ORAL SESSION

ORAL SESSION 1A
BLOOD PRESSURE MEASUREMENT

1A.01 CARDIOVASCULAR EVENTS IN THE SPANISH ABPM REGISTRY

A. De La Sierra1, J. Segura2, JR. Banegas3, M. Gorostidi4, L. M. Ruilope2, N/D SBP 0.96 Night PP 64.0 Night DBP 68.1 Night SBP 132.1 Day DBP 74.6 Day SBP 137.3 24-h DBP 72.8

Background and Aim: Ambulatory Blood Pressure (ABP) is probably a better predictor of cardiovascular events than office blood pressure (OBP), although its role in treated hypertensives in real life conditions is less known. The Cardiorisc Event study aimed to evaluate the association of ABP with the development of cardiovascular events in high-risk patients included in the Spanish ABPM Registry.

Methods: A total of 2115 hypertensive patients with either 3 or more additional risk factors, diabetes, documented target organ damage or previous cardiovascular or renal disease were included. They entered the Spanish ABPM Registry between 2005 and 2006. Vital status and the development of cardiovascular events were checked during 2009. The primary combined endpoint was the sum of death from cardiovascular causes, non-fatal myocardial infarction, non-fatal stroke and coronary or peripheral revascularization procedures.

Results: They were 268 primary events. The relationship between ABP values and the appearance of cardiovascular events is detailed in the Table.

Conclusion: After adjustment for OBP and cardiovascular risk factors and diseases, ABP is related with the development of cardiovascular events. SBP measured 24-hour, daytime and nighttime, all show positive correlations. In the case of DBP, this relationship is only observed with nighttime values.

1A.02 IS BLUNTED HEART RATE DECREASE AT NIGHT ASSOCIATED TO PREVALENT ORGAN DAMAGE IN ESSENTIAL HYPERTENSION?

S. Meani1, C. Cuopidi2, F. Negri3, C. Valerio1, C. Salz4, G. Mancia2. 1Divisione di Cardiologia, Ospedale di Rho, RHO-Italy, 2Dep of Clinical Medicine and Prevention University of Milano-Bicocca-Istituto Auxologico Italiano, Milano-Italy, 3Istituto Auxologico Italiano, Milano-Italy, 4Thoraco-Palm & Cardioirc Dep Fond Polistico-Fiscal Clinica e Iperterpente University of Milano, Milano-Italy

Aim: The association between a blunted decrease in day-night heart rate (HR) and subclinical organ damage has not been previously investigated in human hypertension. Therefore we assessed such association in a cohort of 658 untreated essential hypertensives.

Methods: All subjects underwent procedures including cardiac and carotid ultrasonography, 24-hr urine collection for microalbuminuria, ambulatory blood pressure monitoring (ABPM) with simultaneous assessment of HR, over two-24-h periods within 4 weeks. Non-dipping HR was defined as a mean HR reduction at night lower than 10% compared to day-time values.

Results: A reproducible nocturnal dipping (HR decrease >10% in both ABPM periods) and non-dipping profile was found in 513 (78%) and 76 subjects (12%), respectively; 69 hypertensives (10%) had a variable dipping profile. The three groups did not differ with regard to age, gender, body size, metabolic variables, office and ambulatory BP, left ventricular mass, carotid intima-media thickness, carotid plaque and microalbuminuria. In a univariate analysis, the decrease in nocturnal HR did not correlate with any parameter of subclinical organ damage.

Conclusions: Our findings from a cross-sectional study do not support the view that a flattened HR circadian rhythm is related to a prevalent organ damage in essential hypertension and that this altered pattern is a marker for subclinical cardiovascular disease. The prognostic significance of this finding should be defined by prospective studies.

1A.03 OSCILLOMETRIC ESTIMATION OF CENTRAL BLOOD PRESSURE: VALIDATION OF THE MOBIL-O-GRAPH® IN COMPARISON TO THE SPHYGMOCOR® DEVICE


Objective: Hypertension is a major risk factor for a wide range of cardiovascular diseases and is typically identified by measuring blood pressure (BP) at the brachial artery. Although such a measurement may accurately determine diastolic BP, systolic BP is not reflected accurately. Current noninvasive techniques for assessing central aortic BP require additional recording of an arterial pressure wave using a high-fidelity applanation tonometer. Within one measurement cycle, the mobil-O-Graph® BP device uses brachial oscillometric BP waves for noninvasive estimation of central BP. We therefore validated the mobil-O-Graph® against the SphygmoCor® device, which is widely known as gold standard for noninvasive estimation of central BP.

Methods: For each subject, we compared three readings of central BP values obtained by the mobil-O-Graph® and SphygmoCor® device alternately. 100 subjects (mean age 56.1 ± 15.4 years) were recruited for measurement.

Results: The mean differences (95% CI) for estimated central BP between both devices were –0.43 ± 4.56 mmHg. Comparison of the central BP values measured by the two devices showed statistically significant linear correlation (R = 0.91, p < 0.0001). Intra-rater reproducibility between both devices was also comparable. According to analyses of Bland and Altman, the mean differences (95% CI) between repeated measurements were 1.695 (~0.06 to 3.476) mmHg and 0.97 (~0.64 to 2.58) mmHg, for the SphygmoCor® and mobil-O-Graph® device, respectively. Thus neither of these differences corresponded to the threshold which would necessitate any further action.

Abstract 1A.01

<table>
<thead>
<tr>
<th>Parameter</th>
<th>With CV event</th>
<th>Without CV Event</th>
<th>Unadjusted p</th>
<th>Adjusted by OBP*</th>
<th>Adjusted by confounders**</th>
</tr>
</thead>
<tbody>
<tr>
<td>24-h SBP</td>
<td>136.0 ± 18.0</td>
<td>130.7 ± 15.3</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>24-h DBP</td>
<td>72.8 ± 10.7</td>
<td>73.8 ± 9.9</td>
<td>0.154</td>
<td>0.130</td>
<td>0.119</td>
</tr>
<tr>
<td>24-h PP</td>
<td>63.2 ± 14.8</td>
<td>57.0 ± 12.7</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Day SBP</td>
<td>137.3 ± 18.1</td>
<td>133.4 ± 15.6</td>
<td>0.001</td>
<td>&lt;0.001</td>
<td>0.002</td>
</tr>
<tr>
<td>Day DBP</td>
<td>74.6 ± 11.1</td>
<td>76.3 ± 10.4</td>
<td>0.015</td>
<td>0.730</td>
<td>0.471</td>
</tr>
<tr>
<td>Day PP</td>
<td>62.8 ± 14.9</td>
<td>57.1 ± 13.0</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Night SBP</td>
<td>132.1 ± 20.5</td>
<td>123.5 ± 17.2</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Night DBP</td>
<td>68.1 ± 11.6</td>
<td>66.9 ± 10.4</td>
<td>0.123</td>
<td>&lt;0.001</td>
<td>0.001</td>
</tr>
<tr>
<td>Night PP</td>
<td>64.0 ± 15.7</td>
<td>56.6 ± 13.2</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>N/D SBP</td>
<td>0.96 ± 0.08</td>
<td>0.92 ± 0.09</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>N/D DBP</td>
<td>0.92 ± 0.10</td>
<td>0.88 ± 0.09</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Office SBP, DBP or PP depending on the ABP checked. **Age, gender, diabetes status, and previous CV or renal disease.
Methods:

The oscillometric devices for blood pressure (BP) measurement are regarded as inaccurate in patients with atrial fibrillation (AF). This study assessed the accuracy of a validated oscillometric device for self-home BP measurement that has an algorithm for AF detection (WatchBP100Plus) in subjects with AF. Participants were randomized to perform triplicate BP measurements by 2 observers using Y-tube connected mercury sphygmomanometers or triplicate measurements by a supervisor using the tested device. The alternative method followed until 2 sets of triplicate measurements were obtained by each device. Each set of triplicate mercury or oscillometric device measurements were averaged to give a single systolic and diastolic BP value. The two measurement methods were compared using the European Society of Hypertension International Protocol criteria (mean difference and SD; absolute differences within 5/10/15 mmHg). Twenty-nine patients (mean age 73.8 ± 6.5, 14 men) performed 174 BP measurements by each method. The intraobserver difference was 3.3 ± 4.6/5.2 ± 3.9 mmHg (systolic/diastolic) and the interobserver difference 2.0 ± ≤ 2.2/7.3 ± 4.4 mmHg. The mean difference between the mercury sphygmomanometer and the tested device was 3.1 ± 6.9/7.0 ± 6.5 mmHg. 69% of the BP differences were ≤ 5 mmHg, 85% ≤ 10 mmHg and 93% ≤ 15 mmHg (for diastolic 47%/76%/88% respectively). The tested device successfully detected AF in 90.2% of the BP measurements, in 7.1% AF was missed (false negative) and in 2.7% the measurement was erroneous. These data suggest that the tested oscillometric device has satisfactory accuracy in measuring systolic but not diastolic BP in AF patients. The difficulty in assessing diastolic BP is partially due to the larger interobserver variability. Given that AF affects the elderly population in whom systolic BP carries most of the hypertension induced cardiovascular risk, this device appears to be acceptable for self-home BP monitoring in AF patients in clinical practice.

1A.06 AUTOMATED OSCILLOMETRIC DETERMINATION OF THE ANKLE BRACHIAL INDEX (ABI): A META-ANALYSIS

W. Verberk1, G. Koliias2, G. Stergiou1, 1Microlife Corporation, Taipei-Taiwan, 2Hospital, Athens-Greece

Objective: To investigate the usefulness of automated oscillometric blood pressure (BP) monitors for ankle brachial index (ABI) measurement and peripheral artery disease (PAD) detection.

Methods: Systematic review (Medline/PubMed, Embase and Cochran Library) and meta-analysis of studies comparing automated oscillometric versus conventional Doppler measurements for ABI estimation and PAD detection. Random-effects model analysis of data from 24 identified studies was performed.

Results: Overall, oscillometric ABI was slightly higher than Doppler ABI (mean difference 0.028 [95% CI 0.009, 0.047], p<0.01). The pooled correlation coefficient (r) between oscillometric and Doppler ABI was 0.76 (95% CI 0.70, 0.81). Oscillometric devices specifically developed for ABI measurement compared to the other devices gave lower differences in ABI values versus Doppler (0.012 [95% CI –0.015, 0.040] versus 0.049 [95% CI 0.023, 0.075] respectively, p<0.05) and closer association with Doppler ABI values (r=0.86 [95% CI 0.80, 0.91] versus 0.72 [95% CI 0.66, 0.78] respectively, p<0.03). Oscillometric ABI obtained by simultaneous compared to sequential arm-leg measurements was more closely associated with Doppler ABI (0.85 [95% CI 0.81, 0.89] versus 0.72 [95% CI 0.66, 0.78] respectively, p<0.03). The average sensitivity and specificity of the automated oscillometric ABI estimation in PAD diagnosis was 68% (95% CI 53%, 83%) and 94% (95% CI 93%, 96%) respectively (Doppler method taken as reference).

Conclusions: Automated ABI measurement obtained by oscillometric BP monitors is a reliable and practical alternative to the conventional Doppler measurement for the detection of PAD. Oscillometric devices specifically developed for ABI measurement and providing simultaneous arm-leg measurements appear to provide the closest agreement with the reference Doppler method.

1A.07 A FEW MINUTES REST BEFORE HOME BLOOD PRESSURE MEASUREMENT IS NOT RELEVANT

J.M. Boivin1, E. Boutte2, R. Faye1, P. Rossignol, F. Zannad1, 1CIC-P, Vandoeuvre LesNancy-France, 2Department De Medicine Generale Universite Henri Poincare, Vandoeuvre Les Nancy-France

Background: Home blood pressure measurement (HBPM) is recommended by the European Society of Hypertension (ESH) as well as the French “Haute Autorité de Santé” (HAS), for hypertensive patients diagnosis and follow-up. Measurement protocols are slightly different (2 morning and evening measurements over 3-7 days for the ESH and 3 morning and evening measurements over 3 days for the HAS) but both emphasize preliminary patients education and a few minutes rest before starting the measurements. However, no specific study was designed to evaluate the influence of rest on HBPM.

Objectives and Principal: To determine the influence of rest on the Systolic HBPM reliability, as assessed by its correlation with ABPM (ambulatory blood pressure measurement) as a gold standard; To assess the compliance of rest before HBPM among usual HBPM users.

Methods: 52 treated and controlled hypertensive patients (i.e. casual BP <140/90 mm Hg) were included prospectively in a cross-sectional study. Among them, 38 were usual HBPM users, and were asked about their usual rest compliance before HBPM. A series of 5 morning and evening measurements within three minutes was performed immediately after positioning the cuff (“Rest HBPM”). Then another series was performed five minutes after positioning the cuff (“test HBPM”), over three days. ABPM was also performed within three days before HBPM.

Results: The mean of the 18 SBP NOrest HBPM was closer to the mean daytime ABPM SBP, compared to measurements at rest (p<0.05). An excellent correlation was observed between NOrest HBPM and rest HBPM (r = 0.95, p < 0.0001). A
good correlation was observed between NOrest HBPM, rest HBPM and daytime ABPM (r = 0.71, p < 0.0001). None of 38 interviewed patients declared to respect a few minutes rest before beginning HBPM in current practice, whereas 4 patients respected a measured one minute rest before HBPM.

Conclusions: The recommendation of a few minutes rest before HBPM is not supported by any specific study. Since restless HBPM are more closely correlated to ABPM, these measurements should not be performed after some rest, which is any-way not respected by usual HBPM users.

1A.08 REDUCED NOCTURNAL PULSE PRESSURE DIPPING IN SALT-SENSITIVE MILD HYPERTENSIVE SUBJECTS ALSO DURING HABITUAL DIET. A SCREENING TOOL FOR SODIUM SENSITIVITY?
P. Castiglioni1, G. Parati2, L. Brambilla1, V. Brambilla1, M. Gualerzi1, M. Di Rienzo1, P. Corazzi2. 1Fondazione Don C. Gnocchi, Milan-Italy, 2Dept.Clinical Medicine & Prevention, University of Milano-Bicocca and Istituto Auxologico Italiano, Milan-Italy, 3Fondazione Don C. Gnocchi, Parma-Italy, 4Department of Clinical Sciences/University of Parma, Parma-Italy

Objective: Sodium sensitivity carries an increased cardiovascular risk, which emphasizes the importance of identifying such condition. Unfortunately, the evaluation of a sodium sensitivity status requires a time-consuming protocol that is often challenging for both patients and physicians. Blood pressure (BP) dipping at night is known to be blunted in salt sensitive (SS) subjects during high sodium load. Aim of this study was to evaluate whether nocturnal BP fall is altered in SS mild hypertensive subjects also during the normal sodium load of everyday diet, thus offering an easier way to identify a sodium sensitivity condition.

Design and Methods: We performed 24-hour ambulatory BP monitoring (ABPM) in 46 mild hypertensive subjects under daily-life conditions. Systolic (S) and diastolic (D) BPs, mean arterial (MAP) and pulse (PP) pressures were separately averaged during daytime (8AM –10PM) and night-time (0AM –6AM), defined according to narrow fixed intervals. The corresponding night falls (Sbpnf, Dpbnf, Mapnf, PPNF) were calculated as day-night difference normalized by the daytime value, in percent. All subjects also underwent a sodium sensitivity test. They were classified as SS if MAP was 8 mmHg greater after 1-week of high-salt diet than after 1-week of low-salt diet, otherwise they were classified as salt-resistant (SR). Differences between SS and SR groups were assessed by Mann-Whitney test. Capability to classify a patient as SS or SR was quantified by the daytime value, in percent. All subjects also underwent a sodium sensitivity test. They were classified as SS if MAP was 8 mmHg greater after 1-week of high-salt diet than after 1-week of low-salt diet, otherwise they were classified as salt-resistant (SR). Differences between SS and SR groups were assessed by Mann-Whitney test. Capability to classify a patient as SS or SR was quantified by the daytime value, in percent.

Results: 27 subjects were SR, 19 were SS. The table shows mean (SD) of dipping parameters in SS and SR subjects. Only Pbnpf and Spnpf were significantly reduced in SS vs. SR subjects, with Pbnpf showing the most evident reduction. DBPpbnpf was substantially similar in the two groups.

<table>
<thead>
<tr>
<th>SR</th>
<th>SS</th>
<th>p</th>
<th>AUC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sbpnpf</td>
<td>14.0 (5.1)</td>
<td>10.5 (4.3)</td>
<td>0.02</td>
</tr>
<tr>
<td>MAPnpf</td>
<td>15.5 (5.6)</td>
<td>12.5 (5.2)</td>
<td>0.06</td>
</tr>
<tr>
<td>DBPnpf</td>
<td>16.8 (6.5)</td>
<td>14.4 (5.6)</td>
<td>0.23</td>
</tr>
<tr>
<td>PPNFnpf</td>
<td>8.6 (7.4)</td>
<td>3.2 (5.5)</td>
<td>0.008</td>
</tr>
</tbody>
</table>

Conclusion: The BP dipping pattern at night is reduced in SS subjects even during spontaneous diet, in particular for PP. A blunted PPNFnpf may be related to the need of stimulating the pressure-natriuresis mechanism at night, with impaired Sbpnpf but preserved DBPnpf. Our results suggest that PPNFnpf from 24-hour ABPM may represent a useful tool for an easier identification of SS subjects under spontaneous diet.

1A.09 PROGNOSIS OF ISOLATED SYSTOLIC AND DIASTOLIC HYPERTENSION DETERMINED WITH HOME BLOOD PRESSURE MEASUREMENTS: THE FINN-HOME STUDY
T. Niiranen, A. Aula, J. Johansson, A. Reunanen. National Institute for Health And Welfare, Turku-Finland

Objective: Home blood pressure (BP) measurement is becoming increasingly popular among patients. However, the prognostic significance of home-measured isolated systolic and diastolic BP is somewhat unclear. The objective of this study was to clarify the prognostic significance of isolated systolic and isolated diastolic hypertension as assessed by self-measurement of BP at home, which has a better prognostic value than office BP measurements in the general population.

Design and Method: 2081 randomly selected subjects aged 45 to 74 years from a nationwide cohort were classified into the following 4 groups according to their home BP levels: systolic-diastolic hypertension, isolated systolic hypertension, isolated diastolic hypertension, and normotension. The primary end point was incidence of a cardiovascular event. The prognostic significance of each type of hypertension for the risk of cardiovascular mortality risk was investigated using a Cox proportional hazards regression model adjusted for possible confounding factors.

Results: After a mean follow-up of 6.8 years, 162 subjects had experienced a cardiovascular event. The risk for isolated systolic hypertension (HR 1.58, 95% CI 1.03–2.44, p = 0.04) and systolic-diastolic hypertension (HR 2.13, 95% CI 1.48–3.07, p < 0.001) were significantly higher than for normotension, while isolated diastolic hypertension was associated with no significant increase in risk (HR 0.58, 95% CI 0.19–1.78, p = 0.34).

Conclusions: Isolated diastolic hypertension, as assessed by home BP measurements, carried a low risk of cardiovascular mortality, similar to that found in subjects with normotension, suggesting that the prognosis of hypertension would be improved by treatment focused on systolic rather than on diastolic home BP measurements.

1A.10 BLOOD FLOW IN THE MIDDLE CEREBRAL ARTERY: RELATION TO THE SYSTOLIC AND DIASTOLIC COMPONENTS OF BLOOD PRESSURE IN THE SYSTEMIC CIRCULATION
T. Xu1, Wangxiang Fan1, Jan A Staessen2, Jie Xu3, Fahong Li1, Pingjin Gao1, Jiguang Wang1, Yan Li1. 1Shanghai Institute of Hypertension, Ruijin Hospital, Shanghai Jiaotong University School of Medicine, Shanghai-China, 2The Department of Pharmacology and Toxicology, University of Maastricht, the Netherlands, leuven-Belgium, 3Department of Neurological Surgery, Ruijin Hospital, Shanghai Jiaotong University School of Medicine, shanghai-China

Background: The brain is continually perfused at high-volume flow so that pulsations of pressure and flow originating from the periphery extend well into this organ. We explored the association of the pulsatility of blood flow in the middle cerebral artery (MCA) with the pulsatile and steady components of blood pressure in the systemic circulation.

Design and Methods: We recruited 267 consecutive untreated patients referred for ambulatory blood pressure monitoring (mean age, 51.8 years; 52.4% women). We measured the pulsatility index and resistance index at the MCA (Pimca, Rmca) by transcranial Doppler ultrasonography, and estimated the central mean arterial pressure (MAP) and pulse pressure (PP) using the SphygmoCor system. MAP and PP at the brachial artery in the office and during the ambulatory blood pressure monitoring were measured by the oscillometric devices.

Results: Compared to men, women had faster blood flow at middle cerebral artery (60.5 ± 14.7 vs 59.4 ± 13.3 cm/s, P < 0.001) and lower Pmca (0.76 ± 0.10 vs 0.81 ± 0.15, P<0.001), but similar Rmca (0.52 ± 0.05 vs 0.53 ± 0.06, P = 0.24). In simple correlation analysis, PP, no matter in which way or at which artery it was measured, were significantly (r > 0.33, P < 0.01) associated with Pmca. In contrast, there was no association (P > 0.12) of Pmca and Rmca with central, office and 24-h brachial MAP. After adjustment for sex, age, body mass index, heart rate, MAP, PP (P < 0.001) remained significantly associated with Pmca and Rmca. When central and 24-h brachial PP were included in a single model, only the associations with 24-h PP (P < 0.001) persisted significant.

Conclusion: Increased pulse pressure resulting from arterial stiffening exposes cerebral arteries to higher pulsatile flow, which is transmitted to the small blood vessels in the brain.

1A.11 SUMMER DOES NOT ALWAYS MEAN LOWER: SEASONALITY OF 24 H, DAYTIME AND NIGHT-TIME BLOOD PRESSURE
M. Fedecostante, F. Guerra, P. Barbattelli, L. Lancioni, E. Giannini, E. Espinosa, R. Sarzani, P. Dressi. Poliflucri Internal Medicine Department, University Politecnica Delle Marche, Ancona-Italy

We analyzed data from 4503 ambulatory blood pressure recordings (using Spacelabs 90207) of patients referred to our Hypertension Center between September 2002 and August 2010 to investigate the effects of different seasons on 24-h, daytime and night-time blood pressure. Population was divided by age (younger <65 years of age and elderly ≥65 years of age), sex, and TBS (calculated on the basis of drugs number and dosages). Summer and winter mean temperatures in the Ancona area are usually 24°C and 7°C, respectively, with intermedi- ate temperatures in autumn and spring months. As expected, we found the higher
mean 24h and daytime systolic (SBP) and diastolic blood pressure (DBP) in winter (130.4 ± 13.9/79.3 ± 10.3 mmHg for the 24h, 133.8 ± 14.0/82.5 ± 10.6 mmHg for daytime) and significantly lower in summer (128.6 ± 13.0/77.6 ± 9.8 mmHg for 24 h, 130.9 ± 13.1/80.0 ± 10.0 mmHg for daytime) (p < 0.001). In autumn and spring blood pressure values were not significantly different, even after adjusting for sex, age and treatment. On the other hand, the highest night-time mean SBP was recorded in summer and was significantly different even versus the winter season (123.3 ± 14.5 mmHg in summer vs. 122.0 ± 15.4 mmHg in winter, p = 1) although seasonal differences were less pronounced. This results were confirmed after adjustment for sex, age and TIS. Our data on a very large population confirm that hottest seasons were associated with lower blood pressure compared to coldest confirming the findings of previous scientific studies. However, the inverse relationship found in night-time BP was quite unexpected and might be related to different sleeping behaviors between summer and the other seasons. These data are especially important as night-time BP could become a new therapeutic target given the strong association with organ damage.

**1A.12 ON-TREATMENT AMBULATORY BLOOD PRESSURE IS A POTENT PREDICTOR OF FUTURE CARDIOVASCULAR RISK IN THE DUBLIN OUTCOME STUDY**

E. Dolan1, E O’Brien2. 1Stroke and Hypertension Unit, Connolly hospital, Dublin-Ireland; 2Conway institute, UCD, Dublin-Ireland

**Introduction:** There is increasing acceptance of ambulatory blood pressure (ABP) in clinical practice. Mostly however this is confined to screening for white coat hypertension etc. There is considerable data showing that ABP is superior to office blood pressure (OBP) for predicting future risk and we previously demonstrated that in this cohort. Follow-up ABP may be a more potent predictor of future risk.

**Methods:** At baseline, when not on an hypertensive medica on, 11,291 patients (5526 male, mean age 54.6 years) underwent ABP. Over a mean follow up of 5.3 years there were 566 cardiovascular deaths. 5,326 patients while on treatment had a follow up ABP within 3 years of the initial recording.

**Results:** In a Cox proportional-hazard model, on-treatment 24-hour SBP was an independent predictor of cardiovascular and in particular stroke mortality after adjustment for sex, smoking history, previous cardiovascular events, diabetes, body mass index (BMI), and initial 24-hour SBP. Fall in blood pressure between was two recordings was the strongest measure with a 10mmHg fall in 24 hour SBP reducing risk of stroke deaths by 34% and cardiac by 24%.

**Conclusions:** Response to therapy is an important indicator to outcome. While the greater use of ABP in the initial management of hypertension is to be welcomed it should also be used to monitor progress and response to therapy.
ORAL SESSION

ORAL SESSION 1B

EPIDEMIOLOGY

[1B.01] IMPACT OF NADIR CD4 CELL COUNT AND ANTIRETROVIRAL THERAPY ON HYPERTENSION IN A LONGITUDINAL STUDY OF HIV-INFECTED INDIVIDUALS

I. W. Manner1, M. Baekken2, O. Oektdalen1, I. Os1, 1Faculty of Medicine, University of Oslo, Oslo-Norway, 2Hypertension Unit, H. Clinico SAN Carlos, Madrid-Spain, 3Institute of Clinical Chemistry, H. Clinico SAN Carlos, Madrid-Spain, 4Epidemiology Department. H. Clinico SAN Carlos., Madrid-Spain

Objective: Little is known about the development of hypertension over time in HIV-infected patients. In a longitudinal study of an HIV-infected cohort, the prevalence and new development of hypertension were assessed.

Design and Method: In a cohort of 434 HIV-infected individuals, blood pressure (BP) was measured in duplicate at 3 different visits at baseline and after 18.1/81.6 ± 10.9 mmHg, and HT was present in 34.8%. The prevalence of HT was unchanged during follow-up, 34.8%. In the 127 hypertensive persons without HT at baseline, 29 (22.8%) were no longer hypertensive, while 29 (10.2%) of 283 normotensive developed hypertension.

Methods: This prospective study included 315 pregnant women between weeks 10th and 13th of pregnancy that were referred from the Prenatal Diagnosis Unit of Hospital Clínico San Carlos, Madrid. Exclusion criteria: multiple gestation, chronic hypertension, cardiovascular pathology, creatinine >1.3mg/dL, hypothyroidism, autoimmune diseases, Diabetes Mellitus, previous gestational diabetics, treatment with methotrexate or antiepileptic drugs, previous PIH or PE and maternal age over 40. We measured in every trimester: total cholesterol, HDL-cholesterol, triglycerides, uric acid, creatinine, cystatin-C, CRP, with PAPP-A and free-HCGC being measured only in the first trimester specimen. Samples were obtained on the obstetric visit day. PIH was defined as BP ≥140/90 mmHg and/or ≥200mg/dl (two times with a six hour time interval), after the 20th week of pregnancy. PE was considered as PIH and proteinuria. (≥ 300mg/24hours or ≥30mg/dL). For the statistical analysis c2 (or Fisher’s), t-student, and non parametric median tests were used. ROC and multiple logistic regression analysis were used.

Results: When comparing PIH status (6.1%) vs control pregnant women, the study shows significant statistical differences in the following way: in the first trimester (weeks 10th-13th) in BMI (p = 0.01) and uric acid (p = 0.02), in the second trimester (weeks 20th-22nd) in HDL-cholesterol (p = 0.02) and in the third trimester (weeks 31th-33rd) in total cholesterol (p = 0.04) and uric acid (p<0.001). Moreover results showed an increase in the risk of PIH for Uric acid >3.15mg/dl, in the 1st trimester (p = 0.01) and for creatinine >0.60mg/dl and HDL-cholesterol <66.5mg/dl in the 2nd trimester (p = 0.006 and p = 0.007). In addition, when we considered an increase in the rate of change of uric acid and cystatin-C between 1st and 2nd trimesters we found that the risk of PIH increases (RR = 2.76 and RR = 4.10 respectively).

Conclusion: This study suggests that the renal function biomarkers seem to play a potential role in the early prediction of Pregnancy-induced hypertension.

[1B.02] BIOCHEMICAL PREDICTORS OF PREGNANCY-INDUCED HYPERTENSION

N. Martell-Claro1, M. ABAAD-Cardiel1, F. Blanco-Kelly2, M. A. Herráz1, M. E. Fuentes1, J. M. Torregó1, A. Fernandez-Cruz2, 1Hypertension Unit, H. Clinico SAN Carlos, Madrid, Madrid-Spain, 2Clinical Chemistry Department. H. Clinico SAN Carlos, Madrid-Spain, 3Gynaecology and Obstetrics Department, H. Clinico SAN Carlos, Madrid-Spain, 4Epidemiology and Preventive Medicine Department. H. Clinico SAN Carlos, Madrid-Spain

Pregnancy-induced hypertension (PIH) and Preeclampsia (PE) are multi-system disorders. They contribute substantially to perinatal morbidity and mortality of both mother and fetus. In recent years many biochemical maternal markers have been evaluated, but until now none of them have shown clear reliability for use in practice.

Aim: To evaluate if any of the biochemical markers used in the monitoring of pregnancy can be used as early predictors of the development of pregnancy-induced hypertension.

Methods: This prospective study included 315 pregnant women between weeks 10th and 13th of pregnancy that were referred from the Prenatal Diagnosis Unit of Hospital Clínico San Carlos, Madrid. Exclusion criteria: multiple gestation, chronic hypertension, cardiovascular pathology, creatinine >1.3mg/dL, hypothyroidism, autoimmune diseases, Diabetes Mellitus, previous gestational diabetes, treatment with methotrexate or antiepileptic drugs, previous PIH or PE and maternal age over 40. We measured in every trimester: total cholesterol, HDL-cholesterol, triglycerides, uric acid, creatinine, cystatin-C, CRP, with PAPP-A and free-HCGC being measured only in the first trimester specimen. Samples were obtained on the obstetric visit day. PIH was defined as BP ≥140/90 mmHg and/or ≥200mg/dl (two times with a six hour time interval), after the 20th week of pregnancy. PE was considered as PIH and proteinuria. (≥ 300mg/24hours or ≥30mg/dL). For the statistical analysis c2 (or Fisher’s), t-student, and non parametric median tests were used. ROC and multiple logistic regression analysis were used.

Results: When comparing PIH status (6.1%) vs control pregnant women, the study shows significant statistical differences in the following way: in the first trimester (weeks 10th-13th) in BMI (p = 0.01) and uric acid (p = 0.02), in the second trimester (weeks 20th-22nd) in HDL-cholesterol (p = 0.02) and in the third trimester (weeks 31th-33rd) in total cholesterol (p = 0.04) and uric acid (p<0.001). Moreover results showed an increase in the risk of PIH for Uric acid >3.15mg/dl, in the 1st trimester (p = 0.01) and for creatinine >0.60mg/dl and HDL-cholesterol <66.5mg/dl in the 2nd trimester (p = 0.006 and p = 0.007). In addition, when we considered an increase in the rate of change of uric acid and cystatin-C between 1st and 2nd trimesters we found that the risk of PIH increases (RR = 2.76 and RR = 4.10 respectively).

Conclusion: This study suggests that the renal function biomarkers seem to play a potential role in the early prediction of Pregnancy-induced hypertension.
Noncommunicable diseases, Republic of Seychelles—Seychelles, 3University of T. Lyngdoh1, B. Viswanathan2, G. Myers3, M. Bochud1, P. Bovet1.

LDL, respectively), despite the more intensive therapeutic intervention. Risk (low-moderate: 49% and 53%; very high: 30% and 14%, for HbA1c and beta-blocker or diuretic treatment. Furthermore an inadequate treatment—was unsatisfactory in treated patients without BP control and in those under beta-blocker or diuretic treatment. Metabolic syndrome is worse in higher CV risk categories and in patients without a satisfactory BP control. These adverse relationships may explain the elevated CV morbidity and mortality profile of population living in Central and Eastern European countries.

Conclusions: In Eastern European countries hypertension and CV risk profile are only partly related to altered pressure in LDL. LDL is a high profile. Metabolic syndrome is worse in higher CV risk categories and in patients without a satisfactory BP control. These adverse relationships may explain the elevated CV morbidity and mortality profile of population living in Central and Eastern European countries.

**18.04 IMPACT OF DIFFERENT ADIPOSY MEASURES ON THE RELATION BETWEEN SERUM URIC ACID AND BLOOD PRESSURE IN YOUTH**

T. Lyngdoh1, B. Viswanathan2, G. Myers1, M. Bochud1, P. Bovet1. 1Institute of Social and Preventive Medicine, University of Lausanne & University Medical Center, Lausanne-Switzerland, 2Ministry of Health, Section of Noncommunicable diseases, Republic of Seychelles-Seychelles, 3University of Rochester Medical Center, NY-USA

**Background:** Increasing evidence suggests that serum uric acid (SUA) concentration is independently associated with blood pressure (BP) in adults. We examined this association in young adults at an age where anti-hypertension treatment, other potential confounding factors and co-morbidity are unlikely to occur.

**Methods:** We assessed BP, anthropometric variables including weight, height, waist circumference (WC), body fat percent (using bioimpedance), lifestyle behaviors, and SUA and blood lipids in 549 participants aged 19–20 years from a population-based cohort study (Seychelles Child Development Study).

**Results:** Mean (SD) SUA was higher in males than females, respectively 0.33 (0.08) mmol/L and 0.27 (0.06) mmol/L. SUA was higher in females than males and BP was markedly higher in males than females. Systolic and diastolic BP was significantly associated with SUA. However, the magnitude of the linear regression coefficients relating BP and SUA was attenuated by up to 50% upon adjustment for body mass index (BMI), waist circumference (WC) or body fat percent, while virtually unchanged upon adjustment for body weight-to-height ratio (WHR). Further adjustment for alcohol intake or triglycerides did not alter the association between SUA and BP. In fully adjusted models, SUA remained associated with diastolic BP in the overall sample. SUA levels with both systolic and diastolic BP were inversely correlated in the overall sample. We observed higher prevalences of obesity (42.9% vs 40.7%, p = 0.015) and had a higher BMI (29.6 vs 28.1 kg/m2), all p < 0.001. Prevalence of a high/very high added cardiovascular risk was 46.2% in patients with IFG and 34.8% in NG patients, p = 0.001.

**Conclusions:** In well-controlled hypertensives, IFG was present in nearly 60% of patients. IFG identified patients with an increased need of antihypertensive drugs and a high likelihood of being in a high/very high added cardiovascular risk situation.

**18.06 OBESITY IS ASSOCIATED WITH INCREASED DAYTIME AND NIGHT-TIME PROXIMAL TUBULAR SODIUM REABSORPTION IN THE GENERAL ADULT POPULATION**

M. Bochud1, G. Wuerzner2, M. Maillard2, P. Vollenweider1, F. Paccard1, M. Burnier1, 1Institute of Social and Preventive Medicine, Lausanne-Switzerland, 2Nephrology Division, University Hospital of Lausanne (CHUV), Lausanne-Switzerland, 3Department of Internal Medicine, University Hospital of Lausanne (CHUV), Lausanne-Switzerland

**Background:** Obesity is associated with increased risk of hypertension and with non-dipping. A postulated mechanism is increased sodium retention in the kidney, but population-based data are scarce. We analyzed the association of circadian renal tubular sodium handling with overweight and obesity in the Hercules study.

**Methods:** Of the 437 Caucasian participants randomly selected from the population-based CoLaus study (Switzerland), 380 had data for the present analysis. We estimated proximal tubular sodium reabsorption (RNaprox) using fractional excretion of endogenous lithium, with separate day and night urine collections. Ambulatory blood pressure (BP) was measured using Diays Integra devices. We used multiple linear regression to account for potential confounders.

**Results:** The 193 women and 187 men had mean (SD) age 57.0 (10.1) and 56.1 (10.8) years, with 42.0% overweight, 14.5% obesity and 42.9% hypertension (daytime BP ≥ 135/85 mm Hg). Obesity was associated with hypertension (OR = 3.9, P = 0.001) and reduced nocturnal systolic BP dipping (defined as <10% dipping, P = 0.046). Unadjusted median RNaprox were 87.1%, 88.5% and 90.2% for daytime (P = 0.005) and 87.3%, 88.0%, 90.3% for night-time (P = 0.067), in normal weight, overweight and obese people, respectively. The corresponding adjusted RNaprox (age, sex, smoking, mean BP, urinary Na and K excretion and urine flow rate) were 86.5%, 87.8% and 89.8% for daytime (P = 0.003) and 87.1%, 87.7% and 90.4% for night-time (P = 0.015).

**Conclusions:** At similar BP levels, overweight and obese people have increased day and night proximal sodium reabsorption. This first report of circadian segmental tubular sodium handling in human obesity is consistent with increased BP salt-sensitivity during day and night.

**18.07 INCREASED DAYTIME PROXIMAL SODIUM REABSORPTION IS ASSOCIATED WITH REDUCED NOCTURNAL BLOOD PRESSURE DIPPING IN THE GENERAL POPULATION**

M. Bochud1, G. Wuerzner2, M. Maillard2, A. Beggah1, P. Vollenweider1, F. Paccard1, M. Burnier1, 1Institute of Social and Preventive Medicine, Lausanne-Switzerland, 2Nephrology Division, University Hospital of Lausanne (CHUV), Lausanne-Switzerland, 3Department of Internal Medicine, University Hospital of Lausanne (CHUV), Lausanne-Switzerland

**Background:** The absence of a nocturnal blood pressure (BP) decrease (dipping) is associated with target organ damage, but the determinants of dipping are not well known. We recently showed, in people of African descent, that reduced capacity to excrete sodium during daytime was associated with higher nocturnal BP and reduced dipping. We now explore this relationship in Caucasians.

**Methods:** Among participants to the population-based Hercules study, 351 had data for the present analysis. We estimated proximal tubular sodium reabsorption (RNaprox) using endogenous lithium and creatinine clearances, from separate day and night urine collections. We determined proportional BP dipping from ambulatory BP data measured using Diays Integra devices. We used multiple robust regression to account for potential confounders. We separated participants into tertiles of day-night ratio of urinary sodium excretion rates (UNa_ratio).
Results: The mean ± SD age was 56.7 ± 10.6, mean daytime and nighttime SBP were 120.8 ± 14.8 and 105.5 ± 15.2, respectively. Hypertension prevalence was 43%, half of whom were treated. Proportional BP diurnal variation was 11.1%, 13.1% and 15.8% for systolic and 11.9%, 10.8% and 14.8% for diastolic, in tertiles 1 (poor daytime Na excretors), 2 and 3 (good daytime excretors), respectively (P trend <0.002). In multiple linear regression, UNa_ratio was a significant determinant of nocturnal SBP (P = 0.042) at fixed daytime SBP. Proportional SBP dipping correlated negatively with daytime RNAprox (P = 0.02), even upon adjustment for confounders.

Conclusions: Increased daytime proximal sodium reabsorption is associated with reduced nocturnal BP dipping. Caucasians having difficulties to excrete sodium during daytime have increased nocturnal BP and may therefore be at higher cardiovascular risk.

1B.08 HIGH PLASMA LEPTIN LEVELS PREDICT THE DEVELOPMENT OF INSULIN RESISTANCE IN AN INSELECTED SAMPLE OF ADULT MALE POPULATION. RESULTS OF THE OLIVETTI HEART STUDY (OHS)

F. Galletti, L. D’Elia, G. Rossi, D. De Palma, R. Ippolito, A. Barbato, P. Strazzullo, Dept of Clinical & EXP Medicine, Federico II University of Naples, Naples-Italy

Objective: Elevated levels of plasma leptin (LPT) are associated with overweight and reduced arterial compliance; however, it is not clear whether hyperleptinemia antedates and possibly gives a causal contribution to the development of insulin resistance (IR). Aim of our analysis of the OHS database was to establish whether LPT measured at the 1994-5 examination (baseline) predicts the risk to develop IR over an average follow-up of 8 years. IR was defined as a HOMA index >1.77 (80% percentile for a normal weight adult male Italian population).

Methods: The study population was made of 288 men with normal insulin sensitivity at baseline (HOMA < 1.77) (M ± SE; age: 51.0 ± 0.4 yrs, BMI: 25.9 ± 0.1 kg/m², HOMA: 1.25 ± 0.02) and was stratified by tertile (T) of baseline LPT (T1: age: 50.0 ± 0.7 yrs, LPT: 1.2 ± 0.1 ng/mL; T2: age: 50.5 ± 0.7, LPT: 2.9 ± 0.1; T3: age: 52.5 ± 0.7, LPT: 6.3 ± 0.2).

Results: Body weight, plasma leptin and insulin tended to increase over time. The changes in body weight (BW) and LPT occurred over 8 years were not different between tertiles (M ± SE; DBW: +1.3 ± 0.4, -0.3 ± 0.5 and +0.5 ± 0.4 Kg respectively, p = 0.21; DLPT: +3.4 ± 0.3, +3.1 ± 0.2 and +2.7 ± 0.5 ng/mL, p = 0.49). By contrast, significant differences were detected in the changes occurred in HOMA by tertile of baseline LPT: T1: <0.07 ± 0.07, T2: 0.34 ± 0.10, T3: 0.60 ± 0.12, for p trend = 0.001. The incidence of IR defined as a HOMA >1.77 over 8 years was significantly different between groups: T1 = 19.4%, T2 = 31.5%, T3 = 38.5%, p = 0.01. At multiple linear regression analysis, baseline LPT (ng/mL) was a significant predictor of the risk to develop IR (odds ratio = 1.55, 95% CI: 1 = 1.00-2.50, p = 0.001), upon adjustment for age, basal HOMA, basal BMI and DBW (R² = 13%). In addition LPT was also associated with BP, as a matter of fact, a positive trend between LPT tertile at baseline and BP at the end of the study was detected, but the analysis did not achieve a statistical significance (M ± SE; T1: +3.3 ± 1.3; T2: +3.64 ± 1.6; T3: -1.2 ± 1.7 mmHg; p for trend = 0.14).

Conclusions: In this unselected sample of adult male population with normal insulin sensitivity at baseline, basal plasma leptin was a significant predictor of the risk to develop IR over 8 years, independently of the main potential confounders.

1B.09 INCREASES IN CENTRAL FAT AND DECREASES IN PERIPHERAL FAT MASSES ARE ASSOCIATED WITH ACCELERATED ARTERIAL STIFFENING IN HEALTHY ADULTS. THE AMSTERDAM GROWTH AND HEALTH LONGITUDINAL STUDY

F. Schouten1, J. W. Twisk1, M. De Boer, E. H. Serne1, C. D. Stehouwer2, Y. M. Smulders1, I. Ferreira3, VU University Medical Center Amsterdam- The Netherlands, Maastricht University Medical Centre, Maastricht-The Netherlands

Background & Aims: Central fatness, is associated with higher arterial stiffness, a mechanism that may explain adiposity-related increases in cardiovascular risk. In contrast, peripheral fat mass may counteract such adverse effects, but evidence for this contention, as derived from longitudinal studies at the general population level, is lacking. We have therefore investigated: 1) the associations between changes in central fat (i.e. trunk) vs. peripheral (i.e arms and legs) fat masses with changes in arterial stiffness; and 2) the phenotypes of changes in body composition/fat distribution characterized by the steepest increases in arterial stiffness.

Methods: Longitudinal study among 277 (145 women) healthy adults in whom body composition (dual-energy x-ray absorptiometry) and arterial stiffness estimates (ultrasound imaging), were measured at baseline and repeated at 16, 26, and 36 years. Data were analyzed with the use of multiple linear regression models.

Results: Changes (per 10kg) in trunk fat were positively whereas changes in peripheral fat were inversely associated with the carotid’s Young’s elastic modulus (in 103kPa) [β = 0.14 (95% CI: 0.02; 0.25) and –0.16 (–0.30; –0.01)], and the carotid-femoral pulse wave velocity (in m/s) [β = 1.54 (0.02; 3.07) and –1.46 (–3.48; 0.56), respectively]. These detrimental and additive ‘effects’ of increases in trunk and decreases in peripheral fat masses on arterial stiffness were independent of one another and concomitant changes in lean mass, mean arterial pressure and other risk factors. Notably, this pattern of changes in body fat distribution: was accompanied by only minor increases in body weight (+1.5 Kg) but well within the limits of a normal-weight range (i.e. BMI < 25 kg/m²); occurred in about 1/3 of the study population; and identified a group of individuals exhibiting the steepest increases in arterial stiffness over the 6-yr follow-up period.

Conclusions: Changes in body composition characterized by a combination of increases in trunk and decreases in peripheral fat masses, occur relatively often, are not captured by alarmingly elevated levels of BMI or changes in body weight, but contribute to accelerated arterial stiffening. From a primary prevention point of view, these findings suggest that monitoring changes in body fat distribution, focusing not only in levels of central but also of peripher- nal fat, may help identify those individuals who, even if within the normal-weight range, are in need and can benefit from lifestyle interventions. These findings also provide an additional insight to the aetiology of adiposity- related increases in arterial stiffness and related cardiovascular sequelae.
**ORAL SESSION 1C**

**SMALL VESSELS**

**1C.01 ENHANCEMENT OF ANGIOTENSIN II INDUCED CONTRACTION BY OXIDATIVE STRESS INVOLVES ACTIVATION OF p38 MAPK IN MESENTERIC ARTERIES OF MICE**

A. Patzak1, S. Schmidt1, M. Fuehling1, M. Gaerte1, J. Retting-Zimmermann1, A. Perkowitz1, P. Martin1ka1, 1Charité-Universitätsmedizin Berlin, Berlin-Germany, 2Medical School Hannover, Hannover-Germany

Reactive oxygen species (ROS) are involved in several cell functions and play a role in angiotensin II signaling as well as p38 MAPK activation. We hypothesized that oxidative stress strengthens angiotensin II contractions by activating the p38/MK2 pathway in mesenteric arteries. Oxidative stress was induced by Nadph application. Small mesenteric arteries (SMA) from adolescent (65 ± 6 d) and adult (160 ± 20 d) C57Bl6 mice were investigated under isometric conditions (wire myograph). Concentration-responses (CR) to angiotensin II were similar in both groups under control conditions. Only in adults Nadph treatment increased the maximum contraction to angiotensin II; and L-NAME/Nadph co-treatment shifted the CR to the left. The endothelium dependent relaxation induced by acetylcholine did not differ between Nadph treated and non-treated vessels, while the endothelium independent relaxation by sodium nitroprusside was slightly improved in Nadph treated vessels. Calcium transients did not differ in response to angiotensin II comparing Nadph treated and non-treated adult vessels. Inhibition of p38 MAPK prevented the Nadph effect. Nadph did not affect the angiotensin II responses in MK2-/- mice. Western blots showed increased phosphorylation of p38 MAPK and MLC20 after Nadph + angiotensin II compared to angiotensin II alone in adult wild types. In conclusion, oxidative stress increases angiotensin II responses age dependently in SMA.

**1C.02 RETINAL PULSE WAVE VELOCITY IN MALE SUBJECTS WITH OPTIMAL TO MILD BLOOD PRESSURE VALUES**

K. Kottiar1, H. Hanssen1, K. Berhardt1, W. Vils1, M. Halle1, U. Heemann1, M. Baumann1. 1Department of Nephrology, Munich University of Technology, Munich-Germany, 2Division of Sports Medicine, Institute of Exercise and Health Sciences, University of Basel, Basel-Switzerland, 3Imedos Systems Ung-Jena-Germany, 4Department of Prevention and Sports Medicine, Munich University of Technology, Munich-Germany

Objective: Hypertension is associated with an increase in the wall/lumen ratio of resistance arteries. Increased microvascular stiffness contributes to an increase in wall/lumen ratio. We aimed to investigate the possibility to transform the measurement of macrovascular stiffness into a microvascular environment. Therefore, we assessed retinal pulse wave velocity (pPWV) non-invasively in male normoalbuminuric normotensive to mildly hypertensive subjects.

Design and Method: 65 subjects (age: 28.7 ± 6.0 years) were examined. Time dependent alterations of vessel diameter were assessed by the Dynamic Vessel Analyzer (Imedos Systems, Jena, Germany) simultaneously in different places within a segment of a retinal artery. The data was filtered and evaluated by methods of mathematical signal analysis and pPWVs were calculated. Office blood pressure (BP), albumin/creatinine ratio and augmentation index (AIx) were assessed.

Results: Subjects demonstrated albuminuria below the range of microalbuminuria. pPWV, not AIx, showed a significant association with systolic and diastolic BP (r = 0.63, r = 0.40, p<0.01). As the cohort was divided according to BP, mildly hypertensive patients showed significantly higher pPWV (1554 ± 867 units/second) than subjects with high-normal BP (983 ± 607 units/second, p < 0.01) or normotensive subjects (552 ± 185 units/second, p<0.001).

Conclusions: Applying methodological principles for aortic PWV we consider pPWV as a non-invasive measure of microvascular stiffness. pPWV shows strong association with BP and can differentiate BP in a cohort with optimal to mildly elevated BP. Our results suggest that blood pressure dependent microvascular changes may precede macrocirculatory changes. Moreover, as our study was performed in normoalbuminuric subjects, pPWV may add detailed insights to early microvascular pathophysiology, potentially beyond microalbuminuria.

**1C.03 THE PATTERNS OF THE RETINAL MICROVASCULAR NETWORK ARE NOT RELATED TO THE OVERWEIGHT OR THE OBSESE STATE**

S. Buzzi1, R. Dell’oro1, C. MinEo1, G. Seravalle1, L. Lonati1, G. Brambilla1, C. Giannattasio1, G. Mancia1, G. Grassi1. 1Clinica Medica Ospedale S Gerardo Monza Universita Milano-Bicocca, Monza-Italy, 2Istituto Auxologico Italiano, Milan-Italy

Introduction: Previous studies by our group and others have provided evidence that blood pressure (particularly systolic) is an important determinant of the retinal vascular network characteristics and that the microvascular alterations seen in hypertension are directly related to the severity of the hypertensive state. Whether body weight and body fat depot are also major determinants of the patterns of the retinal microcirculation is debated. It is also debated the impact of the overweight or the obese state on the retinal microvascular network.

Methods: In 278 healthy subjects of both genders (age: 53.4 ± 0.6, mean ± SEM), displaying a wide range of body weight values, we measured anthropometric parameters, clinic and ambulatory blood pressure and metabolic variables (insulin, HOMA index, leptin). Measurements also included arterial-venular ratio (AVR), central retinal artery and vein equivalent (CRAE and CRVE, respectively), assessed via non-myriadic retinography (TopCon TRC-NW200).

Results: In the population as a whole clinic blood pressure values amounted to 134.2/84.6 mmHg, 24-hour blood pressure to 120.9/79.6 mmHg, body mass index (BMI) and abdominal circumference (AC) to 26.1 kg/m2 and 89.4/97.9 (female/male) cm respectively. BMI was < 25 kg/m2 in 115 individuals (classified as lean), while it was between 25 and 30 kg/m2 in 111 overweight and > 30 kg/m2 in 52 obese (the 3 groups were age-matched and displayed systo-diastolic BP values in the normal range with a tendency to greater values in the obese group. In the population as a whole AVR did not show any significant relationship with BMI (r = 0.027, NS ) and AC (r = 0.2, NS), this being the case also for CRAE and CRVE. Furthermore AVR ratio was similar in lean, overweight and obese subjects (0.85 ± 0.01, 0.84 ± 0.005 and 0.87 ± 0.009 a.u., respectively, NS). No significant difference in AVR was also found by subdividing the obese group according to the central or peripheral distribution of the excessive fat depot (0.89 vs 0.84) both in male and female subjects. A similar behaviour was seen for CRAE and CRVE. No relationship was finally found between insulin, HOMA and leptin with the 3 markers of the retinal microvasculature.

Conclusions: Our data show that in contrast to blood pressure body weight is not a major determinant of the patterns of the retinal microcirculatory network. They also show that the obese state does not affect the main features of the retinal microvascular network. Whether body weight and body fat depot are also major determinants of the patterns of the retinal microcirculation and that this is the case independently on the central or peripheral nature of the obese state.

**1C.04 PERIVASCULAR ADIPOSE TISSUE RELAXING FACTOR AND THE BKCA CHANNEL IN MOUSE MESENTERIC SMALL ARTERIES**

F. Lynch, S. Withers, A. Heagerty. University of Manchester, Manchester-United Kingdom

Objective: It has previously been reported that perivascular adipose tissue exerts an anticontractile effect on vascular tone which may provide protection against the development of hypertension. We have shown that this response is dependent on the BKCa channel in isolated small mesenteric arteries from mice. This may be a major influence on blood pressure. Recently, we have identified adiponectin as the vasoactive adipokine in the mouse model. The aim of this study is to
determine whether the BKCa channel is required to transduce the anticontractile signal.

Methods: Male and female, C57BL/6 (Wild type (WT)), BKKb-/- mice, Slo +/- (WT) and slo-/- (12-18 week old ~25g weight) were killed by stunning and cervical dislocation. Cumulative concentration responses (10^-10^-5 M) to norepinephrine (NE) were performed. Solution transfer experiments were performed. Solution was transferred from baths containing preconstricted (10^-5 M NE) WT PVAT arteries and transferred to baths containing PVAT arteries from WT and knockout animals. Responses are expressed as mean change ± SEM in tension (mN/mm) and analysed using student’s t test.

Results: Transfer of bath solution from preconstricted WT PVAT arteries to preconstricted (0.65 ± 0.1mm/nm) WT arteries -PVAT (n = 6) significantly reduced (p<0.05) tension (0.43 ± 0.1nm/mm). However, transfer of solution from preconstricted WT PVAT arteries (n = 6) to preconstricted (0.48 ± 0.2nm/mm) BKKb-/- arteries -PVAT did not significantly alter tension (0.56 ± 0.3nm/mm). Transferral of solution from preconstricted WT PVAT arteries to preconstricted (0.25 ± 0.1nm/mm) slo-/- arteries -PVAT (n = 6) did not significantly alter tension (0.26 ± 0.1nm/mm). Fig 1 shows the transfer-induced change in tension.

Conclusion: These data demonstrate that PVAT releases an anticontractile factor which reduces tension in isolated mouse mesenteric arteries. The effects of this factor are mediated by the BKCa channel. Previous findings suggest that adpinectin is this factor.

1C.05 SIMVASTATIN TREATMENT IMPROVES AUTONOMIC CONTROL OF CIRCULATION AND REDUCES NORADRENALINE-INDUCED CONTRACTION IN RESISTANCE VESSEL FROM HYPERCHOLESTEROLEMIC MICE

I. C. Moraes-Silva1, L. E. Souza1, L.V. Rossoni2, K. De Angelis1, M. C. Iriyogun1,1 Hypertension Unit, Heart Institute (InCor), University of São Paulo Medical School, São Paulo-Brazil,2 Department of Physiology and Biophysics, Institute of Biomedical Sciences, University of São Paulo, São Paulo-Brazil

Statin pleiotropic effects have been widely studied since its targets and mechanisms are not only restricted to the lipids profile improvement. Therefore, our aim was to evaluate the effects of simvastatin treatment (S) in blood pressure (BP) and cardiovascular autonomic control, as well as in the contraction induced by noradrenaline (nor) in mesenteric resistance arteries (MRA) of hypercholesterolemic mice (LDL receptor knock out).

Methods: Male (25-30g), Ldlko mice were treated with S (2 mg/kg, i.p. 7 days; n = 5) or vehicle (n = 5). A third group of C57Bl/6 mice was used as control (CTR; n = 8). Total cholesterol (TC) was measured before and after treatment by Accutrend device (Roche). After the 7-day treatment, carotid artery and jejunal vein were catheterized for hemodynamic measurements (Windaq, 4KHz). Baroreflex sensitivity was evaluated by bradycardic and tachycardic responses to vasoactive drugs. Autonomic modulation was studied in time and frequency domains by spectral analysis, calculated by the fast Fourier’s transform method. MRA (internal diameter ~180-200 μm) were analyzed in a wire myograph. Concentration-response curves to NOR (10^-10^-3 M) were obtained in endothelium-intact rings.

Results: Initial TC was ~3-5 fold higher in Ldlko mice vs. CTR and treatment with S did not alter it. BP was increased in Ldlko mice (systolic:+30%, diastolic:+7% vs. CTR) and there was no significant improvement in this parameter after S treatment. On the other hand, baroreflex sensitivity, which was decreased in Ldlko mice (-45% for bradycardic reflex and -73% for tachycardic reflex vs. CTR), was normalized after S treatment. HR variability was sharply reduced in Ldlko mice (~90%) whereas BP variability was increased by 2-fold in relation to CTR. The Ldlko+S group showed an improvement of ~80% in these parameters; however, they did not reach control values. Cardiac autonomic balance was 3-fold increased in Ldlko vs. CTR, indicating augmented sympathetic modulation. Additionally, the low frequency component to the vessels was 5-fold increased in Ldlko vs. CTR and S treatment reduced it in 82%. Interestingly, NOR-induced contraction in MRA was higher in Ldlko mice vs. CTR, while S treatment restored this contraction to CTR levels.

Conclusion: Treatment with S, even in a subpressor dose, is able to improve autonomic and vascular control of blood pressure in genetically hypercholesterolemic mice.

Financial Support: CNPq, Fapesp and Funderação Zerbini.

1C.06 ALTERATION IN BETA-ADRENERGIC RELAXATION IS ASSOCIATED WITH MYOCARDIAL INFARCTION ADJUSTMENTS IN CORONARY ARTERIES FROM NORMOTENSIVE AND HYPERTENSIVE RATS

G. K. Couto, L. V. Rossoni. University of Sao Paulo, Sao Paulo-Brasil

Objective: Hypertension is an important risk factor to myocardial infarction (MI). Both hypertension and MI are associated with an increment in sympathetic drive. Beta-adrenceptors (beta-AR) are an important vasodilatory pathway in coronary artery (CA) and contributes to the maintenance of the cardiac perfusion. Thus, the aim of this study was to assess the beta-AR relaxation in CA from normotensive and hypertensive rats after MI.

Methods and Statistical Analysis: Male Wistar (WIS) and SHR rats, 9-12 weeks old, were submitted to left coronary artery ligation to produce MI (WIS/inf: n = 14; SHR/inf: n = 10) or sham operation (WIS: n = 15; SHR: n = 13). After 4-8 weeks, rats were anesthetized to assess arterial and left ventricular (LV) hemodynamic parameters. The heart chambers were separated and weighted to evaluate the ventricular hypertrophy (VH). The infarction size was evaluated as a percentage of the LV area. Afterwards, septal CA vascular function was assessed using a wire myograph. After evaluated the active tension induced by KCl (120mM) and acetylcholine- induced endothelial dependent relaxant, concentration-response curves to isoproterenol (ISO, 0.1mM-30mM), a beta-AR agonist, or forskolin (Forsk, 10mM-30mM), an activator of adenylate cyclase, were constructed. One-way Anova, p < 0.05 *vs. WIS; #vs. SHR.

Results: Systolic arterial and LV pressures were greater in SHR as compared to WIS. MI did not change these parameters in WIS/inf; however reduced it in SHR/inf. Hypertension did not change the LV end-diastolic pressure. Nevertheless, MI increased this parameter in both groups, although this increment was biggest in SHR/inf as compared to WIS/inf (WIS/inf: 44%*; SHR/inf: 159%#). The myocardial contraction (dP/dt+) and relaxation (dP/dt-) index were reduced only in SHR/inf (dP/dt+: -25%*# and dP/dt-: -21%*#). MI did not change LV weight, while induced right VH in both groups. In addition, the infarcted area was similar between MI groups (WIS/inf: 30; SHR/inf: 32% of LV). The relaxation induced by ISO in CA from SHR was impaired as compared to WIS (WIS: 82 ± 2 vs. SHR: 40 ± 4% of relaxation). However, this relaxation was increased after MI in WIS/inf (+12%*) as well as in SHR/inf (+108%†). On the other hand, the Forsk-induced relaxation did not alter among groups.

Conclusion: In spite of the same infarcted area, the MI induced more severe cardiac dysfunction in hypertensive than normotensive rats. However, in both animal models MI enhances the relaxation induced by beta-AR agonist in CA. Thus, these results suggest that this vascular adjustment contributes to improve perfusion in the hypertrophied heart after MI in normotensive and hypertensive rats. Financial support: Fapesp and CNPq.

1C.07 RECOMBINANT HUMAN ERYTHROPOIETIN ALTERS SUBCUTANEOUS RESISTANCE ARTERY ENDOTHELIAL FUNCTION THROUGH A MECHANISM INVOLVING OXIDATIVE STRESS AND ENDOTHELIN-1 IN PATIENTS WITH STAGE 4 CHRONIC KIDNEY DISEASE

M. Briet1, T. Barhoumi2, M. Davidman1, D. Bercovitch1, G. Frisch1, S. J. Nessini1, M. L. Lipman1, E. L. Schiffrin1, ‘Division of Nephrology, Jewish General Hospital, McGill University, Montreal-Canada. ‘Vascular and Hypertension Research Unit, Lady Davis Institute for Medical Research, Montreal-Canada. ‘Department of Medicine, Jewish General Hospital, McGill University, Montreal-Canada

Objective: Recent studies have raised concern about the safety of erythropoiesis-stimulating agent because of evidence of an increase in the risk of cardiovascular morbidity and mortality, and hypertension in chronic kidney disease (CKD) patients.
In the present study we investigated the effect of recombinant human erythropoietin (RhuEPO) on the function of resistance arteries isolated from CKD patients.

**Design and Method:** 14 patients (mean age 63 ± 14 years) with stage 4 CKD (mean eGFR 20 ± 5 mL/min/1.73m²), none treated with RhuEPO, were included. Resistance arteries from gluteal subcutaneous tissue were assessed on a pressurized myograph. Endothelium-dependent and independent relaxations were tested with acetylcholine and sodium nitroprusside respectively, with RhuEPO (0, 1, 10 and 20 UI/mL). Tempol (10^(-3) M), a superoxide dismutase mimetic, was used to inhibit oxidative stress. ABT-627 (10^(-3) M) was used as a selective endothelin subtype A receptor antagonist.

**Results:** At 20 UI/mL, RhuEPO had no effect on norepinephrine-induced vasoconstriction [maximal constriction without or with RhuEPO, 70.5 ± 3.05% vs 75.5 ± 2.4% respectively, NS, n = 9] nor on sodium nitroprusside-induced relaxation (n = 9). At 20 UI/mL, RhuEPO impaired endothelium-dependent relaxation [maximal relaxation without or with RhuEPO, 77.7 ± 3.5% vs 40.7 ± 4.6%, <0.01, n = 16]. Increasing concentrations of RhuEPO altered endothelium-dependent relaxation in a dose-dependent manner [maximal relaxation with RhuEPO at 0, 1, 10, 20 UI/mL, 77.7 ± 3.5%, 66.4 ± 6.1%, 50.2 ± 5.3%, 40.7 ± 4.6%, 0.0004, n = 7-14]. Tempol and ABT-627 partially reversed the altered endothelial function in presence of RhuEPO 20 UI/mL, 0.01; n = 8, 0.05, n = 6, respectively).

**Conclusion:** RhuEPO alters endothelial function of subcutaneous resistance arteries in stage 4 CKD patients via a mechanism in part involving oxidative stress and signaling through endothelin subtype A receptors, which could contribute to the deleterious effect of RhuEPO described in large interventional trials.

---

**CLOSE RELATIONSHIP BETWEEN MEDIA TO LUMEN RATIO OF SUBCUTANEOUS SMALL ARTERIES AND WALL TO LUMEN RATIO OF RETINAL ARTERIOLES EVALUATED NON INVASIVELY BY SCANNING LASER DOPPLER FLOWMETRY**


**University of Brescia, Department of Diabetology and Endocrinology, Brescia, Italy.**

**Chair of Ophthalmology, University of Brescia, Brescia-Italy.**

**Chair of Ophthalmology, University of Molise, Campobasso-Italy.**

**Chair of Ophthalmology, University of Ferrara, Ferrara-Italy.**

**Chair of General Surgery, Department of Medical and Surgical Sciences, University of Brescia, Brescia-Italy.**

Structural alterations of subcutaneous small resistance arteries, as indicated by an increased media to lumen (M/L) ratio, are frequently present in hypertensive and/or diabetic patients, and may represent the earliest alteration observed. In addition, M/L of small arteries evaluated by micrography has a strong prognostic significance; however its extensive evaluation is limited by the invasivity of the assessment, since a biopsy of subcutaneous fat is needed. Non-invasive measurement of wall to lumen (W/L) of retinal arteries using scanning laser Doppler flowmetry (SLDF) has been recently introduced (Harazyny J et al. Hypertension 2007; 50:623-629). However, this new technique was never compared with micromycographic measurement, considered the gold standard approach.

**Methods and Results:** We have investigated 18 subjects and patients. Twelve of them were hypertensives and 6 normotensives. Blood pressure values were 131/72 ± 9/8 mmHg (on-treatment values in 7 out of 12 patients) and 113/72 ± 6/6 mm Hg, respectively (p < 0.05). All patients underwent a biopsy of subcutaneous fat bilaterally. M/L of subcutaneous small arteries and W/L of retinal arteries (see Figure): r = 0.82, r = 0.677, <0.001, y = 6.3018x - 0.2208.

**Conclusion:** A non invasive and easily repeatable procedure (intravascular and interobserver variation coefficient <10%) such as an evaluation of the arteries in the fundus oculi by SLDF may provide similar information regarding microvascular morphology compared with an invasive, accurate and prognostically relevant micromycographic measurement of M/L.
Conclusion: Insulin-mediated vasoconstriction in the microcirculation of diabetics is entirely attributable to enhanced ET-1-activity. While in healthy controls ET-B-receptors seem to be responsible for insulin-induced vasoconstriction, in diabetics ET-A-receptors are also involved.
Background: Single nucleotide polymorphisms (SNPs) at the chromosome 9p21.3 locus are strongly and consistently associated with cardiovascular disease (CVD) in multiple populations. The mechanisms by which these SNPs act on CVD risk are unknown. Likewise, the pathophysiology linking CVD to one of its major risk factors, obesity, is largely unknown. Therefore, in the Sib pair population we studied the expression of the positional candidate gene CDKN2B and ANRIL in human subcutaneous adipose tissue (SAT) in relation to two CVD associated SNPs at 9p21.3, as well as to traditional CVD risk factors.

Methodology/Principal Findings: Ninety obesity-discordant sibling pairs, from the Swedish Obese Study (SOS) underwent extensive phenotyping, adipose tissue expression profiling and were genotyped for rs3833207 and rs10757278. Carriers of the risk allelic of rs10757277 showed higher CDKN2B expression among obese individuals (P = 0.042), whereas expression levels in lean subjects were similar across genotypes. CDKN2B expression in SAT was markedly higher in obese subjects as compared to lean subjects (median (interquartile range) 2.0 (1.2–3.3) vs 1.2 (0.7–1.8) respectively (P<0.001). The expression of ANRIL was low and not associated with any clinical or biochemical variance. Further, there were correlations between CDKN2B expression and components of the metabolic syndrome in obese as well as lean subjects.

Conclusions/Significance: We conclude that CVD-associated SNPs at 9p21.3, in interaction with obesity, account for variation of CDKN2B expression in SAT, which in turn correlates strongly with classical risk factors of CVD. We identified no variance in expression of ANRIL. Our data suggest that upregulation of CDKN2B in SAT may be a unifying link between obesity and a cluster of CVD risk factors within the metabolic syndrome.

1D.01 OVERWEIGHT OR OBESITY ARE STRONG PREDICTORS OF HYPERTENSIVE COMPLICATIONS IN YOUNG SUBJECTS WITH STAGE 1 HYPERTENSION

P. Palatini1, F. Saladini1, L. Mos1, M. Santonastaso1, G. Maraglino1, A. Mazzer1, F. Pegoraro1, L. Milan1, D. D’este1, P. Mormino1, E. Cassiglia. 1University of Padova, Padova-Italy, 2Town Hospital, San Daniele del Friuli-Italy, 3Town Hospital, Vittorio Veneto-Italy, 4Town Hospital, Dolo-Italy, 5Town Hospital, San Donà-Italy, 6Town Hospital, Mirano-Italy

Objective: The prevalence of obesity in young people has increased dramatically and little is known about the effect of obesity on the risk of end organ involvement in the early stage of hypertension. Aim of this study was to examine the impact of overweight or obesity on development of target organ damage (TOD) in young subjects screened for stage 1 hypertension.

Design and Method: Participants were 727 never-treated young adults (516 males and 211 females) with a mean baseline age of 33.8 ± 5.3 years (range, 18 to 45 years), who were screened for stage 1 hypertension on at least two occasions two weeks apart. Patients were seen every six months for clinic blood pressure (BP) and global risk assessment to determine which subjects needed drug therapy according to current guidelines. Albumin excretion rate, echocardiographic left ventricular mass and 24h ambulatory BP were measured at entry, every 5 years, and/or just before starting treatment. Subjects were divided according to whether they had normal weight (NW, n = 364), overweight (Ow-W, n = 289) or obesity (Ob, n = 74) at baseline. Microalbuminuria was defined as an albumin excretion rate ≥ 30 mg/24h on two different occasions. Left ventricular hypertrophy (LVH) was defined as a left ventricular mass ≥ 50 g/m2.7 in men and ≥ 47 g/m2.7 in women.

Results: After a median of 8 years, hypertension needing treatment was developed by 54.7% of NW, 66.6% of Ow-W, and 75.0% of Ob subjects (p < 0.001). LVH and/or microalbuminuria at study end was present in 10.7% of NW, 16.4% of Ow-W, and 31.1% of Ob (p < 0.001). These differences remained significant also when adjusted for baseline urinary albumin or left ventricular mass. In a multi-variable logistic analysis, after adjusting for age, sex, lifestyle factors, parental hypertension, 24h BP, clinic BP and heart rate, overweight (p = 0.008) and obesity (p = 0.001) were significant predictors of TOD development with odds ratios (ors) of 2.05 (95%CI, 1.2–3.3) and 4.22 (2.1–8.2), respectively. When baseline TOD was included in the model, these associations remained highly significant with orts of 3.31 (1.5–6.2) and 4.92 (2.0–12.1), respectively. Further inclusion of changes in 24h BP during the follow-up only marginally affected these associations with orts of 3.21 (1.6–6.5) and 5.12 (1.2–17.7), respectively. These relationships were not attenuated by inclusion of follow-up changes in body weight in the models with orts of 3.41 (1.7–6.7) and 5.90 (2.1–16.0), respectively.

Conclusions: These data show that young stage 1 hypertensive subjects with increased body mass index have a much higher risk of target organ damage than NW subjects. This relationship is linear and raises the question about whether in this clinical setting subjects with obesity should be considered at high risk and given early antihypertensive treatment.

1D.02 EXPRESSION OF THE CARDIOVASCULAR SUSCEPTIBILITY GENE CDKN2B IS UP REGULATED IN OBESITY AND ASSOCIATES WITH FACTORS OF THE METABOLIC SYNDROME

B. Wahlstrand1, D. Kellis1, O. Melander1, P-A. Svensson1, A. Walley1, P. Froguel1, L. Carlsson1, T. Hedner1, P. Jacobson3. 1Department of Clinical Sciences, Skåne University Hospital, Malmö, Sweden, 2Sahlgrenska Center for Cardiovascular and Metabolic Research, University of Gothenburg, Gothenburg, Sweden, 3Section of Genomic Medicine, Hammersmith Hospital, Imperial College London, London, United Kingdom

Abstracts e13
and blood pressure values in paediatric age. This finding is evident not only in hypertensive and/or obese children but also in normotensive and/or normal weight peers.

1D.04 EFFECTS OF BARIATRIC SURGERY ON INSULIN SENSITIVITY AND SYMPATHETIC NERVE TRAFFIC IN OBESE SUBJECTS. A LONGITUDINAL STUDY

F. Quarli1, G. Seravalle2, M. Colombo1, P. Perego3, V. Giardini3, M. Volpe1,

Introduction: It has been recently reported that weight loss induced by restrictive bariatric surgery triggers an improvement of both insulin sensitivity and sympathetic balance at the level of the heart. No data, however, are available on the effects of the procedure on a direct index of sympathetic cardiovascular function accurately reflecting more the whole cardiovascular adrenergic drive such as effenter parasympathetic sympathetic nerve traffic and on the inter-relationships between sympathetic and insulin sensitivity changes induced by the intervention.

Methods: In 7 severe obese patients (age 49.8 ± 4.0yrs, 3 male, 4 females) we measured clinic (sphygmonanometric) and beat-to-beat (Finapres) blood pressure (BP), heart rate (EKG), body weight, mass index (BMI), waist-to-hip ratio (WHR), HOME i index and effenter parasympathetic sympathetic nerve traffic (MSNA, microneurography). Measurements were performed 3-4 days before bariatric surgery and repeated 6 and 12 months after the procedure. The same evaluations were performed in 8 age-, gender- and BMI-matched obese patients not undergoing the surgical procedure, thus serving as controls.

Results: Both MSNA and HOME i were significantly related before surgery to BMI and WHR but not to each other. Six months after bariatric surgery BMI and WHR values were significantly reduced (from 43.0 ± 1.9 to 35.3 ± 2.1 kg/m² and 1.02 ± 0.94, respectively, p < 0.05 for both), the weight loss being accompanied by a significant decrease in systolic BP (from 143 ± 2.4 to 134 ± 2.1 mmHg, p < 0.05). HOME i index was also significantly reduced (from 4.7 ± 0.3 to 2.5 ± 0.2, p < 0.05) and this was the case for MSNA (from 69.8 ± 4.0 to 54.3 ± 3.4 bs/100hb, p < 0.05). The weight loss and MSNA reduction were substantially maintained after 12 months from surgery (BMI: 35.9 ± 2.1 kg/m², 53.3 ± 3.1 bs/100hb), while HOME i index showed a tendency to increase again returning toward pre-surgery values (3.9 ± 0.4). No significant changes were observed in the various anthropometric, haemodynamic, metabolic and neural variables in the control group.

Conclusions: These data provide the first evidence that massive weight loss induced by bariatric surgery triggers profound sympathovagal and eumetabolic effects, which however appear to follow a different time course, suggesting their independent behaviour. This is particularly the case in the long-term period, indicating that the sympathovagal accommodation weight loss is more related to the body weight reduction “per se” rather than to changes in insulin sensitivity.

1D.05 ANGIOTENSIN AT2R STIMULATION IMPROVES GLUCOSE TOLERANCE AND INSULIN SENSITIVITY IN OBESE MICE

S. Wardat1, M. Iwai1, M. Horiiuch2, B. Dahlöf1, A. Hallberg1, T. Ungér1, U. Kintscher1, U. M. Steckelings1, A. Foryst-Ludwig1,1Ciberobn, Health Institute Carlos III, Madrid-Spain, 2Cardiovascular Risk Unit Hospital General Universitario University of Valencia, Valencia-Spain, 3Lab Unit Hospital General Universitario, University of Valencia, Valencia-Spain

Objective: The functional role of the AT1-receptor (AT1R) in the development of insulin-resistance (IR) is well understood and it is known that AT1R-blockers (ARBs) improve insulin-tolerance and IR. The metabolic contribution of the AT2-receptor (AT2R) is still controversial. Thus, this study aimed to determine the functional significance of the AT2R for the development of IR and adipose tissue inflammation using the non-peptide AT2R-agonist, Compound 21 (C21).

Design and Methods: Wild type (WT; C57Bl1-6) and AT2R-knockout (AT2R-KO) mice were fed with high fat diet (HFD) or control low fat diet (LFD) (60% kcal from fat or 10% kcal from fat, respectively) for 10 weeks to induce obesity and metabolic changes. Afterwards animals (n = 10 per group) were treated according to the following protocol for 4 weeks in addition to the diet: C21 (0,3mg/kg BW i.p.), the ARB Valsartan (3mg/kg BW i.p.), Hydralazine (250mg/ml drinking water) or vehicle. Glucose tolerance (GT) and insulin sensitivity (IS) were measured by standard ITT and GTT tests, body fat content by NMR, serum markers by magnetic bead-based multiplex assay. The in vivo study was complemented by in vitro experiments in 3T3L-1 adipocytes and THP-1 macrophages.

Results: GT and IS were impaired by HFD-feeding but significantly improved in mice treated with C21. GT was also improved by Valsartan. Furthermore, TNF-α, resistin and serum triglycerides (53.57 ± 5.6mg/dl to 37.16 ± 5.0mg/dl; p<0.05) levels were significantly reduced, and serum levels of incretins GIP and GLP-1 were increased by C21-treatment. Consistent with our in vitro data, C21 treatment increased adiponectin, and decreased leptin serum levels in a significant manner.

HFD-fed AT2R-KO mice showed significantly enhanced body weight gain (+66.6 ± 4.0% vs. +51.2 ± 1.13%) and total body fat content (8.75 ± 1.23g vs. 6.16 ± 0.28g) when compared to WT-HFD-fed mice. Importantly, metabolic outcome of HFD-fed AT2R-KO mice was not altered by the treatment with C21 pointing to AT2R-specificity of C21 effects.

C21 slightly (+6.38mmHg, p<0.05) and Valsartan strongly (+19.37mmHg, p<0.001) lowered blood-pressure in mice of the HFD groups. However, metabolic effects of C21 and Valsartan were blood-pressure-independent as controlled for by the Hydralazine treated group.

Conclusions: The present study demonstrates that direct AT2R-stimulation results in anti-inflammatory actions as well as positive modulation of metabolic markers in a HFD model in mice and related in vitro experiments. These data suggest that the AT2R may be a pharmacological target for improvement of obesity-induced metabolic changes.

1D.06 URINARY ALBUMIN EXCRETION IN OBESE CHILDREN IS DEPENDENT ON METABOLIC FACTORS

E. Lurbe1, I. Torro1, J. Alvarez2, F. Aguilar2, G. Marcada1, J. Redon1,1Ciberobn, Health Institute Carlos III, Madrid-Spain, 2Cardiovascular Risk Unit Hospital General Universitario University of Valencia, Valencia-Spain, 3Lab Unit Hospital General Universitario, University of Valencia, Valencia-Spain

Albunminuria is an integrated marker of cardiovascular and renal morbidity and mortality in adults. Because the roots of these diseases extend back to childhood, assessment of albuminuria has become relevant to child and adolescent clinical care. Very little is known about the association between obesity and urinary albumin excretion (UAE) in the paediatric age.

Objective: To assess the factors associated with UAE and its relation to cardio-vascular risk factors in obese children.

Design and Methods: Obese Caucasian children, (137, 79 males), European origin, mean age 12.5 ± 2.1, were selected. Obesity was defined as BMI >97th percentile, age and sex specific. Degree of obesity was defined using BMI z-score. An oscillometric device measured ambulatory BP (Spacelabs 90207) over 24 hours. Fasting glucose, insulin and lipid profile were measured. UAE was measured in the first voiding urine in the morning, analysed by enzyme-immunoassay and expressed as A/Cr. The value for each subject is the mean over 24 hours. Fasting glucose, insulin and lipid profile were measured. UAE was measured in the first voiding urine in the morning, analysed by enzyme-immunoassay and expressed as A/Cr. The value for each subject is the mean over 24 hours.

Results: Average UAE was 9.82 mg/dg (interquartile range 2.2-6.5 mg/dg). Eleven subjects (7%) had UAE in the microalbuminuric range (>30 mg/dg) and 7% had values in the high-normal range (15-30 mg/dg). When controlled for age and sex, log UAE was significantly related to BMI z-score r = 0.27 (p = 0.003), waist circumference r = 0.31 (p = 0.001), triglycerides r = 0.27 (p = 0.003) and fasting insulin r = 0.21 (p = 0.022). No significant relationship was present for BP. Due to the relationship between metabolic traits and UAE, subjects were grouped by insulin tertiles. Log, UAE, uric acid, triglycerides and HDL-C levels for each insulin tertile can be seen in the figure.
Conclusions: In obese children, a small increment in UAE was associated with metabolic risk factors but not with BP. Whether UAE should be targeted in order to reduce cardiovascular and renal risk in obese children needs to be assessed.

**1D.07**

**FREE RADICAL SCAVENGERS RESCUE OBESITY-INDUCED DAMAGE TO THE ANTICONTRACTILE PROPERTY OF PERIVASCULAR ADIPOSE TISSUE IN RAT AND HUMAN SMALL ARTERIES**

R. Aghamohammadzadeh, A. S Greenstein, A. M. Heagerty. University of Manchester, Manchester-United Kingdom

**Background:** We have previously reported that in human obesity, local inflammation and hypoxia abolish the anticontractile property of perivascular adipose tissue (PVAT). We have also demonstrated that in obese rats, damage to the anticontractile capacity of PVAT strongly correlates with elevation in blood pressure. We aimed to ascertain whether free radical scavengers can rescue PVAT function.

**Methods:** Subcutaneous small artery sections were dissected from gluteal fat biopsy samples of obese patients (n = 18). Proteomic analysis of the adipose tissue was also performed (obese n = 10, control n = 10). 8 Sprague Dawley rats were fed a high fat diet (obese) and 5 fed normal chow (controls) for 16-18 weeks. Mesenteric artery vessels were dissected for the study. In order to assess the PVAT effect, both the human and rat vessels were prepared with and without PVAT intact, and vessel contractility was studied using wire myography by constructing dose response curves to cumulative noradrenaline (NA) to assess the PV AT effect, both the human and rat vessels were prepared with and without superoxide dismutase (SOD) and catalase (CAT) following which the vascular responses to NA were re-examined. Statistical significance was tested using two-way Anova. All other results are reported as mean ± SD.

**Results:** The obese patients had a mean age of 48 (±10) years, body mass index of 48 (±14) kg/m2 and systolic blood pressure of 139 (±21) mmHg. Proteomic analysis of obese human PVAT showed a significant reduction in SOD levels (fold change -2.4, P = 0.0177) as compared with controls. Vessel reactivity to NA was comparable in segments with and without PVAT in the obese group, but after incubation with SOD and catalase, in vessels with intact PVAT, there was a significant reduction in contractility, more apparent at higher concentrations of NA (P = 0.0184). The obese rats weighed significantly more than the control group at the time of sacrifice (835g vs 315g). They developed significantly higher blood pressures (systolic: 147 ± 21 mmHg, P = 0.028). Endothelium-denuded PVAT intact vessels from obese animals showed significantly increased sensitivity to NA as compared with controls (P = 0.003). Incubation with SOD and CAT reduced contractility to NA in endothelium-denuded PVAT intact vessels (P = 0.0142).

**Conclusions:** In health PVAT has an anticontractile effect on adjacent vessels. In human obesity, there is a reduction in SOD levels in PVAT and in both human and rat obesity, incubation with free radical scavengers rescues the PVAT anti-contractile function ex-vivo.

**1D.08**

**CONTRIBUTION OF ABDOMINAL OBESITY AND AMBULATORY BLOOD PRESSURE TO LEFT ATRIUM SIZE: A 10-YEAR FOLLOW-UP OF YOUNG NONMOTIVATIVE SUBJECTS**

A. Rojeck1, M. Chrostowska1, M. Dudziak, B. Krupa-Wojciechowska1, K. Narkiewicz2. 1Hypertension Unit, Department of Hypertension and Diabetology, Medical University of Gdansk, Gdansk-Poland, 2Nonvasive Cardiovascular-Diagnostic Unit, II Chair of Cardiology, Medical University of Gdansk, Gdansk-Poland

**Objective:** Abdominal obesity is one of the main factors contributing to cardio-metabolic risk. Atrial enlargement has been shown to be a strong predictor of morbidity and mortality. The aim of the study was to evaluate the relationship between the development of abdominal obesity and left atrial volume index (LAVI) during a 10-year follow-up from the random sample of young healthy males.

**Design and Method:** The study was carried out in a group of 68 nonobese subjects aged 22.4 ± 2.4 years, mean ± SD, BMI 23.1 ± 2.7 kg/m2, waist circumference (WC) 84.7 ± 8.3 cm, without metabolic risk factors at baseline. They underwent echocardiography (Hewlett-Packard Sonos 1500, Aloka 5000) and ambulatory blood pressure monitoring (ABPM) (SpaceLabs 90207).

**Results:** LAVI was significantly higher in a group whose WC increased during the 10-year follow-up in comparison with the rest of the population (21.8 ± 4.5 vs 18.46 ± 4.0 ml/m2, P < 0.001). In multivariate blood regression analysis, both daytime SBP and WC changes were independent determinants of LAVI (Table). Left atrial systolic function did not differ between the two subgroups (8.56 ± 3.72 vs 7.41 ± 3.24, kdyn, P = NS). No significant correlation between diastolic function and change of WC was found.

**Conclusions:** Development of abdominal obesity and daytime SBP increase contribute to enlargement of left atrium.

**1D.09**

**HIGH LEVELS OF E-SELECTIN ARE ASSOCIATED WITH A REDUCTION OF SIRT1 EXPRESSION IN LYMPHOMONOCYTES FROM SUBJECTS WITH METABOLIC SYNDROME**

A. Cattelan1, G. Cesolot1, A. Bortoluzzi1, A. Fabricio2, E. Squarcina2, M. Giori1, S. Vigili De Kreuztenberg1, A. Avogaro1, A. Semplicini1. 1University of Padova, Padova-Italy, 2Ospedale S. Giovanni E Paolo, Venezia-Italy

**Background:** Endothelial dysfunction and inflammation play a pathophysiological role in the development of metabolic syndrome (MS) and its cardiovascular complications. Recent studies have shown that activation of sirtuins (SIRTs), is reduced in mononuclear cells (PBMC) of patients with MS, but the causes of this alteration is still undefined. The SIRTs are a family of seven enzymes (SIRT1-7) that are activated by caloric restriction and provide resistance to stress, reduced apoptosis and regulate the cell cycle. The purpose of this study was therefore to study the relationship between endothelial dysfunction and markers of inflammation (ICAM, VCAM, E-selectin) and gene expression of SIRT1-7 in patients with MS.

**Patients and Methods:** We studied 85 healthy volunteers (age 47 ± 9, F 64 and F 21), of which 23 met the criteria for MS according to Atpiiu. The plasma concentration of ICAM-1, VCAM-1 and E-selectin were analyzed on the Luminox platform (Bios-Plex system) using the Millipore kit 3-plex Human Panel-1 cardiovascular disease. The sensitivity values obtained are: ICAM-1: 0.08 ng/ml VCAM-1: 0.08 ng/ml E-selectin: 0.5 ng/ml. Gene expression of SIRT (1-7) was determined in mononuclear cells (PBMC) by quantitative real-time PCR analysis.

**Results:** The plasma concentration of E-selectin was significantly increased (from 22.7 ± 1 to 32.2 ± 3 ng/ml, P < 0.001) in subjects with MS than non-MS, while ICAM-1 and VCAM-1 were not different in the two groups of subjects. The plasma levels of E-selectin were positively correlated with blood pressure, waist circumference, triglycerides, blood glucose and insulin. Gene expression of SIRT1-7 was significantly reduced in PBMCs of patients with MS than non-MS (from 0.68 to 1.02 ± 0.1 ± 0.72, P < 0.001), while the gene expression of other SIRT (2-7) was not significantly different. The SIRT1 gene expression was negatively correlated with plasma E-selecitin (r = -0.34, P = 0.012).

**Conclusion:** The metabolic abnormalities seen in patients with MS are associated with increased plasma concentrations of E-selectin and a reduction of gene expression of SIRT1. The inverse correlation between E-selectin and SIRT1 suggesting a link between endothelial dysfunction and the regulation of a gene of importance in MS.

**1D.10**

**THE EFFECT OF ACCELERATED WEIGHT GAIN ON BLOOD PRESSURE, INTRINSIC HEART RATE AND THE FUNCTION OF THE CARDIAC CONDUCTION SYSTEM**

O. Monfredi, A. Mastan, R. Aghamohammadzadeh, I. Egner, M. Boydett, A. Heagerty. University of Manchester, Manchester-United Kingdom

**Introduction:** Obesity is associated with hypertension and the development of cardiac disease, including ischaemia, atrial fibrillation and heart failure, through mechanisms including dyslipidaemia, increased blood volume, increased cardiac output, insulin resistance and overactivity of the sympathetic nervous system. Steatosis within the myocardium can lead to fibrosis, lipotoxicity and apoptosis. Little is known about the direct effect of the combination of accelerated obesity and weight gain on blood pressure and the function of the cardiac conduction system. We set out to investigate these effects further using a rat model of accelerated obesity.

**Methods:** 8 Sprague-Dawley rats were fed a high fat diet (45% calories from fat) and 9 were fed normal chow for 16-18 weeks. Weight and tail-cuff blood pressure were monitored and fasting blood glucose was documented at the time of sacrifice. Rats were sacrificed by approved techniques, and the heart was dissected and transported to a Langendorff apparatus in cold Tyrode’s solution –
Hearts were weighed prior to re-establishment of circulation with oxygenated 37°C Tyrode’s solution. ECG recordings were performed with spring-loaded Ag/AgCl electrodes placed on the right atrium and left ventricle. 500-consecutive beat stationary ECG recordings were made from Langendorff-perfused isolated hearts.

**Results:** Rats fed a high fat diet (obese group) weighed significantly more than the control group at the time of sacrifice (835g vs 315g). The obese rats developed significantly higher systolic (147 vs 121mmHg, P = 0.028) and diastolic blood pressures (113 vs 91 mmHg, P = 0.006) as compared with the control group. There was no difference in blood glucose levels (P = 0.66). Obese rats had significantly heavier hearts compared with lean rats (3.26g vs 2.26g, P<0.05), though their heart weight:body weight ratio was significantly less (0.0040 vs 0.0066, P<0.05). There was no significant difference between the 2 groups in terms of heart weight:body weight ratio (0.646 vs 0.611, P = 0.38). The intrinsic cycle length (RR interval) of obese rats was significantly longer than controls (295ms vs 248ms, P<0.05). There was also a trend towards obese rats having longer PR (49 vs 43ms, P = 0.077), QT (102 vs 66ms, P = 0.051) and QTc (186 vs 138ms, P = 0.083) intervals.

**Conclusion:** Feeding male rats a high fat diet for 16-18 weeks causes significant obesity, systolic and diastolic hypertension and cardiac hypertrophy, with attendant significant changes in intrinsic heart rate and parameters of the conduction system. The effect of hyperglycaemia was eliminated in this study as blood glucose recordings in the two groups were comparable. Further experiments are planned at the functional level to see if the effects on cardiac electrophysiology are acutely pharmacologically reversible, and at the molecular level to investigate whether the changes are due to obesity induced remodeling of cardiac ion channels.

### 10.D.1 SUBCUTANEOUS SMALL RESISTANCE ARTERY MORPHOLOGY AND CIRCULATING INDICES OF INFAMMATION/OXIDATIVE STRESS IN OBES E PATIENTS BEFORE AND AFTER BARIATRIC SURGERY AND CONSISTENT WEIGHT LOSS

C. De Ciuceis1, E. Porteri1, E. La Borla1, G. E. M. Boun1, F. Mittermpergher1, C. Castella2, C. Agabiti Rosei3, G. Buggeri4, D. Rizzoni1. 1Università DI Brescia, Dipartimento DI Scienze Mediche E Chirurgiche, Brescia-Italy, 2Chair of General Surgery, Department of Medical and Surgical Sciences, University of Brescia, Brescia-Italy, 3Chair of Clinical Biochemistry, University of Brescia, Brescia-Italy

**Background:** Structural alterations of subcutaneous small resistance arteries of hypertensive patients, as indicated by an increased media to lumen (M/L) ratio, are frequently present in hypertensive and/or diabetic patients, and may represent the earliest alteration observed. In addition, M/L of small arteries have a strong prognostic significance. Also obesity is associated with an increased M/L. However, no data are presently available about the structure of small resistance arteries of obese patients after weight loss. Therefore, we have investigated 8 patients with severe obesity. All patients underwent a biopsy of subcutaneous fat during bariatric surgery. In addition, M/L of small resistance arteries were dissected and mounted on a wire myograph, and M/L and media cross-sectional area were measured. In addition, circulating levels of C-reactive protein (CRP), total antioxidant power, malonyldialdehyde (MDA) and lipid peroxidation (LPO) were also measured in plasma using spectrophotometric assay. After surgical intervention for abdominoplasty, a biopsy of subcutaneous fat was obtained. In addition, circulating levels of C-reactive protein (CRP), proinflammatory cytokines interleukin-6 (IL-6) and interleukin-18 (IL-18), macrophage chemotactic factor-1 (MCP-1), plasminogen activator inhibitor-1 (PAI-1), soluble vascular cell adhesion molecule 1 (VCAM-1) and soluble Inter-Cellular Adhesion Molecule 1 (sICAM-1) have been measured in plasma by Elisa. Total antioxidant power, malonyldialdehyde (MDA) and lipid peroxidation (LPO) were also measured in plasma using spectrophotometric assay. After surgical correction of obesity and consistent weight loss, a significant improvement of microvascular structure was observed, characterized by a correction of hypertrophic remodeling (reduction in growth index and media cross-sectional area), together with an improvement of endothelial function and a decrease of some indices of inflammation/oxidative stress (see Table: Mean ± SEM, * = p<0.05, ** = p<0.01, ***p<0.001 vs. before weight loss).

**Table:**

<table>
<thead>
<tr>
<th></th>
<th>Obese patients before weight loss (n=8)</th>
<th>Obese patients after weight loss (n=8)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Body mass index (Kg/m²)</strong></td>
<td>31.2 ± 2.1</td>
<td>27.4 ± 1.4 **</td>
</tr>
<tr>
<td><strong>Medians cross-sectional area (mm²)</strong></td>
<td>290 ± 76</td>
<td>363 ± 126 **</td>
</tr>
<tr>
<td><strong>Medians to lumen ratio</strong></td>
<td>0.696 ± 0.03</td>
<td>0.684 ± 0.02 **</td>
</tr>
<tr>
<td><strong>Remodeling index</strong></td>
<td>0.7%</td>
<td>140%</td>
</tr>
<tr>
<td><strong>Glucose index</strong></td>
<td>110%</td>
<td>20%</td>
</tr>
<tr>
<td><strong>LPO (mmol/L)</strong></td>
<td>1.98 ± 0.18</td>
<td>0.97 ± 0.18 **</td>
</tr>
<tr>
<td><strong>MDA (μmol/L)</strong></td>
<td>8.38 ± 10</td>
<td>3.24 ± 6.4 **</td>
</tr>
<tr>
<td><strong>IL-6 (pg/ml)</strong></td>
<td>4.29 ± 1.6</td>
<td>3.18 ± 0.76 **</td>
</tr>
<tr>
<td><strong>sICAM-1 (ng/ml)</strong></td>
<td>635 ± 56.6</td>
<td>497 ± 41.4 **</td>
</tr>
<tr>
<td><strong>CRP (mg/ml)</strong></td>
<td>1465 ± 234</td>
<td>726 ± 300 **</td>
</tr>
</tbody>
</table>

**Conclusion:** Our data suggest that weight loss obtained with bariatric surgery may improve microvascular structure and may decrease indices of inflammation/oxidative stress.

### 10.D.2 IMPLICATION OF THE ADIPOSE TISSUE (PRO)RENNIN RECEPTOR IN THE REGULATION OF BODY WEIGHT AND ADIPOSITY

B. Ahmed1, C. Michel, O. Seda, J. Lavoie. Research Center of the Hospital Center of the Université de Montréal (Crchum), Montreal-Canada

**Objective:** The implication of the renin-Angiotensin system (RAS) in the development of obesity has been previously shown. Binding of renin and prorenin to the (pro)rennin receptor ([P]RR), a recently discovered member of the RAS, increases the activity of the RAS and stimulates angiotensin II-independent signalling. We hypothesize that knocking down the receptor in adipose tissue will decrease weight gain and prevent the development of obesity-related complications.

**Design and Method:** Mice lacking [P]RR specifically in adipose tissue (KO) were created using the CreLox technology. Mice with a floxed [P]RR gene (gracilis) gift from Merck Frost Canada) were bred with mice overexpressing cre-recombinase specifically in adipose (Ap2-Cre, Jackson laboratories). Weekly weight gain, food and water consumption were assessed over 4 weeks in both adult male and female KO and wild-type (WT) littermates. Another group of females were kept for 6 weeks on a high fat diet (HF) to induce obesity. Mice activity and body composition were evaluated using Physioscan cages and echoMRI, respectively. Fat pads were collected, weightied and snap frozen. Circulating leptin was measured in sera.

**Results:** KO mice had significantly smaller body weights compared to their WT littermates, the differences being more pronounced in male KOs since the receptor gene is carried on the Y chromosome. Furthermore, KOs had significant smaller fat mass, visceral adiposity compared to the WTs. This was accompanied in males by an almost 3-fold increase in activity while only a tendency could be observed in partial KO females. In addition,KO females were resistant to develop obesity when placed on a HF diet which was accompanied by lower circulating leptin levels. Interestingly, KOs tended to consume less water while no obvious changes in food intake could be observed.

**Conclusion:** The [P]RR seems to be implicated in body weight control and could be a new therapeutic avenue in the management of obesity and obesity-related complications.
LATE-BREAKER SESSION

LB1.1  LONG-TERM ASSOCIATIONS OF PLASMA RENIN ACTIVITY WITH ALL-CAUSE AND CARDIOVASCULAR MORTALITY

M. Gonzalez1, M. Alderman1, H. Cohen1, J. Sealey2, J. Laragh2. 1Albert Einstein College of Medicine, Bronx-USA, 2NYP-Well Cornell Medical Center, New York-USA

Introduction: Plasma Renin Activity (PRA) has been associated with cardiovascular (CVD) events among hypertensive patients. We now report CVD and all-cause mortality data derived from the National Death Index that show an enduring association of PRA to all-cause and cardiovascular mortality independent of, and in addition to, CVD risk predicted by the Framingham score.

Methods: Study subjects (3791) who participated in a worksite-based hypertension treatment program had entry BP ≥ 140 and/or 90 mmHg, mean age 52. PRA was log transformed and related to CVD and all-cause mortality as a continuous variable, and by tertiles: (T1 = Lowest: 0.05–0.77 (median = 0.36), T2 = Middle: 0.78–2.0 (median = 1.30), and T3 = Highest: > 2.0 (median = 3.30) ng/mL/h. The 10-year Framingham score associations were similarly examined.

Results: Mean follow-up was 16 years. T3, compared to T1, were younger (mean: 50 vs. 53 years, P < 0.001), more likely to be Hispanics [42% (530/1267) vs. 30% (381/1268), P < 0.001], male [77% (971/1267) vs. 56% (707/1268), P < 0.001], and have a higher serum cholesterol (224 vs. 213 mm/dL, P < 0.001). There were 804 deaths, 360 (45%) of which were attributed to CVD. Although T3 vs. T1 had lower mean baseline and follow-up systolic BP [146 vs. 152 mm Hg (P < 0.001) and 135 vs. 139 mm Hg (P < 0.001), respectively], in a Cox model, T3 had a 64% (HR: 1.64, 95% CI: 1.25 – 2.15, P < 0.001) increased risk of CVD mortality and 32% (HR: 1.32, 95% CI: 1.11 – 1.57, P = 0.002) increased risk of all-cause mortality after adjusting for age, gender, race, BMI, eGFR, blood glucose, smoking, LVH by ECG, history of diabetes, and baseline systolic blood pressure. Similarly, those in T3 were more likely than T1 to die from a Myocardial Infarction (HR: 2.92, 95% CI: 1.49 – 5.73, P = 0.002) and Coronary Artery Disease (HR: 1.64, 95% CI: 1.17 – 2.30, P = 0.004). Moreover, in a Cox model adjusting for age, sex, and Framingham score, T3 had greater risk of CVD than T1 (HR: 1.54, 95% CI: 1.19 – 1.99, P < 0.001).

Conclusions: Plasma renin activity has a significant and independent long-term association with all-cause and CVD mortality. Moreover, PRA adds significantly to risk identified by the Framingham score.

LB1.2  HERITABILITY OF BLOOD PRESSURE (BP) PHENOTYPES IN EXTENDED PEDIGREES FROM THE GUBBIO POPULATION STUDY: PRELIMINARY RESULTS

M. T. Bonati1, M. C. Monti1, C. Crocamo1, M. Montomoli2, O. Terradura-Vagnarelli1, M. Mancini1, M. Laurenzi1, A. Zanchetti1, On Behalf of the Gubbio Study Group. 1IRCCS Istituto Auxologico Italiano, Milano-Italy, 2Dipartimento di Scienze Sanitarie Applicate, Università di Pavia, Pavia-Italy, 3On Behalf of the Gubbio Study Group.

Objective: The heritability of SBP/DBP using pedigrees and measurements from a population-based study.

Design and Methods: The Gubbio study consisted of 3 surveys conducted in 1983–86, 1989–91 and 2001–07. The present analyses are derived from 2,749 subjects in 259 pedigrees, 70 nuclear and 189 extended (3–52 members, aged 8–92 years). Clinical records were available for 1074 subjects from the 3rd survey (47% males, mean ± SD age 35 ± 16 years, BMI 25.8 ± 4.3 kg/m², LDL-C 125.4 ± 35 mg/dl and heart rate 68 ± 12 bpm). The average of the 2nd and 3rd measurements of sitting BP was used as the quantitative trait of interest. SBP and DBP values were adjusted for use of antihypertensive therapy (33% of subjects) by adding 10 mm Hg and 5 mm Hg. After this adjustment, mean SBP was 133 ± 21 and mean DBP 77 ± 10 mm Hg. To investigate the proportion of phenotypic variance of BP traits attributable to additive genetic effects, we estimated SBP and DBP heritability (H²) using a quantitative genetic variance component analysis available in the SOLAR program. Clinical, life-style variables and interactions of these were considered as covariates. We adjusted for covariates hierarchically because some may have a genetic basis. We also performed a bivariate variance decomposition analysis to evaluate phenotypic correlation (rhoP) between SBP and DBP, discriminating among the genetic (rhoG) and environmental (rhoE) correlation components.

Results: Low but significant heritability were estimated by a crude model containing only the trait of interest (H² = 0.09, p < 0.0001 for SBP and H² = 0.16, p < 0.0001 for DBP). Adjusting for sex had no influence while accounting for age and age-squared increased H² to 0.29 for both SBP and DBP. After further adjustment for other factors as BMI, LDL, Heart Rate and BMI-age, H² were 0.32 for SBP and 0.35 for DBP. All heritability estimates were significant (p < 0.0001). SBP was positively correlated (rhoP = 0.66) with DBP; decomposition of the phenotypic correlation indicated significant genetic (rhoG = 0.90, p < 0.0001) and environmental (rhoE = 0.55, p < 0.0001) correlations between SBP and DBP.

Conclusions: Our investigation of extended pedigrees confirms the influence of genetic factors on BP and the importance of adjusting heritability estimates through phenotypes considered prognostic factors for BP (as BMI, LDL on both SBP and DBP and age, HR specifically on SBP). Clinical and environmental features account for 37% and 24% of the total variation in SBP and DBP, but a substantial proportion of the unexplained variation appears to be attributable to genetic effects (32% SBP and 35% DBP).

LB1.3  THE ANGLO-SCANDINAVIAN CARDIAC OUTCOMES TRIAL (ASCOT) BIOMARKER PROGRAMME

C. Chan1, N. Poulter1, M. Scanlon1, A. Whitehouse1, P. Welsh2, N. Sattar2, P. Sever1, on Behalf of The ASCOT Investigators. 1Imperial College, London-United Kingdom, University of Glasgow; Glasgow-United Kingdom

Background: We have recently reported that C-reactive protein (CRP) is a poor predictor of future cardiovascular (CV) events in hypertensive patients in ASCOT. We now report the results of 2 case-control studies (CCS) designed to assess the use of serum N-terminal-proBNP (Ni-BNP) as a predictor of CV outcome, and of plasma renin activity (PRA) as a predictor of CV and renal outcomes.

Methods: In UK and Ireland, ASCOT randomised 9098 hypertensive adults to either calcium channel blocker- or beta blocker-based treatment. 4853 patients with total cholesterol ≤ 6.5 mmol/L (250 mg/dL) were further randomised to atorvastatin or placebo. In the Ni-BNP CCS there were 440 CV cases (fatal coronary heart disease, non-fatal MI, coronary revascularization, fatal and non-fatal stroke), over 5.5 years and these were age and sex matched with 1235 controls. In the PRA CCS there were 403 CV cases, 96 cases of new onset renal impairment (50% increase in serum creatinine) and 235 deaths. Conditional logistic regression models were used to evaluate the association between measurements of the biomarkers at baseline and CV and renal outcomes. An additional analysis was undertaken to evaluate the potential association of Ni-BNP with visit-to-visit blood pressure variability.

Results: Ni-BNP strongly predicted CV events (odds ratio[OR] 1.38 [CI 1.23,1.54], per 1 SD increase in log-transformed data, p < 0.0001). In a Framingham model incorporating the PRA into Ni-BNP improved Net Reclassification Index by 11.9% (p = 0.0004). In further analyses there was a highly significant positive relationship between Ni-BNP and measures of systolic blood pressure variability (which we have previously reported to be strong predictors of CV outcomes in ASCOT).

In contrast, PRA negatively predicted CV events (OR 0.84[CI 0.72, 0.99], p = 0.04) in a model fully adjusted for baseline variables including antihypertensive treatment. However, baseline PRA significantly predicted the develop-
ment of renal impairment (OR 1.58 [CI 1.02, 2.45], \( p = 0.04 \), but not all cause mortality (OR 1.12 [0.89, 1.40]) \( p = 0.32 \) in the fully adjusted model.

**Conclusion:** These data support the association of Nt-BNP with increased risk of CV events and its use to improve risk factor prediction in hypertensive subjects. These analyses also support the association of elevated PRA with the subsequent development of renal impairment, but do not support its use to predict future CV events or all cause mortality in hypertensives without pre-existing coronary disease.

**LB1.4 BLOOD PRESSURE AND OTHER DETERMINANTS OF LEFT ATRIAL ENLARGEMENT IN PATIENTS AT HIGH CARDIOVASCULAR RISK: THE ONTARGET/TRANSCEND STUDY**

P. Verdecchia, On Behalf of The ONTARGET/TRANSCEND Investigators, 1Hospital of Assisi, Assisi-Italy

Contemporary evidence on new onset atrial fibrillation (AF) in high-risk vascular patients without heart failure is limited. In the setting of the ONTARGET/TRANSCEND trial, we studied 30,424 patients (mean age ± SD, 66.4 ± 7.0) with vascular disease or complicated diabetes who were in sinus rhythm at entry. Follow-up duration was 4.7 years. New AF was ascertained 2 and 5 years after entry. New AF was detected in 2,092 patients (15.1 per 1000 patient-years). Risk of AF increased with age, systolic blood pressure and pulse pressure, left ventricular hypertrophy, body mass index (BMI), serum creatinine and history of hypertension, coronary artery disease and cerebrovascular disease (all \( p < 0.001 \)). After adjustment for BMI and other variables, AF risk increased with hip circumference. History of hypertension was associated with a 34% higher risk of new AF. New AF portended an increased risk of congestive heart failure (HR 2.89; 95% CI: 2.45–3.30; \( p < 0.001 \)) and cardiovascular death (HR 1.22; 95% CI: 1.05–1.41; \( p < 0.001 \)). The risk of stroke was unaffected (HR 1.14; 95% CI: 0.93–1.40) while that of myocardial infarction was reduced (HR 0.64; 95% CI: 0.50–0.82). Patients with new AF were more likely to receive vitamin K antagonists (\( p < 0.01 \)), statins (\( p < 0.05 \)) and \( \beta \)-blockers (\( p < 0.01 \)) than those in sinus rhythm. In conclusion, new AF is common in high-risk vascular patients and is associated with several risk factors including history of hypertension. Hip circumference was the strongest anthropometric predictor. Despite extensive use of modern therapies, new AF carries a high risk of congestive heart failure and death over a relatively short term.

**LB1.5 NEW ONSET LEFT ATRIAL ENLARGEMENT IN A GENERAL POPULATION: DATA FROM THE PAMELA STUDY**

M. Bombelli1, C. Cuspidi1, D. Fedeli, M. Perononi1, E. Toso1, H. Polo Friz1, G. Brambilla1, L. Primitti1, I. Ronchi1, F. Ganz1, R. Facchetti1, G. Grassi2, R. Sega2, G. Mancia1. 1Department of Clinical Medicine and Prevention, University of Milano-Bicocca, S. Gerardo Hospital, Monza-Italy, 2Department of Internal Medicine, Hospital of Viterbo, Viterbo-Italy

**Background:** Left atrium enlargement is associated with an increased cardiovascular morbidity and mortality. Aim of the present study was to assess the factors involved in the development of left atrial enlargement in a general population.

**Methods:** A sample of 3200 subjects was randomly selected from the general population of Monza (Italy), aged 25–74 years, stratified for sex and decades of age. The participation rate was 64%. In each subject we obtained: office systolic (S) and diastolic (D) blood pressure (BP); home SBP and DBP (mean of 2 self measurements); 24 hour SBP and DBP; office, home and 24 hour heart rate (HR); left ventricular mass index (LVMi) and left atrial diameter (LAD) by echocardiography; height and weight for calculation of body surface area (BSA) and body mass index (BMI). Pathological left atrial enlargement (LAE) was defined as LAD ≥ 3.9 cm in women and ≥ 4.1 cm in men, while left ventricular hypertrophy (LVH) was defined as LVMi ≥ 106 mm²/m² and ≥ 111 g/m² respectively. Reference values for office, home and 24 hour BP (SBP/DBP) were respectively 140/90 mmHg, 132/83 mmHg and 125/79 mmHg. All variables (including blood glucose, total and HDL cholesterol and serum triglycerides) were collected twice, the first at the beginning of the nineties, and the second 10 years later. The analysis was carried out on the individuals without atrial enlargement at the first examination, which accepted to take part in the second survey 10 years later (n = 1045).

**Results:** Among the 1045 subjects without LAE at the first examination, 123 developed LAE during the 10-year time interval (11.8%). The incidence of a new onset LAE was progressively greater from the lowest to the highest tertile of office, home and 24 hour SBP (\( p < 0.0001 \) for trend), and it was also progressively more frequent in subjects with no BP elevation, 1BP elevation and 3 blood pressures (office, home and 24 hour BP) (\( p < 0.0001 \)). The incidence of a new onset LAE was progressively greater from the lowest to the highest tertile of LVMi (\( p < 0.0001 \) for trend), and from the lowest to the highest tertile of BMI, plasma total cholesterol and blood glucose (\( p < 0.001 \) for trend). The factors independently involved with new onset LAE, identified by stepwise selection model, were office SBP, LVMi, age, BSA, and female gender.

**Conclusions:** In the general population, among subjects with a normal sized left atrium, 11.8% developed LAE in 10 year. The factors that independently increase the risk of left atrium enlargement are age, female gender, office SBP, LVMi and BSA.

**LB1.6 BLOOD PRESSURE TREATMENT WITH Candesartan in Acute Stroke: the Scandinavian Candesartan Acute Stroke Trial**

E. C. Sanders1, P. M. W. Bath2, G. Boyesen3, D. Jatuzzi4, J. Körö5, S. Lidens6, G. D. Murray7, P. S. Richter8, R. O. Roine9, A. Terent10, V. Thijss5, E. Berge2, On Behalf of The SCAST Study Group, 1Department of Internal Medicine, Oslo University Hospital, Oslo-Norway, 2Stroke Trials Unit, Division of Stroke, University of Nottingham, City Hospital campus, Nottingham-United Kingdom, 3Department of Neurology, Bispebjerg Hospital and University of Copenhagen, Copenhagen-Denmark, 4Faculty of Medicine and Department of Neurology, Vilnius University Santariskiu Klinikus Hospital, Vilnius-Lithuania, 5Department of Neurology, Tartu University Hospital, Tartu-Estonia, 6Department of Internal Medicine, St Josef Hospital, Cloppenburg-Germany, 7Centre for Population Health Sciences, University of Edinburgh, Edinburgh-United Kingdom, 8Department of Neurology, Institute of Psychiatry and Neurology, Warsaw-Poland, 9Department of Neurology, Turku University Hospital, Turku-Finland, 10Department of Medical Sciences, Uppsala University, Uppsala-Sweden, 11Department of Neurology, University Hospital Leuven, and Vesalius Research Center, VIB, Leuven-Belgium

**Introduction:** Management of elevated blood pressure in acute stroke has long been debated. The ACCESS trial suggested a beneficial effect of candesartan on vascular events in patients with acute ischaemic stroke. We examined whether careful blood pressure lowering treatment with candesartan is beneficial in patients with acute stroke and elevated blood pressure.

**Methods:** The Scandinavian Candesartan Acute Stroke Trial is a North-European, randomised- and placebo-controlled, double-masked trial of candesartan in patients with acute stroke and elevated blood pressure. Patients aged 18 years or older, with acute stroke (ischaemic or haemorrhagic) and systolic blood pressure ≥140 mmHg were included within 30 hours of symptom onset from 146 centres in 9 countries. Patients were randomly allocated to candesartan or placebo for 7 days, doses increasing from 4 mg to 16 mg during the first 3 days. There were two co-primary effect variables: (i) Vascular death, myocardial infarction or stroke during the first 6 months (analysed using Cox proportional hazards regression model), and (ii) Functional outcome at 6 months, as measured by the modified Rankin Scale (analysed using ordinal logistic regression). Analyses were by intention to treat.

**Results:** 2 029 patients were included. The baseline characteristics were well balanced; mean BP: 171/90 mmHg, mean duration of symptoms before randomisation: 18 hours, 85% of the patients had an ischaemic stroke and 14% haemorrhagic stroke. During the 7 days’ treatment period BPs were significantly lower in patients allocated candesartan (\( p < 0.001 \)), mean difference in BP on day seven was 5/2 mm Hg. There was not statistically significant difference between the candesartan and placebo groups in the risk of the composite vascular endpoint (adjusted HR 1.09, 95% CI 0.84–1.41; \( p = 0.52 \)). A non-significant difference with higher risk of poor functional outcome was seen in the candesartan group (adjusted common OR 1.17, 95% CI 1.00–1.38, \( p = 0.048 \)). The effects were similar for all secondary endpoints and there was no evidence of a differential effect in any of the pre-specified subgroups.

**Conclusion:** We see no indication that blood pressure lowering treatment with the angiotensin receptor blocker candesartan is beneficial in patients with acute stroke and elevated blood pressure.
2A.01 THE ANTI-INFLAMMATORY CAPACITY OF HDL IS LOST BY ACCUMULATION OF THE PRO-INFLAMMATORY ACUTE PHASE PROTEIN SERUM AMYLOID A IN THE HDL PARTICLE OF PATIENTS WITH END-STAGE RENAL DISEASE

M. Tölle, M. Schuchardt, T. Huang, J. Prüfer, W. Zidek, M. van der Giet Charité, Berlin-Germany

Objectives: Patients with chronic kidney disease (CKD) have a 10 to 30-times higher risk for cardiovascular mortality compared to the general population. The underlying causes were incompletely understood, given that traditional risk factors like hypertension and hypercholesterolemia do not correlate with mortality in this patient cohort. Epidemiological studies demonstrate that the endogenous molecule – high density lipoprotein (HDL) – loses its anti-inflammatory and cardiovascular protective properties. The aim of this study was to investigate, why HDL is dysfunctional in these patients. Monocyte chemoattractant protein-1 (MCP-1) production is an initial step for inflammatory response in the vascular wall, by recruitment of monocytes in the subendothelial space. Therefore, MCP-1 was used as read-out in this study.

Methods: Rat vascular smooth muscle cells (VSMCs) were used. (MCP-1) expression was detected by real-time PCR and secretion by Luminescent™ technology. Serum amyloid A (SAA) was identified by mass-spectrometry. HDL was isolated from serum of donors via ultracentrifugation in a potassium bromide gradient. SAA level was quantified by Elisa.

Results: HDL isolated from healthy donors dose-dependently reduced the thrombin-induced MCP-1 expression and secretion in VSMCs. This inhibitory capacity of HDL was significantly reduced in HDL isolated from patients with end-stage renal disease (ESRD). To investigate whether accumulation of pro-inflammatory molecules are responsible for this loss of function, we tested the MCP-1 stimulating effects of HDL. HDL from ESRD patients significantly induced MCP-1 secretion, whereas HDL from healthy controls has no effect. Therefore, HDL from ESRD patients was separated in protein/lipid fraction and the stimulatory potential of each fraction was analyzed. The protein fraction strongly induced MCP-1, whereas the lipid fraction showed basically no activity. Further fractionating of protein content of HDL and analysis of MCP-1 inducing potential followed. Mass-spectrometry analysis of the fraction leading to a strong MCP-1 induction identified SAA. SAA levels were markedly increased in serum and HDL of ESRD patients compared to healthy controls.

Conclusions: In summary, we present evidence that HDL from ESRD patients not only have lower anti-inflammatory potential, but also rendered pro-inflammatory. SAA as pro-inflammatory property accumulated in HDL leading to dys-functionality of the particle. The decreased anti-inflammatory properties of HDL may substantially contribute to the excessive cardiovascular morbidity and mortality in ESRD patients.

2A.02 A MYOCARDIAL INFARCTION GENETIC RISK SCORE ASSOCIATES WITH CAROTID ATHEROSCLEROSIS

V. Hamrefoes, B. Hedblad, G. Engstrom, P. Almgren, M. Sjögren, O. Melander. Department of Clinical Sciences, Lund University, Malmö-Sweden

Objectives: To assess whether a score of eleven SNPs, previously associated with myocardial infarction, also is associated with carotid Intima-Media-Thickness (IMT).

Background: Studies have shown strong associations between a number of SNPs, particularly on Chromosome 9p21, and myocardial infarction. Mechanistic insights for many of these SNPs remain elusive and studies of association with atherosclerosis have shown conflicting results.

Methods: We studied a score including eleven SNPs previously associated with MI (Score-MI) in relation to carotid-IMT, a measure of subclinical atherosclerosis, in 3581 middle-aged subjects from the general population.

Results: Score-MI was associated with IMT of the bulb and common carotid artery in unadjusted (P<0.001 and P = 0.005 respectively) and adjusted (P = 0.002 and P = 0.033 respectively) analyses. The effect size of score-MI was similar to that of LDL cholesterol. With exception of the SNPs with known effects on LDL, Score-MI was unrelated to traditional risk factors and CRP.

Conclusions: This genetic risk score was independently associated with carotid atherosclerosis with an effect size similar to that of LDL cholesterol. Our results suggest that the genetic MI risk conferred by the score is related to early atherosclerosis and that the risk score may identify candidates for early primary prevention.

2A.03 THE INFLUENCE OF GENETIC VARIANTS ON BIGLYCAN GENE EXPRESSION

B. Schmitz, A. Rötrige, R. Telgmann, E. Brand, J. Fischer, S. Paul, S.-M. Brand, 1 Medical Faculty of the Westfalian Wilhelms-University, Münster-Germany, 2 Leibniz-Institute for Arteriosclerosis Research, Münster-Germany, 3 University Hospital Münster, Department of Internal Medicine D, Nephrology and Hypertension, Münster-Germany, 4 Institute of Pharmacology, University Hospital Essen, University Duisburg-Essen, Essen-Germany, 5 Faculty of Health, Medicine, and Life Science, University of Maastricht, Maastricht-The Netherlands

Background and Aims: The extracellular matrix proteoglycan biglycan (BGN) is involved in cardiovascular disease (CVD) pathophysiology. It mediates binding of low-density lipoproteins to the artery wall in atherogenesis, exerts pro-inflammatory effects and affects remodelling after myocardial infarction. This project aimed at the specification of BGN gene expression and the impact of molecular promoter haplotypes.

Material and Methods: We screened 1199 bp of the BGN promoter region in 57 high-risk CVD patients (MolProMD Study) to characterize its variant structure. Molecular haplotypes (MolHaps) were identified by subcloning and resequencing of patients DNA. MolHaps and promoter deletion constructs were generated and transfected into EA.hy926 vascular endothelial cells and THP-1 monocytes. Cells were kept under basal conditions or stimulated with TGF-β1 (10ng/ml) for 24 hrs. Transcription start sites were determined by 5’RACE. DNA/protein interactions were analysed by EMSA, competition assays, and ChIP.

Results: We identified three common MolHaps: 1 [G 578 G-151 G+49; wild type (wt)], 2 [G 578 A-151 T+49] and 3 [A 578 G-151 G+94]. Transcriptional activity of MolHaps 2 and 3 was significantly reduced (all p-values <0.05) in EA.hy926 and THP-1 cells. Co-expression with SP1 revealed a significant promoter activation over mock control (p<0.01) and physical interaction of SP1 was demonstrated by ChIP. EMSA experiments revealed binding of c-FOS to the 5’UTR position G+94, TGF-β1 stimulation enhanced SP1 interaction with position G+578A. In THP-1 cells, ETS family member PU.1 bound -578G with higher affinity (4-fold) compared to -578A.

Conclusion: BGN gene expression is under the control of activating transcription factor (TF) SP1. TGF-β1 reinforces SP1 binding and thus enhances transcriptional activity of the BGN promoter. The polymorphic position G+94T reside within a cis-active promoter element were AP-1 complex formation was observed. Cell type-specific regulation of BGN expression is controlled by ETS family members.

2A.04 DECREASED LEVELS OF SOLUBLE RECEPTOR FOR ADVANCED GLYCATION END-PRODUCTS ARE ACCOMPANIED BY PRONOUNCED ARTERIAL STIFFENING, ALBUMINURIA AND ATTENUATED GLOMERULAR FILTRATION RATE IN HYPERTENSION

K. Dimitriadis, C. Tsiodras, M. Poulakis, I. Bafakis, K. KinTis, M. Almyroudi, D. Flessas, C. Stefanadis. First Cardiology Clinic, University of Athens, Hippokration Hospital, Athens-Greece

Abstracts e19
Objective: Emerging evidence implicates the soluble receptor for advanced glycation end-products (sRAGE) in the development of vascular disease, while arterial stiffness, urinary albumin excretion and impaired renal function are associated with atherosclerosis progression. We investigated the interrelationships of sRAGE with urinary albumin excretion, as expressed as the albumin to creatinine ratio (ACR), estimated glomerular filtration rate (eGFR) and arterial stiffness in essential hypertensives.

Design and Method: Our population consisted of 320 newly diagnosed untreated non-diabetic patients with stage I to II essential hypertension [192 males; 242 non-smokers, mean age = 52 years, office blood pressure (BP) = 145/93 mmHg]. In all participants, ACR values were determined as the mean of two non-consecutive morning spot urine samples and aortic stiffness was evaluated on the basis of carotid to femoral pulse wave velocity (PWV), by means of a computerized method (Complior SP). Moreover, eGFR was assessed using the Modification of Diet in Renal Disease equation. The distribution of sRAGE was split by the median (1060.1 pg/ml) and accordingly subjects were stratified into those with high and low values.

Results: Patients with low sRAGE (n = 164) compared to those with high sRAGE values (n = 156) had greater body mass index (29.7 ± 4.5 vs 27.1 ± 2.5 kg/m², p < 0.05) and 24-h systolic BP (139 ± 8 vs 131 ± 6 mmHg, p = 0.001), while did not differ regarding metabolic profile (p = NS). Moreover, patients with low sRAGE compared to those with high sRAGE levels exhibited higher ACR (1.8 ± 1.7 vs 0.9 ± 0.6 mg/g, p = 0.001) and PWV (9.0 ± 1.7 vs 7.5 ± 1.2 m/sec, p < 0.0001), whereas had lower eGFR (65.9 ± 7 vs 92.6 ± 9.1 ml/min/1.73m², p < 0.05), independently of confounders. In the total population, sRAGE was associated with 24-h pulse pressure (r = -0.371, p = 0.001), ACR (r = -0.274, p = 0.019), eGFR (r = 0.236, p = 0.03) and PWV (r = -0.401, p < 0.0001). Multiple regression analysis revealed that body mass index, 24-h systolic BP, ACR and PWV were the independent predictors of sRAGE (R² = 0.57, p < 0.0001).

Conclusions: In essential hypertension, decreased sRAGE levels are associated with increased PWV, pronounced albuminuria and impairment of renal function. Moreover, the close relation of sRAGE with arterial stiffening, ACR and eGFR, supports the potent role of sRAGE in renal and vascular atherosclerotic disease progression.
Design and Method: Our population of 240 newly diagnosed never treated non-diabetics with stage I to II essential hypertension (155 men, mean age = 51 years, office blood pressure (BP) = 150/96 mmHg) with a negative treadmill exercise test (Bruce protocol) was divided into those with HRE (n = 70) (peak exercise systolic BP ≥210 mmHg in men and ≥190 mmHg in women) and those without HRE (n = 170). Arterial stiffness was evaluated on the basis of carotid to femoral pulse wave velocity (PWV) values.

Results: Patients with HRE compared to those without HRE had greater 24-h systolic BP (143 ± 9 vs 131 ± 8 mmHg, p<0.05), while did not differ regarding metabolic profile and left ventricular mass index (p = NS). Patients with HRE as compared to those without HRE exhibited greater levels of ADMA (0.63 ± 0.04 vs 0.52 ± 0.05 μmol/l, p<0.0001), OPG (5.4 ± 0.1 vs 4.1 ± 0.5 pmol/l, p<0.0001) and PWV (8.9 ± 1.7 vs 7.5 ± 0.9 m/sec, p<0.0001), independently of confounders. In the total population, peak exercise systolic BP was related to 24-h systolic BP (r = 0.249, p<0.05), PWV (r = 0.278, p = 0.003), ADMA (r = 0.260, p = 0.007) and OPG (r = 0.214, p<0.05). Regarding OPG, it was associated with 24-h systolic BP (r = 0.285, p<0.0001), ADMA (r = 0.284, p<0.05) and PWV (r = 0.424, p<0.0001). Multiple regression analysis showed that 24-h systolic BP (b = 0.216, p = 0.003), male sex (b = 0.270, p<0.05), ADMA (b = 0.225, p = 0.006) and OPG (b = 0.188, p<0.05) were independent predictors of peak exercise systolic BP.

Conclusions: In essential hypertension, a HRE is accompanied by a state of increased arterial stiffening, endothelial dysregulation and progressive atherosclerosis. The interrelationships of ADMA and OPG with exercise BP response and stiffness support that diffuse vascular dysfunction contributes to HRE-related risk in hypertension.
2B.01 FIBRIN CLOT PROPERTIES IN ARTERIAL HYPERTENSION AND THEIR MODIFICATION BY ANTHYPERTENSIVE TREATMENT

M. Rajzer1, A. Undas2, W. Wojciechowska1, T. Kameczura1, K. Kawecka-Wojciechowska1

Objective: We sought to determine the fibrin clot properties in hypertensive subjects and evaluate the potential effect of antihypertensive therapy on these parameters.

Methods: 61 patients (30 men, 31 women) with essential arterial hypertension stage 1 or 2 (aged 46.6 ± 14.4 years), free of clinically evident vascular disease were randomly allocated for a 6-month monotherapy with one of the 5 antihypertensive agents, i.e. quinapril, losartan, amlopidine, hydrochlorothiazide, or bisoprolol. Office and 24-h ambulatory blood pressure monitoring (ABPM), plasma fibrin clot permeability, turbidimetry and efficiency of fibrinolysis were investigated at baseline and after 6 months of therapy.

Results: On the initial visit the systolic blood pressure in a 24-h ABPM was correlated with the clot permeability (r = 0.37, <0.05), clot lysis time (r = 0.42, <0.05) and maximal D-dimer concentration in the lysis assay (r = 0.45, <0.05). Antihypertensive treatment regardless of the drug class resulted in reduction of systolic/diastolic blood pressure in office measurements and 24-hour monitoring (all <0.001), accompanied by an increase in clot permeability (8.2 ± 0.2 vs. 8.6 ± 0.2 10⁻³ cm², p = 0.02), reduction in clot lysis time (8.5 ± 1.1 vs. 8.0 ± 1.0 min, p = 0.02) and maximal D-dimer concentration (3.8 ± 0.5 vs. 3.6 ± 0.4 mg/l, p = 0.02). The decrease of systolic blood pressure was associated with an increase of clot permeability and decrease in both clot lysis time and maximum D-dimer concentration.

Conclusions: Independently of the used antihypertensive treatment, systolic blood pressure decrease is associated with improved fibrin clot permeation and susceptibility to lysis. Beneficial changes in fibrin clot properties might be a novel anthrombotic mechanism observed during the antihypertensive treatment.

2B.02 OXYTOCIN ROLE IN THE EMBRYONAL DEVELOPMENT OF THE HEART

M. Jankowski, B. A. Danalache, J. Gutkowska. Ruchum, University of Montreal, Montreal-Canada

Background: Oxytocin (OT): synthesized in the heart, has the ability to heal injured hearts and to promote cardiomyogenesis from stem cells. Recently, we reported that the OT-GKR molecule, a processing intermediate of OT, potently increased the spontaneous formation of cardiomyocytes (CM) in embryonic stem D3 cells and augmented glucose uptake in newborn rat CM above the level stimulated by OT. In the present experiments, we investigated whether OT-GKR exists in fetal and newborn rodent hearts, interacts with the OT receptors (OTR) and primes the generation of contracting cells expressing CM markers in P19 cells, a model for the study of early heart differentiation.

Methodology/Principal Findings: High performance liquid chromatography of newborn rat heart extracts indicated that OT-GKR was a dominant form of OT. Immunocytochemistry of mouse embryos (embryonic day 15) showed cardiac OT-GKR accumulation and OTR expression. Computerized molecular modeling revealed OT-GKR docking to active OTR sites and to V1a and V2 receptors of vasopressin. However, in contrast to OT, the OT-GKR injected to Sprague-Dawley rats blocked diuresis, indicating the possible action via AVP receptors. In embryonic P19 cells, OT-GKR induced contracting cell colonies and ventricular CM markers more potently than OT, an effect being suppressed by OT antagonists and OTR-specific small interfering (si) RNA. The V1a receptor antagonist and specific siRNA also significantly reduced OT-GKR-stimulated P19 contracting cells. In comparison to OT, OT-GKR induced in P19 cells less -actinin, myogenin and MyoD mRNA, skeletal muscle markers.

Conclusions/Significance: These results raise the possibility that C-terminally extended OT molecules stimulate CM differentiation from stem cells reserve. OT-GKR by increased glucose uptake and inhibition of oxidative stress in cardiomyocytes exposed to hypoxic conditions can be also important for the cell survival during fetal life.

2B.03 BLOCKADE OF INTERLEUKIN-1 BETA ATTENUATES RENOVASCULAR HYPERTENSION IN MICE

Q. Wang1, A. So2, J. Nussberger1, M. Burnier1. 1Service of Nephrology and Hypertension, CHUV, Lausanne-Switzerland, 2Service of Rheumatology, CHUV, Lausanne-Switzerland

Objective: The NALP3 inflammasome is formed by NALP3, the adaptor ASC, and caspase-1, functions as a sensor of danger signals and triggers processing and release of interleukin-1beta (IL-1β). Recent findings suggest that NALP3 is frequently mutated in some patients with essential hypertension. We have previously shown that NALP3 KO mice do not develop hypertension in two-kidney, one-clip (2K1C) mouse model. The aim of this study is to investigate the role of IL-1β in the development of the 2K1C renovascular hypertension in mice.

Design and Method: Six-week old male C57BL/6J mice were used for generating 2K1C hypertension (n = 6 per group). A U-shaped stainless steel clip was placed on left renal artery under anesthesia. The same surgery without clipping was performed in sham mice. IL-1β antibody (anti-IL-1β) was administered in half of the 2K1C mice by intraperitoneal (IP) injection (200microgram/week). Another half 2K1C mice received only saline injection. At week 6 after clipping and the IP injection, intra-arterial blood pressure (BP) was measured in conscious mice. Blood was collected for plasma renin activity (PRA) and concentration (PRC) measurements. Organ weight indices are used for determining hypertrophy. Data are mean ± SEM treated with Anova one way analysis.

Results: Mean BP (MBP) in anti-IL1b treated 2K1C mice (130 ± 3mmHg) was significantly lower than that in 2K1C mice (146 ± 3mmHg) even if it is still higher than that in sham group (117 ± 3 mmHg). Compared to 2K1C mice, PRA and PRC in anti-IL1b treated 2K1C mice were lower but the difference was not significant. The weight index of the clipped kidney was largely reduced in both 2K1C and 2K1C+anti-IL1b groups when compared to the unclipped kidneys in 2K1C and sham animals, indicating that the clip had a comparable effect on kidney perfusion in the two 2K1C groups. Heart weight (HW) to body weight (BW) ratio was also significantly decreased in 2K1C-anti IL-1b treated mice compared to 2K1C group.

Conclusion: The results show that IL-1beta lowers BP in 2K1C renovascular hypertension in mice and hence prevent the development of cardiac hypertrophy. This may be partly mediated through a renin effect but additional studies are needed to assess the impact of IL-1b on renin synthesis and release.

2B.04 PROBNP GENE DELIVERY PREVENTS HYPERTENSIVE HEART DISEASE IN SPONTANEOUSLY HYPERTENSIVE RATS


Background: Over time, high blood pressure (BP) leads to diastolic dysfunction, cardiac remodeling, fibrosis and progression to congestive heart failure. B-type natriuretic peptide (BNP) has BP lowering, anti-fibrotic and anti-hypertrophic properties, which makes BNP an attractive agent for attenuating the adverse cardiac remodeling associated with hypertension. In the current study, we tested the effects of sustained cardiac proBNP gene delivery on BP, cardiac function and remodeling in spontaneously hypertensive rats (SHR).

Methods and Results: We used the myocardium-tropic adeno-associated virus serotype 9 (AAV9) vector to achieve continuous cardiac rat proBNP expression by OT antagonists and OTR-specific small interfering (si) RNA. The V1a receptor antagonist and specific siRNA also significantly reduced OT-GKR-stimulated P19 contracting cells. In comparison to OT, OT-GKR induced in P19 cells less -actinin, myogenin and MyoD mRNA, skeletal muscle markers.

Conclusions/Significance: These results raise the possibility that C-terminally extended OT molecules stimulate CM differentiation from stem cells reserve. OT-GKR by increased glucose uptake and inhibition of oxidative stress in cardiomyocytes exposed to hypoxic conditions can be also important for the cell survival during fetal life.
In SHR single systemic administration of AA9 vector allowed long-term, cardiac BNP overexpression, resulting in significant reductions in systolic and diastolic BP for nine months after injection. Left ventricular (LV) thickness, LV end-systolic dimensions and LV mass were reduced, while ejection fraction was significantly increased in BNP-treated compared to untreated SHR. Circumferential systolic strain and strain rate of the early phase of diastole were improved in BNP-treated compared to untreated SHR. Importantly, non-cardiac overexpression of BNP via AA2 vector was not associated with changes in BP and plasma BNP in SHR. Furthermore, normal Wistar rats injected with AA9 vector showed significantly reduced heart weights four weeks after injection without BP reduction.

Conclusions: AA9 vector facilitates sustained cardiac proBNP overexpression, resulting in long-term, LV function in hypertensive disease. Long-term proBNP delivery improved both systolic and diastolic function. Importantly, the effects on cardiac structure and function occurred independently of BP lowering effects in normal Wistar rats.

**2B.05**

**AT₁a RECEPTORS TRANSFECTED INTO THE CAUDAL MEDULLA OF AT₁a⁻/⁻ MICE INHIBIT THE CARDIOVASCULAR RESPONSE TO STRESS**

G. Head1, K. Palma-Rigo1, T. Nguyen-Huu1, D. Chen2, A. Allen2. 1Baker IDI Heart and Diabetes Institute, Melbourne-Australia, 2University of Melbourne, Melbourne-Australia.

Brain angiotensin II (AngII) has been recognized as an important neuromodulator of cardiovascular responses induced by stress in several brain regions. The caudal ventrolateral medulla (CVLM) which is important for autonomic regulation is rich in AT₁a receptors. In the present study, we examined whether the expression of AT₁a receptors in the CVLM of AT₁a mice alters the baroreflex sensitivity and cardiovascular responses to stress. Bilateral microinjections of lentivirus with the catecholamine-selective PRSx8 promoter driving expression of either green fluorescent protein (GFPv, -/- n = 9) (control) or AT₁a receptors (AT₁a mice n = 10) were made into the CVLM of AT₁a mice. Telemetry devices were used to record mean arterial pressure (MAP), heart rate (HR) and locomotor activity. No differences in MAP or HR were recorded 6 weeks following lentivirus microinjection. However, baroreflex sensitivity was reduced in AT₁a mice (18.4 ± 3.9 bpm/mmHg < 0.0003). Cogswell stress test for one hour, induced smaller MAP responses in AT₁a mice compared with independently of BP lowering effects in normal Wistar rats.

**2B.06**

**IMPACT OF RENAL NERVE ABLATION ON RENAL PERFUSION AND COMPONENTS OF THE RAAS IN TREATMENT RESISTANT HYPERTENSION**

C. Ot1, A. Schmid1, S. Tzite1, T. Ditting1, U. Ralf1, R. Janka2, K. Hilger3, R. Veelken1, M. Uder1, R. Schmieder1. 1Department of Nephrology and Hypertension, University of Erlangen-Nuremberg, Erlangen-Germany, 2Department of Radiology, University of Erlangen-Nuremberg, Erlangen-Germany.

Background: Renal nerve ablation emerged as a new therapeutic approach for treatment resistant hypertension. Measurement of the renal and sympathetic activity revealed a decrease in sympathetic drive to the kidney and small resistance vessels after renal nerve ablation. The precise mechanism how renal nerve ablation exerts its BP-lowering effects are not yet fully understood.

Methods: In a pilot study 8 patients with treatment resistant hypertension were included and following assessments were done before (day-1), after (day+1) and again after 3 months of renal nerve ablation. Renal plasma flow (RPF) was non-invasively measured by magnetic resonance imaging with arterial spin labeling (MRI-ASI). After 30 minutes of complete rest in supine position blood and urine samples were collected for the determination of the individual components of the RAAS.

Results (median (interquartile range)): Compared to day-1, there was no change in RPF both day+1 (p = 0.811) and 3 months (p = 0.392) after renal nerve ablation. Plasma renin activity and serum angiotensin II levels did not differ between day-1 and day+1 as well as after 3 months of renal nerve ablation. In contrast, there was a significant acute decrease of aldosterone concentration (day-1: 161 (140-265) versus day+1: 110 (101-168) pg/ml, p = 0.012) and in accordance increased urinary sodium/potassium ratio (day-1: 2.41 (1.17-3.44) versus day+1: 6.02 (4.83-7.92), p = 0.028). After 3 months these changes were no longer evident. Urinary angiotensinogen levels, considered as parameter of the local renal RAS activity, tended to be reduced at day+1 (p = 0.116) and was significantly decreased at day+3 (0.02-13.8) versus 16.6 (8.50-37.0) ng/ml, p = 0.046) compared to day-1 levels.

Conclusion: Thus, our data indicate that a decrease of aldosterone with the consequence of a greater urinary sodium excretion occurs after the procedure. However, whether this will lead to a longterm reduction of total body sodium content needs to be established. Renal perfusion did not appear to be significantly changed.

**2B.07**

**URINARY CALCIUM EXCRETION IS RELATED TO PLASMA ALDOSTERONE LEVELS IN HYPERTENSIVE PATIENTS**

L. Marzano, C. Catena, G. L. Colussi, La Sechi. Hypertension Unit, Department of Internal Medicine, University of Udine, Udine-Italy

Objective: Experimental and clinical studies have demonstrated that low renin hypertension and aldosteronism are associated to abnormalities of calcium metabolism. Although these studies suggest a potential role of mineralocorticoid hormones, a direct involvement of aldosterone in calcium metabolism has never been shown in hypertensive patients. The present study was designed to investigate the relationship between aldosterone and calcium metabolism in essential hypertension.

Design and Methods: In 129 patients (age 45 ± 12 yr; 75 M/54 F) with untreated hypertension we measured anthropometric indexes, fasting plasma calcium levels and 24 h urinary calcium excretion, creatinine clearance, plasma renin activity, plasma aldosterone levels, and 24 h urinary cortisol excretion. For statistical analysis, patients were divided according to tertiles of plasma aldosterone levels.

Results: Plasma calcium and plasma phosphate levels decreased progressively and urinary calcium excretion increased progressively and significantly with raising tertiles of plasma aldosterone. Urinary sodium excretion and creatinine clearance did not differ among plasma aldosterone tertiles. Urinary regression analysis demonstrated a direct relationship between urinary calcium excretion and plasma aldosterone levels (r = 0.209; p = 0.017), urinary cortisol excretion (r = 0.243; p = 0.008), and urinary potassium excretion (r = 0.216; p = 0.014). Multivariate analysis including age, body mass index, creatinine clearance, plasma renin activity, urinary potassium and cortisol excretion indicated that urinary calcium excretion is independently associated to plasma aldosterone levels (p = 0.024).

Conclusions: Our results show that aldosterone might be a major player in the mechanisms leading to abnormal calcium metabolism in essential hypertension.

**2B.08**

**AMINO TERMINAL Natriuretic Peptides and Association to Global Cardiovascular Risk in a Male Adult Population from Southern Italy**

A. Barbato1, S. Siccarretà1, S. Marchetti1, R. Iacone1, A. Battistoni2, M. De Giusti3, E. Dito4, A. Marra5, M. Schiano di Cola1, R. Ippolito1, C. Calvieri1, M. Volpe6, P. Strazzullo1, S. Rubatto1, 1Federico II University of Naples Medical School, Frattamaggiore-Italy, 2Dept. Cardiology, Ild School of Medicine, University Sapienza of Rome, 3Ospedale S. Andrea, ROME-Italy, 4Irscc Neumor, Polo Molisano University Sapienza of Rome, Pozzilli-Italy.

Objective: Aminoterminal (NT)-natriuretic peptides (NT-proNPs) have been identified as emerging markers and powerful predictors of cardiovascular disease (CVD). The value of NT-proNP's measurement in the assessment of CV risk among asymptomatic adults free of CV events in the general population is not definitively assessed. We thus aimed to evaluate the association of NT-proNPs levels with CVD risk evaluated by commonly used cardiovascular risk score algorithms in a sample of adult male Italian population.

Design and Method: We performed a statistical evaluation of the association of both NT-proBNP and NT-proANP plasma levels with cardiovascular risk according to three commonly used cardiovascular risk score algorithms (Progetto Cuore, Score, Framingham) in an unsampled selection of adult male population from Southern Italy (n = 630, age range: 35–69 years) participating in the Olivetti Heart Study.

Results: A statistically significant linear increase in CV risk estimated with any of the three algorithms was observed for NT-proANP (<0.001), but not for NT-proBNP.

In order to compare the odds ratio for being at high CV risk, according to different algorithms, for 1 standard deviation (SD) change in NT-proANP (1SD = 1305 fmol/ml) or NT-proBNP (1SD = 119 fmol/ml) level, a logistic regression analysis was performed. Whereas NT-proANP was significant associated to the
probability of being at high CV risk with all three algorithms (Framingham, OR = 1.41; <0.001; Progetto Cuore, OR = 1.40; <0.001; Score, OR = 1.34, <0.001). NT-proBNP was associated with Progetto Cuore estimates (OR = 1.37; p = 0.003), but not with Score (OR = 1.08; p = 0.336) and Framingham (OR = 0.96; p = 0.628). A significant difference between the areas under the receiving operator curve (ROC) of the two peptides was detected when using the Score (<0.05) or the Framingham algorithm (<0.005), with NT-proANP showing better specificity than NT-proBNP in detecting subjects at high cardiovascular risk.

Conclusions: Based on our findings, both NT-NPs are associated with estimates of cardiovascular risk in men using the Progetto Cuore algorithm, probably the one most suitable to the Italian population. By contrast, NT-proANP plasma levels seem to be better than NT-proBNP in detecting subjects at high CV risk when using the Score or the Framingham algorithm. Prospective studies are needed to assess to what extent the predictive capability of NT-proNPs is independent from that of conventional risk factors.

2B.09 ASSOCIATION OF SERUM FETUIN-A WITH CARDIOVASCULAR DISEASE: A SYSTEMATIC META-ANALYSIS
H. Khan, D. F. Freitag, D. Saleheen. Department of Public Health and Primary CARE, University of Cambridge, Cambridge-United Kingdom

Background: Published data on the association between circulating serum Fetuin A levels and fatal or non fatal cardiovascular disease (CVD) are inconsistent. The present meta-analysis was performed to clarify the role of serum Fetuin A in relation to cardiovascular events and type2 diabetes (T2D).

Methods and Results: A systematic search was performed using Medline, and Web of Science database. Effect estimates and 95% confidence intervals (CIs) used to assess the strength of association between levels of serum Fetuin A and CVD related outcomes were extracted from relevant studies. In a total of 14,871 individuals 1756 patients developed fatal and non fatal CVD or T2D. The highest compared with the lowest tertile of plasma Fetuin A significantly increased the risk of developing CVD or mortality 1.22(1.04–1.42) and T2D (RR 1.81(1.4–2.33)). Subgroup analysis by baseline study population selection showed that the risk of developing fatal or non fatal CVD events in healthy population was (RR 2.82(2.16–3.7), for those with stable CVD was RR 0.8(0.65–1.25) and those with renal disease or undergoing dialysis was (RR 0.87(0.55–1.39)). The significant heterogeneity between these underlying population subgroups I2 = 74% suggests that Fetuin A may be involved in the early stages of CVD or atherosclerosis however further investigation needs to undertaken in this regards.

Conclusion: Results of this first systematic analysis show that high circulating levels of Fetuin A are associated with both CVD and T2D independently. However further research is warranted to determine the role of Fetuin A in pathophysiology of cardiovascular disease.
ORAL SESSION

ORAL SESSION 2C

LIFESTYLE CHANGES

2C.01 FATAL AND NONFATAL OUTCOMES, INCIDENCE OF HYPERTENSION, AND BLOOD PRESSURE CHANGES IN RELATION TO URINARY SODIUM EXCRETION IN WHITE EUROPEANS

K. Stolarz-Skrzypek1, T. Kuznetsova2, L. Thijs2, V. Tikhonoff3, J. Seidlerova4, T. Richard1, Y. Fun4, A. Olszecka1, S. Malutina1, E. Casiglia1, J. Filipovsky1, K. Kawecka-Jaszcz1, Y. Nikitin6, J. Staessen2, On behalf of the European Project on Genes in Hypertension (Epogh) Investigators.

1First Department of Cardiology and Hypertension, Jagiellonian University Medical College, Krakow-Poland, 2Studies Coordinating Centre, Division of Hypertension, and Cardiovascular Epidemiology, Maastricht University, Maastricht-The Netherlands, 3Department of Clinical and Experimental Medicine, University of Padova, Padova-Italy, 4Faculty of Medicine in Pilsen, Charles University, Pilsen-Czech Republic, 5Department of Epidemiology, Maastricht University, Maastricht-The Netherlands, 6Institute of Internal Medicine, Novosibirsk-Russia

Objective: Short-term intervention trials support cross-sectional population studies showing positive association between blood pressure (BP) and salt intake. We aimed to investigate in the same cohort various health outcomes in relation to 24 hour urinary sodium excretion (UNa) as index of salt intake in the same cohort of nuclear families prospectively followed-up.

Design and Method: Families were randomly recruited and followed up in the Flemish Study on Genes, Environment and Health Outcomes (1985–2004) and in the European Project on Genes in Hypertension (1999–2001). Participants were predominantly white Europeans. Participants without cardiovascular disease at baseline constituted three cohorts. Main outcome measures were incidence of mortality and morbidity (3681 subjects, Outcome Cohort), incidence of hypertension (2096 subjects normotensive at baseline, Hypertension Cohort) and association between changes in BP and UNa (1499 subjects off treatment at baseline and follow-up, Blood Pressure Cohort). Median follow-up ranged from 6.14 to 7.62 years.

Results: In multivariable-adjusted analyses, baseline UNa did not predict morbidity or mortality except for a weak (P = 0.035) association with cardiovascular mortality. UNa predicted (P < 0.039) the incidence of hypertension (≥ 140/90 mm Hg) in subjects with normal enrollment BP (121-129/80-84 mm Hg). Systolic BP increased by 0.37 mm Hg per year, whereas UNa did not change. At baseline (P = 0.04) and follow-up (P = 0.02), systolic BP correlated with UNa in fully adjusted models. Changes in systolic BP during follow-up were positively related with the changes in UNa. In multivariable-adjusted analyses, a 100 mmol increase in the 24-hour UNa was associated with 1.71 mm Hg increase in systolic BP (P = 0.0003). In relative terms, a doubling of UNa was associated with 2.2% increase in systolic BP (P = 0.0002).

Conclusion: Over and beyond previous cross-sectional studies, our longitudinal study shows for the first time in a general population that systolic BP changes over time in parallel with salt intake. However, high salt intake was not associated with increased cardiovascular risk.

2C.02 BLOOD PRESSURE LOWERING EFFECT OF DIETARY INTEGRATION WITH GRANA PADANO CHEESE IN HYPERTENSIVE PATIENTS

G. Crippa1, M. Bosi2, A. Cassi1, L. Fiorentini1, F. Rossi2, 1Guglielmo DA Saliceto Hospital, AUSL Piacenza, Piacenza-Italy, 2Università Cattolica Del Sacro Cuore, Piacenza-Italy

It has been shown that some tripeptides (mainly valyl-prolyl-proline and iso-leucyl-prolyl-proline), originating from the degradation of milk proteins by proteinases from L. helveticus, has sustained ACE-inhibiting activity and significant antihypertensive effect in SHR. (Yamamoto et al., 1994). The Grana Padano, a typical Italian cow-milk based cheese, at moderate ripening degree (9-12 months), showed a potent (as measured by the spectrophotometric assay) in-vitro ACE-inhibitory effect. (Rossi et al. 2009)

In this study we evaluate whether a daily dietary integration with a small amount of Grana Padano cheese effectively reduced blood pressure (BP). In a randomized, open-label, controlled study, 45 hypertensive patients received a daily dose of 30 grams Grana Padano cheese during a period of 2 months. BP was evaluated before and after treatment by using conventional sphygmomanometry, automated office BP (BpTRU) and ambulatory BP measurements (Takeda, 4220). The results have been compared with those obtained in a homogeneous control group of 15 hypertensive patients. Pharmacological treatments excluded ACE-inhibitors and ARB. A dietary manipulation was performed to maintain unchanged calorie, cholesterol and sodium intake. Preliminary results indicate that the patients who received Grana Padano presented with a statistically significant reduction of systolic and diastolic BP (p<0.05, Student’s t test), while no change was detected in the control group.

No change in LDL-cholesterol, Calcium, Magnesium serum levels and urinary sodium excretion was observed at the end of treatment period.

In conclusion, a moderate intake of mildly seasoned Grana Padano cheese seems to be effective in lowering BP in hypertensive patients. Appropriate (and easily feasible) dietary manipulations can counterbalance the increased intake of cholesterol and sodium due to dietary integration with Grana Padano.

2C.03 CAN OMEGA 3 POLYUNSATURATED FATTY ACIDS SUPPLEMENTATION ACT BLOOD PRESSURE LEVELS IN HYPERTRIGLYCERIDEIMIC PATIENTS, WITH OR WITHOUT METABOLIC SYNDROME AND WITH unconstrained NORMAL-HIGH BLOOD PRESSURE?

M. L. De Rosa. University of Naples Federico II Faculty of Medicine, Naples-Italy

Omega-3 (omega-3) polyunsaturated fatty acids (PUFAs) from fish and fish oils appear to protect against coronary heart disease: their dietary intake is in fact inversely associated with cardiovascular disease morbidity/mortality in population studies. Recent evidence suggests that at least a part of this protective effect is mediated by a relatively small but significant decrease in blood pressure (BP) level. In fact, omega-3 PUFAs exhibit wide-ranging biological actions that include regulating both vasomotor tone and renal sodium excretion, partly competing with omega-6 PUFAs for common metabolic enzymes and thereby decreasing the production of vasoconstrictor rather than vasodilator and anti-inflammatory eicosanoids. PUFAs also reduce angiotensin-converting enzyme (ACE) activity, angiotension II formation.

We retrospectively evaluated the long-term effect of a PUFA supplementation on the blood pressure level of 91 hypertriglycerideemic subjects with untreated normal-high blood pressure that were prescribed a 3 grams PUFAs supplementation in order to improve their plasma lipid pattern.

After 24 months of treatment, systolic blood pressure (SBP) markedly decreased by 2.6 ± 2.5 mmHg (p = 0.001) and diastolic blood pressure (DBP) by 1.4 ± 3.1 mmHg (p = 0.001), while basal heart rate decreased by 4.1 ± 4.6 bpm (p < 0.001). Both SBP and DBP reduction were significantly related to the baseline SBP (p < 0.001) and DBP (p < 0.001), respectively. Diastolic blood pressure change was also inversely related to the patient’s age (p = 0.004). No significant difference was perceived in the metabolic syndrome subgroup.

In our retrospective study, highly purified omega-3 PUFAs long-term supplementation is associated with a significant reduction in SBP, DBP, and basal heart rate in hypertriglycerideemic patients with normal-high blood pressure. No significant difference was perceived in the metabolic syndrome subgroup. The main
determinants of the PUFA anti-hypertensive effect appear to be the basal blood pressure level and age.

Preliminary clinical trials involving normotensive and hypertensive dyslipidaemic patients, diabetics and elderly subjects, confirm this working hypothesis: 3 meta-analyses suggest that PUFAs are able to slightly, but significantly improve arterial hypertension. Future research will clarify if PUFA supplementation could improve the antihypertensive action of specific BP lowering drug classes and of statins.

**Results:**

Patients were instructed to reduce their habitual energy intake in 280Kcal/day.

**Objective:** To avoid weight gain during the study period, all patients received 50g of chocolate 70% cocoa/day (containing 2135mg polyphenols) for 4 weeks. To avoid a expressive reduction, however not statistically significant on plasma biomarkers of endothelial function: vascular cell adhesion molecule-1 (1037 ± 44 vs. 1019 ± 42ng/ml), intracellular adhesion molecule-1 (160 ± 12 vs. 149 ± 10ng/ml), E-selectin (68 ± 7 vs. 64 ± 0ng/ml) and biomarkers of inflammation: high sensitivity C-reactive protein (9.3 ± 2.7 vs. 6.1 ± 1.2mg/l) and interleukin-6 (88 ± 21 vs. 69 ± 15pg/ml). HOMA-IR and serum levels of tumor necrosis factor-α, oxidized LDL, glucose, total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides remained almost unchanged during the study.

**Conclusion:** The results of this study suggest that chocolate 70% cocoa has a beneficial effect on blood pressure.

**Objective:** To evaluate in stage 1 hypertensive subjects, the effects of chocolate 70% cocoa on carotid and cardiac structure and function.

**Results:**

Average intensity of habitual PA was expressed as the average number of accelerometer counts per 1 minute of monitoring time. Freedom’s cut-offs were used to differentiate light, moderate- and vigorous-intensity activity, and minutes of monitoring time spent in moderate-vigorous activity was calculated (M-V PA).

**Conclusion:** In healthy untrained subjects, the average intensity of habitual PA has an independent effect on carotid diameter and stiffness and on systolic myocaridial performance. A low daily level of moderate-vigorous activity does not influence carotid and cardiac structure or function.

**Objective:** Consumption of tomato-derived food products is linked to beneficial outcomes. The aim of this study was to explore the acute and mid-term effects of diet supplementation with tomato paste on the endothelial function and blood pressure of young, healthy volunteers.

**Objective:** To evaluate in stage 1 hypertensive subjects, the effects of chocolate 70% cocoa intake on casual blood pressure, glucose metabolism, lipid profile, oxidative stress and biomarkers of inflammation and endothelial function.

**Methods:** Intervention clinical trial. Twenty stage 1 hypertensive subjects without previous antihypertensive treatment, of both sexes, aged 18-60 years were included in the present study. All patients received 50g of chocolate 70% cocoa/day (containing 2135mg polyphenols) for 4 weeks. To avoid weight gain during the study period, patients were instructed to reduce their habitual energy intake in 290Kcal/day.

**Results:** Comparison of pre versus post intervention data revealed significant reduction in casual blood pressure. Systolic blood pressure decreased from 146.5 ± 1.3 to 136.9 ± 2.6mmHg, p < 0.001; while diastolic blood pressure was considerably reduced from 93.2 ± 0.7 to 87.4 ± 1.8mmHg, p < 0.05. We observed a expressive reduction, however not statistically significant on plasma biomarkers of endothelial function: vascular cell adhesion molecule-1 (1037 ± 44 vs. 1019 ± 42ng/ml), intracellular adhesion molecule-1 (160 ± 12 vs. 149 ± 10ng/ml), E-selectin (68 ± 7 vs. 64 ± 0ng/ml) and biomarkers of inflammation: high sensitivity C-reactive protein (9.3 ± 2.7 vs. 6.1 ± 1.2mg/l) and interleukin-6 (88 ± 21 vs. 69 ± 15pg/ml). HOMA-IR and serum levels of tumor necrosis factor-α, oxidized LDL, glucose, total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides remained almost unchanged during the study.

**Conclusion:** The results of this study suggest that chocolate 70% cocoa has a beneficial effect on blood pressure.
Design and Method: 19 young, healthy volunteers (mean age 39 years, 8 men) were studied following a two week wash-out period in a randomized (sequence of exposure), single-blind (operator), cross-over design. The study consisted of two arms: the tomato paste supplementation arm (70g tomato paste containing 33.3 mg of lycopene) and the control arm. Flow mediated dilatation (FMD) was used as an estimate of endothelial function at day 1 (acute response) and day 15 (mid-term response); peripheral blood pressures were measured by a sphygmomanometer.

Results: Tomato supplementation led to an overall FMD increase compared to control session (P = 0.047 for repeated measures 3x2 Anova). At day 1, FMD was non-significantly increased by 1.4 ± 1.5% at the supplementation arm, and decreased by −0.3 ± 0.6% at the control arm (P = 0.329). By day 15, tomato supplementation resulted in a significant increase in FMD by 3.3 ± 1.4%, while at the control arm FMD declined by −0.5 ± 0.6% (P = 0.03); magnitudes of change are absolute FMD values. Blood pressures did not change.

Conclusions: Daily tomato paste consumption exerts a beneficial mid-term, but not acute, effect on the endothelium of young, healthy volunteers, by ameliorating FMD values. Further studies are warranted in order to explore the endothelial effects of tomato paste of various concentrations in different age groups and comorbidities.

Results: PWV and AIx did not change after the 2-week long daily consumption of either coffee or decaffeinated coffee whereas, caffeine significantly increased both PWV and AIx (maximal change in responses by 0.51 m/sec and 4.3 %, respectively, p<0.05 at the end of the treatment arm). The acute and acute-on-chronic effect of decaffeinated coffee on aortic stiffness and wave reflections was not significant. Coffee with caffeine induced a significant change in PWV and AIx values at the first day (maximal change in responses by 0.54 m/sec and 4.2 %; p<0.05 at 60 min), however, the effect in PWV and AIx at the end of the 2-week therapy (acute-on-chronic) was proportionally less significant (maximal change in responses by 0.13 m/sec and 1.37 %, p = NS at 60 min). On the contrary there were not significant differences in PWV and AIx responses by caffeine between the first day and the end of the 2-week therapy.

Conclusions: Caffeine coffee consumption has a less potent acute-on-chronic effect on aortic stiffness and wave reflections than caffeine given alone. Although mechanisms are not fully known, these findings suggest a separate contribution of an active effect on the intrinsic properties of the elastic arteries already modified by a two-week daily coffee administration.

Introduction: In the last decade it was increasingly noticed that smoking will damage the kidney. However, these data are generated from retrospective analysis of clinical trials. No data on the effect of long-term smoke exposure on the histological outcome in an animal model have been published. The relationship between smoke induced COPD and renal and vascular damage has been investigated.

Material and Method: We analysed 10 months old 129SV and B6 mice that was exposed to 8 months of smoking for 6h 5 days per week. The particle concentration during the smoke exposure was in average 140 mg/m3. After 8 months the kidneys were removed and analysed histological. Additional glomerular filtration rate (GFR) was measured using a FITC-inulin clearance technique and the urine albumin creatinine ratio was obtained.

Results: After 8 months of smoke exposure 129SV and B6 mice showed a mild increase in mesangial tissue expansion compared to control mice. No significant glomerulosclerosis was observed. Albuminuria was significantly higher after 8 months of smoking (17.9 ± 31.5 g/ml vs. 73.3 ± 45.6 g/mol; p<0.01). GFR was reduced by 10% after 2 and 8 month, also this difference was not significant.

Conclusion: Our data suggest that smoking alone is not sufficient to induce histological kidney damage but suggest that vascular damage might lead to the development of albuminuria and changes in GFR. The mechanisms underlying these changes are currently investigated.
ORAL SESSION

ORAL SESSION 2D
SLEEP APNEA

2D.01 INHALATION OF HYDROGEN GAS REDUCES OXIDATIVE STRESS AND ATTENUATES CARDIAC REMODELING INDUCED BY INTERMITTENT HYPOXIA IN MICE

T. Hayashi1, M. Miyamura1, T. Mori1, A. Ukimura1, Y. Okada1, N. Ishizaka1

Methods: Hydrogen (H2) may exert antioxidant effects by selectively reducing hydroxyl radical. Here we have investigated the effect of H2 gas inhalation on lipid metabolism and LV remodeling induced by intermittent hypoxia in mice.

Background: Sleep apnea syndrome (SAS) increases the risk for cardiovascular morbidity and mortality. We have reported that intermittent hypoxia relevant to SAS increases NADPH-dependent superoxide production and accelerates the adverse left ventricular (LV) remodeling. Recent studies have suggested that hydrogen (H2) may exert antioxidant effects by selectively reducing hydroxyl radical. Here we have investigated the effect of H2 gas inhalation on lipid metabolism and LV remodeling induced by intermittent hypoxia in mice.

Methods: Male C57BL/6J mice (n = 62) were exposed to intermittent hypoxia (repetitive 1-minute interval of 5% and 21% oxygen for 8 hours during daytime) for 7 days. H2 gas (1.3 vol%) was given at the timing of reoxygenation, (repetitive 1-minute interval of 5% and 21% oxygen for 8 hours during daytime) for 7 days. H2 gas inhalation significantly suppressed oxidative stress, and attenuated cardiac remodeling in the LV myocardium.

Results: Systemic blood pressure before and after the experiment did not significantly differ. Intermittent hypoxia significantly increased plasma levels of low- and very low-density cholesterol and amount of 4-hydroxy-2-nonenal-modified protein adducts in the LV myocardium. It also upregulated mRNA expression of TNF-α, IL-6, and BNP, increased the production of superoxide, and induced cardiomyocyte hypertrophy, nuclear deformity, mitochondrial degeneration, and interstitial fibrosis. H2 gas inhalation significantly suppressed these changes induced by intermittent hypoxia. Especially, H2 gas inhalation significantly suppressed oxidative stress, and attenuated cardiac remodeling in the LV myocardium.

Conclusion: Inhalation of H2 gas for 7 days was effective in reducing oxidative stress, and in preventing pathological changes induced by intermittent hypoxia.

2D.02 ARTERIAL HYPERTENSION AND SLEEP QUALITY IN THE FRENCH POPULATION IN 2010: THE FLAHS 2010 SURVEY

J. Mourad, N. Postel-Vinay, B. Pannier, O. Hanon, X. Girerd. French League Against Hypertension, Paris-France

Objective: To evaluate the prevalence of sleep disorders according to the presence or absence of arterial hypertension and associated vascular risk factors in a representative sample of the French adult population.

Method: The survey French League Against Hypertension Survey (Flahs) 2010 was conducted among a representative sample of 3718 individuals aged over 35 living in metropolitan France. Taking an antihypertensive treatment qualified the subject as hypertensive (n = 1545 patients). The Epworth Sleepiness Scale was completed. A score between 8 and 12 defined the existence of a sleep deficit, a score> 12 reflected excessive daytime sleepiness. A questionnaire exploring the length and quality of sleep, and cardiovascular risk factors was completed.

Results: The sleep duration is longer in hypertensive (8.5 h ± 1.3 vs. 8.1 h ± 1.2 p <0.01). The prevalence of snoring was higher in hypertensives than non hypertensives (58.1% vs. 51.3%, p <0.01). The prevalence of apneas was higher in hypertensives than non hypertensives (4.9% vs. 3.4%, p <0.01) and was positively correlated with BMI and waist circumference. Patients treated for sleep apnea are 1.1% in the population without any vascular risk factor, 2.7% among those with hypertension alone, and 10.9% in those with diabetes hypertension and dyslipidemia. 65.3% of the population has an Epworth score> 8, including 11.3%> 12. The prevalence of disorders by the presence of hypertension alone or in combination is detailed in the table.

Conclusions: The quantity and quality of sleep are not comparable in subjects treated for hypertension and / or CV risk factors compared to the rest of the population. The prevalence of sleep apnea treatment increases with the number of cardiovascular risk factors. An assessment of sleep quality should be part of the management of hypertension. The French League Against Hypertension adopted the theme of quality of sleep in hypertensive patients for its national campaign in 2011.

2D.03 NOCTURNAL HOME BLOOD PRESSURE AND OBSTRUCTIVE SLEEP APNEA

A. Destounis1, K. Cholodou2, A. Kollas1, N. Karpettas1, E. Markozannes2, E. Alchanatis2, G. S. Stergiou1. Hypertension Centre, Third University Department of Medicine, Sotiria Hospital, Athens-Greece, First University Department of Respiratory Medicine, Sotiria Hospital, Athens-Greece

Studies have shown a causal relationship between obstructive sleep apnea (OSA) syndrome, renal dysfunction and nocturnal ambulatory blood pressure (BP). This study assessed the relationship between OSA severity, indices of renal function and BP assessed in the clinic (CBP) and by patients at home (HBP) during daytime and nighttime. Subjects referred to an OSA clinic were assessed with polysomnography, serum creatinine and spot urine for albumin/creatinine ratio (AC). HBP was measured using a validated oscillometric device designed for automated nocturnal BP monitoring (Microlife WatchBP HomeN). Duplicate morning and evening self-measurements were taken during the day (dHBP), and 3 automated programmed measurements at 60-min intervals during sleep (nHBP). CBP was measured in 2 visits (triplicate measurements) using the same device as HBP. Forty-three subjects were included (mean age 49 ± 13.1[SD] years, 32 men, apnea-hypopnea index [AHI] 35.4 ± 27.1, BMI 34.8 ± 8.3 kg/m2, CBP 134 ± 15/285.3 ± 9.5 mmHg (systolic/diastolic), dHBP 132 ± 12/98 ± 9.1 mmHg, nHBP 117 ± 11.8/69 ± 8.7 [n = 24]). AHI was correlated with body weight (r = 0.42, p<0.05) and was higher in men (p<0.05). AHI was not associated with CBP and dHBP (systolic and diastolic) or systolic nHBP. However, AHI was associated with diastolic nHBP (r = 0.57, p<0.01), serum creatinine (r = 0.34, p<0.05) and AC (r = 0.31, p = 0.09). Diastolic nHBP was also associated with saturation <90%/min (r = 0.52, p<0.05), desaturation index/hour (r = 0.57, p<0.05), duration of desaturation/hour (r = 0.55, p<0.05) and maximum duration of desaturation/sec (r = 0.56, p<0.05), whereas systolic nHBP was also associated with desaturation index/hour (r = 0.42, p<0.05). Daytime sleepiness (Epworth scale) was associated with systolic dHBP (r = 0.34, p<0.05) and nHBP (r = 0.42, p<0.05) but not with CBP. These data suggest that nighttime HBP measurements obtained by a low-cost home monitor are superior to daytime HBP or CBP measurements in terms of their association with OSA severity. Furthermore, OSA is associated with markers of renal function which may be involved in the pathogenesis of OSA induced hypertension.
and as obese subjects without (n = 10) or with (n = 15) OSA we measured arterial blood pressure (Finapres), heart rate (ECG), venous plasma norepinephrine (high-performance liquid chromatography) and postganglionic sympathetic nerve traffic in the skeletal muscle and skin areas (MSNA and SSNA respectively, microdialysis). MSNA and SSNA measurements were made in a randomized sequence over two periods of 30 min each, spaced by a 20-30-min interval. Measurements also included evaluation of skin sympathetic responses to emotional stimuli (acoustic stimulus).

Results: The 4 groups were matched for age, gender and BP values, the 2 obese groups without and with OSA showing a similar significant (P<0.05) increase in body mass index (33.1 versus 32.3 kg/m², respectively) and waist-to-hip ratio (0.97 versus 0.96, respectively) compared with the 2 lean groups with or without obstructive sleep apnoea (body mass index 24.0 versus 23.5 kg/m² and waist-to-hip ratio 0.76 versus 0.76, respectively). While MSNA was greater in OSA lean subjects as compared with the non-OSA lean individuals (61.8 ± 2.9 vs 42.4 ± 3.8 bs/100 hb, p<0.04), SSNA was superimposable in the two groups (12.4 ± 1.6 vs. 12.3 ± 0.9 bursts/minute, P = NS), paralleling the behaviour of plasma norepinephrine values which failed to show significant differences in the OSA and non-OSA lean subjects (268 ± 39 vs 220 ± 28 pg/ml). Similarly, while MSNA was greater in OSA obese subjects as compared with the non-OSA individuals (72.8 ± 4.2 vs 59.4 ± 3.1 bs/100 hb), p<0.04), SSNA was superimposable in the two groups (13.5 ± 1.4 vs. 12.6 ± 1.1 bursts/minute, P = NS). Also in this instance venous plasma norepinephrine values were not significantly different in the two groups (40 ± 4 vs 38.7 pg/ml). SSNA responses to emotional arousal were similar for magnitude in the 4 groups.

Conclusions: These data provide evidence that the sympathetic activation characterizing OSA is not generalized to the entire cardiovascular system. This phenomenon, which takes places both in lean and obese subjects with OSA, may depend on the fact that skin and muscle sympathetic neural districts are governed by mechanisms that are differently affected by the OSA syndrome.

2D.05 OBSTRUCTIVE SLEEP APNEA IS MAINLY DETERMINED BY GLUCOSE ABNORMALITIES IN OBSESE WOMEN

L. Gilardini1, C. Lombardi2, G. Redaelli1, L. Vallone1, GF Parati2, C. Invitti1.
1DEPT Medical Sciences and Rehabilitation, Istituto Auxologico Italiano, Milano-Italy, 2DEPT Cardiology, Istituto Auxologico Italiano, Milano-Italy

Objective: The relationships between obstructive sleep apnea (OSA), obesity and cardio-metabolic abnormalities have been demonstrated in men, but remain uncertain in women. We therefore assessed the concomitants of OSA in obese women.

Design and Methods: We examined the associations between apnoea/hypopnoea index (AHI) calculated from the results of the polysomnography, anthropometric measures, blood pressure (BP), glucose and insulin levels, in 93 obese women (35 ± 13.5 yr, BMI 36.3 ± 6.4 kg/m²) who underwent a 3-month weight loss intervention (diet + physical activity) and repeated all baseline measurements at the end of intervention. The relationship between weight loss and changes in AHI, BP and metabolic variables were analysed.

Results: AHI was correlated with age (r = 0.270, p<0.01), BMI (r = 0.270, p<0.01), neck circumference (r = 0.312, p<0.01 after adjustment for BMI) and fasting glucose (FPG, r = 0.465, p<0.001), but not with BP and lipids. In the multivariate analysis, AHI remained independently associated with BMI and FPG (β = 0.461, p<0.001 and 0.205, p<0.05). Neck circumference was correlated with FPG (r = 0.258, p<0.05) and insulin (r = 0.471, p<0.001) (not with age). AHI>10 (used as definition of OSA) was present in 24% of obese women (9.6% of those in pre-menopause). Women with OSA compared with those with AHEI<10, were older (61.4 ± 9.8 vs 50.7 ± 13.6, p<0.05), had more frequently menopause (86.1% vs 57.1%, p<0.05), diabetes (18.2% vs 4.3%, p<0.05), hypertension (72.0% vs 50.0%, p = 0.06), and a greater neck circumference (38.6 ± 1.8 vs 37.3 ± 2.3 cm, p<0.05). In OSA women, the intervention induced, a significant decrease in BMI, waist and neck circumference (p<0.001 for all) and sBP (p<0.05), but not in FPG, insulin and AHI, though 37.5% of OSA women reduced the AHI below 10.

Conclusions: In obese women 1) AHI is related to hyperglycemia independent of degree of obesity, 2) OSA is associated with menopause as in general population and with cardio-metabolic complications, 3) a moderate weight loss, though associated with BP reduction, does not induce a significant decrease in AHI.

2D.06 ENDOTHELIAL FUNCTION AND RENAL VASODILATION, BUT NOT ARTERIAL STIFFNESS, ARE IMPAIRED IN LEAN, NORMOTENSIVE PATIENTS WITH SLEEP- APNEA SYNDROME

University of PISA, PISA-Italy

Background: Patients with obstructive sleep apnea syndrome (OSAS), a condition with a strong comorbidity with hypertension and obesity, exhibit an accelerated vascular aging and renal damage. The aim of the study was to evaluate endothelial function, arterial stiffness, and renal vasodilating response to glyceryl trinitrate (GTN), a new parameter of renal vascular damage, in lean, normotensive patients with OSAS.

Methods: 21 patients with moderate-severe OSAS (AHI 31 ± 19) and 21 matched healthy controls were recruited. Renal resistive index (RI) was obtained by Duplex ultrasound at baseline and after sublingual GTN (25 μg), evaluating renal vasodilation as percent RI change. Endothelium-dependent (flow-mediated-dilatation, FMD) and independent (response to GTN) vasodilation in the brachial artery was assessed by computerized edge detection system. Arterial stiffness was assessed as carotid-femoral pulse wave velocity (PWV).

Results: OSAS patients and controls presented similar RI (0.61 vs 0.59, p = ns), but impaired renal vasodilatation to GTN (~5.7 ± 6.2% vs -10.3 ± 4.6%, p<0.05). FMD was reduced (~4.1 ± 2.2% vs 6.2 ± 3.3%, p<0.05), while GTN-dependent brachial artery vasodilation was preserved. PWV was different between OSAS and controls (7.9 ± 1.5 vs 7.7 ± 1.4 m/s, p = ns).

Conclusions: Even in the absence of hypertension and obesity, OSAS is characterized by endothelial dysfunction and impaired renal vasodilating capacity. Thus, OSAS could predispose per se to vascular dysfunction and renal vascular damage.

2D.07 PREVALENCE OF OBSTRUCTIVE SLEEP APNEA SYNDROME IN HYPERTENSIVE PATIENTS REFERRED TO A SPECIALIZED OUTPATIENT CLINIC AND ASSOCIATION WITH PRIMARY ALDOSTERONISM

G. P. Rossi, G. Pitter1, V. Gallina1, G. Rossitto1, A. C. Pessina1.
1Department of Clinical and Experimental Medicine-Internal Medicine 4, University of Padova, Padova-Italy

Objective: To prospectively determine the prevalence of obstructive sleep apnea syndrome (OSAS) and its predictors, including its association with primary aldosteronism (PA) and resistance to treatment, in hypertensive patients referred to a specialized outpatient hypertension clinic.

Design and Methods: We systematically investigated the occurrence of OSAS in 340 consecutive hypertensive patients (170 women and 170 men, age 58.6 ± 15.8 yrs) referred to the High Blood Pressure Centre of the University of Padova between April 2008 and August 2010. All underwent a protocol for the ascertainment of any secondary form of arterial hypertension, which included history, physical examination, a simplified sleepness questionnaire, and measurement of plasma aldosterone concentration (PAC), renin activity (PRA), 24-hr urinary Na’ and K’ and metanephrine excretion. The patients were selected to undergo multi-parameter poly-somnographic recording (PSG) based on a higher probability of OSAS. The diagnosis of PA and aldosterone-producing adenoma was based on the PAPY Study criteria and that of resistant hypertension was according to the ESH/ESC guidelines.

Results: Overall 20.1% of the patients had resistant hypertension and 6.5% had OSAS. In OSAS patients the average AHI was 38.5 ± 4.8; the total number of apneas was 158 ± 31 with a predominance of obstructive apneas (135 ± 29, 82.4% of all apneas). As compared to the patients without OSAS, the OSAS patients were mostly male (77.3% vs 22.7% female, p = 0.008), had a higher BMI (29.7 ± 4.0 vs 27.5 ± 3.5, p = 0.005) and a 20-fold increased rate of chronic obstructive pulmonary disease or asthma (COOPD, 13.6% vs 0.7%, p<0.001). Unlike resistant hypertension that occurred similarly among those with and without OSAS, the prevalence of PA was higher among those with than without OSAS (22.7% vs 13.8%), but this difference did not achieve statistical significance. At regression analysis (backward) the predictors of OSAS were BMI, the presence of COOPD, and PAC (F = 7.96, p<0.0001); a model with these 3 variables accounted for 10% of OSAS variance.

Conclusions: OSAS is common among referred hypertensive patients and can be overlooked if not systematically searched for. The non-significant association with PA and resistant hypertension is at variance with some previous findings and might be due to insufficient statistical power and/or to a selection bias. The identification of predictors of OSAS can improve its detection thus opening the way to specific treatment.
ORAL SESSION 3A
THERAPEUTIC ASPECTS

3A.01 INADEQUATE MANAGEMENT OF UNCONTROLLED HYPERTENSIVES UNDER BITHERAPY: THE SEVICAP STUDY

B. Pannier1, P. Poncelet2, P. Clerson3, C. Koch4.

Objective: To describe practitioners’ management, according to patient individual risk and characteristics, for uncontrolled blood pressure in patients currently treated with bitherapy including calcium channel blocker in France.

Design and Method: Observational retrospective study by French GP (n = 353) and cardiologists (n = 271), to assess the management of uncontrolled hypertensives currently treated with bitherapy including calcium channel blocker in homogeneous subtypes of patients resulting from non supervised classification procedure. (Faslicus procedure in SAS 9.2). Strategies were classified as follows: 1) no treatment (Non TT) and 2) treatment (TT). Strategies were classified as follows: i) treatment with at least one drug from the same pharmacological family; ii) modification without increase (Mod TT): change of one and/or two drugs in the same pharmacological family; ii) modification without increase (Mod TT): changing of one and/or two drugs by other compound from other class; iii) enhancement (EnhTT): increasing dosage of one and/or two drugs, addition of a third drug. Strategies were described according to patients subtypes.

Results: 1851 hypertensives were included (men: 62%, 64 ± 11 years, BMI 27.9 ± 4.5 kg/m², SBP 159 ± 11 mmHg, DBP 92 ± 8 mmHg). Five subtypes of patients were observed (Calinski’s criteria): C1: 22% (uncomplicated young males with risk factors), C2: 20% (metabolic: diabetes, hyperlipidemia), C3: 16% (vascular disease: elderly, hyperlipidemia, cardiac, coronary artery, cerebro-vascular diseases), C4: 9% (severe BP), C5: 33% (low risk, no target organ damage (TOD)). The observed strategy was C1, C2, C3, C4, C5, Total; SimTT: 32%, 30%, 36%, 31%, 31%, 35%; ModTT: 22%, 24%, 30%, 43%, 19%, 24%; EnhTT: 46%, 39%, 36%, 26%, 47%, 41%; Cardiologists enhanced treatment twice as much than GP.

Conclusion: 5 subtypes of uncontrolled hypertensives treated with bitherapy are observed according to age, levels of BP, TOD. The practitioners’ strategy to control BP is clearly inadequate in 35%, and delayed in 41%. The enhancement of pharmacological power is observed in only 24%, and large differences are observed according to types of patients, but also between GP and cardiologists. More directive recommendations for treatment strategy are needed particularly for these second/third lines management of hypertensives.

3A.02 ALISKIREN PENETRATES ADIPOSE AND SKELETAL MUSCLE TISSUE, AND REDUCES RENIN–ANGIOTENSIN SYSTEM ACTIVITY IN OBSESE HYPERTENSIVE PATIENTS


Objective: To describe practitioners’ management, according to patient individual risk and characteristics, for uncontrolled blood pressure in patients currently treated with bitherapy including calcium channel blocker in France.

Design and Method: Observational retrospective study by French GP (n = 353) and cardiologists (n = 271), to assess the management of uncontrolled hypertensives currently treated with bitherapy including calcium channel blocker in homogeneous subtypes of patients resulting from non supervised classification procedure. (Faslicus procedure in SAS 9.2). Strategies were classified as follows: i) no treatment (Non TT) and 2) treatment (TT). Strategies were classified as follows: i) treatment with at least one drug from the same pharmacological family; ii) modification without increase (Mod TT): change of one and/or two drugs in the same pharmacological family; ii) modification without increase (Mod TT): changing of one and/or two drugs by other compound from other class; iii) enhancement (EnhTT): increasing dosage of one and/or two drugs, addition of a third drug. Strategies were described according to patients subtypes.

Results: 1851 hypertensives were included (men: 62%, 64 ± 11 years, BMI 27.9 ± 4.5 kg/m², SBP 159 ± 11 mmHg, DBP 92 ± 8 mmHg). Five subtypes of patients were observed (Calinski’s criteria): C1: 22% (uncomplicated young males with risk factors), C2: 20% (metabolic: diabetes, hyperlipidemia), C3: 16% (vascular disease: elderly, hyperlipidemia, cardiac, coronary artery, cerebro-vascular diseases), C4: 9% (severe BP), C5: 33% (low risk, no target organ damage (TOD)). The observed strategy was C1, C2, C3, C4, C5, Total; SimTT: 32%, 30%, 36%, 31%, 31%, 35%; ModTT: 22%, 24%, 30%, 43%, 19%, 24%; EnhTT: 46%, 39%, 36%, 26%, 47%, 41%; Cardiologists enhanced treatment twice as much than GP.

Conclusion: 5 subtypes of uncontrolled hypertensives treated with bitherapy are observed according to age, levels of BP, TOD. The practitioners’ strategy to control BP is clearly inadequate in 35%, and delayed in 41%. The enhancement of pharmacological power is observed in only 24%, and large differences are observed according to types of patients, but also between GP and cardiologists. More directive recommendations for treatment strategy are needed particularly for these second/third lines management of hypertensives.
inhibitor therapy (delta SBP 1st month, delta DBP 1st month). We evaluated in 175 essential hypertensive patients the role of the renin-angiotensin system, we performed genetic and pharmacogenetic analysis of the renin gene and glomerulonephritis using Genome-Wide Analysis. As expected in our sample a considerable variability of blood pressure response is present with approximately three fourth of responders (delta SBP 1st month < -12.6 mmHg, delta DBP 1st month < -9 mmHg). The systolic and diastolic blood pressure response is greater in patients with higher baseline renin values (p = 0.003) and also directly depends on the values of baseline blood pressure (p < 0.001). Among the candidate genes (genes related to sodium sensitivity, to renal sodium transporters and to renin-angiotensin system) only the renin gene was relevant: in patients carrying the homozygous mutated genotype, deltaSBP 1st month is -21.6 mmHg compared to -4.2 mmHg in patients with wild-type genotype (ANOVA p = 0.01 model R² = 26.5%). Genome-Wide Analysis allowed us to identify 4 significant top SNPs (corrected p = 4.3 × 10E-6); 2 top SNPs for delta SBP 1st month (genes HAS2 and MUC16) and 2 top SNPs for delta DBP (MUC16 genes and SNW1). Patients carrying the mutated genotype for each top SNPs have a decrease in blood pressure (systolic and diastolic) twice than population average. Instead, top SNPs interaction leads to a decrease in blood pressure threefold then the population average. These data are a first step towards building a genetic profile to predict the variation in the response to therapy with ACE-inhibitor.

**3A.05 ACETAZOLAMIDE CONTRASTS AMBULATORY BLOOD PRESSURE INCREASE UNDER ACUTE EXPOSURE TO HIGH ALTITUDE**


**Background:** We have shown that exposure to high altitude (HA) induces an increase in blood pressure (BP), partly counteracted by beta-blockers or angiotensin receptor antagonists.

**Aim:** To assess the effect of acetazolamide (AC), a drug used in acute mountain sickness, on ambulatory BP under acute exposure to hypoxia at HA.

**Methods:** 43 healthy normotensives were randomized in double-blind design to receive AC 250 mg b.i.d. or placebo (PL). Study tests including ambulatory BP monitoring (ABPM; AND TM2430) were performed at sea level (SL) before (BAS-SL) and after 2 days of treatment (T-SL); and on 2nd full day of acute exposure to HA (Monte Rosa, 4559 m). 24h, day and night BP and HR mean levels and nocturnal fall (%) were computed in each condition.

**Results:** All subjects (age 36.8 ± 8.9, 22M/21F, BMI 21.8 ± 2.6 kg/m²) but one completed the study. There were no significant differences between groups at BAS-SL. BP and HR increased at HA in PL while a minor increase in diastolic (D)BP and HR but not in systolic (S)BP occurred in AC group (Table). AC had little influence on study variables at T-SL except for an increase in daytime HR.

**Table:** Mean ± SD values of SBP, DBP (mmHg) and HR (bpm) and their nocturnal reductions (dip) in the study conditions (°p < 0.05, °°°p < 0.01 vs. BAS; °p < 0.05, °°°p < 0.01 vs. SL).

**3A.06 NON-Steroidal ANTI-INFLAMMATORY DRUG (NSAID) RELATED INHIBITION OF ALDOSTERONE GLUCURONIDATION AND ARTERIAL DYSFUNCTION: A PROOF OF CONCEPT STUDY**

M. Cilly, A. Mangoni. Aberdeen University Medical School, Aberdeen-United Kingdom

**Background:** Patients with rheumatoid arthritis (RA) are at an increased risk of cardiovascular (CV) disease and are commonly prescribed non-selective non-steroidal anti-inflammatory drugs (ns-NSAIDS). New in vitro evidence suggests that this increased CV risk may be mediated through aldosterone glucuronidation inhibition (AGI), which differs between NSAIDS (in the order of diclofenac > naproxen > indomethacin > ibuprofen). Our aim was to explore the association between ns-NSAID-related-AGI and arterial dysfunction in patients with RA.

**Methods:** The extent (augmentation index, AIX%) and timing (reflected wave transit time, RWT, msec) of arterial wave reflection (measured using radial aplanation pulse wave analysis, PWA, Sphygmocor device) were assessed in 114 consecutive RA patients without overt CV disease aged 40-65 years. A ‘higher AIX%’ and ‘lower RWT’ indicate arterial dysfunction. All patients were assessed by a single research nurse after having rested supine for 10-15 minutes. Assessment also included a fasting blood sample, and self-completed patient questionnaire. A detailed medical record review was undertaken by a rheumatologist. Participants were similar to patients receiving outpatient care elsewhere in the UK. Multivariate analysis was used to adjust for age, sex, mean arterial pressure, smoking status, cumulative erythrocyte sedimentation rate (ESR-years) and Stanford HAQ disability score.

**Results:** We identified 60 patients taking ns-NSAIDS for 3 months or more and 25 non-users. Using a ns-NSAID with the highest AGI was associated with a higher AIX% (and lower RWT) versus treatment with a ns-NSAID with the lowest AGI (diclofenac AIX%: 32.3, RWT 132.7 msec; versus ibuprofen AIX% 23.8, RWT 150.9 msec): adjusted mean difference AIX%: 6.5% (95% CI 1.0 to 11.9; p = 0.02); RWT = 14.2 milliseconds (95% CI –22.2 to –6.3; p = 0.001). Multivariate analysis explained a high proportion of the variability in arterial dysfunction among users of ns-NSAIDS or indomethacin demonstrated intermediate levels of arterial dysfunction.

**Conclusion:** ns-NSAID-related AGI appears to be independently associated with arterial dysfunction in patients with RA. These findings provide a novel insight into the CV toxicity of commonly used ns-NSAIDS.

**3A.07 SYSTEMATIC REVIEW OF THE EFFECT OF ANTI-HYPERTENSIVE DRUG THERAPY ON ARTERIAL STIFFNESS**

L. D’Elia, R. Ippolito, M. Schiano di Cola, G. Rossi, D. De Palma, F. Galletti, P. Strazzullo. Dept of Clinical & Exp Medicine, Federico II University of Naples, Naples-Italy

**Objective:** Several studies investigated the effect of anti-hypertensive therapy on arterial stiffness (AS) and their results were not univocal. We performed a systematic search of the literature using on-line databases (1966–December 2010) to assess the effect of different classes of anti-hypertensive drugs on arterial stiffness through a meta-analysis of the available studies.

**Design and Methods:** Criteria for inclusion were adult population study, measures of Pulse Wave Velocity (PWV, m/s - expression of AS) and blood pressure (BP-reported as continuous variable) obtained at the beginning and at the end of study, time of run-in, outcome expressed as difference between the effects of single drug vs baseline or placebo. For each study, mean difference in PWV and 95% confidence intervals were extracted and pooled using a random effect model.

**Results:** Twenty-one studies were identified providing 40 cohorts that included 1,375 male and female participants. Only one study was a randomised controlled trial, in all the others the effect of therapy being evaluated versus baseline. The mean time of observation was 17 weeks (range 3-208). Arterial stiffness was assessed by different devices: Sphygmocor (n = 18), Compilor (n = 9), Colin (n = 9), and Doppler methods (n = 4). In the pooled analysis, there was a significant mean difference (MD) in PWV after therapy with renin-angiotensin system (RAAS) blockers = -1.27 m/s (95% CI: -1.85, -0.69; p=0.001), in particular with ACEI = –1.39 (–1.97, –0.82; p=0.001) and ARBs = -1.46 (–2.68, –0.25; p = 0.02); Beta-blockers = –1.03 (–1.23, –0.82; p=0.001). The pooled analysis of Ca-antagonist and
Diuretic therapy showed a non signicant decrease, MD = -0.88 (-1.84, 0.08; p = 0.07) and -0.62 (-1.56, 0.33), respectively. There was significant between-studies heterogeneity, but no evidence of publication bias. In meta-regression analysis, blood pressure at baseline, changes in blood pressure, age and different device utilised, were significant sources of heterogeneity. The comparison between drug classes did not show significantly different effects (heterogeneity p=0.10).

Conclusions: This systematic review showed in the first place that there is a lack of randomised controlled trials of the effect of anti-hypertensive therapy on arterial stiffness. Based on the available methodologically faulted studies, our meta-analysis suggests that anti-hypertensive treatment might improve arterial stiffness probably in relation to the effect on blood pressure. Possible differences in the effect of different drug classes were not apparent.

3A.08 WHY DO BLACK PEOPLE RESPOND BETTER TO CALCIUM BLOCKERS AND DIURETICS? A SYSTEMATIC REVIEW

L. Brewster1, Y. Seedat2. 1AMC, Amsterdam-The Netherlands, 2University of Kwa Zulu Natal, Durban-South Africa

Background: Mortality of hypertension is greater in black people. Importantly, adequate responses to calcium blockers and diuretics are reported, with attenuated responses to beta blockers and ACE inhibition. Knowledge of the biomarkers that affect these differential responses might better guide individual therapy and reduce mortality. Therefore, we conducted a systematic review of factors that predict the differential response of black people to antihypertensive drugs.

Methods: We sought to identify published or unpublished studies that considered explanations for the differential clinical efficacy of antihypertensive drugs in blacks, including systematic literature searches in Pubmed, Embase, Lilacs, and the African Index Medicus.

Results: Retrieved papers: 1180, included 35. Table shows reported causes for the differential drug responses.

Conclusion: Mortality of hypertension could be better reduced with effective, individual treatment options. We systematically assessed environmental, pharmacokinetic, and pharmacodynamic factors that may explain the differential response to antihypertensive drugs in black people. Aside small effects of genetic polymorphisms, ethnic differences in pharmacodynamics were most prominent, related to low renin, low NO bioavailability, and potentially, high activity of the ATP regenerating enzyme creatine kinase (CK) associated with enhanced vascular contractility and salt retention. Aside renin, biomarkers for NO bioavailability and ATP regeneration might prove to be useful to predict blood pressure responses.

3A.09 EFFECTS OF NEBIVOLOL AND ATENOLOL ON CENTRAL AORTIC PRESSURE IN HYPERTENSIVE PATIENTS

J. Redon1, E. Rodilla2, J. M. Pascual3, A. Vicente4, J. Olivan5, J. Bonet1, P. Torguet1, J. Almirall6. 1Hospital Clínico, Incliva. Universitat de Valencia. Valencia-Spain, 2Hospital de Sagunto, Sagunto-Spain, 3Hospital Universitario Virgen Macarena, Sevilla-Spain, 4Hospital Universitari Germans Trias i Pujol, Badalona-Spain, 5Hospital Universitari de Girona Dr. Josep Trueta, Girona-Spain, 6Corporació Sanitària Parc Taulí de Sabadell, Sabadell-Spain

The study analyzes the impact of a beta-blocker with vasodilatory properties, nebivolol, in central pressure parameters.

Methods: The study was a randomized, double blind, with parallel arms of 10 weeks of active treatment. Hypertensives, 40 to 65 years with mild or moderate essential and uncomplicated hypertension, who showed a sitting SBP ≤140 mmHg to ≤179 mmHg and a sitting DBP ≤90 mmHg to ≤109 mmHg after two weeks of run-in placebo treatment were included. Patients received Nebivolol 5 mg or Atenolol 50 mg gid as starting dose that could be increased after 3 weeks of treatment to 100 mg/day for not responders in atenolol group. Hydrochlorothiazide 25 mg could be added for not responders after 6 weeks of treatment. Mean change in augmentation index (AI), assessed by Sphygmocor from radial pulse, was considered the primary objective. Anova was used and level of significance was two-sided 0.05.

Results: 166 patients were screened and 138 randomized (52.6 yr, 80 men, 60%. SBP/DBP 153/95 mmHg). 131 (65 nebivolol and 66 atenolol) completed the protocol. In the absence of differences in baseline characteristics, 16.2% patients in the nebivolol group and 27.5% in the atenolol needed the addition of diuretic to reduce BP below 140/90 mmHg (p ns). In the absence of differences in brachial SBP nor DBP, no changes in AI were observed with Nebivolol based treatment while a significant progressive increment was observed with atenolol (p = 0.027) in both intention to treat and per protocol analysis. The changes of AI from baseline to the end of the study were in the figure.

Conclusion: The study results confirm superiority of Nebivolol vs Atenolol in the reflecting waves in hypertensive patients.

![Graph](image-url)
6-MERCAPTOPURINE INCREASES MINERALIZATION OF VASCULAR SMOOTH MUSCLE CELLS IN VITRO


Objectives: Arteriosclerosis is a major problem in advanced chronic kidney disease (CKD) and in kidney transplanted patients contributing to high cardiovascular mortality. Vascular calcification has long been considered to be a passive process; however recent studies indicates actively induced changes in vascular smooth muscle cell (VSMC) behavior toward an osteoblast-like phenotype. There is evidence that different immunosuppressive therapy affect the development of arteriosclerosis. Here, the influence of 6-mercaptopurine (6-MP), a member of the thiopurine class of immunosuppressive drugs, were investigated by proving arteriosclerotic properties of this substance.

Methods: In vitro calcification in rat VSMCs were induced with calcification medium (CM) (DMEM containing 4.5 g/L glucose supplemented with 15% FCS, 10 mmol/L sodium pyruvate, 50 μg/mL Vitamin C, and 10 mmol/L β-glycerophosphate). Calcium deposition was monitored by Alizarin staining and quantified by O-cresolphthalic complexone method. ALP gene expression was measured by real-time PCR.

Results: CM induced mineralization of VSMC visualized by Alizarin Red staining and quantified by O-cresolphthalic complexone method. ALP gene expression was increased in VSMCs after 48 h.

Conclusions: In this study we were able to show that 6-MP increases calcification of VSMCs in vitro. The data let suggest that 6-MP treatment may contribute to the high cardiovascular risk by enhancing vascular mineralization and arterial stiffening.

PHENOTYPE SWITCH OF VASCULAR SMOOTH MUSCLE CELLS UPON UP4A INDUCED P2Y2/6 ACTIVATION


Objective: Mineralization of the vasculature is a major risk factor in patients with chronic kidney disease (CKD) patients and contributes to the increased cardiovascular mortality. Recent evidence indicates that vascular calcification is an actively induced process, where smooth muscle cells (VSMCs) differentiate toward an osteoblast-like phenotype. Core binding factor-α subunit-1 (cbfa1) is a key regulatory transcription factor involved in osteogenic differentiation. The dinucleoside polyphosphate uridine adenosine tetraphosphate (Up4A) has previously shown to be a potent calcification inducing substance. The aim of this study was to investigate the mechanisms for the Up4A-mediated vascular calcification.

Methods: Expression of cbfa1, Mx2, OCN, OPG was measured in rat VSMCs after stimulation with Up4A (10 μmol/L) in the presence or absence of inhibitors via real-time PCR. Protein content in the nuclear fraction of cells was measured by proving a specific anti-cbfa1 antibody using Western Blot technique. Phosphorylation of MEK and ERK1/2 was detected via Luminex™ technology.

Results: Up4A led to a dose-dependent and significant increase in cbfa1 expression in VSMCs. Furthermore, the protein content of cbfa1 significantly increased in the nuclear protein fraction of the cells when they were stimulated with different Up4A concentrations. The non-selective P2Y inhibitors suramin, Ppad, and RB-2 as well as MR52578, which antagonizes P2Y6, have a significant inhibitory effect on the Up4A-stimulated cbfa1 expression; whereas MR52179, a P2Y1 antagonist, has no significant effect. ATP5 and IDP mimics the effect of Up4A on cbfa1 expression. Other osteogenses like Mx2, OCN and OPG are also affected by Up4A stimulation of VSMCs. In the intracellular signaling cascade, the phosphorylation of MEK and ERK1/2 seems to be involved. Up4A time-dependently induce MEK and ERK1/2 phosphorylation. An inhibition of MEK/ERK phosphorylation by U0126 significantly diminished the Up4A-induced cbfa1 expression.

Conclusions: Our results demonstrated that Up4A-mediated P2Y2/6 activation stimulate expression of osteogenses in VSMCs. In the downstream signaling of P2Y, the phosphorylation of MEK/ERK is involved. This study demonstrates that the endothelium-derived factor Up4A has influence on vascular mineralization and therefore, the putendergning signaling might be involved in arteriosclerotic processes.

THE PREDICTIVE CAPACITY OF AORTIC PULSE WAVE VELOCITY FOR MAJOR CARDIOVASCULAR EVENTS IS STRONGER IN LOW CARDIOVASCULAR RISK PATIENTS. A SUB-ANALYSIS OF THE EDIVA STUDY

J. Maldonado1, T. Pereira2, J. Polonii3, J.A. Silva4, J. Moraís5, M. Marques6. 1Instituto DE Investigação E Formação Cardiovascular, Coimbra-Portugal, 2Escola Superior De Tecnologia DA Saúde, Coimbra-Portugal, 3Hospital Pedro Hispano, Matosinhos-Portugal, 4Hospital S. Andre, Leiria-Portugal, Universidade De Lisboa, Lisboa-Portugal

Objective: To demonstrate the importance of PWV in cardiovascular risk stratification in the general population.

Methods and Results: A prospective, multicenter and observational cohort study included 22,000 Portuguese nationals (58.6% male) aged between 18 and 91 years (mean 46.33 ± 13.76 years). They underwent clinical assessment and annual PWV measurement using a Complior device, and major cardiovascular events (MACE) - death, cerebrovascular accidents, accidents, coronary, peripheral arterial disease and renal failure – were recorded. During a mean follow-up of 21.42 ± 10.76 months, there were 47 non-fatal MACE (2.1% of the sample). PWV was significantly higher in individuals with events than in those without events (11.76 ± 2.13 m/s vs 10.01 ± 2.1 m/s, p < 0.001). For absolute PWV, the adjusted HR (per 1 m/s change) was 1.316 (CI: 1.13–1.53, p<0.001). The Cox regression analysis (with deviation from mean coding) applied to PWV categorized by quintiles (Q) allowed to demonstrate a curvilinear relationship with cardiovascular risk: Q1 HR = 0.24 (CI:0.04–1.12); Q2 HR = 0.78 (CI:0.33–1.85); Q3 HR = 1.00 (CI:0.47–2.11); Q4 HR = 1.78 (0.91–3.46); Q5 HR = 2.92 (CI:1.49–5.71). Subgroup analysis showed that PWV discriminates cardiovascular risk more robustly in individuals with lower cardiovascular risk (see Figure). The HR per 1 m/s increase in PWV was 1.74 (CI:1.47–2.08) for ages <50 years, higher than that found in ages 50-60 years (HR = 1.51, CI:1.19–1.93) and ages >60 years (HR = 1.182, CI:0.90–1.85). The association was also relatively more pronounced in individuals without hypertension and without diabetes compared with the hypertensive and diabetic ones (see Figure).

Conclusion: The findings illustrate a consistent and robust clinical relevance of PWV as a marker of cardiovascular risk, expressing a tendency of particular validity in the context of primary prevention, where the predictive capacity of PWV seems to be enhanced.

ORAL SESSION

ORAL SESSION 3B
LARGE ARTERIES

3B.01 6-MERCAPTOPURINE INCREASES MINERALIZATION OF VASCULAR SMOOTH MUSCLE CELLS IN VITRO

3B.02 PHENOTYPE SWITCH OF VASCULAR SMOOTH MUSCLE CELLS UPON UP4A INDUCED P2Y2/6 ACTIVATION

3B.03 THE PREDICTIVE CAPACITY OF AORTIC PULSE WAVE VELOCITY FOR MAJOR CARDIOVASCULAR EVENTS IS STRONGER IN LOW CARDIOVASCULAR RISK PATIENTS. A SUB-ANALYSIS OF THE EDIVA STUDY
THE CHANGE IN PULSE WAVE VELOCITY OVER THE CARDIAC CYCLE IS INDEPENDENTLY ASSOCIATED WITH LEFT VENTRICULAR MASS INDEX IN MIDDLE-AGED HEALTHY SUBJECTS


Objective: To investigate the association of the pressure dependency of arterial stiffness, expressed as the difference between systolic and diastolic pulse wave velocity (DPWV), with left ventricular mass index (LVMI). Biomechanically, an increase in DPWV is directly linked to enhanced increases in systolic blood pressure during e.g. daily activities and exercise. Aortic PWV (aoPWV), currently recommended in the guidelines for hypertension management, is measured at diastolic pressure and, hence, may inadequately reflect the impact of arterial stiffness on LV afterload. We hypothesized, therefore, that DPWV is more strongly associated with LVMI than aoPWV.

Design and Methods: We studied 1776 subjects from the Asklepios cohort (healthy, age 35-55 yrs). DPWV was obtained from combined carotid artery ultrasound and tonometry recordings by calculation of distensibility coefficients over the diastolic and systolic pressure range separately. Multiple linear regression analysis was performed to investigate the associations of DPWV with sex (r of 0.05, p = 0.06). DPWV was significantly associated with LVMI (β of 0.68 g/m1.7 per 0.18 vs 0.59 g/m1.7 per 0.009 mm for IMT; p < 0.001 for both). Both the vascular functional (PWV) and structural (IMT) parameters correlated with LVMI (r = 0.16, p<0.001 for PWV, and r = 0.27, p<0.001 for IMT). The subgroup of patients with LVMI but without LVH (n = 236; 32% of the population, 49% of patients without LVH) showed PWV and IMT values significantly greater than patients without LVMI (10.6 ± 0.18 vs 10.19 ± 0.16 m/sec for PWV, and 0.6 ± 0.012 vs 0.59 ± 0.009 mm for IMT; p < 0.001 for both). In this group without LVH but with LVMI, 48 patients (20.3%) had values of PWV >12 m/sec and 32 patients (13.6%) had values of IMT > 0.9 mm and thus displayed vascular target organ damage.

Conclusions: These data provide the first evidence that LVMI is 1) of frequent detection in treated hypertensive patients, even when LVH is not present and 2) associated with profound alterations of the functional and structural characteristics of the left arteries. This association may participate at the increased cardiovascular risk seen in this condition.

INAPPROPRIATE LEFT VENTRICULAR MASS IS ASSOCIATED WITH VASCULAR ORGAN DAMAGE INDEPENDENTLY ON LEFT VENTRICULAR HYPERTROPHY IN HYPERTENSION

C. Giannattasio1, F. Cesana1, F. Soriano2, M. Allon2, M. Cairo2, G. Colombi2, M. Pozzi2, C. Menni1, G. Trocino1, A. Fontana1, A. Capra1, P. Canova2, G. Grassi1, C. Mancia2.

Objective: It has been previously shown that left ventricular hypertrophy is frequently associated with both functional and structural alterations of the large arteries. Whether this is the case for the condition characterized by an inappropriate left ventricular mass (LVMI, i.e. a LVMI > 128% of the value predicted by an equation including age, sex and stroke work), known to carry an increased cardiovascular risk independently on the presence of left ventricular hypertrophy, is still undefined.

Design and Methods: In 739 treated hypertensives aged 53.8 ± 13.7yrs (mean ± SD, 57% males) we measured, with a non-invasive device, aortic PWV (aPWV), currently recommended in the guidelines for hypertension management, is measured at diastolic pressure and, hence, may inadequately reflect the impact of arterial stiffness on LV afterload. We then calculated ILVM as the ratio between LV observed mass and LV predicted mass (derived from the formula 55.37 + 6.64 x β2 + 0.64 x SW - 18.07 x gender, where SW (stroke work) = systolic blood pressure x stroke volume x 0.0144 and gender = 1 (male) or 2 (female); h = m). ILVM was considered abnormal when the ratio is higher than 1.28.

Results: Mean systolic and diastolic BP were 142 ± 18/86 ± 10.4 mmHg. ILVM was detected in 67% of patients, while, according to reference values of ESH-ESC Guidelines, in 264 patients (36%) LV hypertrophy was found. Patients with ILVM showed values of PWV and IMT significantly greater than patients without ILVM (11 ± 0.13 vs 10 ± 0.15 m/sec for PWV, and 0.68 ± 0.009 vs 0.59 ± 0.009 mm for IMT; p<0.001 for both). Both the vascular functional (PWV) and structural (IMT) parameters correlated with ILVM (r = 0.16, p<0.001 for PWV, and r = 0.27, p<0.001 for IMT). The subgroup of patients with ILVM but without LVH (n = 236; 32% of the population, 49% of patients without LVH) showed PWV and IMT values significantly greater than patients without ILVM (10.6 ± 0.18 vs 10.19 ± 0.16 m/sec for PWV, and 0.6 ± 0.012 vs 0.59 ± 0.009 mm for IMT; p < 0.001 for both). Both the vascular functional (PWV) and structural (IMT) parameters correlated with ILVM (r = 0.16, p<0.001 for PWV, and r = 0.27, p<0.001 for IMT). The subgroup of patients with ILVM but without LVH (n = 236; 32% of the population, 49% of patients without LVH) showed PWV and IMT values significantly greater than patients without ILVM (10.6 ± 0.18 vs 10.19 ± 0.16 m/sec for PWV, and 0.6 ± 0.012 vs 0.59 ± 0.009 mm for IMT; p < 0.001 for both). Both the vascular functional (PWV) and structural (IMT) parameters correlated with ILVM (r = 0.16, p<0.001 for PWV, and r = 0.27, p<0.001 for IMT). The subgroup of patients with ILVM but without LVH (n = 236; 32% of the population, 49% of patients without LVH) showed PWV and IMT values significantly greater than patients without ILVM (10.6 ± 0.18 vs 10.19 ± 0.16 m/sec for PWV, and 0.6 ± 0.012 vs 0.59 ± 0.009 mm for IMT; p < 0.001 for both). Both the vascular functional (PWV) and structural (IMT) parameters correlated with ILVM (r = 0.16, p<0.001 for PWV, and r = 0.27, p<0.001 for IMT).

Conclusions: These data provide the first evidence that ILVM is 1) of frequent detection in treated hypertensive patients, even when LVH is not present and 2) associated with profound alterations of the functional and structural characteristics of the large arteries. This association may participate at the increased cardiovascular risk seen in this condition.

THE LONGITUDINAL ASSOCIATION BETWEEN ARTERIAL STIFFNESS AND RENAL DAMAGE IN A PRIMARY CARE POPULATION

B. van Vark1, H. Stoffers1, F. Soomere1, A. Plat1, P. de Leeuw2, A. Koom3,1Maastricht University, Maastricht-The Netherlands, 2Maastricht University Medical Center, Maastricht-The Netherlands

Background: Increased arterial stiffness is commonly observed in chronic kidney disease (CKD) and cardiovascular disease and is an independent predictor of outcome. Arterial stiffening has been proposed to be a major common pathophysiological process linking CKD and cardiovascular outcome. The present study aims to prospectively evaluate whether carotid-femoral Pulse-Wave Velocity (cfPWV) is associated with renal function decline and to assess to what extent age and other traditional cardiovascular risk factors determine this association.

Methods: In 83 participants from the ongoing Hippocrates study we prospectively measured arterial stiffness, renal function and microalbuminuria. Arterial stiffness was assessed by measuring the cfPWV using a Complior device. We estimated the Glomerular Filtration Rate (eGFR) using the CKD-EPI equation.

Results: The median follow-up duration was 5.2 years. The mean cfPWV increased significantly from 10.8 ± SD 1.8 m/sec at baseline to 12.3 ± 2.5 m/sec at follow-up (P < 0.001). The eGFR fell slightly from 87.7 ± SD 11.1 to 82.5 ± SD 13.6 ml/min/1.73m2 (P < 0.001). In a multivariable linear regression model,
we observed a significant inverse association between baseline cfPWV and annual change in eGFR (\(\beta = -0.32; P = 0.004\)), independent of age, gender, BMI, mean arterial pressure and annual change in cfPWV. There was no association between cfPWV and change in microalbuminuria.

Conclusion: These preliminary results demonstrate an independent, significant inverse association between cfPWV and annual decline in renal function, but not with incident microalbuminuria. More follow-up measurements are being performed.

**3B.07** THE PRESSURE DEPENDENCE OF ARTERIAL STIFFNESS AS A NOVEL MARKER OF VASCULAR FUNCTION: OBTAINED FROM PWV AND BRACHIAL BP TAKEN AT DIFFERENT ARM HEIGHTS

G. Schillaci1, B. Gavish2, G. Pucci1, L. Settimi1, E. Mannarino1. 1Università DI Perugia, Perugia-Italy, 2InterCure Ltd, Lod-Israel

Background: The increase of arterial stiffness with blood pressure (BP) reflects the nonlinear increase of BP with volume. Stiffness can be representated by the square of the pulse wave velocity (PWV), and is currently measured for the diastolic BP (DBP). By analyzing the changes in DBP and diastolic PWV (PWVd) induced by changing arm position, we evaluated a linear relation between stiffness and DBP in individual subjects, and used it for calculating systolic stiffness.

Methods: In 27 healthy subjects (66% men, age 51 ± 17 years, BP 134/78 ± 17/12 mmHg), we measured brachial BP and carotid-radial PWVd in supine position with arm supported at 3 postures: below-, at- and above the heart level. The linearity of PWVd-versus DBP was evaluated by the correlation coefficient. PWVd was expressed by the model 0.127(\(\beta DBP - 6\), where the parameters \(\beta\) and \(\alpha\) were best fitted for each subject, and then used for determining the systolic stiffness PWVd from the SBP, according to the model 0.127(\(\beta SBP - 6\). \(\beta\) (stiffness constant), or the change in PWVd for a given change in DBP expresses the steepness of the pressure-volume exponential curve.

Results: PWVd highly correlated with DBP for individual subjects (\(r = 0.95 \pm 0.03\)). \(b\) increased significantly at older age (\(r = 0.49, p<0.001\)). While diastolic PWV increased linearly with age (\(r = 0.64\)), calculated systolic PWV increased with age exponentially (\(r = 0.65, p<0.001\)) and became steep over age 50 years (Figure).

Conclusions: (1) The gravity effect on brachial DBP generated by arm height variation induces linear changes in diastolic PWV, which increase steeply with age. (2) The dynamic changes of PWV and DBP with the cuff height provide a novel and simple measure of systolic PWV in an individual subject, which shows greater age sensitivity than diastolic PWV.

**3B.08** ARTERIAL STIFFNESS, CENTRAL BLOOD PRESSURE AND MICROCIRCULATION EVIDENCE FOR A CLOSE RELATIONSHIP IN HYPERTENSIVE PATIENTS

M. L. Muiesan, D. Rizzoni, M. Salvetti, A. Paini, C. Agabiti Rosei. 3B.08 ARTERIAL STIFFNESS, CENTRAL BLOOD PRESSURE AND MICROCIRCULATION EVIDENCE FOR A CLOSE RELATIONSHIP IN HYPERTENSIVE PATIENTS

Background: The possible relationships between indicators of small resistance artery structure and of large artery distensibility have not yet been evaluated.

Aim: to assess the relationship between carotid-femoral pulse wave velocity (CF-PWV), central blood pressure (cBP) and structural alterations of small resistance arteries (media to lumen ratio, M:L) in patients with primary and secondary hypertension.

Patients and Methods: In 65 patients (mean age 53 ± 14 years, 31 F, 21 with diabetes mellitus type 2, 14 never treated) with essential (n = 32) and secondary (n = 33) hypertension, pulse wave velocity was measured (Compilor) and PWV analysis was performed (SphygmoCor). In all patients small-resistance arteries were dissected from subcutaneous fat biopsies and mounted on an isotonic myograph, for the measurement of the M:L.

Results: Mean values of CF-PWV and of M:L ratio were 11.4 ± 2.6 m/s and 0.09 ± 0.019, respectively. M:L ratio was significantly related to brachial systolic blood pressure (SBP) and pulse pressure (PP) (\(r = 0.40\) and 0.39, \(p < 0.001\), respectively) and to central SBP and PP (\(r = 0.44\) and 0.46, \(p < 0.001\), respectively). A positive correlation was observed between M:L and CF-PWV (\(r = 0.43, p < 0.001\)); this correlation remained statistically significant after adjustment for augmentation pressure (\(r = 0.42, p < 0.001\)); again this correlations remained statistically significant after adjustment for age, gender, mean BP and also for CF-PWV.

Conclusions: In hypertensive patients the presence of structural alterations of small resistance arteries may be associated with the increase in large arteries stiffness and, possibly contribute to an increase in central pressure by earlier wave reflections.

**3B.09** EFFECT OF AGING ON AORTIC STIFFNESS IN CAMEROONIAN PYGMIES

D. Lemogoum1, W. Ngatchou1, C. Janssens1, M. Leeman1, L. Van Bortel1, J. P. Degauve1, Ph. Van de Borne1. 1Erasme Hospital, Free Brussels University, Brussels Belgium, 2Heymans Institute of Pharmacology, Gent Belgium

Objective: To investigate whether aortic pulse wave velocity (PWV), a direct measure of arterial stiffness (AS), which reflects the true arterial wall damage and its dynamic properties with aging in Cameroonian traditional pygmies (TP) living in tropical forest on hunter-gather (HG) subsistence mode.

Design and Method: We determined aortic PWV (Compilor), brachial blood pressures (BP), and lipid profile in 78 TP, carefully matched for age and gender to 43 contemporary pygmies (CP) who migrated to sub-urban area and 43 Bantu farmers (BF) sharing the same environment with CP.

Results and conclusions: TP were shorter than CP and BF (\(P = 0.02\)). They had lower LDL cholesterol as compared to CP and BF (\(P<0.01\)), while their mean BP (MAP) was greater than that of CP (\(P = 0.04\)), but lower compared to that of BP (\(P = 0.01\)). TP PWV (6.99 ± 2.23 m/s) was slower (\(P = 0.02\)) than that of CP (7.72 ± 2.15 m/s) and BF (8.06 ± 2.30 m/s). In univariate analysis, PWV increased with age in TP, CP and BF (\(\beta = 0.047; 0.095;\) and 0.127, respectively, all \(p<0.01\)). In the whole study population, multivariate analysis including CV variables of interest revealed age, MAP, LDL cholesterol and short stature as independent determinants of PWV (\(R^2 = 0.48, P = 0.03\)). By contrast, in multivariate analysis restricted to TP, height (\(P = 0.02\)) and MAP (\(P = 0.01\)), but not age (\(P = 0.12\)) emerged as independent determinants of PWV (\(R^2 = 0.56, P = 0.02\)); suggesting a blunting effect of aging on arterial distensibility in TP. In conclusion TP on HG subsistence mode have more distensible aorta that remains less stiffer even with advancing age. It seems likely that the observed age dependent increased aortic stiffness in the whole study population may be attributed to environmental factors rather than early vascular aging.
**ORAL SESSION**

**ORAL SESSION 3C**

**GENETICS/MOLECULAR BIOLOGY**

**3C.01 A WEIGHTED GENETIC RISK SCORE PREDICTS OBESITY POORLY IN TWO DIFFERENT SPANISH POPULATIONS**

F. Martínez1, M. L. Mansego2, G. Rojo3, G. De Marco3, S. Morcillo3, Valencia-Spain, 2Genotyping and Genetic Diagnosis Unit and Ciber of Valladolid-Spain, 3Department of Preventive Medicine and Epidemiology, Loyola University Medical School, Maywood-USA, 6Genotyping and Genetic

**Background:** In the last few years GWAS have successfully discovered several loci associated to obesity, the majority of them acting through regulation of the appetite. Some of them such as variants of FTO have been widely replicated, but for other variants the association is not as clear.

**Objective:** To investigate the association between BMI and obesity and single variants and haplotypes identified in obesity-related genes in two Spanish populations. The predictive value of a weighted obesity genetic risk score was also analyzed.

**Subjects and Methods:** Forty SNPs in 23 obesity-related genes were evaluated in a rural population characterized by a high prevalence of obesity (869 subjects, mean age 46y, 62% women, 36% obese) and in an urban population (1425 subjects, mean age 54y, 50% women, 19% obese). Genotyping was made with SNPlex. A genetic risk score was constructed from the beta coefficients associated with each variant in the pooled analysis and the number of risk alleles for each subject and a ROC analyses was performed.

**Results:** We found association between polymorphisms in FTO and obesity that was more prominent in the rural population. A combination of risk alleles in FTO had an additive effect on BMI and obesity in our population. There was an increase in BMI and in the prevalence of obesity from the lowest to the highest quartile of the score, but obesity predictive value overall was low (0.85%).

**Conclusions:** The principle loci associated with BMI and obesity in this study were FTO, MC4R, MTCH2 and HTR2C. Among the newly discovered loci, ATXN2L, NEGR1 and SH2B1 might be also associated with BMI and obesity in Spanish population. Baseline characteristics of the populations, mainly age and grade of obesity, have a strong influence in the genetic association results. The risk associated with these polymorphisms is low and the overall effect in BMI or obesity prediction is minimal. A weighted genetic risk score based on known and frequent polymorphisms constructed with genes mainly acting through central nervous system mechanisms was associated with BMI and obesity but it yields minimal clinical prediction in general population.

**3C.02 SYNERGIC EFFECT OF TWO QTLS ON CHROMOSOME 1 AND 18 ACCOUNTS FOR THE DIFFERENCE OF STROKE-SUSCEPTIBILITY BETWEEN SHR AND SHRSR; A STUDY ON DOUBLE-CONGENIC STRAINS**

T. Nabiha, Z-H. Cai, T. Ogawa, T. -A. Gandolgor, K. Kawakami, H. Ohara. Shimane University School of Medicine, Izumo-Japan

**Background:** The stroke-prone spontaneously hypertensive rat (Shrsp) is a genetic model for severe hypertension and hypertension-related cerebral diseases. In contrast, its parental strain, SHR, is known to be ‘resistant’ to cerebral stroke in addition to milder hypertension when compared with Shrsp. In this study, we attempted to isolate genetic factors accounting for the stroke-susceptibility in Shrsp using a QTL analysis and the congenic strategy.

**Methods:** F2 rats (n = 299) were obtained between Shrsp and SHR. At 12 week old, blood pressure (BP) was measured, and salt-loading was started using 1% salt water as drinking water. A number of days before identification of symptoms of stroke (stroke-latency) was quantified on each F2 rat. A QTL analysis was performed on BP and the stroke latency using about 100 microsatellite markers. Based on the results of the QTL analysis, genomic fragments on Chr 1 and 18 were exchanged between Shrsp and SHR using the speed congenic strategy; two pairs of reciprocal congenic strains for each of Chr-1 and -18 QTLs, SHRSRpch1.0 and SHRPch1.0, and SHRSRpch18.0 and SHRPch18.0, were constructed. Further, through crossing SHRpch1.0 and SHRPch18.0, we constructed a double-congenic strain (SHRPch1_18) in which both the Shrsp-fragments of Chr 1 and 18 were introgressed on the SHR background. BP and the stroke-latency was evaluated in these congenic strains.

**Results and Discussion:** The genetic analysis indicated that two QTLs with large genetic effects on the stroke-latency were identified on Chr 1 and 18. In addition, a QTL for BP was found in the region on Chr 1 overlapping with the QTL for the stroke-latency. Phenotyping of the four congenic strains conformed the effect of the Chr-1 and Chr-18 QTLs on the stroke-latency in SHRSRpch1.0 and SHRPch18.0. In contrast, the two SHR-based congenic strains (SHRPch1.0 and SHRPch18.0) did not show significant effects of the two QTLs on the stroke-latency, suggesting ‘context-dependent’ effects of those QTLs. In a double-congenic strain, however, introduction of the two Shrsp-fragments on Chr 1 and 18 greatly and significantly reduced the stroke-latency. This result indicated that the synergistic interaction between the two QTLs accounted for most of the difference in the stroke-susceptibility between Shrsp and SHR.

**3C.03 ANGIOTENSIN-(1-7) INDUCES MAS RECEPTOR INTERNALIZATION**

M. Gironacci1, H Adamo2, G. Corradi1, R. Santos2, P. Ortiz3, O. Carretero4, 1Iqafú–Conicet, Fac. Farmacia y Bioquímica, Univ De Buenos Aires, Buenos Aires–Argentina, 2Department of Physiology, Federal University of Minas Gerais, Belo Horizonte-Brazil, 3Hypertension and Vascular Research Division, Henry Ford Hospital, Detroit-USA

**Objective:** Angiotensin (Ang) (1-7) is the endogenous ligand for the G protein-coupled receptor Mas, a receptor (R) coupled to cardiac, renal and cerebral protective responses. Physiological evidence suggests that Mas R undergoes agonist-dependent desensitization, but underlying molecular mechanism regulating R activity is unknown. We investigated the hypothesis that Mas R desensitizes and internalizes upon stimulation with Ang-(1-7).

**Design and Method:** We generated a chimera between the Mas R and the fluorescent protein YFP (Mas-YFP R). Mas-YFP transfected HEK 293T cells were incubated with Ang-(1-7) and the relative cellular distribution of Mas-YFP R was observed by confocal microscopy.

**Results:** In resting cells, Mas-YFP R was mostly localized on the cell membrane. Ang-(1-7) induced a redistribution in fluorescent after 5 min stimulation changing the localization of Mas-YFP R to intracellular vesicles of various sizes. Following the time course of [125I]Ang-(1-7) endocytosis we observed that up to 65.1±8.7 % of Mas-YFP R underwent endocytosis after 20 min from the plasma membrane which was blocked by the Mas receptor antagonist. Mas-YFP R colocalizes with Rab5, the early endosome antigen I and AP-50, indicating that Mas-YFP R is internalized through clathrin-coated pits and targeted to early endosomes after Ang-(1-7) stimulation. Mas-YFP R also colocalized with caveolin-1 suggesting that at some point of R trafficking Mas-YFP R traverses caveolin-1 positive compartments.
Conclusion: Mas R undergoes endocytosis upon stimulation with Ang-(1-7) and this event may explain the desensitization of Mas R responsiveness. In this way, Mas R activity and density may be tightly controlled by the cell.

**3C.04 NETWORK OF SALT-SENSITIVE HYPERTENSION: TIME EFFECT ON A GENETIC HUB**

M. Simonini, G. Gatti, S. Delli Carpini, S. Pozzoli, L. Citterio, C. Lanzani, E. Brioni, L. Zagato, P. Manunta. SAN Raffaele Scientific Institute, Universita’ Vita-Salute, Milano-Italy

The central roles of salt (NaCl) and the kidneys in the pathogenesis of most forms of hypertension are well established. The linkage between NaCl retention and blood pressure (BP) elevation is often referred to as “whole body autoregulation”. We previously showed how Adducin affects natriuresis control.

**Aim:** to study whether ADD1 and ADD2 mutated allele interact with other genes affecting the Pressure Natriuresis relationship (PNat). We performed a Na load test (iv. infusion of 2L of 0.9% NaCl2h) in 513 new diagnosed, never treated hypertensive patients and monitoring of BP and blood/urine collection every 120 min. The slopes of P Nat at the end of infusion time (T120) and after recovery (T240) were studied. No differences are identifiable under the ADD1 and ADD2 wild-type allele background. However, a time effect of ADDs genes was detected. We observed an episodic (p < 0.001) effect on P Nat of ADD2 with the recessive alleles of ADD1, PKD2, SLC8A1 (NCX1), and LSS all related to vascular component at T120. However, after recovery (T240) we found an episodic interaction on P Nat (p < 0.01) between ADD1 and genes related to tubular transporters (WNK1, MDR1, NEDD4L) and MYLK gene, encoding myosin light chain kinase which is a calcium/calmodulin dependent enzyme. Our findings suggest that Adducin may be consider a hub, connecting genes involved in both vascular and tubular transporter involved in pressures natriuresis control.

**Methods:** Total RNA was purified from the hearts of postnatal day 2 HHR (n = 6) and NHR (n = 6) using TRIzol reagent. RT-PCR was performed using random hexamer primers. Quantitative real-time PCR was performed using miScript System and SybrGreen probes.

**Results:** Expression levels of miR-133a and miR-15b in HHR and NHR normalized to Gapdh are shown in the figure. Error bars indicate the SEM. We found that both miR-15b and miR-133a were significantly suppressed in the hearts of neonatal HHR.

**3C.05 THE ROLE OF MICRORNA IN CARDIAC HYPERTROPHY INDEPENDENT OF BLOOD PRESSURE**

F. J. Charchar1, E. Porrello2, L. M. Delbridge3, S. B. Harrap1. 1University of Ballarat, Ballarat-Australia, 2University of Texas Southwestern Medical Center, Texas-USA, 3University of Melbourne, Melbourne-Australia

**Objectives:** MicroRNAs (miRNAs) are short non-coding RNAs that inhibit mRNA translation or promote mRNA degradation but little is known of their roles or their target genes in the development of the common forms of primary cardiac hypertrophy. We have a unique normotensive model of human polygenic cardiac hypertrophy - the Hypertrophic Heart Rat (HHR) - in which the heart has a reduced complement of terminal differentiated cardiomyocytes, evident soon after birth. In the current study we determined cardiac expression in neonatal HHR and its control model the NHR (Normal Heart Rat) of i) miR-15b, an miRNA associated with regulation of cell cycle and falls within quantitative trait loci Lvm1; ii) miR-133a, which regulates ventricular development and promotes proliferation of cardiomyocytes.

**Methods:** Total RNA was purified from the hearts of postnatal day 2 HHR (n = 6) and NHR (n = 6) using TRIzol reagent. RT-PCR was performed using random hexamer primers. Quantitative real-time PCR was performed using miScript System and SybrGreen probes.

**Results:** Expression levels of miR-133a and miR-15b in HHR and NHR normalized to Gapdh are shown in the figure. Error bars indicate the SEM. We found that both miR-15b and miR-133a were significantly suppressed in the hearts of neonatal HHR.

**3C.06 PATHOLOGICAL INCREASE IN LEFT VENTRICULAR MASS INDEX AND CHANGING MICRORNA PROFILE IN STROKE-PHONE SPONTANEOUSLY HYPERTENSIVE RAT**

A. Monkeviciute, D. Graham, A. F. Dominiczak, S. A. Nicklin, M. W. McBride. Institute Of Cardiovascular AND Medical Sciences, BHF GCRC, University OF Glasgow, Glasgow-United Kingdom

**Background and Objective:** The stroke-prone spontaneously hypertensive rat (ShrSp) is a model of human essential hypertension with increased incidence of stroke which develops increased left ventricular mass index (LVMI) prior to the onset of hypertension. MicroRNAs (miRs) are small 21-23 nucleotide long single strand non-coding RNA molecules involved in post-transcriptional regulation of gene expression. Differential expression of microRNAs has been reported in various conditions. Importantly miRs have been implicated in the development of cardiovascular pathophysiology including LVMI. The aims of our study were to establish expression patterns of novel and previously published microRNAs and their roles in pathological increase in LVMI in the Shrsp prior to the onset of hypertension in this model.

**Design and Method:** We performed microRNA microarray profiling in hearts of 5 week old Shrs and WKY (Wistar Kyoto rats; normotensive reference strain) animals using LC Sciences multispecies chips based on Sanger miRbase 11.0 with probes for 1307 miRNAs. Significantly differentially expressed microR-NAs were identified by Rank Products analysis. Total RNA was extracted from whole hearts of neonatal, 5 and 16 week old animals to confirm miR expression patterns using TaqMan® microRNA assays.

**Results:** Our screen identified 72 miRs that were significantly differentially expressed in the heart (FDR < 0.05) between the Shrsp and WKY in 5 week old animals. Based on the results of our screen and published data we selected miR-195, miR-329 and miR-451 for further analysis. TaqMan® microRNA assays confirmed that miR-195 was significantly upregulated (p < 0.01) in Shrsp compared to WKY but miR-129 and miR-451 were not different. However miR-195, miR-329 and miR-451 were significantly upregulated (p < 0.02, p < 0.03 and p < 0.04 respectively) in neonatal animals, but showed no differences in 16 week old ShrSp compared to WKY.

**Conclusions:** We have identified significant differences in microRNA expression patterns of miR-195, miR-329 and miR-451 in hearts of neonatal animals and for miR-195 in 5 week old Shrsp and WKY rats. Understanding the underlying cause for differential expression of individual microRNAs or the genes they target in the heart prior to onset of hypertension will help further our understanding of the pathophysiology of cardiovascular disease development in this rat model of human hypertension.

**3C.07 DYNAMIC GENETIC LINKAGE OF BLOOD PRESSURE PHENOTYPES**

I. Arenas1, J. Tremblay1, B. Deslauriers1, J. Sandoval1, O Šedá1, D Gaudet1, E Merlo1, T Kotchen1, AW Jr Cowley1, P Hamet1. 1Centre hospitalier de l’Université de Montréal, Montréal-Canada, 2École Polytechnique de Montréal, Montréal-Canada, 3Ecogene-21 and lipid clinic, Université de Montréal, Montréal-Canada, 4Medical College of Wisconsin, Milwaukee-USA

**Conclusions:** Our studies show that dysregulation of miR-15 and miR-133 in neonatal HHR could predispose the hearts to hypertrophy without affecting blood pressure.
Blood pressure (BP) is a complex trait and its levels are regulated by environmental and genetic factors. The majority of studies searching for genetic determinants of BP have been conducted with measurements in the sitting position. Here, we used posture as a tool to demonstrate the dynamics of the genetic regulation of BP in humans.

**Methods and results:** This study was conducted in sib-pairs from families with early-onset hypertension. Extensive phenotyping for hemodynamic and neuroendocrine intermediate BP phenotypes measured while lying supine and upon standing upright was performed. 196 genes involved in BP regulation were tested for linkage using the Haseman-Elston’s regression. Permutations were designed to calculate empirical estimates of significance for each posture and a permutation test was implemented to test for differences in linkage between postures. Linkage was influenced by the change in posture: 13% of genes showed evidence of linkage with any phenotype only during supine but not upon standing, whereas 6% of genes were specifically linked to standing phenotypes. In effect, linkage of genes located under previously published BP QTLs on chromosomes 1 (e.g. KCNH1) and 3 (e.g. SLC2A2), and highly significant novel findings such as linkage of Ednra with systolic BP (P = 10^-8), KCNH8 (P = 10^-16) with cyclic GMP were only evident through this dynamic approach. An additional major finding was the relationship between the renalase gene, cGMP and stroke volume. A genetic profile showing genetic interactions among intermediate BP phenotypes and genes specific to each posture was constructed.

**Conclusions:** Important genetic component of BP is missed by performing genetic studies exclusively in a single posture. Supine and standing BP have distinct genetic signatures. The use of standardised maneuvers influences the results of genetic studies for BP reflecting its dynamic architecture.
ORAL SESSION

ORAL SESSION 3D HEART

3D.01 THE MECHANISM OF CARDIOPROTECTIVE ACTION OF OXYTOCIN
J. Gutkowska, A. Menouar, M. Jankowski. CR-CHUM, Montreal-Canada

Objective: We have previously demonstrated that the release of oxytocin (OT) system, synthesized in the rat and human heart is implicated in several cardiac functions including stem cells differentiation into cardiomyocytes (CM) and increased CM survival. OT treatment has beneficial effect on myocardial infarct, normalized heart work by decreasing inflammation and increasing angiogenesis. Therefore, OT has cardioprotective role which requires mechanistic explanation. OT translocates glucose transporter type 4 (GLUT4) to the plasma membrane in human endothelial cells. OT is also involved in cell metabolism. We therefore hypothesize that the role of OT may be implicated in the regulation of myocardial glucose uptake under physiological conditions and during metabolic stress, such as hypoxia. Furthermore the cardioprotective effect of OT may be mediated by decreasing cardiac hypertrophy.

Design/Methods: Primary cultures of rat cardiomyocytes (CM) were used. The glucose uptake was measured using labelled glucose (0.5 μCi/well). The cardiac hypertrophy, induced by endothelin-1 (ET-1, 10 nM) was studied in newborn and adult CM by an increased cell surface (70%) area and protein synthesis (30%) over 24h.

Results: OT (10 nM) increased basal glucose uptake in newborn rat CM to 4.0 ± 0.2 fmol/mg protein in comparison to 2.2 fmol/mg in control cells (P < 0.001). OT had a moderate synergistic effect with 0.1 mM 2,4-dinitrophenol (hypoxia-inducing agent), augmenting basal glucose uptake to 5.5 ± 0.5 fmol/mg. The increase in glucose uptake by OT was associated with increased phosphorylation of phosphatidylinositol-3-kinase (PI3K), the recognized cardioprotective pathway. Wortmannin (0.1 μM), an inhibitor of PI3K, significantly suppressed the effects of OT and insulin (10 nM) (p<0.001) on glucose uptake, indicating a common pathway. The activation of PI3K pathway suggested the role of OT in prevention of CM hypertrophy. Indeed, the pre-treatment of cells with OT (10 nM) completely inhibited the hypertrophic effect of ET-1. In the newborn and adult rat CM, the OT receptor antagonist (OTA) completely abrogated the anti-hypertrophic effect of OT. Western blot analysis indicated that OT treatment modulates phosphorylation of proteins downstream of PI3K such as PKB/Akt. Like ET-1, OT dose-dependently increased atrial natriuretic peptide (ANP) release 24h after OT treatment, however without changes in the cell volume and protein synthesis. Inhibition of ANP guanylyl cyclase receptor by the specific inhibitor, anantin, blocked the effect of OT on CM hypertrophy.

Conclusions: These findings indicate that OT cardioprotective actions involve stimulation of PI3K signalling pathway. Further more ANP released from the cells treated with OT inhibits ET-1-induced CM hypertrophy.

3D.02 PREVALENCE OF LEFT VENTRICULAR HYPERTROPHY IN HYPERTENSION: AN UP-DATED ANALYSIS OF ECHOCARDIOGRAPHIC STUDIES
C. Cuspidi1, F. Negri1, C. Sala1, M. Masaidi2, G. Mancaia. 1Dept of Clinical Medicine and Prevention University of Milano-Bicocca-Instituto Aziologico Italiano, Milano, Italy, 2Thorax-Pulm & Cardiologie, Dept Fond Polietchnico-Fisiot Clinica e Iperzione University of Milano, Milano-Italy

Aim: Left ventricular hypertrophy (LVH) is a cardinal manifestation of hypertensive organ damage associated to an increased cardiovascular (CV) risk. We reviewed recent literature on the prevalence of LVH, as assessed by echocardiography, in order to offer an updated information on the magnitude of subclinical alterations in LV structure in contemporary human hypertension.

Design: A Medline search using key words “left ventricular hypertrophy”, “hypertension”, “echocardiography”, “cardiac organ damage” was performed in order to identify relevant papers. Full articles published in English language in the last decade, (January 1st 2000-December 1st 2010), reporting studies in adult or elderly individuals, were considered.

Results: A total of 30 studies, including 37,700 untreated and treated patients (80.3% Caucasian, 52.4% men, 9.6% diabetics, 2.6% with CV disease) were considered. LVH was defined as 23 criteria; its prevalence ranged from 36% (conservative criteria) to 41% (less conservative criteria) in the pooled population. LVH prevalence tended to be higher in women than in men (range 37.9- 46.2% versus 36.0-43.5%, respectively). Eccentric LVH was more prevalent than concentric hypertrophy; this latter adverse phenotype was found in a consistent fraction (20%) of both genders.

Conclusions: Despite an improved management of hypertension in the last decade, LVH remains a highly frequent biomarker of cardiac damage in the hypertensive population. Our analysis calls for a more aggressive treatment of hypertension and related CV risk factors leading to LVH.

3D.03 CARDIOTROPIN-1 IS A NEW KEY PLAYER IN CARDIAC AND VASCULAR FIBROSIS AND IN CARDIOVASCULAR DYSFUNCTION BEYOND HYPERTENSION
N. Lopez-Andres1, L. Calvier1, C. Inigo1, C. Labat1, N. Sloboada1, M.A. Fortuno2, J. Diez2, F. Zannad3, P. Lacolley1, P. Rossignol1. 1Inserm U961, Nancy-France, 2Division of Cardiovascular Sciences, Centre for Applied Medical Research. University of Navarra, Pamplona-Spain, 3Inserm Clinical Investigation Centre, CIC9501, Nancy-France

Aims: Cardiotrophin-1 (CT-1), a cytokine belonging to the interleukin-6 family, is increased in hypertension and in heart failure, although its precise role in the cardiovascular system is unknown. In this study we analysed CT-1 effects on cardiovascular remodelling and function in two experimental models without hypertension: rats subjected to chronic CT-1 administration and mice lacking CT-1.

Methods: CT-1 (20 μg/Kg/day) or vehicle were administrated to Wistar rats for 6 weeks. 30 months-old WT and CT-1-null mice were used. Left ventricular (LV) dimensions and cardiac function were analysed using M-mode echocardiography, Doppler assessment and PFT-scan, and vascular function by echotracking device. Cardiovascular morphology and fibrosis were assessed by RT-PCR, Western Blot and immunohistochemistry.

Results: CT-1-treated rats presented increased LV systolic and diastolic volumes and E/A ratio, and reduced fractional shortening and ejection fraction, without modification in blood pressure levels. CT-1-infused rats showed LV dilatation and increased myocardial fibrosis. The incremental elastic modulus (Einc)-circumferential wall stress (WS) curve was shifted leftward in CT-1-treated rats compared to control, indicating an increased stiffness. CT-1-treated rats showed increased carotid media thickness and vascular collagen content. CT-1-null mice exhibited decreased LV systolic and diastolic volumes and slightly increased ejection fraction, accompanied by decreased myocardial fibrosis. Compared to WT group, the Einc-WS curve of CT-1-null mice was shifted rightward, indicating decreased stiffness. Carotid media thickness and vascular fibrosis were lower in CT-1-null mice.

Conclusions: CT-1 is a new key player in cardiovascular remodelling and function whilst modulating cardiac and vascular fibrosis, independently from blood pressure levels. Thus, CT-1 could be a new biotarget to reduce the remodelling process in cardiovascular diseases.
Abstract 3D.04 – Table 1: Echocardiographic parameters in groups with PH and in control.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>IPH (M ± m)</th>
<th>CTD</th>
<th>SS</th>
<th>CORD</th>
<th>CHD</th>
<th>RPH</th>
<th>CG</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAV, ml</td>
<td>79.44 ± 7.17</td>
<td>77.09 ± 5.92</td>
<td>56.61 ± 6.96</td>
<td>50.25 ± 6.54</td>
<td>64.61 ± 6.38</td>
<td>72.35 ± 7.27</td>
<td>36.47 ± 3.14</td>
</tr>
<tr>
<td>EDV, RV, ml</td>
<td>80.18 ± 8.62</td>
<td>80.44 ± 9.71</td>
<td>55.96 ± 5.41</td>
<td>63.92 ± 9.91</td>
<td>79.9 ± 9.16</td>
<td>70.22 ± 8.06</td>
<td>34.52 ± 3.73</td>
</tr>
<tr>
<td>EF RV, %</td>
<td>35.22 ± 2.06</td>
<td>42.14 ± 3.75</td>
<td>52.9 ± 2.5</td>
<td>55.78 ± 2.40</td>
<td>48.95 ± 3.52</td>
<td>52.14 ± 2.77</td>
<td>64.27 ± 1.2</td>
</tr>
<tr>
<td>EDV LV, ml</td>
<td>45.67 ± 5.66</td>
<td>61.51 ± 7.85</td>
<td>60.48 ± 6.73</td>
<td>67.53 ± 6.49</td>
<td>52.46 ± 7.58</td>
<td>88.5 ± 10.27</td>
<td>103.27 ± 5.12</td>
</tr>
<tr>
<td>SPAP, mm Hg</td>
<td>91.8 ± 5.5</td>
<td>59.9 ± 7.1</td>
<td>55.7 ± 6.7</td>
<td>51.1 ± 4.9</td>
<td>71.9 ± 8.2</td>
<td>45.2 ± 5.9</td>
<td>20.6 ± 2.3</td>
</tr>
<tr>
<td>ε max b,%</td>
<td>25.5 ± 2.1</td>
<td>27.0 ± 2.8</td>
<td>23.3 ± 1.6</td>
<td>25.7 ± 2.9</td>
<td>28.0 ± 3.0</td>
<td>33.7 ± 3.4</td>
<td>22.8 ± 1.4</td>
</tr>
<tr>
<td>ε max m,%</td>
<td>20.6 ± 2.5</td>
<td>19.4 ± 4.0</td>
<td>25.1 ± 3.1</td>
<td>30.9 ± 2.9</td>
<td>28.6 ± 2.6</td>
<td>21.2 ± 4.9</td>
<td>28.1 ± 2.0</td>
</tr>
<tr>
<td>α max a,%</td>
<td>43.0 ± 2.4</td>
<td>38.7 ± 3.1</td>
<td>35.8 ± 2.8</td>
<td>40.5 ± 3.6</td>
<td>44.8 ± 3.0</td>
<td>23.6 ± 3.5</td>
<td>28.1 ± 2.5</td>
</tr>
</tbody>
</table>

b-basal, m-medial, a-apical segment. *p < 0.05 versus control; ^- IPH; $- CTD; &- SS; /- CORD; #- CHD.

Materials and Methods: In the study we included: 29 pts with idiopathic pulmonary hypertension (IPH) at age of 33.07 ± 1.93 years, 15 pts with chronic thromboembolic disease (CTD) of 52.07 ± 2.88 years, 18 pts with pulmonary hypertension (PH), associated with systemic sclerosis (SS) of 52.39 ± 3.08 years, 13 pts with PH, associated with chronic obstructive respiratory disease (CORD) of 66.09 ± 2.7 years, 15 pts with PH, associated with congenital heart disease (CHD) of 43.2 ± 3.38 years, 12 pts with residual PH after 6-8 years after surgical closing of septal defects of 51.42 ± 2.08 years. 21 healthy volunteers served as control group (CG). Echocardiographic, complete conventional and Tissue Doppler Imaging (TDI) were operated (Vivid 7, G.E.). Left and right atrial volumes (LAV and RAV), end systolic and diastolic volumes (ESV and EDV) of right and left ventricles (RV and LV), ventricular ejection fractions (EF) and ventricular deformation were assessed. The mean pulmonary arterial pressure (SPAP), systolic pulmonary artery pressure (SPAP) were assessed. Regional systolic strain was expressed as the percentage of right ventricular myocardial deformation (ε max).

Conclusions: Hypoxia increased CT-1 levels in cardiac cells (in vitro and in vivo) through a direct regulation of CT-1 promoter by hypoxia inducible factor-1 (HIF-1α). This CT-1 activation by hypoxia may protect cells from apoptosis, thus supporting a protective role for CT-1 as a survival factor for cardiomyocytes.

3D.05 UP-REGULATION OF CARDIOTROPHIN-1 IN THE SURVIVAL RESPONSE OF CARDDIOMYOCYTES TO HYPOXIA


Objective: Cardiotrophin-1 (CT-1) is a cytokine of the interleukin-6 superfamily which is upregulated in cardiac diseases, in part via hypoxia-dependent mechanisms. However, no evidence for a direct regulation of CT-1 gene (CTF1) promoter by hypoxia inducible factor-1 (HIF-1α) has been provided. Constructs containing deleted CTF1 promoter sequences were used for luciferase assay in experiments involving decay experiment and mutagenesis.

Design and Method: The murine cardiomyocyte cell line HL-1 or a murine model were exposed to hypoxia and RNA samples were collected for RT-PCR. In some experiments with the HL-1 cells siRNA interference technology or specific inhibitors of signaling pathways were used. Interaction between HIF-1α and CTF1 promoter was analysed by EMSA. The role of CT-1 in the hypoxic induced apoptosis in HL-1 cells was evaluated by annexin V and caspase 3/7 activities. Finally, constructs containing deleted CTF1 promoter were use for luciferase assays in experiments involving decay and mutagenesis.

Conclusions: Hypoxia increased CT-1 mRNA levels in the rat adult cardiomyocyte cell line HL-1 in a time-dependent manner. Interestingly, in C57BL/6 mice we show that systemic hypoxia also significantly up-regulated CT-1 in myocardial tissue. The effect of hypoxia on CT-1 expression was mediated through a transcriptional mechanism, since hypoxia increased luciferase activity of constructs containing CTF1 promoter sequences. The increase in CT-1 levels was significantly reduced by drugs that prevent calcium mobilization, such as lercanidipine, or that inhibit the activation of the PI3K/ Akt pathway (wortmannin) or MITOR (rapamycin). The CT-1 elevation was similarly induced by HIF-1α over-expression in co-transfection experiments and prevented by HIF-1α silencing. The direct interaction of HIF-1α with the CTF1 promoter was confirmed through both site-directed mutagenesis of hypoxia response elements and electrophoretic mobility shift assays. Hypoxia induced HL-1 apoptosis (measured as annexin-V binding or caspase 3/7 activity) which was increased when CT-1 was silenced in knock-down cells by lentiviral vectors.

3D.06 STAT3 MEDIATED ACTIVATION OF PROAPOPTOTIC GENES IN DIABETIC CARDIOMYOPATHY

G. E. Cambi, McH. Djeokeng, G. Lucchese, M. Bonacchi, G. Sani, A. Modesti, P. A. Modesti

Objective: Clinical benefits of Angiotensin (Ang II) inhibition in diabetic cardiomyopathy are now well recognized and different mechanisms have been demonstrated to play a role at the cellular level. In particular Ang II stimulation of AT1 receptors in the presence of high glucose (HG) may induce JAK2 phosphorylation with consequent activation of transcription factors of the STAT family. The present study was designed to clarify the effect of STAT3 activation on downstream gene expression.

Design and Methods: The study was performed on cardiomyocytes isolated by enzymatic digestion method from control rats. Myocytes were preincubated for 2 h in the presence and in the absence of 25 mM glucose. Then the cells were stimulated with Ang II (100 nM) for 0,15,30, and 60 min. Pro-inflammatory (IRF-1), pro-apoptotic (Fas-L), and anti-apoptotic (Bcl-XL) genes were investigated by RT-PCR with Gusb as housekeeping gene. STAT3 phosphorylation was investigated in Western blot studies.

Results: STAT3 phosphorylation was induced by Ang II in the presence of HG (+57%, *p<0.05 vs. Ang II at 30 min, left panel) with a contemporary significant increase of Fas-L gene expression (+11%, *p<0.05 vs. Ang II, right panel). Fas-L gene expression was abolished by JAK2 antagonist (AG490, 10 μM), whereas a mild enhancement was induced by ERK inhibition (PD98059, 30 μM) (+100%, *p<0.05 vs. Ang II). The inhibitory effect of p38-MAPK antagonist (SB203580, 10 μM) reveals the convergence of two different pathways in Fas-L gene expression (Figure).
Conclusions: Present findings support the participation of STAT3 in the pro-apoptotic effects of Ang II in diabetic cardiomyopathy.

**3D.07 ETANERCEPT INDUCES A DECREASE IN LEFT VENTRICULAR MASS IN PATIENTS WITH RHEUMATOID ARTHRITIS**

C. Immediato Daïen, I. Morel, G. du Cailar, A. M. Dupuy, J. P. Cristol, Montpellier-France

**Background:** Mortality in patients with rheumatoid arthritis (RA) is higher than in the general population, mainly due to premature cardiovascular disease. RA is associated with increased cardiac mass (left ventricular [LV] hypertrophy) which is a strong marker of cardiovascular morbidity and mortality. Experimental studies suggest that tumour-necrosis factor alpha (TNFα) may induce LV hypertrophy.

**Aim:** To assess the influence of etanercept (ETN, TNFα inhibitor) or synthetic drug-modifying anti-rheumatic drugs (sDMARD) on LV morphology in RA patients.

**Methods:** Thirty-eight female patients with active RA were included and allocated to sDMARD (n = 17; methotrexate, sulfasalazine, leflunomide) or ETN (n = 21), according to current guidelines. Exclusion criteria were diabetes, obesity, previous cardiovascular events, cardiopathy, uncontrolled hypertension, alcohol abuse and renal disease. Clinical and biological monitoring and echocardiography were performed at inclusion and after 3 months of etanercept or sDMARD therapy. All determinations of LV mass were performed on an offline station by the same operator who was blind to treatment assignment.

**Results:** (mean ± SEM) In sDMARD allocated subjects, age was 50 ± 4 yrs and RA duration was 1.7 ± 0.5 yrs. At baseline, DAS28 was 4.2 ± 0.3, LV mass index was 86 ± 7 g/m² and LV hypertrophy (LV mass>110 g/m²) was present in 23% of subjects. In ETN allocated subjects, age was 56 ± 3 yrs and RA duration was 9.5 ± 2 yrs. At baseline, DAS28 was 4.8 ± 1.1, LV mass index was 94 ± 4 g/m² and LV hypertrophy was present in 19% of subjects. In patients on sDMARD, LV mass did not change significantly after 3 months (~1.4 ± 3.4 g/m²; p = 0.70), whereas in patients on ETN, LV mass decreased by 5.31 ± 1.7 g/m² (p = 0.007) without change in blood pressure (~3.7 ± 2.3 mmHg NS).

**Conclusion:** In this longitudinal prospective comparative study conducted in RA, etanercept induced a significant decrease of LV mass whereas sDMARD did not influence cardiac remodeling. Those results suggest that TNFα may be a main factor of LV hypertrophy. This could partly explain the previously reported benefit of TNF inhibitors on cardiovascular morbi-mortality in RA.

**3D.08 INCREASED LEFT VENTRICULAR APOCAL Rotation UNDER EXPOSURE TO HYPOBARIC HYPOXIA AT VERY HIGH ALTITUDE: A SIGN OF SUBENDOCARDIAL ISCHEMIA? DATA FROM THE HIGHCARE PROJECT**

G. Osculati1, M. Revera1, G. Branzi1, A. Faini1, F. Ciambelliotti1, G. Bilo1, G. Mancia1, G. Parati1, on behalf of Highcare investigators. 1Dept. Cardiology, Ospedale San Luca, Istituto Auxologico Italiano, Milan-Italy, 2Dept. of Clinical Medicine and Prevention Univ. Milano-Bicocca, Milan-Italy, 3University of Milano-Bicocca & Istituto Auxologico Italiano, Milan-Italy

**Background:** It has been suggested that exposure to hypobaric hypoxia at high altitude (HA) is associated with an increase in global left ventricle (LV) function in healthy subjects. However, in cultured myocytes a reduced contractility has been described with low levels of oxygen pressure. The discrepancy between in vivo and in vitro results could be explained by a different behavior of LV subepicardial and subendocardial layers. Occurrence of an increased LV torsion could unveil even small alterations of subendocardial LV contractility. Our aim was thus to explore possible subendocardial LV contraction abnormalities in subjects exposed to HA through analysis of LV apical rotation patterns.

**Design and Methods:** In 46 healthy volunteers (31 males, age 39.9 ± 10) participating in Highcare project, 2D cross-sectional echocardiographic images at apical level were repeatedly recorded at sea level (SL); during acute exposure to HA (3500 m a.s.l, HA); at very HA (Mt. Everest Base Camp, 5400 m a.s.l.) both after 1-3 days (VHA1) and 7-9 days (VHA2); after return to SL (SLR). 2D echo images were analyzed by using speckle tracking technique to evaluate the apical rotation. For each step systolic (S), diastolic (D) blood pressure (BP), heart rate (HR), oxygen saturation (SpO2) and plasma norepinephrine were assessed.

**Results:** HR, SBP, DBP and plasma noradrenaline increased progressively with altitude, whereas SpO2 decreased. The corresponding values of apical LV rotation and its values corrected for concomitant LV radius changes are shown in the table. A strong inverse linear correlation was found between SpO2 and LV apical rotation (p<0.002).

<table>
<thead>
<tr>
<th>SL</th>
<th>HA</th>
<th>VHA1</th>
<th>VHA2</th>
<th>SLR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rot max°</td>
<td>9.10 (6.4)</td>
<td>10.4 (1.05)</td>
<td>11.7 (1.07)**</td>
<td>11.4 (1.08)**</td>
</tr>
<tr>
<td>Rot/deltar °/cm</td>
<td>3.2 (3.7)</td>
<td>19.7 (3.15)</td>
<td>18.7 (1.62)</td>
<td>22.6 (2.68)**</td>
</tr>
</tbody>
</table>

**Conclusion:** Our data show a depressant effect of HA hypoxia on subendocardial LV fibers contractility, possibly related to sympathetic activation, unveiled by a significant increase in LV apical rotation, inversely related to SpO2.

**3D.09 LEFT ATRIAL STRAIN IN NORMAL INDIVIDUALS IS INFLUENCED BY AGE AND LEFT ATRIAL VOLUME: IMPLICATIONS FOR EVALUATION OF ATRIAL FUNCTION IN HYPERTENSIVE PATIENTS WITH DIASTOLIC DYSFUNCTION**

M. Chinali1, G. P. Aurigemma1, U. Khan1, J. C. Hill1, G. De Simone1, D. A. Tighe1, 1Umass Medical School, Worcester-USA, 2Federico II University Hospital, Naples-Italy

**Background:** Left atrial (LA) geometry and function are independent predictors of atrial fibrillation and heart failure. We and others have shown that LA strain (SLA) by speckle tracking imaging (STI) is a descriptor of atrial reservoir function, and is reduced in hypertensive patients with diastolic dysfunction. However, SLA might physiologically decrease with aging and be significantly influenced by LA size. Our goal was to arrive at a model for SLA that accounted for age and size, so as to more accurately determine LA dysfunction.

**Methods:** 100 healthy volunteers (NLS; 50 ± 15yrs; 58 women) underwent standard echocardiography with complete evaluation of diastolic function, LA volume and SLA. LA volume was calculated by the area-length method. Multivariate regression models were derived from normals to generate regression equations that were then tested in 50 hypertensive patients with grade 1-2 diastolic dysfunction (HTN; 76 ± 4yrs; 72% females) without significant valvular disease or cardiac rhythm abnormalities.

**Results:** Reduced LA function was defined as SLA ≤24.4% (5th percentile in normals). In stepwise multiple regression analysis, SLA was significantly and negatively associated with older age (b = −0.288; p<0.01) and bigger LA volume (b = −0.252; p<0.01) with low collinearity among covariates (tolerance >0.80). Surprisingly, no independent association was observed for gender, body size and left ventricular mass or relative wall thickness. The following regression equation was derived to correct SLA (SLA -c) for age and LA size: SLA c[%] = SLA [%] + 0.198 x (age - 50) + 0.155 x (LAvol - 45) + 3.54; where age is expressed in years and LAvol is unadjusted LA volume in mL (R = 0.42, SEE = 3.95, p<0.001). SLA c was normally distributed with a mean value of 41.1%. We then repeated the analysis using this ‘corrected’ SLA -c, with a partition value of <29.4% (i.e. 5th percentile of distribution in normal individuals). Prevalence of reduced LA function was significantly higher in HTN as compared to NLS by both classifications (p<0.01). However as compared to classification by unadjusted SLA prevalence of LA dysfunction was significantly lower when defined by SLA -c (16% vs 47%; p<0.001).

**Conclusions:** Atrial function by SLA decreases physiologically with ageing and increasing LA size. This phenomenon should be taken into account when evaluating LA function to avoid misdiagnosis of LA dysfunction and correctly stratify cardiovascular risk in individuals with hypertension.
**ORAL SESSION 4A**

### 4A.01 TRANSCUTANEOUS ELECTRICAL NERVE STIMULATION - SAFE BUT NO ANTI-HYPERTENSIVE ALTERNATIVE

J. Silverdal, G. Mourtzini, E. Stener-Victorin, C. Mannheimer, K. Manhem. 1Department of Internal Medicine and Geriatrics, Sahlgrenska University Hospital/Ostra, Goeteborg-Sweden, 2Department of Internal Medicine, Sahlgrenska University Hospital/Molndal, Molndal-Sweden, 3Department of Physiology, Sahlgrenska Academy, University of Gothenburg, Goeteborg-Sweden, 4Multidisciplinary Pain Center, Sahlgrenska University Hospital/Ostra, Goeteborg-Sweden, 5Department of Internal Medicine, Sahlgrenska University Hospital/Sahlgrenska, Goeteborg-Sweden.

**Objective:** Blood pressure (BP) is often unsatisfactory controlled, partly due to side effects. Transcutaneous electrical nerve stimulation (TENS) is well tolerated and has in pilot studies reduced BP. Patients with refractory angina use TENS for symptom alleviation and might concurrently be BP sensitive due to drug treatment. This randomized cross-over investigation compared the BP lowering effect of TENS with felodipine in hypertensive patients.

**Design and Methods:** In 32 subjects (mean age 55 years, mean BP 152.7/90.0 mmHg) four weeks of 2.5 mg felodipine once daily and 30 minutes of bid- dally TENS was compared. Office BP and 24-hour ambulatory blood pressure measurements (ABPM) were performed initially and at the end of treatment periods and four weeks intervening washout periods.

**Results:** Office BP (in mmHg, with levels of significance vs. Baseline; n.s.=non significant, * p < 0.05, ** p < 0.01, *** p < 0.001) after felodipine treat- ment was 142.7±83.7***, after felodipine washout 145.8***/86.9***; after TENS 148.0****/88.5 n.s. and after TENS washout 145.6****/87.2*. ABPM revealed a sig- nificant systolic reduction of 4 mmHg by felodipine, but no changes after TENS.

**Conclusions:** Felodipine reduced systolic and diastolic office BP. TENS slightly reduced systolic office BP but the further reduction found after TENS washout was similar to BP after felodipine washout and therefore reasonably caused by factors other than the treatment. ABPM failed to identify changes by TENS which also supports the conclusion that TENS does not reduce BP. This is for safety reasons important in patients with coronary heart disease and refractory angina.

### 4A.02 COMPARISON OF BLOOD PRESSURE, POTASSIUM, RENIN AND ALDOSTERONE EFFECTS OF ALDOSTERONE SYNTHASE INHIBITION vs. MINERALOCORTICOID BLOCKADE IN PATIENTS WITH PRIMARY ALDOSTERONISM

L. Amar, M. Azizi, J. Menard, S. Peyrard, P.F. Plouin. Hôpital Européen Georges Pompidou, Paris-France

**Objective:** To compare the hemodynamic, potassium (K) and hormonal effects of aldosterone synthase inhibition with those of mineralocorticoid receptor blockade in patients with primary aldosteronism (PA).

**Design and Methods:** After a two-week placebo run-in, 14 patients with PA received oral LCI699 (0.5 mg b.i.d.) from day 1 to 14, LCI699 (1 mg b.i.d.) from day 15 to 29, and placebo from day 29 to 36. The first part of the study on LCI699 has been reported elsewhere (Hypertension 2010; 56:831). Once BP, plasma K and hormone concentrations had returned to baseline levels on day 36, patients were treated with eplerenone for four weeks (50 mg b.i.d. increasing to 100 mg b.i.d. in 12/14 patients after 2 weeks), in addition to their previous antihypertensive treatment, which was maintained unchanged. We compared changes in BP, plasma K, renin (PRC) and aldosterone (PAC) concentrations after LCI699 (day 29) and four weeks of eplerenone administration.

**Results:** At baseline, patients (13 men, age: 50.3±6.7 years) had high 24h ambulatory SBP/DBP (145±9/89±7 mmHg), low plasma K concentra- tion (3.27±0.31 mmol/L), high PAC (540±50 mmol/L [95% CI: 394; 739]), high urinary aldosterone concentration (82 mmol/24h [95% CI: 61; 109]) and low PRC (11 ml/L [95% CI: 8.15]). LCI699 reduced 24h ambulatory SBP/DBP by 4.1% (95% CI: -8.1; -0.1) and 1% (95% CI: -.45; -0.3) mmHg (P = 0.046/P 0.08 day 29 vs. baseline). Eplerenone further decreased 24h ambulatory SBP/ DBP by 5.3% (95% CI: -.10; -0.4/ 3.1 95% CI: -.6; -0.3) mmHg (P = 0.027/ P = 0.06 vs. day 29 on LCI699). Plasma K concentration reached 3.89±0.35 mmol/l on 1 mg LCI699 treatment (P < 0.001) day 29 vs. baseline), then decreased to 3.38±0.35 mmol/L (P < 0.0001) day 36 vs. day 29 before increasing to 4.30±0.45 mmol/L after four weeks of eplerenone treatment (P = 0.009 vs. day 29 on LCI699). The increase in PRC was significantly greater after eplerenone (+131% [95% CI: 61; 231]) treatment than on day 29, after treatment with 1 mg LCI699 (+39% [95% CI: 5; 86]; P = 0.023). Treatment with 1mg LCI699 markedly decreased PAC, by 75% (95% CI: -.84; -63), whereas eplerenone markedly increased PAC from day 36, by 89% (95% CI: 40;154; P < 0.0001 vs. LCI699).

**Conclusion:** In patients with PA, the BP, potassium and PRC effects of four weeks of eplerenone treatment (up to 100 mg b.i.d.) are greater than those of four weeks of LCI699 treatment (0.5 to 1 mg b.i.d.). These drugs had opposite effects on PAC.

### 4A.03 THERAPEUTIC INERTIA FOR CARDIOVASCULAR PREVENTION IN HYPERTENSIVE PATIENTS: PLATELET AGGREGATION INHIBITORS PRESCRIPTION


**Aim:** To study the prevalence of therapeutic inertia (TI) in hypertensive patients not treated with Platelet Aggregation Inhibitors (aspirin or clopidogrel) despite of guideline recommendation. To analyze associated factors to TI.

**Methods:** Observational, cross sectional, multicentre, study setting in Pharmacy practices. A consecutive sample of 525 patients was included. The criteria for Aggregation Inhibitors Prescription (AIP) with aspirin or clopi- dogrel were according to Spanish Committee of Cardiovascular Prevention Guideline 2009. A multivariable analysis was performed.

**Results:** AIP was indicated in 18.5% (IC95% 15.2-21.8) of hypertensive patients. TI was 51.5% (IC95% 41.6-61.4). In the multivariable analysis a sign- ificative association was found (p = 0.000) with a variability explanation of 49.5%. Associated factors were not having dyslipidemia p = 0.031, OR = 0.28 (0.09–0.89); not having stroke (p = 0.007), OR = 0.13 (0.03-0.58); not having coronary heart disease (p = 0.000), OR = 0.12 (0.04-0.37); and lower diastolic blood pressure (p = 0.006), OR = 0.92 (0.86–0.97). Of those taking Aggregation Inhibitors only 14.9% (4.7-25.1) reached systolic blood pressure target.

**Conclusion:** There is therapeutic inertia for Aggregation Inhibitors Prescription in hypertensive patients, having more than 50% without treatment despite of recommendation. TI is associated to patients with lower cardiovascular risk. For those taking Aggregation Inhibitors, the most do not have their systolic blood pressure controlled.

### 4A.04 EFFICACY AND TOLERABILITY OF TRIPLE COMBINATION THERAPY (TCT) WITH OLMESARTAN MEDIXOMIL (O) PLUS AMLODIPINE (A) PLUS HYDROCHLOROTHIAZIDE (H) COMPARED WITH DUAL COMBINATION THERAPY (DCT) WITH O PLUS A

M. Volpe1, A. Januszewicz2. 1University of Rome - Sapienza, Sant’Andrea Hospital, Rome-Italy, 2Institute of Cardiology, Warsaw-Poland

**Purpose:** To compare the efficacy of triple combinations of O/A/H with dual combinations of O/A in pts with moderate to severe hypertension.

**Methods:** This was a multinatural, randomised, double-blind, parallel-group study in patients (N = 2690) with moderate-to-severe hypertension. At baseline, pts with seated SBP ≥160 and DBP ≥100 mmHg were randomly allocated to treatment sequences in which they initially received 2 weeks of DCT with...
O/A (20/5, 40/5 or 40/10 mg). Pts then entered an 8-week double-blind period in which they continued the DCT or received TCT (20/5/12.5, 40/5/25, 40/10/12.5 or 40/10/25 mg) containing the dose of O/A that they had received during the first 2 weeks. The primary efficacy parameter was the change from baseline in DBP at the end of double-blind treatment (Week 10); changes in SBP were also measured.

**Results:** At Week 10, significant, dose-related, reductions in DBP and SBP from baseline were seen in each group (p < 0.0001 for each). The O/A 20/5 mg group showed the smallest reductions in DBP and SBP (19.9±3.1 mmHg), and the O/A/H 40/10/25 mg group showed the largest (23.0±3.7 mmHg) reductions. Each TCT group showed significantly greater reductions in DBP and SBP compared with the group treated with the corresponding DCT (table). All treatments were well-tolerated, with a low rate of adverse events across the groups (19.9–32.2%).

**Conclusion:** In patients with moderate-to-severe hypertension, the tripe combination of O/A/H demonstrated a positive, statistically significant contribution in efficacy by adding H 12.5 and 25 mg to the dual combination of O/A, and demonstrated comparable tolerability.

**4A.06 INFLUENCE OF RENAL ARTERY DENERVATION ON BLOOD PRESSURE VARIABILITY AND BAROREFLEX SENSITIVITY: A PROSPECTIVE CONSECUTIVE CASE-SERIES**

V. Baudrie1, M. Frank1, O. Steichen2, J.L. Elgboz1, M. Sapoval2, G. Bobrie2, P.F. Plouin3, M. Azizi4. 1Pyrac, Insarm U970, Paris-France, 2HEGP, APHP, Paris-France

**Objective:** Catheter based renal artery denervation is a new therapeutic approach in resistant arterial hypertension. Its effect on blood pressure variability and baroreceptor sensitivity is unknown. We report here the effects of renal denervation on spontaneous baroreflex sensitivity and beat-to-beat blood pressure variability in patients with resistant arterial hypertension.

**Methods:** Six patients with resistant hypertension enrolled in the multicenter randomized controlled Simplicity HTN-2 trial in our center (3 assigned to the renal denervation group and 3 assigned to the control group) had measurements of spontaneous baroreflex sensitivity and instantaneous blood pressure variability with the Finapres device before randomisation and at 6 months. After 6 months, those assigned to the control group were offered denervation and had new measurements.

**Results:** Mean age of patients was 41.5±13.4 yrs, with a male/female ratio of 2/4 and mean BMI of 29.3±6.2 kg/m². Systolic Blood Pressure (SBP) levels, sympathetic activity (Low Frequency (LF) component of SBP variability) and baroreflex sensitivity (transfer function, LF range) remained unchanged at month 1 (148.2±18.9 mmHg, 22.9±4.9 mmHg², 6.6±1.9 ms/mmHg²) and 6 (152±14.4 mmHg, 34±2.1 mmHg², 5.1±0.2 ms/mmHg²) for the patients of the control group in comparison to baseline (157.5±2.6 mmHg, 19.3±3 mmHg², 5.2±0.8 ms/mmHg²). In the 2 patients with significant decreases in blood pressure after the procedure (SBP change between baseline and month 6 being -57.4 mmHg), there was a major decrease in sympathetic activity (LF SBP at baseline 19.5; 1 month 7.9; 6th month 4.7 mmHg²), together with a spontaneous baroreflex sensitivity increase after denervation (baseline 5.9; month 1 13.2; 6th month 12.1 ms/mmHg). In patients with persistent hypertension, sympathetic activity and baroreceptor sensitivity remained unchanged.

**Conclusion:** Our observations suggest that successful renal denervation may be associated with a decreased blood pressure variability and an increased baroreflex sensitivity. One can hypothecize that an efficient renal denervation determined an increased baroreflex sensitivity which may be causally related to the blood pressure decrease.

**4A.07 DIRECT ANGIOTENSIN AT2-RECEPTOR STIMULATION IMPROVES SURVIVAL AND NEUROLOGICAL OUTCOME IN EXPERIMENTAL STROKE (MCAO) IN MICE**

K. Schwengel1, C. Thöne-Reinke1, K. Luchi1, P. Namsolleck1, S. Müller1, M. Horiuichi1, M. Iwai1, B. Dahlöf1, A. Hallberg1, T. Unger1, U.M. Steckelings1, 1Center for Cardiovascular Research, CCR, Charité Universitätmedizin Berlin, Berlin-Germany, 2Charité Universitätmedizin Berlin, Center for Stroke Research Berlin (CSR), Berlin-Germany, 3Ehime University School of Medicine, Department of Molecular and Cellular Biology, Ehime-Japan, 4Sahlgrenska University Hospital/Ostra, Gothenburg-Sweden, 5Uppsala University, Department of Medicinal Chemistry, Uppsala-Sweden

**Objective:** Previous studies have provided indirect evidence suggesting a beneficial effect of AT2 receptor (AT2R) stimulation on stroke outcome. The aim of this study was to investigate the effect of direct AT2R stimulation with the novel specific and selective non-peptide AT2R agonist Compound 21 (C21) on infant size, survival and neurological outcome after middle cerebral artery occlusion (MCAO) in mice.

**Design and Method:** C57BL/6 or AT2R knockout (on C57BL/6 background) mice underwent MCAO for 30 minutes followed by reperfusion. Starting 45 minutes after MCAO, mice were treated daily with either vehicle (0.9% NaCl i.p.) or C21 (0.03 mg/kg i.p.) for a period of 4 days. Garcia neurological score was performed daily to assess the severity of neurological deficits. Infarct volumes were measured in vivo 96 hours post-stroke by MRI. Expression levels of the neurotrophin BDNF, the neurite outgrowth marker Gf3, the inhibitor of axonal growth NogoA and its receptor NogoR and the pro-inflammatory cytokine interleukin-6 were measured in brain samples by quantitative RT-PCR and Elisa.

**Results:** While having no effect on blood pressure, treatment with C21 significantly attenuated neurological deficits when compared to vehicle-treated
mice. Mortality in vehicle-treated mice amounted to 57% and was significantly lowered to 26% in C21 treated mice (p < 0.016). There were no effects of C21 on neurological outcome and survival in AT2-KO mice. Pharmacological AT2R stimulation by C21 did not significantly reduce infarct size. However, mean infarct size in AT2R-deficient mice was significantly larger than in wild-type mice (79.6 mm3 vs. 51.4 mm3 (p < 0.03)). Gene expression of BDNF and Gap43 were significantly increased whereas NogoA and its receptor NogoR were significantly downregulated. IL-6 gene expression was significantly lower in the infarcted brain areas of C21-treated mice compared to the vehicle group, while there were no changes in AT2R-deficient mice. BDNF protein levels were significantly enhanced after C21 treatment compared to the vehicle group.

Conclusions: Our data demonstrate for the first time that direct AT2R-stimulation by C21 improves survival and neurological deficits after experimental stroke through neuroprotective, anti-inflammatory, blood-pressure independent mechanisms, and that these effects are indeed AT2R-specific.

**4A.08 CARDIOVASCULAR PROTECTION BY INITIAL AND SUBSEQUENT COMBINATION OF ANTIHYPERTENSIVE DRUGS IN DAILY LIFE PRACTICE**

G. Mancia1, F. Nicotra2, A. Parodi3, A. Zamboni4, F. Heiman5, L. Merlino6, I. Ferretti1, C. Ferracuti1, C. Caruso1, Gerardo Hospital, Milano-Italy, 2Department of Statistics, Unit of Biostatistics and Epidemiology, University of Milano-Bicocca, Milano, Italy, 3Cegedim Strategic Data, Epidemiology and Health Economics Manager, BKL Consulting s.r.l., Milano, Italy, 4Operative Unit of Territorial Health Services, Lombardy Region, Milano-Italy

**Background:** Guidelines recommend combination of two drugs to be used as first step treatment strategy in high risk hypertensive individuals to achieve timely blood pressure control and avoid early events. The evidence that this is associated with cardiovascular (CV) benefits compared to initial monotherapy is limited, however.

**Objectives:** To assess whether, compared with antihypertensive monotherapy, combination of antihypertensive drugs provides a greater CV protection in daily clinical practice.

**Methods:** A population-based, nested case-control study was carried out by including the cohort of 209,650 patients from Lombardy (Italy) aged 40-79 years who were newly treated with antihypertensive drugs between 2000 and 2001. Cases were the 10,688 patients who experienced a hospitalization for CV disease from initial prescription until 2007. Three controls were randomly selected for each case. Logistic regression was used to model the CV risk associated with starting on and/or continuing with combination therapy. A Monte-Carlo sensitivity analysis was performed to account for unmeasured confounders.

**Results:** Patients starting on combination therapy had a 11% CV risk reduction with respect to those starting on monotherapy (95% CI: 5% to 16%). Compared to patients who maintained monotherapy also during follow-up, those who started on combination therapy and kept it along the entire period of observation had 26% reduction of CV risk (95% CI: 15% to 35%).

**Conclusions:** In daily life practice combination of antihypertensives drugs is associated with a greater reduction of CV risk than monotherapy. This is the case also for use of drug combination as first step treatment strategy.

**4A.09 Efficacy and safety of azilsartan medoxomil/chlorthalidone with olmesartan/hydrochlorothiazide combinations in stage 2 systolic hypertension**

W. C. Cushman1, D. Sica2, G. L. Bakris3, M. A. Weber4, W. B. White5, C. Forte6, R. L. O. R. S. K. L. K. S. University of Tennessee College of Medicine, Memphis, USA, 2Virginia Commonwealth University Health System, Richmond, USA, 3University of Chicago Pritzker School of Medicine, Chicago, USA, 4New York, New York-USA, 5University of Connecticut School of Medicine, Farmington-USA, 6Takeda Global Research & Development Center, Deerfield-USA

**Background:** Azilsartan medoxomil (AZL) is a new highly potent, long-acting angiotensin II receptor blocker (ARB), and chlorthalidone (CLD) is a highly potent, long-acting thiazide-like diuretic.

**Methods:** We compared fixed-dose combinations (FDCs) of AZL/MCLD 20/12.5 mg QD titrated to 40/25 mg if needed or AZL/MCLD 40/12.5 mg QD titrated to 80/25 mg if needed and an FDC of the ARB olmesartan medoxomil (OLM) plus the thiazide diuretic hydrochlorothiazide (HCTZ) 20/12.5 mg QD titrated to 40/25 mg if needed. This was a randomized, double-blind, 8-week study of 1085 subjects with mean clinic systolic BP (SBP) 160-190 mm Hg and diastolic BP ≤119 mm Hg. Titration to higher doses occurred at week if BP was above target. The primary endpoint was change from baseline in clinic seated trough SBP; 24-hour ambulatory BP monitoring was also conducted.

**Results:** Patient characteristics: mean age 56 years, 48% women, 26.7% black, 62.7% white, BMI 31.8 kg/m², 22.9% current smokers, and 17.3% diabetes mellitus. Changes in clinic SBP were greater with AZL/M/CLD than with OLM/HCTZ despite less titration to higher doses (Table). At 8 weeks, both AZL/MCLD FDCs reduced 24-hour mean SBP more than OLM/HCTZ (-26.4 and -27.9 versus -20.7 mm Hg; both p < 0.001). Adverse events leading to temporary or permanent drug discontinuation occurred in 6.2%, 9.5%, and 3.1% of the AZL-M CLD 40/25 mg, AZL/MCLD 80/25 mg, and OLM/HCTZ 40/25 mg groups, respectively. No deaths occurred.

**Conclusions:** AZL-M/CLD FDCs reduced office and ambulatory SBP significantly more than OLM/HCTZ in this titration-to-target study.

**4A.10 Cardiorespiratory response to exercise after renal sympathetic denervation in patients with resistant hypertension**

C. Ukena1, F. Mahfoud2, I. Kindermann3, M. Kindermann1, M.-C. Brandt3, U. Hoppe4, H. Krum5, M. Esler6, P. Sobotka7, M. Böhm1, 1Universitätssklinikum DES Saarlandes, Homburg/Saar-Germany, 2Centre of Cardiovascular Research and Education in Therapeutics, Melbourne-Australia, 3Baker IDI Heart and Diabetes Institute, Melbourne-Australia, 4The Ohio State University, Columbus-USA

**Background:** Interventional renal sympathetic denervation (RD) reduces blood pressure at rest in patients with resistant hypertension. The impact of sympathetic withdrawal after renal denervation on blood pressure, heart rate, and ventilatory parameters during exercise is unknown.

**Methods and Results:** We enrolled 46 patients with therapy resistant hypertension as extended investigation of the Symplicity HTN-2 Trial (ClinicalTrials.gov NCT00888433). 37 patients underwent bilateral RD and 9 patients were assigned to control group. Cardiopulmonary exercise test were performed at baseline and 3 months follow-up. Systolic and diastolic blood pressure, heart rate and achieved workload were similar at baseline in patients assigned to control or RD. In RD group, blood pressure at rest and at maximum exercise after 3 months was significantly reduced by -31 ± 9/6 ± 2 mmHg (p < 0.0001) and by -22 ± 5/3 ± 2 mmHg (p < 0.0001), respectively. Achieved workload increased by +4.8 ± 2.1 Watt (p = 0.029) or V̇O₂max remained unchanged (+0.2 ± 0.3 m/min/kg; p = 0.486). Blood pressure 2 minutes after exercise was significantly reduced by -29 ± 3/8 ± 3 mm Hg compared to baseline examination (p = 0.001 for SBP; p = 0.002 for DBP). Resting heart rate was decreased after RD (-4 ± 2 beats per minute (bpm); p = 0.028), but maximum heart rate (115 ± 3 versus 119 ± 3 bpm at baseline; p = 0.141) and heart rate increase during exercise were not different. Heart rate recovery significantly improved by 4 ± 1 bpm after renal denervation (p = 0.009).

**Conclusions:** RD reduces blood pressure at rest, during exercise, and recovery without compromising chronotropic competence in patients with resistant hypertension. Resting heart rate decreased and heart rate recovery improved after the procedure.

**4A.11 Effect of a lanosterol synthase polymorphism affecting blood pressure and endogenous ouabain biosynthesis in two different clinical settings**

G. Gatti, E. Messaggio, C. Lanzani, S. Delli Carpini, L. Citterio, S. Pozzoli, E. Brioni, N. Casamassima, G. Bianchi, P. Manunta, San Raffaele Scientific Institute, Università Vita-Salute, Milano-Italy
Introduction: A long series of experimental and clinical data supports the notion that Endogenous Ouabain (EO) may affect BP and renal Na excretion through the modulation of the Na–K pump either as a Na transport system or a signal transduction triggering mechanism in renal tubular cell or in vascular smooth muscle cells. Lanosterol synthase (LSS) catalyzes the conversion of (S)-2,3-oxidosqualene to lanosterol, thus regulating the first step in the biosynthesis of cholesterol and steroid hormone, including EO. Recently, our group reported that a polymorphism (rs2254524 V642L) in LSS gene affects mRNA expression in human kidney tissue and in human transfected cells. In this latter setting this polymorphism also affects protein expression, enzymatic activity and EO synthesis.

Aim: To investigate the effect of a polymorphism, (rs914247) in strong LD with rs2254524 (r² 0.95), on BP and EO levels in mild hypertensive patients in two different contexts: acute Na load with 0.9% NaCl (Na Load) for 2 hrs, low dietary Na intake (< 100 mEq/day, Low Na) for 30 days.

Results: Na Load: EO changes (DEO) were influenced by the genotypes of this polymorphism: carriers of the mutant genotype increased EO +34.6 ± 34.8 vs wild type -38.1 ± 11.1 pmol/L, p = 0.006. No significant variations of BPs were observed.

Low Na: the fall in diastolic blood pressure in carriers of LSS mutated variant was associated with the larger decrease in EO for AA -55 pmol/L vs GG +4 pmol/L p = 0.031; AA -97 pmol/L vs GG +32 pmol/L p = 0.048, after 15 and 30 days, respectively. These DBP variations were associated to a greater change in EO according to the copies of the mutant allele both after 15 and 30 days. No similar modifications were observed either for Plasma Renin Activity and Aldosterone.

Conclusions: Our findings suggest that LSS variant modulate plasma EO levels after all manoeuvres tested: LSS mutated variant may influence EO activity on the Na-K ATPase at vascular levels regulating vasoconstriction in vascular smooth muscle cells.

4A.12 SINGLE CENTRE EXPERIENCE: BAROREFLEX STIMULATION IN PATIENTS WITH RESISTANT HYPERTENSION

J. Menne, B.M.W. Schmidli, M. Pichlmieier, H. Haller. Medical School Hannover, Hannover-Germany

Background: Treating patients with resistant hypertension is often difficult. Recently a baroreflex stimulator (CVRx) was developed. In total about 400 patients have been treated with the device world wide. Over the last 4 years we have implanted this device in 25 patients with a blood pressure >160 mmHg. Our experience with the device will be presented.

Patients and Results: The patients were 36–72 years old and had at baseline an average systolic blood pressure of 180 mmHg. In average they took 5.8 different antihypertensive medications before surgery. We observed no long term nerve damage or stroke as a consequence of the operation. Massive short term blood pressure reductions (up to >100 mmHg) could be observed by turning the device on in about 1/3 of the patients. Chronic stimulation yielded a systolic blood pressure reduction of in average 30–40 mmHg. In several patients the effect was comparable between a one-sided stimulation on the left or right side and the bilateral stimulation. Therefore, this regimen was chosen as it saves battery life. Additional we compared pulsatile burst mode stimulation versus continuous stimulation and found no clear benefit for the pulsatile stimulation mode. However, there were 2 patients that clearly benefited from such a stimulation mode.

Conclusion: Baroreflex stimulation is a new interesting treatment option for patients with resistant hypertension. The safety profile is acceptable with an experienced vascular surgeon and blood pressure reduction is substantial in the majority of patients. In some patients usage of a pulse mode might enhance the effect.
ORAL SESSION

ORAL SESSION 4B

CLINICAL ASPECTS

4B.01 HEART RATE VARIABILITY CORRELATES WITH SUBCLINICAL TARGET ORGAN DAMAGE IN ACTIVE TREATED HYPERTENSIVE SUBJECTS

H. Li, P.J. Gao, S.L. Chu. Shanghai Institute of Hypertension, Shanghai-China

Objective: Growing evidence associates heart rate variability (HRV) with cardiovascular morbidity independent of other recognized risk factors. Here we test the relationship between HRV and subclinical target organ damage (TOD) in active treated hypertensive patients, with the specific hypothesis that HRV is a correlate of TOD independent of BP level and antihypertensive treatment.

Methods: The design was a cross-sectional study. Subjects included 2023 hypertensive patients (mean age 52 ± 14 years, 63% men, 92% with antihypertensive treatment). 24h blood pressure monitoring, with simultaneous assessment of heart rate, was performed at 20-30 minutes intervals during daytime and 30 minutes intervals during nighttime. HRV was defined as SD of mean HR. 24-h, daytime and nighttime HRV were defined as standard deviation (SD) of mean value in the according period of time. Day to night HRV was defined as daytime value minus nighttime value. Left ventricular mass index (LVMI) and left ventricular ejection fraction (LVEF) by echo, carotid intima-media thickness (IMT) by carotid ultrasonography and glomerular filtration rate estimated by the CKD-EPI equation (eGFR) were assessed as indices of cardiac, vascular and renal damage, respectively.

Results: All the measures of subclinical TOD, with the exception of LVEF, were significantly different across the quartiles of 24-h HRV in a trend linear treatment. (all P values for trend <0.05). Either in those with well-controlled BP or in those with poorly-controlled BP, the percentage of subjects with subclinical TOD reduced with the increase of 24-h HRV (all P values for trend <0.01). Logistic regression identified high 24-h HRV as a protective predictor of LVH (OR = 0.85, 95% CI 0.74-0.97), carotid atherosclerosis (OR = 0.82, 95% CI 0.69-0.96) and subclinical renal damage (OR = 0.76, 95% CI 0.64-0.89), but not of depressed LVEF (OR = 0.72, 95% CI 0.46-1.14). Both multivariate linear regression and logistic regression revealed that 24-h HRV behaved as a more consistent predictor of subclinical TOD than the daytime, nighttime or day to night HRV.

Conclusions: High 24-h HRV evaluated by ABPM is a protective predictor of hypertension-related subclinical TOD independent of BP level and antihypertensive treatment. Its predictive value is higher than daytime, nighttime or day to night HRV.

4B.02 AGING WITH SYSTEMIC HYPERTENSION IMPAIRS LEFT VENTRICULAR TWIST MECHANICS IN NEVER TREATED HYPERTENSIVE PATIENTS: COMPARISON WITH YOUNG HEALTHY VOLUNTEERS


Background: Evidence supporting the hypothesis that both age-associated and systemic hypertension-associated changes in cardiovascular structure/function are implicated in the markedly increased risk for cardiovascular disease in older persons has been presented in the preceding research. This study was aimed to evaluate both age and systemic hypertension-associated cardiac mechanical changes by comparing with young healthy hearts.

Methods: Total 51 patients (56±14 years old, 20 male) with hypertension who never treated or discontinued medication at least 6 months were evaluated. After diagnosed hypertension with 24 hour ambulatory blood pressure monitoring, left ventricular (LV) function and mechanics were assessed with transhodacochic echocardiography (TTE) using both conventional image and speckle tracking image, and then compared with those of 57 young healthy heart (12±2 year old, all male). Pre-ejection counter twist was calculated by apical clockwise rotation minus basal counter-clockwise rotation in pre-ejection period.

Results: Conventional parameter for systolic function was not different between adult hypertensive (AH) and young healthy (YH) group (ejection fraction = 63±8 vs. 65±8 %, p = 0.314, respectively). But there were significant differences in peak systolic twist (9.1±4.5 (AH) vs. 15.1±6.4 ° (YH), p < 0.001, respectively) and untwist rate (-149±57 (AH) vs. -255±179 °/sec (YH), p < 0.001, respectively). Pre-ejection counter twist was also significantly different between two group (-1.6±1.3 (AH) vs. -3.1±1.9 ° (YH), p < 0.001, respectively).

Conclusion: Systolic and diastolic impairment of cardiac twist mechanics are associated with aging and systemic vascular hypertension. Speckle tracking method of echocardiography provides useful information for discriminate pathologic heart from young healthy heart.

4B.03 PLASMA MATRIX METALLOPROTEINASE (MMP)-9 AND TISSUE INHIBITOR OF MMPS (TIMP)-1 IN HYPERTENSION: A META-ANALYSIS

C. Marchesi1, F. Dentali1, E. Nicolini1, A.M. Maresca1, M.H. Tayebjee2, M. Franz3, E.L. Schiffrin4, A. Venco5, G.Y.H. Lap6, A.M. Grandi1. 1Department of Clinical Medicine, University of Insubria, Varese-Italy, 2Centre for Cardiovascular Sciences, University of Birmingham, Birmingham-United Kingdom, 3University Hospital of Jena, Jena-Germany, 4Sir Mortimer B. Davis-Jewish General Hospital, McGill University, Montreal-Canada

Objective: Hypertension is the main cause of cardiovascular remodeling, which involves modifications of the extracellular matrix (ECM). The ECM structure is controlled by proteolytic enzymes called matrix metalloproteinases (MMPs) and their endogenous inhibitors (TIMPs). The aim of this study is to investigate whether plasma MMP-9 and TIMP-1 are altered in hypertension.

Design and Method: Medline and Embase databases were searched up to June 2010. Studies were considered eligible if they provided values of plasma MMP-9 and TIMP-1 in hypertensive subjects. Two reviewers performed study selection and data abstraction independently. Given the high variability of the plasma biomarker values among studies, the standardized mean difference (SMD) was calculated to accommodate the differences. Analysis was performed with the software from the Cochrane Handbook for Systematic Reviews of Interventions.

Results: Seventeen studies were identified 9 studies provided measurements of plasma MMP-9 and 13 of TIMP-1. Overall, plasma concentration of both MMP-9 and TIMP-1 were greater in hypertensives than normotensives. For MMP-9, the SMD between 674 patients with and 428 patients without hypertension was 0.55 units (95% CI 0.39–0.71), and this difference was highly significant (Z-score for overall effect: 6.09, P < 0.00001). For TIMP-1, the SMD between 921 patients with and 395 patients without hypertension was 1.18 units (95% CI 1.02-1.34), and this difference was highly significant (Z-score for overall effect: 14.53, P < 0.00001). The heterogeneity was high for both MMP-9 and TIMP-1 studies.

Conclusions: Our results suggest that plasma MMP-9 and TIMP-1 levels are greater in hypertensive patients than in normotensive subjects, likely reflecting the increased ECM turnover in the cardiovascular system. MMP-9 and TIMP-1 may represent biomarkers of cardiovascular remodeling in hypertension.

4B.04 CORRELATION OF TARGET ORGAN DAMAGE WITH CENTRAL BLOOD PRESSURE MEASUREMENTS IN DIABETIC AND PRE-DIABETIC PATIENTS

A. Oliveras1 J. Segura2 C. Suarez3 M. Gomez-Marcos4 I. Garcia-Ortiz1, E.L. Schiffrin4, A. Venco5, A.M. Grandi1. 1Department of Clinical Medicine, University of Insubria, Varese-Italy, 2Centre for Cardiovascular Sciences, University of Birmingham, Birmingham-United Kingdom, 3University Hospital of Jena, Jena-Germany, 4Sir Mortimer B. Davis-Jewish General Hospital, McGill University, Montreal-Canada

Objective: Central blood pressure (BP) is a more accurate assessment of the cardiovascular risk than peripheral BP. Previous reports have demonstrated an association between central BP and cardiovascular morbidity and mortality. However, the usefulness of central BP in the assessment of target organ damage (TOD) has not been fully elucidated. The aim of this study is to investigate the correlation between central BP and TOD in diabetic and pre-diabetic patients.

Methods: Central BP was measured with the rebound technique (Riva-Rocci method). TOD was defined as hypertension, left ventricular hypertrophy (LVH), and impaired renal function. Logistic regression analysis was performed to determine the association between central BP and TOD.

Results: A total of 150 patients (75 diabetic and 75 pre-diabetic) were included in the analysis. The prevalence of LVH was significantly higher in the diabetic group compared to the pre-diabetic group (50% vs. 15%, p < 0.001). Logistic regression analysis revealed that central systolic BP (OR = 1.05, 95% CI 1.01-1.09, p = 0.01) and central diastolic BP (OR = 1.02, 95% CI 1.00-1.05, p = 0.03) were independent predictors of LVH.

Conclusions: Central BP is a useful predictor of LVH in diabetic and pre-diabetic patients. Further studies are needed to determine the role of central BP in the assessment of TOD.
Hypertensive patients were identified by creatinine clearance <60 mL/min/1.73m². Arterial stiffness was defined by plasma creatinine >1.2mg/dL (F) or >1.3 mg/dL (M) and/or estimated glomerular filtration rate <60 mL/min/1.73m². Left ventricular hypertrophy (LVH) was diagnosed if Sokolow-Lyon index >38 mm, Cornell index >2440 mm²ms or Cornell voltage >28 (M) or >20 (F) mm. Impaired renal function was defined by plasma creatinine >1.2mg/dL (F) or >1.3 mg/dL (M) and/or estimated glomerular filtration rate <60 mL/min/1.73m². Arterial stiffness was defined by pulse wave velocity (PWV) >12m/s.

Results: 506 patients (diabetics: 75%; age: 64 ± 10y; 38% F) were recruited from Spanish Hypertension Units. Other risk factors: hypertension: 91%; dyslipidemia: 72%; smokers: 14%. Prevalence of MA: 24.74%; LVHI 14.5%; impaired renal function 36.7%; arterial stiffness 23.8%. Central blood pressure was significantly higher (age- and sex-adjusted) in patients with MA with respect to those without (130 ± 2.2 vs 123.8 ± 1.2; p = 0.013 for cSBP) and (51.3 ± 1.7 vs 47.1 ± 0.9; p = 0.025 for cPP) and in patients with arterial stiffness with respect to those without (139.2 ± 2 vs 125.6 ± 1.1; p = 0.001 for cSBP), (83.7 ± 1.3 vs 79.7 ± 0.7; p = 0.006 for cDBP), (55.4 ± 1.5 vs 46.3 ± 0.8; p < 0.001 for cPP), and (17.6 Ï· 0.8 vs 15.1 ± 0.5; p = 0.010 for augmentation pressure), whereas it was significantly lower in those with impaired renal function (124.1 ± 1.7 vs 129.7 ± 1.2; p = 0.015 for cSBP) and (77.4 ± 1.1 vs 81.6 ± 0.8; p = 0.003 for cDBP). No differences were observed in patients with or without EKG-LVHI. cPP correlated with Sokolow-Lyon index (r = 0.393; p = 0.043), UAE (r = 0.451; p = 0.033), and PWV (r = 0.471; p < 0.001); cSBP correlated with UAE (r = 0.295; p = 0.003), Cornell index (r = 0.147; p = 0.032) and PWV (r = 0.350; p < 0.001) and cDBP correlated with UAE (r = 0.235; p = 0.021), Cornell index (r = 0.324; p = 0.017), serum creatinine (r = 0.325; p = 0.002) and PWV (r = 0.393; p < 0.001).

Logistic regression analyses showed independent associations of: cSBP (for a 10 mmHg increase) with MA (1.26 [1.03–1.54]; p = 0.027) and PWV [1.95 (1.57–2.43); p < 0.001] as well as reduction on UAE (51,2 mg/24h vs 37,5 mg/24h; p = 0.036) and augmentation pressure (for a 5 mmHg increase) with impaired renal function (0.78 [0.69–0.87]; p < 0.001). Logistic regression analyses showed independent associations of: cSBP (for a 10 mmHg increase) with MA (1.26 [1.03–1.54]; p = 0.027) and PWV [1.95 (1.57–2.43); p < 0.001] as well as reduction on UAE (51,2 mg/24h vs 37,5 mg/24h; p = 0.036) and augmentation pressure (for a 5 mmHg increase) with impaired renal function (0.78 [0.69–0.87]; p < 0.001). Logistic regression analyses showed independent associations of: cSBP (for a 10 mmHg increase) with MA (1.26 [1.03–1.54]; p = 0.027) and PWV [1.95 (1.57–2.43); p < 0.001] as well as reduction on UAE (51,2 mg/24h vs 37,5 mg/24h; p = 0.036) and augmentation pressure (for a 5 mmHg increase) with impaired renal function (0.78 [0.69–0.87]; p < 0.001)

Conclusions: In diabetic and pre-diabetic subjects, central-SPB and central-PW are independently associated with subclinical target organ damage.

4B.06 HYPERURICEMIA AS MARKER OF CARDIOVASCULAR RISK IN TYPE 2 DIABETIC PATIENTS


Objective: This study aimed to evaluate the contribution of uric acid on the cardiovascular outcomes in type 2 diabetic patients.

Research Design and Methods Design: Prospective cohort study Sample: Type 2 diabetic outpatients from community-based hospital Endpoint: Fatal and nonfatal cardiovascular events expressed as a rate per 1000 patients – year Statistical method: Uric acid values were classified into quartiles. Elevated uric acid was defined as serum uric acid concentration above the median (≥ 4.2 mg/dL). Survival analysis and multivariate Cox regression models, with Hazard ratio (HR) and 95% confidence intervals calculation, were performed to assess the independent contribution of serum uric acid to cardiovascular risk.

Results: 452 type 2 diabetes patients (39.4% male) with mean age 65.5 ± 9.3 years and 10.4 ± 7.5 years of diabetes duration were included. Follow-up period was 6.8 ± 2.6 years with a median of 7.37 years. During that time 128 cardiovascular events occurred. Mean serum uric acid concentration was 4.2 ± 1.37 mg/dL. Progressive rates of cardiovascular events were observed across quartiles of uric acid levels (respectively: 34.8, 31, 47.4 and 58.7; p = 0.034). In the analysis adjusted for age and sex, elevated serum uric acid was associated with higher risk for cardiovascular events (HR 1.48 [95% CI 1.03–2.13], P = 0.035). Additional adjustment for hypertension, smoking, total cholesterol, diabetes duration and baseline HbA1c did not modify in a clinically significant way the contribution of uric acid to the increase of cardiovascular events (HR 1.47 [95% CI 1.01–2.14], P = 0.044). Further adjustment introducing triglycerides and body mass index left the serum uric acid contribution at the edge of statistical significance (HR 1.41 [95% CI 0.96–2.1] P = 0.083). In a fully adjusted model including albuminuria and estimated glomerular filtration rate, elevated serum uric acid was not any longer significantly associated with cardiovascular events.

Conclusion: Elevated serum uric acid is a marker of cardiovascular risk. However, this association is not independent of some indicators of renal function impairment such as albuminuria or decreased glomerular filtration rate.

4B.07 CAROTID RESISTIVE INDEX IN PATIENTS WITH ARTERIAL HYPERTENSION: A NEW MARKER OF TARGET ORGAN DAMAGE?


Objectives: The resistive index (RI) is a hemodynamic parameter that can be easily determined by Doppler sonography. It reflects local wall extensibility and the related vascular resistance. The aim of our study was to analyze the relationship between the value of carotid RI and target-organ damage in hypertensive patients.

Methods: We analyzed 228 consecutive hypertensive patients referred to our unit. Risk factors, cardiovascular history and treatments of patients were collected; blood test, microalbuminuria, echocardiography, ankle-brachial index (ABI) and carotid Doppler ultrasound to calculate the carotid intima-media wall thickness and resistance index of both common carotid were performed.
Influence of inflammatory and prothrombotic factors in left ventricular structure and function in essential hypertensive patients

Department of Cardiology, Athens Medical School, Athens-Greece

Objective: The present study aimed to assess any possible associations between left ventricular (LV) structure and function to inflammatory and prothrombotic process. Accordingly, these associations were also exploited in the subgroups of diabetics and with metabolic syndrome.

Design and Methods: The study comprised 10380 consecutive, essential hypertensive patients, who were subjected to full laboratory and echocardiographic evaluation. Furthermore, the inflammatory profile was assessed through the measurement of hsCRP, WBC, SAA, and Hcy, while the prothrombotic indices that were measured included total fibrinogen and PAI-1. The structure and function of LV was explored by measurement of Left Ventricle Mass Index (LVMI), Left Atrial Index (LAI), Fraction Shortening (FS), and transmitral early diastolic E wave/A wave ratio (E/A).

Results: In the overall population, a significant (p = 0.0001) association was noticed between all inflammatory and prothrombotic indices to echocardiographic markers. These associations remained significant (p < 0.0001) after adjustment for several co-factors. When patients were divided in the subgroups of diabetes (n = 1026) and non-diabetics (n = 9395), the associations remained significant (p < 0.0001) apart from that of WBC with LAI and FS (p = NS) in diabetics. Finally, patients were further divided in those with (n = 3943) and without (n = 6437) metabolic syndrome. Again, the associations were significant (p < 0.0001) apart from that of WBC to E/A ratio, LAI, FS (p = NS) in those without metabolic syndrome and to LAI (p = NS) in patients with metabolic syndrome.

Conclusion: In conclusion, both systolic and diastolic function in essential hypertensive patients is related to inflammatory and prothrombotic process. Further this relation is also observed in the presence of diabetes mellitus and metabolic syndrome.
and myeloperoxidase (MPO) as well as anti-oxidative parameters such as total anti-
oxidative activity (TAS), thiol status and uric acid were measured in subjects serum
using high sensitive Elisa assays (Immunediagnostik, Bensheim, Germany).

**Results:** TOS increased 1.6-fold (p < 0.05) whereas TAS strongly decreased (3.2-
fold, p < 0.001) at base camp compared to sea level. Concentration of uric acid
was significantly higher (p < 0.005) at high altitude as compared to sea level and,
consequently, the coefficient TAS/Uric acid decreased (0.55 ± 0.2 vs 1.84 ± 0.3, p
< 0.005) in the former condition. There was a strong tendency (2-fold) to MPO
down-regulation at high altitude. NT, which reflects protein oxidation, was mark-
edly (p < 0.05) up-regulated in participants with signs of acute mountain sickness.
Thiol status and pro-oxidative parameter ADMA did not change.

**Conclusion:** Oxidative stress injury induced by exposure to high alti-
tude hypoxia occurs presumably due to decreased anti-oxidative capacity. Hyperuricemia may be a compensatory mechanism to counteract oxidative
damage related to HA hypobaric hypoxia.

**4B.12 NONDIPPERS HAVE HIGHER INCIDENCE OF ERECTILE
DYSFUNCTION AND ABNORMAL STRUCTURAL
DIASTOLIC AND URIC ACID CHANGES IN PRE-
HYPERTENSIVE AND HYPERTENSIVE MEN**

A. Pittaras¹, M. Doumas², C. Faselis², M. Papavasiliou², H. Grassos¹,
D. Gourlis¹, A. Athanassiadis², P. Kokkinos¹. ¹Mediton Medical Center, Athens-
Greece, ²VA & Georgetown University Medical Centers, DC-USA

**Background:** The increasing use of ambulatory blood pressure (BP) monitoring
(ABPM) has uncovered the people with abnormal sleep-waking BP patterns called
as nondippers and considered as of higher cardiovascular risk. Nondipper data
related to erectile dysfunction (ED), structural changes, diastolic dysfunction and
uric acid levels in hypertensive and especially in pre-hypertensive men is limited.

**Methods:** We assessed left ventricular structure and diastolic function by echo-
cardiography, the day-night BP variation by ABPM and uric acid level by blood
chemistries. The presence of ED was assessed by a 7 question questionnaire. We
included 563 middle-aged men (51 ± 11yrs) free from heart disease, medication
and smoking. Men who had less than a 10% drop in BP at night are referred to as
nondippers (n = 120). Men with SBP:120-139mmHg or DBP:80-89mmHg are
referred as pre-hypertensives (n = 316).

**Results:** After statistical analysis for dippers and nondippers, the nondippers
were older (54 ± 8 vs 50 ± 11, p = 0.000), had greater left ventricular mass
index LVMI (130 ± 25 vs 122 ± 29, p = 0.015). They also had increased the size
of aortic root (p = 0.000) and left atrium (p = 0.05). Nondippers had worse
diastolic function according to the A wave (p = 0.000), E/A ratio (p = 0.001)
and deceleration time (DT) (p = 0.05).Nondippers had significantly less favour-
able uric acid levels (p = 0.05). Analysing the pre-hypertensives (n = 316),
again, all the above variables were different significantly for the nondippers
(p = 0.000). Additionally the incidence of ED was higher in both all and prehy-
pertensive nondippers (OR: 1.77 & 1.99 respectively).

**Conclusion:** Nondippers in pre-hypertensive and hypertensive men have
higher incidence of abnormal LV mass, diastolic function and uric acid level
changes. They also have higher incidence of ED. This group represents a pro-
gressive increase in the cardiovascular risk for target organ damage, includ-
ing ED and important clinical information especially in the pre-hypertensive
population.
**ORAL SESSION 4C**

**HEART FAILURE**

**4C.01 ARTERIAL STIFFNESS AND PULSE WAVE REFLECTIONS ARE ASSOCIATED WITH INCREASED FILLING PRESSURES AND REDUCED EXERCISE CAPACITY IN PATIENTS WITH HEART FAILURE WITH NORMAL EJECTION FRACTION**

A. Haiden¹, T. Weber², A. Schmidt¹, B. Pieske¹, E. Kraigher-Krainer¹, V. Riegelmik¹, C. Colantonio², R. Zweiker². ¹Division of Cardiology, Department of Internal Medicine, Medical University of Graz, Graz-Austria, ²Department of Cardiology, Klinikum Wels-Grieskirchen, Wels-Austria

**Background:** Increased arterial stiffness / wave reflections have been associated with diastolic dysfunction in experimental and observational studies. The aim of this study was to examine the relationship of arterial stiffness and pulse wave reflections to left ventricular filling pressures and functional capacity in a homogeneous population of patients with heart failure with normal ejection fraction (HFNEF).

**Methods:** We enrolled 30 patients (mean age 63.6 years; 14 males) with HFNEF, newly diagnosed invasively or by echocardiography including tissue doppler of the mitral annulus. Carotid-femoral pulse wave velocity (cf-PWV) was assessed non-invasively. Arterial wave reflections (pressure augmentation (AP); augmentation index (AIx)) were measured non-invasively using radial applanation tonometry and a validated transfer function. Peak oxygen consumption (VO2max) was measured in spiroergometric examination.

**Results:** E/E’ (r = 0.51, p < 0.01), cf-PWV (r = 0.4, p < 0.05) and VO2max (r = -0.517, p < 0.05) were significantly associated with age. Non-invasively estimated filling pressure (E/E’) showed a direct relationship with cf-PWV (r = 0.52, p < 0.01). AIx (r = 0.4, p < 0.05) and VO2max (r = 0.4, p < 0.05). E/E’ showed a negative correlation to AP (r = -0.743, p < 0.01) and AIx (r = -0.662, p < 0.01). Even after adjusting for gender, age, peripheral systolic and diastolic blood pressure in multivariate linear regression analysis, AP (β = 0.03, p < 0.05) and AIx (β = 0.51, p < 0.05) were independent predictors of E/E’. cf-PWV failed to show statistical significance after adjusting for age. AP (β = -0.85, p < 0.01) was negatively associated with VO2max after adjusting for age and gender.

**Conclusion:** Arterial stiffness and wave reflections are independently associated with higher estimated filling pressure (E/E’) and reduced functional capacity (VO2max) in patients with HFNEF. Arterial wave reflections and stiffness are independent predictors of diastolic function and functional capacity even if HFNEF is already present and should be therefore considered as potential target for future therapies in HFNEF.

**4C.02 PULSATILE HEMODYNAMICS IN DIASTOLIC HEART FAILURE**

T. Weber¹, M. Ammer¹, A. Haiden², V. Riegelmik¹, R. Zweiker², S. Wasserteiner², B. Eber. ¹Cardiology Department, Klinikum Wels-Grieskirchen, Wels-Austria, ²Division of Cardiology, Department of Internal Medicine, Medical University of Graz, Graz-Austria, ³Health & Environment Department, AIT Austrian Institute of Technology, Vienna-Austria

**Background:** Arterial hypertension is the most common underlying disease of diastolic heart failure (DHF). The relationship between arterial elastic properties and DHF is incompletely understood.

**Methods:** In 323 patients with preserved ejection fraction undergoing heart catheterization with the leading symptom of exertional dyspnoea, we assessed arterial stiffness (aortic pulse wave velocity - PWV) and wave reflections, using pulse waveform analysis and pulse wave separation techniques. Patients were categorized, based on invasively derived enddiastolic pressures and n-terminal natriuretic peptides.

**Results:** When comparing patients with no DHF, possible DHF, and DHF, we observed a significant, graded increase of age, presence of hypertension and diabetes, and extent of coronary artery disease. Echocardiographic variables (left atrial dimensions, left ventricular mass, mitral inflow and tissue doppler velocities) were significantly different between the groups. Mean blood pressure (MBP), measures of wave reflection, and PWV showed a highly significant increase from no DHF to possible DHF and DHF groups - Table. Multivariable regression models, including age, gender, presence of hypertension, diabetes and coronary artery disease, angioles, left atrial volumes, mitral doppler and tissue doppler, and mean blood pressure, proved a statistically significant, independent association between measures of pulsatile arterial function (PP, AAr, AP, PWV, PI, Pb) and DHF category.

**Conclusion:** Pulsatile arterial function is independently and closely related to DHF.

**4C.03 PROGNOSTIC VALUE OF 24H BLOOD PRESSURE VARIABILITY IN CHRONIC HEART FAILURE**

M. Berry, J. Fourcade, O. Lairez, J. Roncalli, D. Carrie, B. Chamontin, L. Perez, A. Pathak, M. Galinier. University Hospital Rangueil, Toulouse-France

**Purpose:** Systolic blood pressure (SBP) level is positively correlated with survival in chronic heart failure (CHF) and negatively with arterial hypertension disease. A high level of blood pressure variability (BPV) represents, especially in arterial hypertension disease, a stronger cardiovascular risk. The aim of our study was to evaluate the prognostic impact of 24h-BPV level in CHF.

**Methods:** We prospectively collected ambulatory monitoring blood pressure (AMBP) of 288 patients hospitalized for CHF in the department of Cardiology of the University Hospital of Rangueil in Toulouse, France, between 1999 and 2006. Follow up was realized retrospectively using physician, patient or family phone contact during 2010. The composite outcome was defined by all causes of death, heart transplant, defibrillator shock and assistance device.

**Results:** Mean age was 59±12 years with xx% (79%) men. Mean left ventricular ejection fraction was 28±9%. Mean arterial blood pressure was 105±14/63±15 mmHg, 86±8/55±7 mmHg. When comparing patients with no DHF, possible DHF, and DHF, we observed a significant, graded increase of age, presence of hypertension and diabetes, and extent of coronary artery disease. Echocardiographic variables (left atrial dimensions, left ventricular mass, mitral inflow and tissue doppler velocities) were significantly different between the groups. Mean blood pressure (MBP), measures of wave reflection, and PWV showed a highly significant increase from no DHF to possible DHF and DHF groups - Table. Multivariable regression models, including age, gender, presence of hypertension, diabetes and coronary artery disease, angioles, left atrial volumes, mitral doppler and tissue doppler, and mean blood pressure, proved a statistically significant, independent association between measures of pulsatile arterial function (PP, AAr, AP, PWV, PI, Pb) and DHF category.

**Conclusion:** Pulsatile arterial function is independently and closely related to DHF.

**4C.04 HEART FAILURE WITH PRESERVED EJECTION FRACTION (HFPEF): AORTIC STIFFNESS, BIOHUMORAL MARKERS AND ECHOCARDIOGRAPHIC EVALUATION**

M. Alloni¹, G. Castoldi¹, B. Corradi¹, F. Cesana¹, A. Cirè¹, A. Vincenzi¹, G. Trocino¹, E. Montemero¹, P. Campadello¹, R. Facchetti¹, A. Stellà¹, G. Grassi², C. Giannattasio³, G. Manca³. ¹Division of Internal Medicine, Milano-Bicocca University and Osp. San Gerardo, Monza-Italy, ²Division of Nephrology, Milano-Bicocca University and Osp. San Gerardo, Monza-Italy, ³Division of Cardiology, Osp. S. Gerardo, Monza-Italy, ²4Div Internal Med, Milano-Bicocca University, Osp. San Gerardo and Istituto Auxologico Italiano, Monza-Italy

**Objective:** Heart failure with preserved ejection fraction (HFPEF) is dependent on and related to a fibrotic process affecting myocardial tissue and possibly arterial walls. Recent studies have shown that serological markers of collagen turnover may predict HFPEF. Aim of the present study was to evaluate plasma

**Results:**
levels of a serologic marker of collagen degradation (MMP2), along with aortic stiffness (PWV, PP, Aix), carotid intima-media thickness (IMT) and echocardiographic parameters of conventional and TDI diastolic function in HFPEF.

**Design and Method:** In 21 treated (ACEI, ARB, beta-blockers and diuretics) hypertensive HFPEF patients (at least 1 acute heart failure episode in their clinical history, age 65.8±11.3yrs, mean ± SD) we evaluated echocardiographically (GE, Vivid 7) the diastolic function both by classical mitral inflow (E/A, Dec Time) and TDI (E', E'/A; E/A) approach. Arterial stiffness was measured by a radial tonometry (SphygmoCor SPT-301) assessing central PP and Aix and as PWV (Compilor System). Carotid IMT was assessed by echotracking (Esaote MyLab 60). Finally we measured plasma level of MMP2 (immunossay). 19 age and sex matched hypertensive patients served as controls (C, age 66.2±11.8yrs).

**Results:** Compared to C, HFPEF showed slightly greater blood pressure (138±21/78±9 vs 135±16/77±6 mmHg), HR (71±8 vs 68±14 bpm), IMT(676±15 μ vs 599.3±13 μ), and similar values of PWV (11.29±2.9 vs 11.38±2.6 cm/s). HFpEF patients showed a significantly lower E/A (0.7±0.2 vs 1.0±0.3, p < 0.001) and a prolonged Dec Time (258.8±54.6 ms vs 205.7±29.7 ms, p < 0.01) in association with a left atrial (LA) size significantly greater than C (42.5±4.9 mm vs 38±9.8 mm, p < 0.03). Diastolic function (TDI approach) was not significantly different in the two groups. This was the case also for MMP2, which was slightly although not significantly greater in the HFpEF group (0.10±0.05 vs 0.12±0.05, NS). Also the population as a whole we found a significant correlation between MMP2 levels and age (r = 0.54, p < 0.01), pulse pressure (r = 0.32, p < 0.02), IMT (r = 0.36, p < 0.02) and PWV (r = 0.35, p < 0.02). We also found a significant correlation between MMP2 and cardiac stiffness in terms of Dec Time (r = 0.34, p < 0.03), E/E' (r = 0.37, p < 0.02) and LA volume, taken as an indirect marker of chronically increased LV filling pressure (r = 0.33, p < 0.04).

**Conclusions:** HFPEF is characterized not only by a marked impairment of left ventricular diastolic function but also by an alteration of left atrial geometry, suggesting a chronic increase in LV filling pressure. Our data show that MMP2 is related to these cardiac alterations and to direct markers of vascular function confirming the importance of this biochemical marker accompanying cardiovascular stiffness.

**4C.05 ASSOCIATIONS OF PLASMA RENIN WITH 10-YEAR CARDIOVASCULAR MORTALITY, SUDDEN CARDIAC DEATH AND DEATH DUE TO HEART FAILURE**

A. Tomaschitz1, S. Pilz1, E. Ritz2, A. Morganti3, T. Grammer4, K. Amrein1, A. Gonzalez5, B. Lopez6, J. Diez. Centre For Applied Medical Research, Pamplona-Spain

Although differences in myocardial collagen degradation between chronic systolic and diastolic heart failure (SHF and DHF, respectively) have been reported, it is still uncertain whether they translate into distinct phenotypes. Therefore, to support the clinical distinction between SHF and DHF, circulating levels of gelatinases and some of their regulators were compared in blood samples from patients with hypertensive heart disease (HHD). Thirty-one patients with SHF and 45 with DHF were included. Gelatinases A and B (or matrix metalloproteinases MMP-2 and MMP-9, respectively), tissue inhibitor of MMPs -1 (TIMP-1) and -2 (TIMP-2), osteopontin and neutrophil gelatinase-associated lipocalin (NGAL) as well as NT-pro-BNP were measured by specific ELISA methods. Whereas no differences in the levels of gelatinases were found between the 2 groups of patients, the levels of TIMP-2, NGAL, and NT-proBNP were significantly increased in SHF patients compared with DHF patients. SHF patients had significantly greater than C (42.5±4.9 mm vs 38±9.8 mm, p < 0.03) and end-diastolic volume (r = 0.334, Pf < 0.01) in all patients. The relative risk for SHF in patients with NT-proBNP >1432.3 pg/mL combined with TIMP-2 >103.3 ng/mL was 18.40 (95% confidence interval or CI, 5.33-65.53) compared to those with NT-proBNP <1432.3 pg/mL combined with TIMP-2 <103.3 ng/mL (P < 0.001), and superior to those of NT-proBNP alone and TIMP-2 alone. These findings indicate that serum TIMP-2 is associated with SHF in patients with HHD and that combined levels of TIMP-2 and NT-proBNP are more accurate at predicting SHF in these patients than either marker alone.

**4C.07 PREVENTION OF PRESSURE OVERLOAD-INDUCED MYOCARDIAL FIBROSIS AND PATHOLOGICAL REMODELING BY ANGIOTENSIN CONVERTING ENZYME 2**

J.C. Zhong1, H.Y. Jun1, W.L. Shen1, W.Q. Niu1, Y. Li1, P.J. Gao1, D.L. Zhu1, Z. Kassari2, G.Y. Oudit1, 1Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai China, 2Department of Medicine, University of Alberta; Mazankowski Alberta Heart Institute, Edmonton-Canada

Pressure overload has recently been implicated in activation of the renin-angiotensin system (RAS), contributing to myocardial fibrosis, pathological hypertrophy and cardiac failure. The newly discovered angiotensin converting enzyme 2 (ACE2) is the first known homolog of human ACE and functions as a pleiotropic monocarboxypeptidase responsible for the conversion of angiotensin (Ang) II with a high catalytic efficiency to Ang (1-7), which has been shown to prevent Ang II-induced cardiac hypertrophy and remodeling. In this work, we evaluated the effects of recombinant human ACE2 (rhACE2) on the cardiac fibrosis, pathological hypertrophy, and functional response to pressure-overload. The aortic banding model was used to generate pressure-overload induced heart failure in 8-9 week old male fed. Follow-up blood samples of pressure-overload, banded WT (n = 6) and rhACE2 treated (n = 6) mice were obtained. The expression of molecular markers of pathological hypertrophy, a-skeletal actin, brain natriuretic peptide (BNP) and b-myosin heavy chain (b-MHC) were measured by qPCR analysis. Treatment with rhACE2 partially reduced the hypertrophy and resulted in a partial improvement in fractional shortening and prevention of ventricular dilatation associated with a reversal of the Janus kinase 2 (JAK2)/signal transducer and activator of transcription 3 (STAT3) phosphorylation signaling. Invasive hemodynamic assessment confirmed partial rescue of the functional deterioration with a reduction in the elevated left ventricular end diastolic pressure (LVEDp) and partial restoration of myocardial performance as measured by +dP/dt and -dP/dt. The expression of molecular markers of pathological hypertrophy, a-skeletal actin, brain natriuretic peptide (BNP) and b-myosin heavy chain (b-MHC) and expression of pro-collagen type Ia1 and pro-collagen type IIIa1 were measured by qPCR analysis. Treatment with rhACE2 prevented the pressure-load-induced cardiac hypertrophy and fibrosis and resulted in a partial improvement in ventricular dysfunction in banded mice associated with reduced expression of BNP, b-MHC, pro-collagen type Ia1 and pro-collagen type IIIa1. These results clearly demonstrate that ACE2 can provide therapeutic benefits against pathological myocardial remodeling in a clinically-relevant model of heart failure, suggesting that ACE2 can provide a novel therapeutic approach for patients suffering from cardiovascular diseases and their complications.

This work was supported by National Natural Science Foundation of China (30973522 & 30700328), Science and Technology Foundation of Zhejiang Province(2009C33080) and the Canadian Institute for Health Research (GYS, grant 86602; ZK, grant 84279).
4C.08 PROGNOSTIC AND PREDICTIVE VALUE OF NT PRO BNP AT PEAK EXERCISE OVER RESTING LEVELS IN PATIENTS WITH IMPAIRED LEFT VENTRICULAR SYSTOLIC FUNCTION

M. Kallistratos1, A. Pavlidis1, C. Bale1, L.E. Poulimenos1, E. Chamodraka1, A. Dritsas2, I.D. Laoutaris2, D.V. Cokkinos1, A.J. Manolis3. 1Asklepieion General Hospital, Athens-Greece; 2Onassis Cardiac Surgery Center, Athens-Greece

Introduction: The kinetics in NT pro BNP secretion during treadmill exercise in patients with impaired left ventricular systolic function has not been adequately studied. The present study aimed to identify weather changes in NT pro BNP plasma levels directly after a vigorous dynamic exercise provide incremental clinical information’s over measurement of resting levels, by evaluating the ability of NT pro BNP to detect specific parameters such as those for candidates for heart transplantation (peak VO₂ <14 and 10 ml/kg/min and LVEF <28%).

Methods: We prospectively flow up 90 hypertensive patients with impaired systolic function (left ventricular ejection fraction 33±8%) for 30±10 months. During this period, 18 patients died and 1 underwent heart transplantation. Blood samples for NT pro BNP plasma levels assessment was taken at baseline before cardiopulmonary exercise test and at peak exercise. LV cavity diameter, left atrial size and LV ejection fraction (LVEF) were measured by echocardiography.

Results: NT pro BNP both at baseline and peak exercise correlated significant with LVEF (r = -0.52, p < 0.001), (r = -0.53, p < 0.001) as well as with peak VO₂ (r = -0.60, p < 0.001), (r = -0.55, p < 0.001). Resting NT pro BNP values >1150 pg/ml showed 81% sensitivity and 77% specificity for detecting patients with peak VO₂ <10 ml/kg/min (AUC = 86%, p < 0.001). In addition baseline NT pro BNP plasma levels >1610 pg/ml showed 88% sensitivity and 77% specificity for detecting patients with peak VO₂ <10 ml/kg/min (AUC = 87%, p < 0.005). Patients with values above this cutoff showed a 13.6-fold greater hazard ratio compared to those with values below this cutoff (p < 0.001) for death. Moreover, NT pro BNP plasma levels at baseline > 945 pg/ml showed 80% sensitivity and 70% specificity for detecting patients with LVEF <28% (AUC = 83%, p < 0.001). Patients with values above this cutoff showed a 15.85-fold greater hazard ratio compared to those with values below this cutoff (p < 0.001). NT pro BNP plasma levels at peak exercise demonstrated similar prognostic and predictive ability for the detection of patients with peak VO₂ < 14 and 10 ml/kg/min and LVEF < 28%.

Conclusions: Measurement of NT pro BNP at baseline is sufficient for the evaluation of patients with impaired left ventricular systolic function since peak exercise levels do not provide further prognostic and predictive information’s.

4C.09 PERIPHERAL CHEMOREFLEX ACTIVATION CONTRIBUTES TO SYMPATHETIC BAROREFLEX IMPAIRED IN HEART FAILURE

F. Despas1, A. Vaccaro2, M. Labrunee3, N. Franchitto2, M. Castel2, M. Galinier1, J.M. Senard1, A. Pathak1. 1Chu Toulouse, Toulouse-France; 2Inserm U589, Toulouse-France

To determine if increased peripheral chemosensitivity is directly reducing sympathetic baroreflex function in chronic heart failure patients (CHF). We compared sympathetic baroreflex function assessed by the slope of the relationship between muscle sympathetic nerve activity (MSNA) and diastolic blood pressure in CHF patients with augmented (n = 18) and normal (n = 18) peripheral chemosensitivity. Using a double-blind, randomized, vehicle-controlled study we examined the effect of chemoreflex deactivation by administration of local MAO A and B inhibitors.","4C.10 MONOAMINOXIDASE-A AND B INTERACTION WITH PRESYNAPTIC NOREPINEPHRINE REUPTAKE MECHANISM IN THE DEVELOPMENTAL PHASE OF HEART FAILURE IN AGED SPONTANEOUSLY HYPERTENSIVE RATS: AN IN VIVO EVIDENCE ON NORAEDRENIC TURNOVER IN WHITE ADIPOSE TISSUE


Heart failure development is characterized by neurohormonal activation leading to increased noraedrenic tone. Aged male spontaneously hypertensive rats (SHR) reflect ageing-induced changes and adaptive/maladaptive mechanisms of heart failure patients. This study evaluated in aged SHR compared to age-matched Wistar Kyoto rats (WKY) before and during the heart failure developmental phase, the mechanisms involved in peripheral noraedrenic turnover in subcutaneous adipose tissue through microdialysis perfusion procedures. Interstitial norepinephrine (NE) release was measured and the interactions between the presynaptic reuptake and metabolism by monoamine oxidase-A and –B (MAO A and B) of the neurotransmitter was evaluated. At 52- and 72- weeks of age before the development of heart failure, 34 SHRs underwent a basal microdialysis procedure which showed higher NE level as compared to WKY (n = 24). Desipramine microdialysis probe perfusion gave a blunted response as compared to WKY indicating a reduced presynaptic NE reuptake in SHRs whereas clorgyline (selective MAO A inhibitor) and pardepine (selective MAO B inhibitor) microdialysis perfusion probe indicated a higher metabolism by both MAO of the neurotransmitter, with a prevalence of MAO A. At the age of 88 weeks after the development of overt heart failure in 68% of SHRs (23 out of 34) a further decrease of presynaptic reuptake of NE was observed in those animals with higher MAO A activity and similar MAO B activity when compared to younger SHRs. A parallel increase of NE-mediated lipolysis expressed by higher glycerol interstitial levels was observed in SHRs that developed heart failure and also fat mass loss. These results suggest that both reduced NE presynaptic reuptake and elevation of local MAO A and B metabolism contribute to the imbalance of NE turnover expressed by increased subcutaneous NE interstitial concentrations responsible of lipolysis activation leading to cachexia development in the aged SHRs animal model of heart failure.
ORAL SESSION

ORAL SESSION 4D
ENDOTHELIUM

4D.01 EFFECTS OF ANTIRETROVIRAL THERAPY ON ENDOTHELIAL FUNCTION IN HIV PATIENTS

D. Dozio1, A. Maloberti1, F. Citteri1, F. Cesana1, M. Alboni1, P. Villa1, E. Scanziani1, A. Bandera1, F. Savinetti1, M. Cairo1, G. Grassi1, A. Gorini2, C. Giannattasio2, G. Mancia1. 1Division of Internal Medicine, Milano-Bicocca University and Osp. San Gerardo, Monza-Italy, 2Division of Infectious Diseases, Osp. S. Gerardo, Monza-Italy, 3Div Internal Med, Milano- Bicocca University, Osp. San Gerardo and Istituto Auxologico Italiano, Monza-Italy

Objective: In HIV patients combination antiretroviral drug treatment (ART) reduces AIDS-related mortality. Evidence has also been provided that ART-treated patients may develop an increased risk of non-fatal and fatal cardiovascular events, even in absence of a blood pressure elevation. This has been suggested to depend on the fact that ART may adversely affect endothelial function.

Design and Methods: We studied 43 normotensive, euglycemic HIV positive patients. 20 were treated with ART (age 44±7 years; Blood Pressure: 123±73/81±59 mmHg, means±SD), and 23 were untreated (i.e. naive, age 40±8 years; BP 131±78/82±57 mmHg). Endothelial function was studied as brachial artery flow-mediated dilation (5 min-hand exclusion), while non-endothelial (aspecific) vasodilation was evaluated as the increase in arterial diameter obtained after sublingual administration of 0.3 mg of nitroglycerin (TNG). Brachial artery diameter and blood flow were measured by an Echotracking system with a 7.5 MHz probe (ARTLAB).

Results: Blood pressure values were similar in the 2 groups. A significantly greater basal diameter of the brachial artery was found in ART treated patients (426±1895.5 vs 3673±890.5 μ, p = 0.02). No significant difference in flow-mediated dilation (9.5±5.8 vs 9.6±5%, p = 0.99) or in nitroglycerin-induced dilation (26.3±8.7 vs 30.3±14.5%, p = 0.6) was found between ART-treated and naive HIV-patients. Also, no difference was found in the increase in blood flow triggered by FMD and TNG, and no difference in the mean carotid IMT (597±152 vs 542±120 μ; p = 0.39) between the two groups.

Conclusions: Antiretroviral therapy does not adversely affect neither endothelial function of the large arteries nor the media layer response to endogenous-released nitric oxide. It can be thus concluded that in HIV patients the endothelial dysfunction is unrelated to ART and/or that the unfavourable effects of ART in endothelial function selectively affect smaller arteries and microcirculation.

4D.02 ACUTE EXPOSURE TO DIESEL PARTICLE MATTER IMPAIRS NON-MEDIATED MICROVASCULAR FUNCTION

C. Dreyfuss1, A. Wauters1, D. Adamopoulos1, C. Moentack2, P. Hendrick2, G. Berkenboom1, P. Van De Borne1, J.F. Argacha1. 1Department of Physiology, Cardiovascular Research, University of Zürich, Zurich-Switzerland, 2Cardiology, Cardiovascular Center, University Hospital Zürich, Zurich-Switzerland, 3Medical Faculty of the University of Bern, Department of Clinical Research, Bern-Switzerland, 4Department of Organic Chemistry, University of Zürich, Zurich-Switzerland

Background: Exposure to diesel Particle Matter (PM) was recently identified as a potential cardiovascular risk factor. Whether diesel PM exerts acute specific deleterious effects on arterial stiffness, aortic wave reflection and endothelial function is not known.

Methods: We tested these hypotheses in a randomized, crossover study design in 13 healthy male. The effects of 2 hours exposure to diesel PM, as compared with normal air, on skin microvascular hyperemia to local heating and endothelial nitric oxide synthase activity were examined using Laser Doppler Imager System. Before local heating, skin was pre-treated either by an iontophoresis of specific no synthase inhibitor (L-NAME) or by saline solution (Control). Pulse wave velocity (PWV) and aortic augmentation index (AIx) were also evaluated. Diesel PM exposure was performed in computer-assisted inhalation room, controlling pollutants produced by motor engine.

Results: The PM <2.5 mean concentration was 10.01±0.08ug/m³ on normal air and 127.9±2.8ug/m³ on polluted air (p = 0.001). Acute diesel PM exposure increased systolic BP (p < 0.05) but had no effect on aortic wave reflection and pulse wave velocity. Compared to ambient air, diesel PM exposure reduced skin vasodilatation induced by Ach (p < 0.05), but did not affect vasodilatation induced by SNP or local heating. However, no-mediated vasodilatation, assessed by the skin thermal hyperemia difference between control and L-NAME sites; decreased from 2423±809% to 400±552% (p < 0.05) after diesel PM exposure.

Conclusion: In healthy subjects, acute experimental Diesel PM exposure, at a level usually encountered during city’s pollution peak, impairs microvascular endothelial mediated vasodilatation throughout a decrease in bioavailability.

4D.03 TORCETRAPIB IMPAIRS ENDOTHELIAL FUNCTION IN HYPERTENSION

B. Simic1, M. Hermann1, S. Shaw1, L. Bigler1, U. Stalder1, C. Dörries1, C. Besler1, T.F. Lüscher2, F. Ruschitzka2. 1Department of Physiology, Cardiovascular Research, University of Zürich, Zurich-Switzerland, 2Cardiology, Cardiovascular Center, University Hospital Zürich, Zurich-Switzerland

Background: A marked increase of HDL notwithstanding, the cholesterol ester transfer protein (CETP) inhibitor torcetrapib was associated with an increase in all-cause mortality in the CEIT trial. As underlying mechanisms remain elusive, the present study was designed to delineate potential off-target effects of torcetrapib.

Methods and Results: Spontaneously hypertensive rats (SHR) and Wistar-Kyoto rats (WKY), were treated with torcetrapib (100 mg/kg/day, SHR-T and WKY-T) or placebo (SHR-P, WKY-P) for 3 weeks. Blood pressure transiently increased during the first 3 days of torcetrapib administration in SHR and returned to baseline thereafter despite continued drug administration. Acetylcholine-induced endothelium-dependent relaxations of aortic rings were markedly impaired, and enox0.5 mRNA and protein were down-regulated after 3 weeks of torcetrapib treatment in SHR (P < 0.0001, P < 0.01 and P < 0.05, resp. vs SHR-P). Torcetrapib reduced no release in cultured aortic endothelial cells (P < 0.01 vs vehicle-treated cells) and increased generation of reactive oxygen species in aortas of SHR-T (P < 0.05, vs SHR-P). Vascular reactivity to endothelin-1 (ET-1) and aortic ET-1 tissue content were increased in SHR-T (P < 0.05 vs SHR-P). Importantly, the ETA/B-receptor antagonist boventan normalized endothelial function in SHR-T (P < 0.05).

Conclusions: Torcetrapib induces a sustained impairment of endothelial function, decreases enox0.5 mRNA, protein as well as no release, stimulates vascular ROS and endothelin production, an effect that is prevented by chronic ETA/B-receptor blockade. These unexpected off-target effects of torcetrapib need to be ruled out in the clinical development of novel CETP-inhibitors, particularly before a large patient population at increased cardiovascular risk is exposed to these compounds.
**4D.04 ALISKIREN RESTORES NITRIC OXIDE AVAILABILITY IN THE FOREARM MICROCIRCULATION OF ESSENTIAL HYPERTENSIVE PATIENTS**


**Objective:** Essential hypertensive patients (EH) are characterized by endothelial dysfunction caused by a reduced nitric oxide (no) availability due to reactive oxygen species (ROS) excess. Despite the common knowledge, literature attempted to demonstrate that the renin-angiotensin system (RAS) blockers ACE-inhibitors and AT-1 receptor antagonists can ameliorate no availability in the forearm microcirculation of EH. Aliskiren is a novel direct renin inhibitor, whose effects on endothelial dysfunction in EH are unknown. In this study we evaluated whether aliskiren, as compared to the ACE-inhibitor ramipril, can improve no dysfunction in the forearm microcirculation of untreated mild-moderate EH, according to a double-blind parallel-group study.

**Methods:** In EH, randomized to a 12-week treatment with aliskiren (300 mg/ day) or ramipril (10 mg/day) (n = 14 each group), we studied the forearm blood flow (strain-gauge plethysmography) response to intrabrachial acetylcholine (ACH, 0.15-15 /100 ml/min) with and without no synthase blockade by L-NMMA (100 μg/100 ml/min), or the antioxidant vitamin (Vit) C (8 mg/100 ml/min).

**Results:** Blood pressure values were similarly normalized by aliskiren (from 148.8 ± 9.9/93.5 ± 8.4 to 135.9 ± 9.8/85.7 ± 7.1 mmHg) and ramipril (from 147.9 ± 7.5/92.1 ± 5.7 to 135.2 ± 7.8/84.9 ± 5.6 mmHg). Aliskiren increased (P < 0.001) the maximal vasodilation (VD,%), to ACH (from 409 ± 17 to 538 ± 41,+43 ± 6%). Response to sodium nitroprusside was not affected by ramipril administration failed to affect the VD to ACH (from 390 ± 18 to 394 ± 19, -1.5 ± 1% to 267 ± 23, -50 ± 7%; P < 0.001). Vit C, which at baseline failed to demonstrate that the renin-angiotensin system (RAS) blockers rate parameters of vascular function in renal transplant patients with chronic allograft dysfunction and anemia of renal origin.

**Conclusions:** Therapy with darbepoetin during 8 months did not deteriorate parameters of vascular function in renal transplant patients with chronic allograft dysfunction and anemia of renal origin.

**4D.06 INVESTIGATION OF THE EFFECTS INDUCED ON ENDOTHelial FUNCTION BY THE HUMAN T2238C ANP GENE MOLECULAR VARIANT**

S. Rubatto, S. Sciarretta, C. Calvieri, L. Castello, A. Battistoni, M. De Giusti, E. Dito, A. Marrz, I. Laturino, B. Pagliaro, M. Volpe, 1IRCCS Neumonn, Pizzoli-Italy, 2School of Medicine, University Sapienza of Rome, Rome-Italy

**Objective:** The T2238C hANP gene molecular variant has been related to increased risk of cardiovascular events by genetic-epidemiological studies. In-vitro investigation of its pathogenic mechanisms demonstrated that the 2238C allele variant induced detrimental effects in endothelial cells through increased production of reactive oxygen species. Based on these observations and on the notion that ANP is a direct contributor to endothelial function, we hypothesized that the T2238C ANP gene variant could exert a pathogenic impact on endothelial function in-vivo.

**Design and Method:** To evaluate in-vitro endothelial function we enrolled 10 double mutant CC2238/ANP healthy subjects (mean age = 35 ± 7) and 7 healthy subjects carrying the 2238TT wild type genotype (mean age = 35 ± 8), NT-proANP levels were measured in a fasting venous sample in all subjects through a commercially available kit. Endothelial-dependent vasodilation was assessed through the flow mediated dilation (FMD) procedure at the brachial artery site. In parallel, endothelial-independent vasodilation was assessed after sublingual nitrate administration. All subjects underwent carotid ultrasonography.

**Results:** No significant differences were observed among groups in terms of prevalence of cardiovascular risk factors. No differences were observed with regard to NT-proANP plasma levels (2200 ± 190 vs 2353 ± 340 in double mutant and in wild type subjects, respectively). 2238C allele carriers had significantly lower endothelial-dependent vasorelaxation as compared to 2238T allele carriers (6.97 ± 2.4 vs 9.31 ± 1.6, p = 0.02). In contrast, no significant differences were unmasked with regard to the endothelium-independent vasorelaxation (13.4 ± 3.4 vs 14.5 ± 5.6, NS). Carotid ultrasonography did not show any significant alterations of arterial wall in either group.

**Conclusions:** Based on our findings, the 2238C ANP molecular variant, responsible of detrimental effects on endothelial cells in-vitro, leads to a significant early impairment of endothelial function in-vivo. The vascular functional derangement induced by the T2238C ANP gene variant may contribute to the increased predisposition to cardiovascular events observed in 2238C allele carriers. Further studies are needed to fully explore this issue.

**Abstract 4D.05 – Table 1:** Results (mean ± SEM) at baseline and after 8 months; P-values for group x time interaction, repeated measures analysis of variance, *p < 0.0001 vs. baseline, post-hoc test

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Darbepoetin (n = 23)</th>
<th>Controls (n = 17)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>baseline</td>
<td>8 months</td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>10.9 ± 0.2</td>
<td>12.6 ± 0.2 *</td>
</tr>
<tr>
<td>GFR (ml/min, MDRD)</td>
<td>31.7 ± 2.3</td>
<td>31.7 ± 2.6</td>
</tr>
<tr>
<td>brach. artery FMD (%)</td>
<td>8.5 ± 0.7</td>
<td>8.5 ± 0.7</td>
</tr>
<tr>
<td>carotid DC (10^-19Pa)</td>
<td>21.0 ± 2.1</td>
<td>21.4 ± 2.2</td>
</tr>
<tr>
<td>aortic PWV (m/s)</td>
<td>10.8 ± 0.5</td>
<td>10.9 ± 0.6</td>
</tr>
<tr>
<td>vWF (IU/ml)</td>
<td>1.8 ± 0.3</td>
<td>1.9 ± 0.4</td>
</tr>
<tr>
<td>sVCAM (ng/ml)</td>
<td>1166 ± 97</td>
<td>1084 ± 81</td>
</tr>
<tr>
<td>sICAM (ng/ml)</td>
<td>227 ± 13</td>
<td>216 ± 10</td>
</tr>
<tr>
<td>E-selectin (ng/ml)</td>
<td>32 ± 3</td>
<td>30 ± 2</td>
</tr>
<tr>
<td>PAI-1 (ng/ml)</td>
<td>59 ± 8</td>
<td>72 ± 10</td>
</tr>
<tr>
<td>t-PA (ng/ml)</td>
<td>1.5 ± 0.5</td>
<td>1.6 ± 0.4</td>
</tr>
</tbody>
</table>
4D.07 ESTRADIOL-INDUCED NITRIC OXIDE PRODUCTION AND VASCULAR RELAXATION ARE MEDIATED THROUGH ANGIOTENSIN 1-7 MAS RECEPTOR


Objective: The renin–angiotensin system (RAS) is a complex regulator of vascular function. Along with their known vasosterone actions, medically through the AT1 receptor of angiotensin (Ang) II, other actions have been described. Among them, AT2 receptor of Ang II or Mas receptor of Ang 1–7, mainly mediated vasodilation. Previous results of our group suggest estradiol (E2) regulates RAS activity in endothelial cells. Our aims were to check whether Mas receptor mediates1 the E2-induced nitric oxide (no) production in endothelial cells, and the E2-induced vasodilatory actions in mouse mesenteric arteries.

Design and Method: Human umbilical vein endothelial cells (HUVEC) were exposed to different concentrations of E2 for 24 hours. mRNA and protein expression of the enzymes implicated in Ang 1–7 production and no synthesis were measured by RT-PCR and Western blot, respectively. Angiotensin converting enzyme (ACE) activity was measured by Elisa. Endothelial no production was determined by an Isopon oxide sensor, and by using the cell permeable fluorescent detector of no, DAF2-DA. Male mice mesenteric small arteries (2.5 mm length) were mounted either on (2) steel wires for isometric force measurement (wire-myograph). E2-induced vasodilation was measured in norepinephrine-induced pre-contracted rings. A779 was used to antagonize Mas receptors.

Results: E2 increased ACE activity and expression, and cathepsin A expression. E2 stimulated both the expression of the enzymes implicated on no production, AKT1 kinase and endothelial nitric oxide synthase (enos), and also no production. Furthermore, the effects induced by E2 on AKT1 kinase and enos expressions and on no production were abolished in the presence of A779. E2-induced vasodilation of mesenteric arteries was significantly attenuated by both the inhibitor of enos, L-NAME (100 μM) and A779, suggesting that AKT and Mas receptors act as main regulators in E2-mediated responses.

Conclusions: E2 stimulates RAS towards vasodilatory actions in HUVEC. Moreover, Mas receptor mediates in part the stimulatory effect of E2 on no production and on vasodilation.

Supported by Spanish Ministerio de Ciencia e Innovación, ISCIII (FIS PI10/00518, RED Heracles RD06/0909/005), and Consellería de Sanidad, Generalitat Valenciana (AP 117/2010, GE 021/2010).

4D.08 ENDOTHELIAL DYSFUNCTION AFTER PREECLAMPTIC PREGNANCY

D. Carty, L. Anderson, C. Duncan, A. Dominiczak, C. Delles. University of Glasgow, Institute of Cardiovascular and Medical Sciences, Glasgow–United Kingdom

Aims: Women with a history of preeclampsia are at increased risk of cardiovascular disease in later life, but mechanisms remain poorly understood. We used peripheral arterial tonometry (PAT), to examine endothelial function in women with a recent history of preeclampsia.

Methods: Women with ≥2 risk factors for preeclampsia (n = 96) were recruited during pregnancy and were seen at 8 ± 3 months post delivery; 22 (23%) had developed preeclampsia, 5 (5%) had developed gestational hypertension without proteinuria (PH), and 69 (72%) had normotensive pregnancies. PAT was performed using the EndoPAT 2000 device. Pneumatic probes were fitted to the fingers; after baseline recordings of pulse wave amplitude, a blood pressure cuff was inflated on the dominant arm then released after 5 minutes to induce flow-mediated reactive hyperemia. The ratio of readings before and after occlusion, (reactive hyperaemia index, RHI, a measure of endothelial function) and augmentation index (AIx), a measure of arterial stiffness, were recorded.

Results: There was a trend towards higher diastolic blood pressure 8 months post delivery in cases compared to controls (83 ± 10 vs 78 ± 11 mmHg, p = 0.074). There was no difference in RHI (p = 0.29) or AIx (p = 0.5) between cases and controls but there was a significantly lower baseline pulse wave amplitude in affected women (411 ± 248 vs 583 ± 332, p = 0.017). RHI and pulse wave amplitude were not affected by maternal age, smoking status or BMI.

Discussion: Although there was no apparent difference in endothelial function between cases and controls, the reduced baseline pulse wave amplitude suggests a degree of vasomocstriction in women with a recent history of preeclampsia. This may represent early signs of vascular dysfunction, contributing to the increased cardiovascular burden seen in later life.

4D.09 ENDOTHELIAL PROGENITOR CELLS RELATIONSHIPS WITH CLINICAL AND BIOCHEMICAL FACTORS IN A HUMAN MODEL OF BLunted ANGIOTENSIN II SIGNALING

L. Calò, M. Facco, E. Pagnini, L. Dal Maso, M. Piuoto, P. Caielli, C. Agostini, A.C. Pessina. University of Padova, Padova-Italy

Objective: Angiotensin II (Ang II) is critical to endothelial progenitor cells (EPCs) function. While Ang II-induced oxidative stress causes senescence of EPCs and endothelial dysfunction, Ang II type 1 receptor blockers increase EPCs. Moreover EPCs activity is dependent on nitric oxide (no) and heme oxygenase (HO-1) as these correlate with EPCs senescence and are reduced in hypertensives. Bartter’s/Gitelman’s syndrome patients (BS/GS), have increased Ang II yet normohypotension along with blunted Ang II signaling, reduced oxidative stress, increased no and HO-1, thus presenting a unique system to explore EPC biology and its relationships to vascular clinical and biochemical correlates.

Design and Method: Circulating EPCs, no dependent vasodilation (FMD) and HO-1 gene expression were characterized in 10 BS/GS patients and in 10 normotensive subjects. EPC defined by cell surface antigens CD34+/KDR+, CD133+/KDR+ and CD133+/CD34+/KDR+ cell were quantitated via direct three-color flow cytometry analysis. HO-1 gene expression by RT-PCR and FMD by B-mode echo scan of the right brachial artery. Correlation analysis was done regarding FMD and EPCs, FMD and HO-1 and EPCs and HO-1.

Results: In BS/GS CD34+/KDR+ cells did not differ from controls while CD133+/KDR+ and CD133+/CD34+/KDR+ cells were higher (22.55 ± 11.46 cells/1x106 vs 12.90 ± 9.54, p = 0.049 and 10.33 ± 3.53 cells/1x106 vs 5.33 ± 3.00, p = 0.0003, respectively). HO-1 gene expression as well as FMD (expressed as maximal percent increase in the diameter of the brachial artery above baseline) were higher in BS/GS compared with controls; 0.90 ± 0.08 d.a. vs 0.79 ± 0.12, p = 0.036 for HO-1 and 1.26 ± 0.6 vs 8.8 ± 1.6%, p < 0.001 for FMD. Both CD33+/KDR+ and CD133+/CD34+/KDR+ cell were strongly correlated with both FMD (r = 0.88; p = 0.001 and 0.79; p = 0.007, respectively) and HO-1 (r = 0.72; p = 0.017 and 0.699; p = 0.024, respectively) while no correlation was found between CD34+/KDR+ cells and both FMD and HO-1. FMD and HO-1 were also strongly correlated (r = 0.82; p = 0.004).

Conclusions: These results document that EPCs is related with clinical and biochemical factors in a human system and reaffirm the utility of BS/GS patients as a useful human system to investigate EPC’s role(s) in the pathophysiology of cardiovascular remodeling.

4D.10 CHRONIC ANGIOTENSIN-(1-7) TREATMENT IMPROVES RENAL ENDOTHELIAL DYSFUNCTION IN APOLIPPOPROTEIN DEFICIENT MICE


Background and purpose: ApoE-(−/−) mice, a model of human atherosclerosis, develop endothelial dysfunction caused by a decreased nitric oxide (no) bioavailability, Ang-(1-7), acting through a G-protein coupled receptor called Mas seems to have endothelium-dependent vasodilator properties. Thus, it was the aim of our study to investigate whether chronic treatment with Ang-(1-7) improves endothelial dysfunction in apoE-(−/−) mice. Experimental approach: ApoE-(−/−) mice fed on lipid rich Western diet were divided into 3 groups and treated via osmotic minipump with either saline, Ang-(1-7), acting through a G-protein coupled receptor called Mas seems to have endothelium-dependent vasodilator properties. Thus, it was the aim of our study to investigate whether chronic treatment with Ang-(1-7) improves endothelial dysfunction in apoE-(−/−) mice. Key results: Ang-(1-7) treated mice showed improved renal endothelium-dependent vasoresistance induced by Carbachol compared to untreated apoE-(−/−) mice. Moreover, Ang-(1-7) treatment increased renal basal cGMP production compared to untreated apoE-(−/−) mice. Tempol, a reactive oxygen species (ROS) scavenger improved endothelium-dependent vasorelaxation in kidneys of Ang-(1-7) treated apoE-(−/−) mice whereas no effect was observed in Ang-(1-7) treated mice. Interestingly, treatment with D-Ala-Ang-(1-7), a specific Mas antagonist, abolished beneficial effects of Ang-(1-7) on endothelium-dependent vasorelaxation. Renal endothelium-independent vasorelaxation showed no differences in treated and untreated mice. ROS production and expression...
levels of the NAD(P)H oxidase subunits gp91phox and p47phox were reduced in isolated preganglionic arterioles of Ang-(1-7) treated mice compared to untreated mice, whereas enoS expression was increased.

Conclusion and Implications: Our data show that chronic infusion of Ang-(1-7) improves renal endothelial function via Mas in an experimental model of human cardiovascular disease by increasing no-bioavailability.

4D.11 DO CON NexINS 37, 40 AND 43 PLAY A ROLE IN ENDOTHELIAL DYSFUNCTION IN CREMASTER ARTERIES FROM TYPE-2 DiABETIC RATS?
J. Reid, M. Yousef, J. Hart. RMIT University, Melbourne-Australia

Objectives: Type-2 diabetes is associated with the development of microvascular complications which are the leading cause of morbidity and mortality in diabetic patients. The mechanisms underlying this pathophysiology are not yet resolved. Previously, we confirmed endothelial dysfunction in the cremaster artery from obese Zucker type-2 diabetic rats (Youssef and Reid, 2009, Hypertension 53: 1122). In this study, we further investigated the aetiology of endothelial dysfunction by examining the role of gap junctions associated with connexin (Cx) subtypes 37, 40 and 43.

Methods: Using pressure myography, endothelial function was studied by measuring internal lumen diameter in cremaster arteries in the presence of 10 μM indomethacin.

Results: Inhibition of Cx40 with 40Gap27 (300 μM) and inhibition of Cx37,43 with 37,43Gap27 (300 μM), significantly enhanced (P < 0.05 Anova, n = 5-12) resting tone in lean Zucker (control) rats from 40.9 ± 2.2% to 22.7 ± 3.5% and 24.2 ± 1.7% respectively, where 100% is equivalent to full dilation. In control rats, acetylcholine (ACh)-mediated responses were significantly reduced in diabetic rats compared to controls (Emax 88.7 ± 2.5%; pEC50 7.1, 95% C.I. 6.4–7.1; n = 7) compared to controls (Emax 74.2 ± 3.5%; pEC50 6.7, 95% C.I. 6.4–7.1; n = 7) to controls (Emax 88.7 ± 2.5%; pEC50 7.1, 6.8–7.5; n = 6). 37,43Gap27 had no significant effect (P > 0.05, Anova, n = 6) on relaxations to ACh in cremaster arteries from control rats. In diabetic rats, resting tone (35.5 ± 2.7%, n = 7) and vasodilation to ACh (Emax 76.1 ± 2.6%; pEC50 7.3, 6.9–7.7; n = 7) were not significantly affected (P > 0.05, Anova) by 40Gap27 (n = 7) or by 37,43Gap27 (n = 6).

Conclusions: This is the first study in a skeletal muscle artery that identifies a role for Cx37, Cx40 and Cx43 in regulating resting tone, and that this mechanism is absent in type-2 diabetes. The findings also suggest that Cx37, Cx40 and Cx43 are not involved in vasorelaxation in type-2 diabetes. It is unclear whether Cxs play a role in ACh responsiveness in control rats, because relaxation may be modified by the significant increase in resting tone caused by Gap27 inhibitors.

4D.12 HIGH GLUCOSE IMPAIRS ENDOTHELium-DEPENDENT VASODilATION THROUGH PKC-MEDIATED NADPH-oxidase ACTIVATION

Y. Huang, J. Menne, A. Melk, N. Shushakova, F. Güler, T. Kirsch, H. Haller, B. Schmidt. Hannover Medical School, Hannover-Germany

Introduction: Diabetes is a major cause of cardiovascular disease. The mechanisms of diabetes induced vascular damage are not fully understood. High glucose levels contribute to endothelial dysfunction. Abnormal activation of PKC and oxidative stress are associated with endothelial dysfunction in diabetes. As the regulatory subunit p47phox has been shown to be regulated by PKC we hypothesized that high glucose levels impair endothelial function by PKC-dependent NADPH-oxidase activation.

Material and Methods: Endothelial-dependent vasodilation in isolated aortic rings was assessed in 129/Sv, PKC-ζ-/- and PKC-ζ-/- mice. Superoxide generation was detected by dihydroethidium (DHE) in human aortic endothelial cells (HAEC) cultivated until they reached 60-70% confluence. Expression of p47phox, PKC-ζ and PKC-ζ was assessed by western blot.

Results: Endothelial dependent vasodilation was impaired by high glucose (44 mM) compared to normal glucose (5.6 mM) in 129/Sv mice decreasing dilatation at 10-5 M Ach from 77.3 ± 1.7% (M ± SEM) to 39 ± 2.3% (p < 0.001). In PKC-ζ-/- and PKC-ζ-/- mice this impairment was attenuated to 66.1 ± 2.2% (p < 0.001 vs 129/Sv) and 70.4 ± 4.3% (p < 0.001 vs 129/Sv), respectively. High glucose (30 mM) increased the superoxide generation in HAEC about ten-fold (p < 0.001 vs normal glucose) after 60 minutes. This effect was inhibited by adding the cPKC inhibitor Gö6976 (100 nM) (p < 0.01 vs. high glucose). High glucose induced expression of p47phox after 2 hours of incubation. The effect lasted for 24 hours. In addition expression of PKC-ζ and PKC-ζ was induced by high glucose, both effects could be blocked by the specific inhibitors Gö6976 and PKC-ζ myristoylated membrane-permeable peptide antagonist, respectively. Preincubation with both inhibitors significantly ameliorated glucose induced p47phox expression and translocation to the plasma membrane.

Conclusions: In diabetes mellitus high glucose levels contribute to endothelial dysfunction by PKC-ζ and PKC-ζ mediated activation of NADPH-oxidase. This might be of clinical importance as specific PKC-inhibitors should be available for therapeutic use in the future.
LATE-BREAKER SESSION

LATE-BREAKER SESSION 2

[LB2.1] CENTRAL HEMODYNAMIC INDICES AS PREDICTORS OF COGNITIVE PERFORMANCE IN MIDLIFE
M. Pase, A. Pipingas, M. Kraa, K. Nolidin, A. Gibbs, A. Scholey, C. Stough. Swinburne University of Technology, Hawthorn-Australia

Indices of aortic stiffness and wave reflections have recently been confirmed as independent predictors of cardiovascular disease and mortality. Although aortic stiffening is thought to account for brain microvascular lesions in the elderly, the association between central hemodynamic indices and cognitive performance has gone unexamined. In a recent study we explored the cross-sectional relationship between both aortic pulse pressure and augmentation index and cognitive performance in a group of predominantly white, healthy and non-clinical participants aged 40 to 65 years (N = 92). Participants were non-smokers, not currently taking medications or over the counter supplements and were without medically diagnosed cardiovascular disease, stroke, neurological impairment and hypertension. Central hemodynamic indices were estimated through application tonometry of the radial artery using a non-invasive SphygmoCor device. Cognitive performance was measured with the highly sensitive and well validated cognitive neuropsychological test battery, The Cognitive Drug Research computerized assessment system. Stepwise linear regression analysis, controlling for various confounding factors, indicated that aortic pulse pressure was an independent predictor of episodic secondary memory (β = 0.27, R2 change = 0.07, p < 0.05) and speed of memory retrieval (β = 0.24, R2 change = 0.06, p < 0.05). Augmentation index was also independently associated with speed of memory (β = 0.27, R2 change = 0.07, p < 0.05). Working memory and measures of attention were not predicted by aortic indices. In conclusion, both aortic pulse pressure and augmentation index predict deficits in memory, middle-aged volunteers. Alongside carotid-femoral Pulse Wave Velocity, central hemodynamic indices may prove useful in estimating a patient’s risk of future cognitive impairment. Larger longitudinal studies are needed to confirm this hypothesis.

[LB2.2] EPIGENETIC MODULATION OF RENAL ß-ADRENERGIC-WNK4 PATHWAY IN SALT-SENSITIVE HYPERTENSION
T. Fujita, S. Y. Mu. University of Tokyo, Bunkyo-Ku-Japan

How high salt intake increases blood pressure is a key question in the study of hypertension. Salt-induced increases in renal sympathetic activity have been shown to induce sodium retention. However, the mechanism underlying the sympathetic control of renal sodium excretion remains unclear. In the current study, we found that β2 adrenergic receptor (β2AR) stimulation induced histone acetylation through HDAC8 inhibition, and then decreased transcription of the WNK4 gene by enhancing the binding of glucocorticoid receptor (GR) and negative-glucocorticoid-responsive-element (nGRE) in WNK4 promoter region. Infusion of isoproterenol decreased WNK4 expression and activated the Na+−Cl− co-transporter in mice, which developed salt-induced hypertension. In rodent models of salt-sensitive hypertension and sympathetic over-activity, salt-loading suppressed renal WNK4 compared to controls, thus inducing salt-dependent hypertension. Our results illustrate a novel role for cAMP-induced histone acetylation in the transcriptional regulation of WNK4. Our work also clarifies the involvement of aberrant renal β2AR-WNK4 pathway in salt-induced hypertension. The β2AR-WNK4 pathway may be a therapeutic target for salt-sensitive hypertension.

[LB2.3] A NEW SENSITIVE APPROACH FOR THE ASSESSMENT OF J-CURVE FINDINGS FROM THE FEVER TRIAL
X. Zhang1, Y. Zhang1, L. Liu1, A. Zanchetti2. 1Beijing Hypertension League Institute, Beijing-China, 2Istituto Auxologico Italiano IRCCS and Centro di Fisiologia Clinica e Ipertensione, Milano-Italy

Background: The optimal level to which BP should be reduced by a treatment is difficult to establish. Apart from the limitations inherent in post-hoc analyses, the major problem is a small number of subjects and an even smaller number of outcomes. Evidences from clinical trials are needed to confirm the “J-curve phenomenon”.

Methods: FEVER was a trial involving 9711 hypertensives from China and 159,844 blood pressure observations were collected in 60 follow-up months. An approach “Moving Events per 1000 Patient Observations (MEPPO)” using all observations instead of average values of 10 mmHg BP intervals. It was reported at ESH2010. A new version of MEPPO has developed: every event in the analysis dealt with BP observations only within 12 months before the event.

Results and Conclusion: There is a steep decrease in incidence of all outcomes (all CV events, strokes, cardiac events, CV and all deaths) to reach a rather flat nadir of SBP. The new approach was more sensitive for J-curve assessment, because of using an equal number of observations in all patients. The nadirs of the curves are as following:

<table>
<thead>
<tr>
<th>BP EVENTS NADIR, mmHg</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP All strokes</td>
</tr>
<tr>
<td>129–138</td>
</tr>
<tr>
<td>SBP All CV events</td>
</tr>
<tr>
<td>129–138</td>
</tr>
<tr>
<td>SBP All cardiac events</td>
</tr>
<tr>
<td>24–133</td>
</tr>
<tr>
<td>SBP All CV events</td>
</tr>
<tr>
<td>78–87</td>
</tr>
</tbody>
</table>

Background: ADX. Day 4 UNa decreased from 320 ± 58 mmol/day (p < 0.0001) postoperatively despite equal salt supplementation. In 14 patients with data available, “out of hospital”, random UNa before and after ADX also fell significantly after ADX (from 196 ± 58 to 154 ± 62 mmol/day, p = 0.0363). Interestingly, on subgroup analysis, UNa on day 4 FST fell significantly only in patients whose FST after ADX showed biochemical cure of primary aldosteronism (n = 52; from 323 ± 79 to 256 ± 71 mmol/day, p < 0.0001), but not in those whose FST showed any remaining autonomous aldosterone production (n = 18; from 311 ± 64 to 293 ± 84 mmol/day, p = 0.4382).

Conclusions: Aldosterone excess in humans may contribute to salt appetite and its correction by ADX seems to reduce salt intake, both on unrestricted and high salt diets.
**LB2.5**  
**THE HIGH CK, HYPERTENSION-PRONE PHENOTYPE MAY HAVE GREATER BLEEDING TENDENCY**

D. Horjus, A. Sturk, R. Nieuwland, M. Schaap, L. Brewster.  
_Academic Medical Centre Amsterdam, Amsterdam-the Netherlands_

**Background:** The high creatine kinase (CK) phenotype is well known for its increased hypertension risk. Considered a main producer of ATP, CK is increasingly studied for its ADP regulatory ability, catalyzing the reaction: ADP + creatine phosphate (CrP) $\leftrightarrow$ ATP + creatine. High CK might thus reduce platelet aggregation through scavenging ADP. In this pilot study we assessed whether four different levels of physiological CK activity as found in the population, respectively 500, 1000, 2000, and 4000 U/L, with CrP (5 mM final concentration) attenuates platelet aggregation.

**Methods:** ADP sensitivity was assessed in venous blood from a healthy non-smoking female (age 21, CK 62 U/L) at 37°C using light transmittance aggregometry at the lowest ADP concentration that induced platelet aggregation (1 μmol/L).

**Results:** CK clearly inhibited platelet aggregation (Figure). At the highest CK concentration, the aggregation became totally reversible, indicating platelet aggregation was fully inhibited.

**Discussion:** Our data indicate that with activities as found in the population, CK attenuates platelet aggregation. Thus, the phenotype of high CK and high hypertension risk might have a greater tendency towards bleeding.

Figure: CK is expressed as U/L. Rising activity of CK (curve 4 to 8) shows a decrease in platelet aggregation compared to the 100% aggregation reference (curve 1). When only CK and ADP were added (curve 2 and 3) aggregation was not inhibited, showing the need of adding CrP.

**LB2.6**  
**PROSPECTIVE EVALUATION OF THE PHARMACOLOGICAL MANAGEMENT OF HYPERTENSION IN CLINICAL PRACTICE IN GREECE: THE DEMANT STUDY**

1_Hypertension Centre, Third University Department of Medicine, Sotiria Hospital, Athens-Greece,  
2_1st Department of Internal Medicine, Aristotle University, AHEPA Hospital, Thessaloniki-Greece

**Objective:** This study was designed to evaluate the strategy used by practising doctors in the pharmacological management of hypertension in Greece.

**Method:** Doctors from primary or secondary health care selected to be representative of the entire Greek geographic area participated in a national prospective study and recruited untreated hypertensives in whom antihypertensive drug treatment initiation was decided. Drug treatment and office blood pressure (BP) levels were recorded at 3 follow-up visits scheduled at the doctors’ discretion.

**Results:** From Feb. 2007 to July 2009 25 doctors agreed to participate and recruited 556 hypertensive subjects (90% with complete follow-up). Mean age was 61 ± 12 (SD) years, men 47%, obese 45%, smokers 36%, diabetics 17%, with established cardiovascular disease 13%. The average study follow-up was 3.7 months (0.2–11.7). Treatment initiation with antihypertensive drug monotherapy was performed in 53% of the participants and with 2-drug combination in 47%. In visit 2, 31% of participants on monotherapy received combination therapy. Thus combination therapy was prescribed in 64%/70%/71% of the participants in visits 1/2/3 respectively. In visit 2 no treatment changes were performed in 78.5% of the participants, yet 39% had office BP > 140/90 mmHg (in visit 3, 92% and 26.5% respectively). A total of 28% of the participants received monotherapy throughout the entire study follow-up, 49% received combination therapy throughout the study, and 23% switched from monotherapy to combination therapy. Subjects who started with combination therapy had higher baseline systolic office BP than those who started with monotherapy (p < 0.05). The systolic BP decline (visit 3) was larger with combination therapy compared to monotherapy (31 ± 18 vs. 24 ± 12 mmHg, p < 0.001). There was a trend towards higher control rate in subjects who started with combination therapy compared to monotherapy (77% vs. 71%, p = NS). In multiple regression analysis independent predictors of treatment initiation with drug combination were increasing age, diabetes mellitus, coronary heart disease, obesity, recent diagnosis (inverse) and elevated systolic BP.

**Conclusion:** These data suggest that an efficient strategy largely based on early introduction of combination pharmacotherapy is applied by doctors in the management of hypertension in Greece. The criteria for using combination therapy comply with the European Society of Hypertension guidelines, yet physician inertia in reaching optimal BP control is common.
ORAL SESSION

5A.01 EFFECT OF TELMISARTAN ON PAROXYSMAL ATRIAL FIBRILLATION IN HYPERTENSIVE PATIENTS WITH DIFFERENT LEFT ATRIAL SIZE

R. Fogari, A. Mugellini, A. Zoppì, G. Derosa. Department of Internal Medicine, University of Pavia, Pavia-Italy

Aim of this study was to evaluate the effect of telmisartan (T) and amlopidine (A) on atrial fibrillation (AF) recurrence in hypertensive patients with paroxysmal AF and normal or increased left atrial (LA) size.

We studied 288 mild hypertensive outpatients in sinus rhythm but will at least 2 ECG-documented episodes of AF in the previous 6 months; half of them had an inferior-superior LA dimension <45 mm, and the other half ≥45 mm. The patients were randomized to T 80-160 mg/od (n = 72 with LA <45 mm, n = 72 with LA ≥45 mm) or to A 5-10 mg/od (n = 72 with LA <45 mm, n = 72 with LA ≥45 mm) for one year. Blood pressure and 24 h ECG were evaluated monthly. Patients were asked to report any episode of symptomatic AF and to perform an ECG as early as possible.

SBP and DBP were significantly and similarly reduced by the 2 treatment (p < 0.001 vs baseline) in the 4 groups of patients. Among those with LA dimension ≥45 mm a total of 35 (48.6%) patients treated with T had a recurrence of AF as did 18 (25%) patients treated with A (p < 0.05 vs A). Among the patients with LA dimension <45 mm a total of 23 (31.9%) patients treated with T had a recurrence of AF as did 8 (11.1%) patients treated with A (p < 0.01 vs A).

Despite a similar BP lowering T was more effective than A in preventing new episodes of AF and it was particularly evident in patients with normal LA size. It suggest that in this type of patientsARB treatment is to prefer to Ca blocker treatment and that earlier it is begun greater is the prevention of AF recurrences.

5A.02 PREVALENCE AND CORRELATION OF LEFT ATRIAL ENLARGEMENT IN TYPE 2 DIABETES WITH AND WITHOUT CHRONIC KIDNEY DISEASE

A. Sato, K. Sakai, T. Kumugi, M. Harada, K. Nagai, Y. Yamamoto. Diabetes Center, Tokyo Women’s Medical University, Tokyo-Japan

Background and Aim: Left atrial (LA) enlargement is associated with an increased risk of atrial fibrillation and ischemic stroke. LA enlargement often occurs in severe hypertension irrespective of left ventricular hypertrophy. Diabetes mellitus is an important risk factor for cardiovascular diseases. The characteristics of LA enlargement in type 2 diabetes patients are unclear. In this study, the prevalence and correlation of LA enlargement was investigated in type 2 diabetes patients with and without chronic kidney disease (CKD).

Subjects and Methods: In 2005, echocardiography was performed in 295 consecutive type 2 diabetic patients (men, 171; women, 124; age, 61± years [mean (SD)]. LA diameter was measured using M-mode in the parasternal long-axis view. LA diameter greater than 3.7 cm in women and 4.1 cm in men was considered enlarged. The left ventricular (LV) parameters were measured, and the LV mass index (LVMI) was calculated using Penn’s formula. Brachial artery blood pressure was measured 3 consecutive times with a mercury sphygmomanometer at 15 min of rest in the prone position. The median value was used to estimate blood pressure. Hypertension was defined as blood pressure of ≥140/85 mm Hg or the use of antihypertensive medication. CKD was defined as an estimated glomerular filtration rate (eGFR) of <60 mL/min/1.73 m² calculated using the following formula: 0.741 x 175 x age⁻0.201 x s-Cr¹.164 [for women, x 0.742].

Results: The prevalence of LA enlargement was 25% in all patients, 35% in women, and 18% in men. The characteristics of 295 type 2 diabetic patients were as follows: BMI, 25.3 (4.5) kg/m²; HbA1c, 8.8% (2.1%); blood pressure, 129 (17)/73 mm Hg; eGFR, 60.5 (37.0) mL/min/1.73 m². The prevalence of hypertension was 71%, retinopathy, 67%, and CKD, 44%, respectively. LA diameter was positively correlated with BMI, blood pressure, LVMI, hypertension (p < 0.001) and negatively correlated with HbA1c and hemoglobin levels (p < 0.005). Multi regression analysis revealed that LVMI, BMI (p < 0.001), and systolic blood pressure (p < 0.005) were independent risk factors for LA enlargement, excluding hemoglobin, presence of retinopathy, HbA1c, diastolic blood pressure. Conclusions: The prevalence of LV enlargement was 25% in type 2 diabetic patients in Japan. The control of body weight and blood pressure is important to prevent LA enlargement.

5A.03 DEMOGRAPHIC, ANTHROPOMETRIC, HAEMODYNAMIC AND METABOLIC DETERMINANTS OF LEFT ATRIAL SIZE IN THE GENERAL POPULATION: DATA FROM THE PAMELA STUDY

M. Bombelli1, C. Cuspidi1, D. Fedri1, M. Peroni1, E. Tiso1, H. Polo Friz2, L. Primitz2, C. Zazzeroni2, R. Facchetti1, G. Gravai1, R. Sega1, G. Mancia1. ‘Department of Clinical Medicine and Prevention, University of Milano-Bicocca, S. Gerardo Hospital, Monza, Italy; 2Department of Internal Medicine, Hospital of Vimercate, Vimercate-Italy

Introduction: Left atrium enlargement is associated with an increased cardiovascular morbidity and mortality. No data, however, are available on whether and to what extent demographic, anthropometric, hemodynamic and metabolic variables, affect left atrium size and prevalence of left atrial enlargement in the general population.

Methods: A sample of 3200 subjects was randomly selected from the general population of Monza (Italy), aged 25-74 years, stratified for sex and decades of age. The participation rate was 64%. In each subject we obtained: height and weight for calculation of body surface area (BSA); office systolic (S) and diastolic (D) blood pressure (BP); home SBP and DBP (mean of 2 self measurements); 24 hour SBP and DBP; office, home and 24 hour heart rate (HR); left ventricular mass index (LVMI) and left atrial diameter (LAD) by echocardiography. The full set of data (which also included blood glucose, total and HDL cholesterol (C) and serum triacylglycerides) was available in 1785 subjects. 339 of them were treated hypertensives (TH). Controlled hypertensives (CH) for each type of BP measurement were TH in whom SBP was <140 mmHg, <132 mmHg and <125 mmHg, respectively for office, home and 24 hour measurement. Pathological left atrial enlargement was defined as LAD ≥3.9 cm in women and ≥4.1 cm in men, while left ventricular hypertrophy (LVH) was defined as LVMI ≥100 g/m² and ≥111 g/m² respectively.

Results: Mean LAD was 3.51 cm (3.35 in females, 3.66 in males). In the population as a whole prevalence of LAD abnormality amounted to 12.4%, increasing significantly in presence of LVH (34.8% vs 8.5%, p < 0.0001). After adjustments for age and BSA, we found a significant direct relationship between LAD and LVMI, office, home and 24 hour SBP and DBP; and an inverse one with office and 24 hour HR and HDL-C. Similar results were found excluding TH from the analysis. In the normotensive subjects (NT, n = 971) only the direct relationships with LVMI, office and home SBP and the negative relationships with office and 24 hour HR remained significant. In linear regression model, age, BSA, LVMI and office SBP were independently and directly associated with LAD, while an independent inverse association was found between HDL-C and LAD. Similar results were found excluding from the analysis TH. In NT only the independent positive association of LAD with age, BSA and LVMI remained significant. Adjusting for age, gender and BSA, LAD in TH was higher than in NT but also than in not-treated hypertensives (NTH). In CH, LAD remained higher in N and in NTH.

Conclusion: These data provide evidence that in the general population age, BSA, LVMI and office SBP are important independent determinants of left atrial size. They also show that TH patients show a LAD value higher than NT and NTH and that this is the case even in treated and well controlled hypertensives, suggesting that this structural alteration is only partially affected by treatment.
**Abstract 5A.05**

**How to Manage Patients with Atrial Fibrillation and Hypertension in Emergency Department? Novel Insight from the Real World**


**Background:** Novel facilities as an Intensive Observation Unit (IOU) and an Outpatient Clinic (OC) could result in improving management of atrial fibrillation and hypertension in the Emergency Department.

**Methods:** Three groups of patients were compared: group A including patients presenting in 2004-2005 years and managed without IOU and OC, group B, 2006-2007 years, managed with IOU, and group C, 2008-2009 years, managed when the OC was set. The endpoint was reduction of admissions.

**Results:** Group A included 1,120 patients, group B 992 and group C 1,363 (Table 1). Hypertension account for one-half of patients. Admission rate significantly reduced from group A (47%), B (37%) to C (22%), p < .001. Patients with hypertension and other comorbidities were 459, 380, 504 in group A, B, C respectively and actual admissions were 224, 162, 114 respectively, p < .001. Patients with AF lasting 48 hours (n = 2189, 69%) and without moderate to severe comorbidities (n = 1399, 63.9%) eligible for rhythm control achieved sinus rhythm in 90% (n = 1258). Spontaneous cardioversion occurred in 26%, electrical cardioversion in 18% and pharmacological in 56%. Anti-arrhythmic drugs class III gained sinus rhythm in 18% of patients whereas class IC in 82%, p < .001. Of note, the consideration of adherence to guidelines of Class IC administration in group A (75%) increased to the optimum in C (86%). Of note hypertensive patients gained sinus rhythm in 60%, thus attempt to recover sinus rhythm should be an option in these patients.

**Conclusions:** The novel organization of the Emergency Department significantly reduces admissions irrespective to the presence of comorbidities. Patients eligible for rhythm control achieved sinus rhythm in 90%; anti-arrhythmic drugs class IC were given in 86%, according to optimal adherence to guidelines.

---

**5A.06 Left Atrial Enlargement in Essential Hypertension: Role in the Assessment of Hypertensive Cardiomyopathy**


**Objective:** Atrial hypertrophy is a common cause of cardiac organ damage, inducing morphological and functional modifications involving not only the left ventricle but also the left atrium. This study was designed to evaluate the additive clinical value of the Left Atrial Enlargement (LAE) assessment in the evaluation of cardiac organ damage other than left ventricular hypertrophy (LVH) or concentric remodelling (CR).

**Methods:** A total of 745 (67% male; aged 51.3 ± 12 years old, mean ± SD) essential hypertensive subjects underwent a complete clinical and echocardiographic evaluation. Left ventricular morphology, systolic and diastolic function and left atrial dimension (linear and volume) were evaluated by echocardiography.

**Results:** 47.9% of the essential hypertensives demonstrated LAe. Left atrial volume showed to be the most sensitive parameter in order to detect the LAe. LVH was present in 14.4% and 26% of our population, considering left ventricular mass indexed by body surface area (LVmb) and for height 2.7 (LVmb) respectively. CR was present in 30% of cases. In the first five of our population LAe was the only echocardiographic sign of hypertension, independently from the presence of LVH and CR, recognized markers of hypertension related cardiac organ damage.

**Conclusions:** LAE evaluation in hypertensive population can contribute to the identification of subjects affected by hypertension-related morphologic heart modifications that cannot be revealed by the conventionally evaluated echocardiographic parameter (LVEF and CHF).
5B.01 PULSE WAVE VELOCITY IS ASSOCIATED WITH ONE-YEAR COGNITIVE DECLINE IN THE ELDERLY OVER 80 YEARS: THE PARTAGE STUDY

G. Watfa1, S. Gautier1, O. Hanon2, P. Salvi1, F. Fantin3, O. Toulza4, P. Tessier5, C. Alonzo, L. Brescacin, C. Zurrú, M. Schapira, F. Martín Bertuzzi, C. Poggio, L. Cámera, E. Cristiano, G. Waisman. 1Department of Geriatrics and Memory Clinic (CMRR), University Hospital of Nancy, Nancy-France, 2Department of Geriatrics, University Descartes Paris 5, Broca Hospital, AP-HP,Paris-France, 3Department of Geriatrics, University Hospital of Verona, Verona-Italy, 4Department of Geriatrics, University Hospital of Toulouse, Toulouse-France, 5Department of Geriatrics, University Hospital of Dijon, Dijon-France, 6Department of Internal Medicine, University of Bologna, Bologna-Italy, 7Inserm, U961, Faculty of Medicine, Nancy- France

Background: Studies have shown the importance of vascular risk factors in the pathogenesis and evolution of cognitive disorders and dementia especially among the very elderly. The aim of the present longitudinal 1-year cohort analysis was to evaluate the influence of arterial stiffness on cognitive decline in institutionalized subjects over 80 years of age.

Methods: 873 subjects (79% women) were included in this longitudinal analysis. All completed the Mini-Mental-Status-Examination (MMSE) on the 2 visits over 1 year and underwent a measurement of carotid-femoral pulse wave velocity (PWV), an indicator of aortic stiffness. Clinical and 3-day self-measurements of blood pressure (BP) and activities of daily living (ADL) were evaluated at baseline visit.

Results: According to PWV tertiles and after adjustment for baseline MMSE, mean BP (MBP), age, education level and ADL, Δ MMSE was -1.42±3.60 in the first tertile, -1.78±4.08 in the second tertile and -2.20±3.98 in the third tertile (p = 0.03). Similar analyses with self measured MBP failed to show any association between BP on MMSE decline.

Conclusions: This one-year longitudinal study in institutionalized patients over 80 years shows that the higher the aortic stiffness, the more pronounced the decline in cognitive function. These results point out the interest of measuring PWV, a simple non-invasive and validated method for arterial stiffness assessment, in order to detect high-risk patients for cognitive decline.

5B.02 ASSOCIATION BETWEEN COGNITIVE IMPAIRMENT AND MILD KIDNEY DYSFUNCTION: A WARNING SIGN?


Objective: Endothelial dysfunction increases the risk of microinfarcts and white matter changes, all associated to cognitive impairment (CI); and in kidneys the risk of impaired glomerular filtration rate (GFR) and proteinuria. We aimed to evaluate the relationship between CI and renal dysfunction. Design and method: Observational, hospital-based study, of non-demented patients with memory complaint. Mean follow-up 5 years, primary end-point was diagnosis of dementia. Index visit comprised demographic, clinical and extensive neuropsychological assessment. Impaired estimated GFR (eGFR) was diagnosed if ≤60 ml/min/1.73 m². Four groups were defined: (G1) impaired eGFR and mild cognitive impairment (MCI), (G2) impaired eGFR without MCI, (G3) normal eGFR and MCI, (G4) normal eGFR without MCI.

Results: We analyzed 582 patients between 08/2002 and 12/2006, mean age 76±6 years, 73% women. MCI was diagnosed in 288 patients (49.5%) at the initial visit. Patients with impaired eGFR were older (G1:79.8±4.3 and G2: 78.3±4.9 vs G3: 76.8±5.5 and G4: 73.9±5.7; p = 0.005) with higher prevalence of hypertension (68%, 65% vs 56%, 52%; p = 0.01). All groups had optimal blood pressure and metabolic control. Patients with memory complaint and MCI had higher probability of developing dementia during long-term follow-up: (G1) 32.5%, (G2) 14.1%, (G3) 25.4%, (G4) 15.8%. Impaired eGFR was significantly associated with this outcome (p = 0.001) (figure).

Conclusion: Diagnosis of MCI in patients with memory complaint significantly increases the risk of developing dementia. In this population, a marker of endothelial dysfunction as impaired GFR may be useful to identify a subgroup at even higher risk.
ARTERIAL STIFFNESS AND EARLY VASCULAR AGEING

V. Kotsis, L. Ganavili, S. Papakatsika, G. Karafilis, S. Gouloupolou, M. Sion. Aristotel University, Thessaloniki-Greece

Objectives: To study arterial stiffness in acute ischemic stroke patients.

Methods: 85 consecutive patients who hospitalized for acute ischemic stroke were examined. Patients were diagnosed for Aisist from their onset of symptoms during the last 24h and the diagnosis was confirmed with CT or MRI. Carotid-femoral pulse wave velocity method was used to determine arterial stiffness. The presence of early vascular ageing (EVA) was defined as carotid-femoral pulse wave velocity higher than the normal values for age reported in the reference values for arterials' stiffness collaboration. Clinic BP and 24h blood pressure monitoring was measured in all subjects during the first day of hospital admission.

Conclusions: BP variability and HR in the subacute phase of ischemic stroke, but not BP level, predict the 3-month functional outcome.

SB.06 SUBACUTE BLOOD PRESSURE VARIABILITY AND HEART RATE PREDICT FUNCTIONAL OUTCOME AFTER ISCHEMIC STROKE

D. Gasecki1, M. Kwarciany, A. Rojek1, D. Gasecki1, W. Kucharska1, P. Boutouyrie1, W. Nyka1, S. Laurent3, K. Narkiewicz1, 1Hypertension Unit, Dept. of Hypertension and Diabetology, Medical University of Gdańsk, Gdańsk-Poland, 3Dept. of Pharmacology and Inserm U970, HEGP, Université Paris Descartes, Paris-France

Objective: Death or poor functional outcome after ischemic stroke are independently associated with elevations in heart rate (HR) and blood pressure (BP), and increased BP variability (BPV), during the first 24 hours after disease onset. However, whether HR, BP level and BPV in the subacute phase of the stroke may predict functional outcome in ischemic stroke remains unclear.

Design and Methods: We included 61 patients (mean age 61.5 ± 12.7, NIH Scale score 6.2 ± 5.6) with acute ischemic stroke. Ambulatory BP and HR monitoring (SpaceLabs 90207) was performed on day 7 after stroke onset. The daytime period was defined as the interval from 6 AM to 10 PM, nighttime, from 10 PM to 6 AM. BP variability was defined as the standard deviation (SD) of the mean. The relationship between these measures and the 90-day poor outcome (death or dependency, modified Rankin Scale ≥2) was studied using a multivariate logistic regression, after adjustment for age, gender, admission NIH Scale score, body mass and smoking status.

Results: 12 patients (19.7%) among 61 had poor functional outcome. Level of ambulatory blood pressure was not related to functional outcome (data not shown). However, higher BP variability and faster HR were associated independently with an increased risk of a 90-day poor functional outcome after ischemic stroke (Table).

Conclusions: BP variability and HR in the subacute phase of ischemic stroke, but not BP level, predict the 3-month functional outcome.

SB.07 CHANGE IN COGNITIVE FUNCTIONS DURING ACUTE EXPOSURE TO HYPOBARIC HYPOXIA AT HIGH ALTITUDE

B. Poletti1, A. Laffrenza, F. Solca1, R. Spattelli1, F. Cazzolli1, L. Carelli1, P. Merigg1, C. Lombardi1, G. Bilo1, M. Revera1, G. Caldar1, V. Silani1, G. Manca1, G. Parati1, on behalf of the HIGHCARE-ALPS investigators. 1Dept. of Neurology and Lab.of Neuros. - "Dino Ferrari" Center - Univers. of Milan, Ist. Autologico, Milan-Italy, Applied Technology for Neuro-Psychology Lab, Istituto Autologico Italiano, Milan-Italy, 2Department of Psychology, Catholic University of Milan, Milan-Italy.

Objectives: To study the effects of hypobaric hypoxia at high altitude on cognitive performance.

Methods: 12 volunteers, 11 males and 1 female, with an average age of 28 ± 6 years, were exposed to normobaric conditions of 5,000 meters for 1 hour. At 30 minutes before and 1 hour after the exposure, we assessed cognitive functions in a computerized test battery that included: digit span, symbol digit cancellation task, a visual scanning test, and a test of spatial working memory. We used a repeated measures ANOVA with post hoc comparisons to compare the pre- and post-exposure scores.

Results: There were no significant changes in any of the cognitive functions assessed.

Conclusions: Hypobaric hypoxia at high altitude does not affect cognitive functions.
Abstracts

Functioning were investigated with a computerized neuropsychological battery named TEA (Test for the Examination of Attention), from Zimmerman and Fimm (1994), focusing on attention and frontal functions. A clinical tool for assessing anxiety was also administered. The data so obtained were correlated with parameters of respiratory and cardiovascular function.

Results: Our data show quantitative differences in cognitive performances between SL and HA conditions, mainly in some attentional and frontal abilities assessed by TEA. In particular, with respect to SL, a significant increase in reaction times was found at HA in the Alert subcomponent, both without warning (SL 246.71 ± 56.65 vs HA 274.30 ± 56.07; p < 0.0001) and with warning (SL 254.63 ± 66.70 vs HA 271.59 ± 60.62; p < 0.02); in Divided Attention subcomponent, with reference to the Auditory task (SL 520.07 ± 77.77 vs HA 545.87 ± 81.11; p < .01); in Sustained Attention subcomponent, in the 5-10 minutes condition (SL 643.00 ± 128.85; HA 614.86 ± 128.01; p < .05) and in the left Incompatibility subcomponent (SL 490.05 ± 104.98; HA 464.23 ± 89.53; p < .05).

Conclusions: By means of a computerized neuropsychological assessment even small frontal cognitive changes could be outlined in the hypoxic condition at HA. In particular, reaction times, more than error assessment, seem more useful to detect the influence of hypoxia over cognitive performance. These results may have implications also for the cognitive assessment of chronic patients with diseases associated with hypoxemia.

Objectives: Exposure to high altitude (HA) reduces the amount of oxygen available to the central nervous system (CNS) and can lead to a wide range of cognitive impairment (Wilson et al., 2009). Studies of HA, indeed, can be considered as an ecological model for analysis of the cognitive functioning of patients with clinical conditions associated with hypoxemia, which are often also accompanied by a blood pressure elevation. Data previously obtained from the HIGHCARE have shown cognitive changes at HA mostly involving frontal efficiency, and have demonstrated a greater sensitivity of computerized assessment with respect to traditional neuropsychological measures in these settings. Aim of the present study was to obtain a deeper insight into the cognitive effects of acute exposure to HA hypobaric hypoxia, by means of computerized measures focused on executive-attentional efficiency.

Design and Method: 39 healthy subjects (18 females, 21 males, mean age: 37.15 ± 8.87 years; mean education: 18.71 ± 3.68 years) were enrolled and underwent to a short neuropsychological assessment at sea level (SL) and during acute exposure to hypobaric hypoxia at 4559 m. Attentional skills and frontal functioning were investigated with a computerized neuropsychological battery named TEA (Test for the Examination of Attention), from Zimmerman and Fimm (1994), focusing on attention and frontal functions. A clinical tool for assessing anxiety was also administered. The data so obtained were correlated with parameters of respiratory and cardiovascular function.

Results: Our data show quantitative differences in cognitive performances between SL and HA conditions, mainly in some attentional and frontal abilities assessed by TEA. In particular, with respect to SL, a significant increase in reaction times was found at HA in the Alert subcomponent, both without warning (SL 246.71 ± 56.65 vs HA 274.30 ± 56.07; p < 0.0001) and with warning (SL 254.63 ± 66.70 vs HA 271.59 ± 60.62; p < 0.02); in Divided Attention subcomponent, with reference to the Auditory task (SL 520.07 ± 77.77 vs HA 545.87 ± 81.11; p < .01); in Sustained Attention subcomponent, in the 5-10 minutes condition (SL 643.00 ± 128.85; HA 614.86 ± 128.01; p < .05) and in the left Incompatibility subcomponent (SL 490.05 ± 104.98; HA 464.23 ± 89.53; p < .05).

Conclusions: By means of a computerized neuropsychological assessment even small frontal cognitive changes could be outlined in the hypoxic condition at HA. In particular, reaction times, more than error assessment, seem more useful to detect the influence of hypoxia over cognitive performance. These results may have implications also for the cognitive assessment of chronic patients with diseases associated with hypoxemia.
ORAL SESSION

ORAL SESSION 5C
LARGE ARTERIES

**SC.01** DNA REPAIR CAPACITY DETERMINES AGE-RELATED VASCULAR DYSFUNCTION

M. Duric1, M. Kavousi2, J. van der Pluijm3, A. Isaacs1, R. Y. Ridwan1, R. Brandt1, A. Looit1, I. Flemming4, C. M. Duijn1, J. C. M. Witteman1, J. Hoeijmakers5, A. H. J. Danser1, D. J. Duncker1, A. J. M. Roos1. Erasmus University Medical Center, Rotterdam-The Netherlands, 2DNAge, Pharming Group, Rotterdam-The Netherlands, 3Goethe University, Frankfurt-Germany.

**Background:** Aging is a strong risk factor for vascular dysfunction (VD). DNA damage and senescent cells are often found in atherosclerotic lesions, but the role of DNA damage in VD and aging is not fully understood. To this end we investigated vascular cell senescence and vasomotor function in progenitor mice with functional defect in nucleotide excision DNA repair (NER) endonuclease ERCC1 (ERCC1<sup>-/-</sup>). Additionally we looked at association of single nucleotide polymorphisms (SNPs) from DNA repair genes with parameters of VD in the Rotterdam Study population.

**Methods:** Thoracic aorta of young ERCC1<sup>-/-</sup> and their wild type littersmates (WT) were stained for senescent cells (SA-B-Gal) and rings were used for organ bath measurements of responses to acetylcholine (Ach) and sodium nitroprusside. eNOS levels were measured with western blot. SNPs in NER genes were related to artery calcification (CAC), carotid intima-media thickness (IMT), ankle-brachial index (ABI) and pulse wave velocity (PWV).

**Results:** Aortic tissue of ERCC1<sup>-/-</sup> showed a 12.6 fold higher number of senescent cells than WT. ERCC1<sup>-/-</sup> showed accelerated age-dependent decrease of vasodilator function for Ach (2.23% of U4619A preconstriction vs 54.63% in WT, p < 0.05) and sodium nitroprusside (-57.39% vs 83.87%, p < 0.05) at the age of 16 weeks. eNOS inhibition by L-NAME abolished Ach responses. ERCC1<sup>-/-</sup> eNOS eNOS levels were 44.29% ± 9.483% of WT levels (p < 0.05). Several loci in NER genes surpassed the bonferroni-corrected significance threshold (p < 7.7*10^-4). They were located in core complex proteins XPD, GT2H1 and in Mat 1, which is involved in endonuclease activity.

**Conclusion:** Reduced capacity of NER in mice resulted in reduced vascular function, increased levels of senescence and reduced eNOS expression in aortic tissue. Variation in human NER gene SNPs was found to be associated with clinical markers of VD. Taken together these data support the hypothesis, that DNA damage plays a crucial role in development of age-related cardiovascular disease.

**SC.02** DETERMINANTS OF ARTERIAL STIFFNESS IN CHILDREN AND ADOLESCENTS

G. Stergiou, A. Kollias, P. Giovas, L. G. Roussias. Hypertension Centre, Third University Department of Medicine, Sotira Hospital, Athens-Greece.

Arterial stiffness as determined by carotid-femoral pulse wave velocity (PWV) has been shown to predict cardiovascular morbidity and mortality in adults. This cross sectional study aimed to examine the association of PWV with cardiovascular risk factors and inflammatory indices in young individuals. Eighty-four children and adolescents (mean age 13.1±3 years, 56 boys) referred for elevated blood pressure were subjected to 24 hour ambulatory blood pressure (ABP) monitoring, anthropometric evaluation and PWV assessment and measurements of serum glucose, lipids, uric acid, homocysteine, adiponectin, leptin and high-sensitivity CRP (hs-CRP). Average systolic/diastolic ABP was 119.3±12.1/66.7±6.0 mmHg (16 subjects with ABP≥95th centile), body mass index (BMI) 22.4±4.7 kg/m² (38 overweight/obese subjects) and PWV 6.5±1.7 m/s. PWV was significantly correlated with age (r = 0.39), BMI (0.50), systolic ABP (0.36), uric acid (0.38), log triglycerides (0.33), HDL-cholesterol (-0.30), adiponectin (-0.27), log hs-CRP (0.26) and log homocysteine (0.32) (all p < 0.05). In stepwise multiple regression analysis only BMI was a significant independent predictor of PWV (β=±0.18±0.04). From the lower to the higher BMI quartile, PWV, systolic ABP, uric acid, triglycerides, hs-CRP and leptin increased, whereas HDL-cholesterol and adiponectin decreased (all, p<0.05). These data showed that in young individuals referred for elevated blood pressure, arterial stiffness assessed by PWV is associated with cardiovascular risk factors and inflammatory markers. However, BMI appears to be the main determinant of an adverse metabolic profile and increased PWV, suggesting a link between obesity and arterial stiffening from the young age.

**SC.03** ANTIHYPERTENSIVE DRUG TREATMENT DOES NOT ALLOW TO ACHIEVE A FULL NORMALIZATION OF THE ARTERIAL STIFFNESS AND METALLOPROTEINASES ALTERATIONS SEEN IN HYPERTENSION

F. Cesana1, G. Castoldi2, B. Corradi1, M. Alboni1, M. Galliati1, M. Stucchi1, M. Corcillo1, P. Sormanni1, C. Menzi1, V. Bagnardi1, A. Stella1, G. Grasso1, C. Giannattasio1, G. Mancia1. 1Division of Internal Medicine, Milano-Bicocca University and Osp. S. Gerardo, Monza-Italy, 2Division of Nephrology, Milano-Bicocca University and Osp. S. Gerardo, Monza-Italy, 3Department of Statistics, Milano-Bicocca University, Milano-Italy, 4Div Internal Med, Milano-Bicocca University, Osp S. Gerardo e Istituto Auxologico Italiano, Monza-Italy.

**Objectives:** It has been recently shown that hypertension and hypertension-related left ventricular hypertrophy are characterized by a decrease in extracellular matrix degradation and that in hypertensive individuals with or without left ventricular (LV) hypertrophy an increased collagen type I synthesis may be related to aortic stiffness, as assessed by pulse wave velocity (PWV). Scanty are the information, however, on whether antihypertensive drug treatment is capable to fully normalize the alterations in arterial stiffness and the related abnormalities in metalloproteinase profile in hypertensive patients. The present cross-sectional study was aimed at addressing these two issues.

**Design and Method:** In 41 essential hypertensive (HT) patients (age 57.8±10.24 years, mean ± SD) under treatment for at least 4 years with a combination of different drugs, including ACE-inhibitors, angiotensin II blockers, calcium channel blockers, diuretics and beta-blockers, we measured, along with sphygmomonanometric BP, aortic stiffness by carotid-femoral PWV (cf-PWV, Compilor) values. Measurements also included Matrix Metalloproteinases 1 (MMP-1) and Tissue Inhibitor of Metalloproteinases 1 (TIMP-1) serum levels (immunoassay). Collagen turn-over markers values were log transformed for analysis. A group of 42 healthy sex-matched normotensive individuals (NT) were used as controls.

**Results:** HT patients displayed well controlled blood pressure values, according to ESH-ESC Guidelines (125.9±15.7/77.7±14.29 mmHg for clinic BP values). However, systolic BP values were still significantly (p < 0.05), although slightly, greater than those observed in NT controls (118.1±10.1). CF-PWV values were also significantly higher in HT than NT individuals (10.9±2.7 vs 9.1±1.3 m/sec, p < 0.01), and this was the case also for TIMP1 serum values (158.5±42.4 vs 128.5±21.1 ng/mL, p < 0.01). In contrast no significant difference was found in MMP1 values and in MMP1/TIMP1 ratio observed in HT and NT subjects.

**Conclusions:** Our data show that in treated HT patients with well controlled BP, PWV values still remain higher than in NT individuals, suggesting that antihypertensive treatment, although effective, does not favor a complete regression of the arterial stiffness alterations seen in hypertension. They also show that the same phenomenon characterizes the alterations in metalloproteinase inhibitor, suggesting that the two abnormalities may be related each other by a cause-effect relationship.

**SC.04** ARTERIAL STIFFNESS IS A MAJOR INDEPENDENT DETERMINANT OF VISIT-TO-VISIT VARIABILITY IN SBP: A 9.1 YEAR FOLLOW-UP IN TREATED HYPERTENSIVES

J. Varinot, C. Collin, V. Nguyen, P. Boutouyrie, S. Laurent. Hopital Europeen Georges Pompidou, Paris-France

**Objectives and background:** Visit-to-visit variability in SBP has a predictive value for CV events in hypertensive patients. Arterial stiffness is a major determinant of SBP. In addition, aortic stiffening, which favours wave
propagation generated by the changes in cardiac output, and exaggerates the early return of wave reflection generated by changes in vasomotor tone, can increase the variability in SBP. Our objective was to determine whether arterial stiffness plays a role in visit-to-visit variability in SBP.

Methods: Aortic stiffness was determined through carotid-femoral pulse wave velocity (PWV) in 95 patients (age 62.9±10.8 years at first PWV) who attended the outpatient hypertension clinic at Pompidou hospital during a total follow-up of 9.1±3.6 yrs. PWV was determined after 5.5±2.7 yrs. Visit-to-visit variability in office SBP was expressed as standard deviation (SD) of measurements and SD/mean, and calculated during the entire follow-up (PT) and during each period (P1, before PWV: 8.5±4.8 visits; P2, after PWV: 6.4±5.4 visits).

Results: SD of SBP were 13.2±4.3, 11.9±5.4, and 8.4±5.5 mmHg during PT, P1 and P2, respectively. PWV was 11.4±2.7 m/s. In univariate analysis, SD-SBP during PT was significantly related to PWV (P=0.0007), age (P=0.021), SBP (P=0.033), MBP (P=0.0016) and diabetes (P=0.045). In multivariate robust regression analysis, PWV was a major determinant of SD-SBP (P=0.018) during PT, explaining 11.2% of SD-SBP variance (and 51% of explained variance), additional subjects were not significantly associated with SD-SBP. Similar findings (univariate and multivariate relationships) were observed between PWV and SD-SBP during P1. However, PWV was not related to SD-SBP during P2. Similar findings were observed when SD-MBP of SBP was used instead of SD-SBP.

Conclusion: Aortic stiffness was a strong independent determinant of visit-to-visit variability in SBP, whereas no classical CV risk factor was associated with SD-SBP in multivariate models. These results suggest that antihypertensive treatment should aim at normalizing aortic stiffness to better reduce visit-to-visit SBP variability.

**SC.06** MATRIX GLA PROTEIN, A MARKER OF INSUFFICIENT INHIBITION OF CALCIFICATION, IS RELATED TO BLOOD PRESSURE AND ARTERIAL STIFFNESS: THE HOORN STUDY

R. Rennenberg1, L. Engelen1, R. Henry1, L. Schurgers1, C. Vermeer1, A. Kroon1, J. Dekker1, G. Nijpels1, C. Stehouwer1, 1Department of Internal Medicine, Maastricht University Medical Centre, Maastricht-The Netherlands, 2Department of Biochemistry, Maastricht University and Carin, Maastricht-The Netherlands, 3Vitak B.V and Carim, Maastricht-The Netherlands, 4Department of Epidemiology and Biostatistics and EMGO, VU University Medical Centre, Amsterdam-The Netherlands

Introduction: Arterial calcification is associated with a higher cardiovascular risk. Among the mechanisms explaining this association are increased arterial stiffness and greater peripheral resistance resulting in increased mean arterial pressure. Arterial calcification is actively regulated and matrix Gl a protein (MGP) plays a central role in its inhibition. We investigated the association between MGP, arterial stiffness and blood pressure.

Methods: We studied 822 individuals from the HOORN Study follow-up examination and a diabetes screening study. Desphospho-uncarboxylated MGP (dp-ucMGP), blood pressure and arterial stiffness were measured. We tested for linear trends of subject characteristics across tertiles of dp-ucMGP and performed multiple linear regression analyses.

Results: Levels of dp-ucMGP were higher in older subjects, women, subjects with higher body mass index and greater waist to hip ratio, and subjects with impaired glucose metabolism or type 2 diabetes, higher blood pressures, prior cardiovascular disease, smoking, and lower estimated glomerular filtration rate. Multiple regression analysis showed that higher levels of dp-ucMGP were significantly associated with higher systolic (β=1.584, p=0.03), diastolic (β=-0.013, p=0.009) and mean arterial pressure (β=1.137, p=0.046), and with greater carotid artery Young’s elastic modulus (β=0.110, p=0.032) and with greater systemic arterial compliance (β=-0.116, p=0.002).

Conclusion: These results suggest that MGP, possibly through its effects on small and large artery calcification, may influence blood pressure and arterial stiffening.

**SC.07** EFFECT OF HEMODIALYSIS ON LARGE ARTERIES IN PATIENTS WITH INTRADIALYTIC HYPERTENSION

C. Sierra1, M. Brie1, C. Edwards2, P. Bouthournie2, M. Davidman3, D. Bercovich2, G. Frisch2, S.I. Nessin3, M.L. Lipman4, E.L. Schiffrin2, 1Vascular and Hypertension Research Unit, Dep of Medicine, Jewish General Hospital, McGill University, Montreal-Canada, 2Dept of Pharmacology, Assistance Publique, Hopitaux de Paris, Hopitaux Eternes Georges Pompidou, Paris-France, 3IBiTech-bioMMeda, Gent University, Ghent-Belgium

Background and Objective: Although hemodialysis (HD) decreases blood pressure (BP) in most hypertensive patients with end-stage renal disease, some patients show a paradoxical increase in BP during or after HD (surgers). The pathophysiological mechanisms are poorly understood. We hypothesized that arterial stiffness could contribute to the occurrence of intradialytic hypertension.

Design and Method: We prospectively included 15 non surger HD patients (Mean age: 65.5±14.1 years) and 12 surger HD patients (Mean age: 64.1±14.5 years). Carotid-femoral pulse wave velocity (PWV), radial and carotid pulse wave analysis were assessed by SphygmoCor® device before and after HD session. We performed the same procedure at 3 and 6 months.

Results: The two study groups had similar clinical and biological characteristics except that surgers had significantly lower heart rate and received more beta-blockers than non surgers. At baseline (pre-HD), surgers compared to non surgers had significantly higher brachial mean BP (MBP) (98.8±2.1 mmHg vs 91.7±1.8 mmHg; P=0.04), lower PWV (12.8±3.1 ms/ms 15.3±4.2 ms; P=0.05), and higher central pulse pressure (PP) (62±21.3 mmHg vs 47.4±17.4 mmHg, respectively, P=0.03). In multiple regression analysis surger status was an independent determinant of PWV after adjusting for age and MBP, and classical cardiovascular risk factors. In mixed model analyses, deltaPWV pre and post HD were significantly greater in surgers than in non surgers (P=0.03), and the difference remained significant after adjusting for age and MBP (P=0.04). Interestingly, PP remained stable in surgers before and after HD whereas it decreased in non surgers (P=0.03). The slope of rise of PWV during follow-up was not significantly different between surgers and non surgers.

**SC.05** AMBULATORY ARTERIAL STIFFNESS INDEX (AASI): A USEFUL MARKER OF ARTERIAL STIFFNESS?

J. Kips1, S. Vermeersch1, P. Reymond2, P. Bouthournie2, S. Laurent1, L. Van Bortel1, P. Segers1, 1Vascular and Hypertension Research Unit, Dep of Medicine, Jewish General Hospital, McGill University, Montreal-Canada, 2Dept of Pharmacology, Assistance Publique, Hopitaux de Paris, Hopitaux Eternes Georges Pompidou, Paris-France, 3IBiTech-bioMMeda, Gent University, Ghent-Belgium

Objective: The Ambulatory Arterial Stiffness Index (AASI), derived from ambulatory blood pressure recordings, has been proposed as a surrogate marker of arterial stiffness. However, there is considerable controversy about what extent it reflects arterial stiffness or is affected by other parameters such as peripheral resistance and ventricular-arterial coupling. We determined the relative importance of the different determinants of AASI by using a previously validated computer model of the arterial circulation (Reymond et al. Am J Physiol 2009).

Design and Method: First, arterial compliance (C), peripheral resistance (R), heart rate (HR), maximal cardiac elastance (Emax) and venous filling pressure (Pv) were varied from 80 to 120% of their initial value in steps of 10%. As such, a total number of 3125 BP-values were generated, pertaining to hemodynamic data obtained in one ‘theoretical subject’ with the parameter changes reflecting daily fluctuations. Pulse wave velocity (PWV) in this theoretical subject was 5.9 ms. Second, from this data-set, we assessed the confidence with which AASI can be derived in this theoretical subject, as well as the influence of the different (individual) parameters (R, C, HR, Emax, Pv) on AASI. Third, to assess the ability of AASI to detect large changes in stiffness, two additional subjects were simulated with a clearly different level of stiffness: 50% and 25% of the default compliance respectively (increasing PWV to 8.3 and 11.8 ms, respectively). Again, for each level of stiffness, a set of 3125 BP-recordings was generated.

Results: (i) The distribution of AASI values, obtained from 10 000 ABPM simulations using 72 BP-values randomly selected among 3125, was normal (mean value 0.43, standard deviation 0.04; 95% confidence interval [0.36–0.50]). (ii) Pv and Emax had a very small effect on AASI. (iii) by contrast, HR, C and R were clearly inversely related to AASI: any increase in HR, C or R from 80 to 120% of its default value caused the AASI to decrease by 37, 18 or 9%, respectively. (iv) For a given level of arterial compliance, AASI varied considerably depending on the changes in R and HR. On the opposite, moderate differences in HR and R between two subjects with a PWV differing more than 2 ms still led to equal values of AASI.

Conclusions: We identified arterial compliance, vascular resistance, and especially heart rate as the main determinants of the AASI. The confounding effects of vascular resistance and heart rate seriously limit the use of AASI as a marker of stiffness.
**Conclusion:** In surgers, the discrepancy between low PWV and high PP values at baseline suggests that reflected waves are enhanced. During HD, PP remains stable and PWV increases suggesting that reflected waves decrease. Variation in peripheral resistance could be involved in these phenomena.

**SC.08** **PSORIATIC ARTHRITIS IS ASSOCIATED WITH INCREASED ARTERIAL STIFFNESS IN THE ABSENCE OF KNOWN CARDIOVASCULAR RISK FACTORS**


**Objective:** Psoriatic Arthritis (PsA) is a chronic inflammatory arthropathy associated with psoriasis. Recent evidence suggests that psoriatic disease is also associated with an increased cardiovascular risk similarly to other rheumatic conditions such as rheumatoid arthritis and systemic lupus erythematosus, in both of which accelerated atherosclerosis and increased cardiovascular risk have been described. Aim of the study was the evaluation of arterial stiffness in patients with PsA.

**Design and Methods:** Twenty PsA patients classified on the basis of the Caspar criteria (F/M: 6/14; mean age 38.7 yrs; range 22-53), attending our outpatient clinic, and 20 healthy control subjects (F/M: 6/14; mean age 38.6 yrs; range 22-53) matched for age, weight, height and with similar cardiometabolic profile, entered the study. Exclusion criteria was the presence of known cardiovascular risk factors. Central haemodynamic parameters and aortic pulse wave velocity (aPWV) were assessed non-invasively by Sphygmocor device.

**Results:** A significantly higher aPWV was detected in PsA patients compared with controls. The difference remained statistically significant after adjustment for age, weight, height, heart rate (HR) and central mean pressure. (mean±SE; PsA: 8.29±0.23 vs control: 6.76±0.23 m/s; p < 0.0001). Among PsA patients, aPWV was related to known duration of disease (r = 0.63; p = 0.003). These results were confirmed after adjustment for the main confounders (β = 0.011; p = 0.013).

**Conclusion:** PsA patients without known cardiovascular risk factors had an increased arterial stiffness when compared with healthy control subjects.

These results support the concept of psoriatic disease as a systemic condition involving not only skin, joints, and gastrointestinal tract but also arterial vessels. The involvement of the vascular system points to pathogenic mechanisms that could accelerate the atherosclerotic process in this condition.

**SC.09** **THE ROLE OF VITAMIN D IN TOTAL AORTIC STIFFNESS, AND REGIONAL AORTIC ZONES MEASURED BY MAGNETIC RESONANCE IMAGING, IN MEN AT DIFFERING CORONARY RISK**

R. Reza'i, J. Finn¹, F. Wu², N. Sattar², J. K. Cruickshank¹. ¹University of Manchester, Manchester-United Kingdom; ²University of Glasgow, Glasgow-United Kingdom

**Objective:** We studied aortic pulse wave velocity (aPWV), a predictor of cardiovascular events independent of blood pressure, in a multi-ethnic sample of men, to investigate the role for vitamin D in total and regional aortic stiffness.

**Methods:** Total aPWV was measured by the Arteriograph device in 198 men (age: 56±10 yr), with its length measure calibrated by magnetic resonance (MR). PWV over the arch (archPWV) and descending aorta (descPWV) were measured by MR in a subsample (n = 47) and 25(OH)D3 using liquid chromatography-tandem mass spectrometry.

**Results:** Mean(95%CI) total aPWV in South Asians (SA, n = 68, age: 55±10yr), at known higher CHD risk than others, was 0.5(0.1–0.9)m/s higher than in African-Caribbeans (AfC, n = 67, 55±10yr) and Europeans (n = 63, 57±8yr), adjusted for age, SBP and diabetes (p = 0.01). By MR, descPWV in SA was 0.7(0.1-1.3) and 0.8(0.2-1.4) m/s higher than in AfC and Europeans; archPWV was not different. SA and AfC had 21(3) and 14(3) nmol/L lower mean(SE) 25(OH)vitaminD than Europeans. 25(OH)vitaminD was negatively correlated with aPWV adjusted for age and SBP, and weakened/removed cross-ethnic aPWV differences in regression models.

**Conclusions:** These data suggest aortic stiffness as aPWV parallels CHD risk in ethnic groups, improving risk from distending pressure alone, descending but not arch PWV has this feature, and serum 25(OH)vitaminD is an independently and inversely related to aPWV, and may partly explain ethnicity-related differences in aPWV and CHD risk.
Introduction: As compared to normal pregnancy circulating components of the renin-angiotensin-aldosterone system (RAAS) are decreased, whereas the vasocostrictor response to angiotensin II (Ang II) is increased in preeclampsia. We hypothesized that the increased Ang II vasocostrictor response relates to a change in function of the Ang II subtype 2 (AT2) receptor, mediating vasoconstriction instead of vasodilation.

Objective: To study the function of AT2-receptors in subcutaneous resistance vessels from women with a normal or preeclamptic pregnancy.

Methods: Blood and subcutaneous fat were collected at the time of emergency or elective cesarean section from women with a healthy (n = 7) or pre-eclamptic (n = 8) pregnancy. Tissue was kept in cold Krebs solution, and subcutaneous arteries with a diameter of 50-200 μm were isolated, cut in segments of 1-2 mm in length and mounted in a Mulvany wire myograph. Concentration-response curves (CRC) were constructed to Ang II in the absence or presence of the AT1 receptor antagonist irbesartan or the AT2 receptor antagonist PD123319 (both; 1 μM). Data are expressed as a % of the absence or presence of the AT1 receptor antagonist irbesartan or the AT2 receptor antagonist PD123319 (both; 1 μM). Data are expressed as a % of the maximum response to Ang II

Results: Plasma renin, angiotensin I, angiotensin II and aldosterone parameters were elevated in healthy vs. pre-eclamptic women. The Ang II constrictor response was enhanced in pre-eclampsia (Emax: 257 ± 42% vs. 121 ± 26%, p = 0.018), whereas the Ang II potency was unchanged (pEC50: 8.9 ± 0.15 vs. 9.0 ± 0.13, p = 0.324). In the presence of PD123319, the Ang II CRCs of resistance vessels of pre-eclamptic women were flatter compared to healthy pregnant women. Ang II-mediated constrictions were completely abolished by irbesartan.

Conclusion: A change in function of the AT2 receptors to a vasocostrictor phenotype may explain the enhanced constrictor response to Ang II in preeclampsia. Co-stimulation of the AT1 receptor is a prerequisite for this response, as Ang II-mediated constrictions were completely blocked by irbesartan.

Conclusions: The ability of the aorta nerve varicosities to load 3H-NA is the same in neonates and young adult rabbits. The higher aorta endogenous NA content in neonates is the result of a greater biosynthetic activity in the nerves. The fractional rate of loss is higher in neonates because the varicosities in the aorta wall are closer to the surface, and thus more accessible to the surrounding media. It can be concluded that at birth the rabbit possess its aortic nerves at a fully developed state. As in other species, post-junctional α1-adrenoceptor-mediated responses are also fully developed at birth in rabbits.

Abstracts e77 ORAL SESSION 5D BASIC PHARMACOLOGICAL ASPECTS

5D.01 IS THE ENHANCED VASOCONSTRICTOR RESPONSE TO ANGIOTENSIN II IN PREECLAMPSIA MEDIATED BY AT2 RECEPTORS?


Objective: To compare the role of AngII and AT1 receptors in the vasocostrictor response to AngII in normotensive and preeclamptic pregnant women.

Methods: Blood and adiposities were collected at the time of cesarean section from normotensive (n=7) and preeclamptic (n=9) pregnant women. Tissue was kept in cold Krebs solution, and subcutaneous arteries with a diameter of 50-200 μm were isolated, cut in segments of 1-2 mm in length and mounted in a Mulvany wire myograph. Concentration-response curves (CRC) were constructed to AngII in the absence or presence of the AT1 receptor antagonist irbesartan or the AT2 receptor antagonist PD123319 (both; 1 μM). Data are expressed as a % of the maximum response to AngII

Results: Plasma renin, angiotensin I, angiotensin II and aldosterone parameters were elevated in normotensive vs. preeclamptic women. The AngII constrictor response was enhanced in preeclampsia (Emax: 257 ± 42% vs. 121 ± 26%, p = 0.018), whereas the AngII potency was unchanged (pEC50: 8.9 ± 0.15 vs. 9.0 ± 0.13, p = 0.324). In the presence of PD123319, the AngII CRCs of resistance vessels of preeclamptic women were flatter compared to normotensive pregnant women. AngII-mediated constrictions were completely abolished by irbesartan.

Conclusion: A change in function of the AT2 receptors to a vasocostrictor phenotype may explain the enhanced constrictor response to AngII in preeclampsia. Co-stimulation of the AT1 receptor is a prerequisite for this response, as AngII-mediated constrictions were completely blocked by irbesartan.

Conclusions: The ability of the aorta nerve varicosities to load 3H-NA is the same in neonates and young adult rabbits. The higher aorta endogenous NA content in neonates is the result of a greater biosynthetic activity in the nerves. The fractional rate of loss is higher in neonates because the varicosities in the aorta wall are closer to the surface, and thus more accessible to the surrounding media. It can be concluded that at birth the rabbit possess its aortic nerves at a fully developed state. As in other species, post-junctional α1-adrenoceptor-mediated responses are also fully developed at birth in rabbits.

P. Melo1, M. Moreira-Rodrigues2, M. Pereira1, P. Mendes1, L. Graça1, S. Becker1, K. Schwengel1, K. Lucht1, S. Slavic1, E. Kaschina1, J. Leonhardt1, S. Becker1, K. Schwengel1, K. Lucht1, S. Slavic1, E. Kaschina1, J. Leonhardt1, 1Institute of Pharmacology and Therapeutics, FMUP, Porto-Portugal, 2Neuropharmacology, IBMC, Porto-Portugal

Objective: To compare, in the same species, the maturation of pre and post-junctional α1-adrenoceptor mediated responses.

Methods: We investigated 3 groups of male adult rats (n = 10) each: control, L-NAME (50 mg/kg/day) and L-NAME + compound 21 (0.3 mg/kg/day). Blood pressure was measured non-invasively by tail-cuff plethysmography each week. After 6 weeks intra-aortal pulse wave was recorded by two catheters in the aorta (proximal and distal) simultaneously and the PWV was calculated. Wall thickness and inner diameter were determined by morphometry in hematoxylin-eosin-stained aortic cross-sectional slices.

Results: L-NAME-induced hypertension was associated with increased PWV, reduced inner diameter and aortic wall thickening. Compound 21 minimally reduced blood pressure, PWV and arterial remodelling in L-NAME-treated NO-deficient rats. L-NAME-induced hypertension was associated with increased PWV, reduced inner diameter and aortic wall thickening. Compound 21 minimally reduced blood pressure, PWV and arterial remodelling in L-NAME-treated NO-deficient rats. L-NAME-induced hypertension was associated with increased PWV, reduced inner diameter and aortic wall thickening. Compound 21 minimally reduced blood pressure, PWV and arterial remodelling in L-NAME-treated NO-deficient rats.

Conclusions: Blood and subcutaneous fat were collected at the time of emergency or elective cesarean section from women with a healthy (n = 7) or pre-eclamptic (n = 8) pregnancy. Tissue was kept in cold Krebs solution, and subcutaneous arteries with a diameter of 50-200 μm were isolated, cut in segments of 1-2 mm in length and mounted in a Mulvany wire myograph. Concentration-response curves (CRC) were constructed to AngII in the absence or presence of the AT1 receptor antagonist irbesartan or the AT2 receptor antagonist PD123319 (both; 1 μM). Data are expressed as a % of the maximum response to AngII

Results: Plasma renin, angiotensin I, angiotensin II and aldosterone parameters were elevated in normotensive vs. preeclamptic women. The AngII constrictor response was enhanced in preeclampsia (Emax: 257 ± 42% vs. 121 ± 26%, p = 0.018), whereas the AngII potency was unchanged (pEC50: 8.9 ± 0.15 vs. 9.0 ± 0.13, p = 0.324). In the presence of PD123319, the AngII CRCs of resistance vessels of preeclamptic women were flatter compared to normotensive pregnant women. AngII-mediated constrictions were completely abolished by irbesartan.

Conclusion: A change in function of the AT2 receptors to a vasocostrictor phenotype may explain the enhanced constrictor response to AngII in preeclampsia. Co-stimulation of the AT1 receptor is a prerequisite for this response, as AngII-mediated constrictions were completely blocked by irbesartan.

Conclusions: The ability of the aorta nerve varicosities to load 3H-NA is the same in neonates and young adult rabbits. The higher aorta endogenous NA content in neonates is the result of a greater biosynthetic activity in the nerves. The fractional rate of loss is higher in neonates because the varicosities in the aorta wall are closer to the surface, and thus more accessible to the surrounding media. It can be concluded that at birth the rabbit possess its aortic nerves at a fully developed state. As in other species, post-junctional α1-adrenoceptor-mediated responses are also fully developed at birth in rabbits.
Objective: Angiogenesis inhibition has become an established treatment for several tumor types. Unfortunately, this therapy is associated with side effects, including hypertensive renal toxicity. Recent studies have demonstrated that the multi-target tyrosine kinase inhibitor sunitinib induces a rise in blood pressure (BP), and causes renal functional as well as histological changes associated with increased circulating endothelin 1 (ET-1) levels. The aim of the current study was to explore the role of ET-1 and the nitric oxide (NO)/reactive oxygen species balance in sunitinib-induced hypertension and renal dysfunction in Wistar Kyoto rats.

Design and Method: BP and heart rate (HR) were monitored telemetrically during 8 days of administration of sunitinib alone by oral gavage (n = 10), the combination of sunitinib and the dual endothelin receptor antagonist macitentan (n = 8), or sunitinib by gavage and tempol, a superoxide dismutase mimetic (n = 6), subcutaneously via an osmotic minipump. At baseline and at the end of treatment 24-hour urine samples were collected.

Results: During administration of sunitinib BP rose from 95.6±1.1 mmHg to 127.7±1.5 mmHg, whereas BP rose from 97.7±2.7 mmHg to 112.3±2.7 mmHg (p = 0.008) during co-administration of macitentan and from 97.3±2.6 mmHg to 125.3±2.4 mmHg (p = 0.008) during co-administration of tempol. The previously reported sunitinib-induced decrease in HR was not affected by either compound. Urine nitrates decreased during sunitinib administration from 5.0±0.8 pg/day to 1.3±0.8 pg/day, p < 0.001 and were not reversed by macitentan or tempol. Urinary thromboxane B2 reactive substances did not change. Macitentan and tempol did not reverse the sunitinib-induced rise in serum creatinine, but significantly decreased sunitinib-induced proteinuria and urinary ET-1 excretion (Δ1±0.6±0.9 μg/day, p < 0.001 & Δ1±2.0±0.8 μg/day, p < 0.05 for macitentan, and Δ13±6.3±2.4 μg/day, p < 0.05 Δ1±2.9±1.3 μg/day, p < 0.05 for tempol) compared to rats on sunitinib alone (Δ12.8±0.4 μg/day Δ2.8±1.3 μg/day). Neither macitentan nor tempol significantly changed sunitinib-induced renal histological abnormalities.

Conclusions: The endothelin system, rather than oxidative stress, plays an important role in the development of sunitinib-induced hypertension, whereas both systems play a role in the development of sunitinib-induced renal functional abnormalities.

5D.05 INTERMITTENT TREATMENT WITH VALSARTAN CHRONICALLY ENHANCES SBP AMPLITUDE AND FAILS TO PREVENT END ORGAN DAMAGES IN SPONTANEOUSLY HYPERSTENIC RATS

C. Bouisssou-Schurz1, H. Dubire1, Y. Zhang1, M. Safar1, D. Laude2, P. Lacolley1, Y. Bezie3, InsERM U661, Maison-Alfort-Paris, France, 1Hôpital-Dieu Hospital, Diagnosis center and Université René Descartes, UFR Médecine, Paris-France, 2Inserm U872, Paris-France, 3Inserm U864, Nancy-France, 4Groupe hospitalier Paris Saint-Joseph, Paris-France

Objective: A few experimental rat models of short-term variability are well characterised but none is available to characterise the impact of long term blood flow amplitude in vivo on end-organ damage. Our aim is to develop a new experimental rat model by evaluating long-term arterial pressure variations in relation to chronic sustained anti-hypertensive therapy in spontaneously hypertensic rats (SHR).

Design and Methods: Thirty-eight SHR were divided into 3 groups treated randomly allocated (5 animals in each group) to twice daily application on oral valsartan (30 mg/kg, po) daily (continuous therapy; CT) or every 3 days (discontinued therapy; DT). Five rats of each group were used and the other 8 rats of each group were used to evaluate end-organ damage. For the other 8 rats of each group, end organ damage was evaluated by pulse wave velocity (PWV) and cardiac hypertrophy measurements.

Results: During the 8 weeks of the experiment, mean systolic blood pressure (SBP) was equally reduced in DT (113±1.3 mmHg) and CT (117±1.1 mmHg) compared to PT rats (160±2.2 mmHg; p < 0.01). In accordance with the SBP decrease, the sympathetic tone was lower in the treated groups compared to PT. The baroreflex sensitivity was restored in CT compared with PT but not in DT rats. Radiotelemetry monitoring showed increased amplitude of variations in SBP in DT rats (16.3±0.8 mmHg) compared with CT (12.9±1.1 mmHg; p < 0.01) and PT rats (15.3±0.8 mmHg). PWV was reduced in CT compared with PT rats (729±24 cm/sec vs. 935±103 cm/sec; p < 0.01). In contrast, PWV in DT rats was not different compared to PT rats, but slightly increased compared to CT rats (759±31 cm/sec; p = 0.06). Valsartan prevented the development of cardiac hypertrophy in CT rats compared with PT (Heart weight: 1.50±0.03 g vs. 1.42±0.02 g; p < 0.01) but not with DT rats (1.51±0.03 g, p < 0.05 with CT). Conclusion: Our results demonstrate that a chronic intermittent treatment with valsartan is able to reduce the SBP in the same extent as a continuous one. Nevertheless, the increased arterial stiffness and cardiac hypertrophy observed in DT rats compared with CT rats indicate that despite the same decrease of SBP, an intermittent treatment with valsartan may not achieve the full cardiovascular benefits observed with a continuous treatment. Our results suggest that this experimental model is useful to investigate the impact of chronic increased amplitude of variations in SBP on target organ damage. These results that mimics partial adherence to therapy may have important clinical implications in hypertensive patients.

5D.06 SELECTIVE SEROTONIN REUPTAKE INHIBITORS EXERT A NEGATIVE EFFECT ON PERIPHERAL WAVE REFLECTIONS

V. Katsi1, G. Souretis1, K. Kontouggeous1, K. Koundi1, I. Vlasseros1, A.N. Koumoudi1, M. Divani1, S. Christakopoulos1, P. Sakka1, C. Stefanidis1, G. Papadimitriou2, I. Kallikazaros1, 1Hippokration Hospital, Athens-Greece, 2Eginisto Hospital, Athens-Greece

Background: In view of the high likelihood that hypertensives will have comorbid anxiety and depression, all hypertensives should be screened for concurrent psychiatric illnesses and treatment. We hypothesized that there is a relationship between the administration of selective serotonin reuptake inhibitors (SSRIs) and arterial stiffness, a hallmark of the cardiovascular aging process.

Methods: We studied 210 consecutive untreated stage 1 to 2 essential hypertensive (aged = 62±9 years; 110 female, office blood pressure (BP) = 163/91 mm Hg). The participants were divided into group A (n = 83), those receiving SSRIs and group B (n = 127), those without taking any antidepressant therapy. Arterial stiffness was evaluated on the basis of carotid to femoral pulse wave velocity (c-f PWV) by means of a computerized method (Compilor SP). Venous blood sampling was performed for the estimation of routine metabolic profile.

Results: The two groups did not differ regarding age, gender, office systolic/diastolic BP as well as serum glucose and triglycerides levels (83± vs 84± mg/dl and 128± vs 119± mg/dl, respectively; p = NS in all cases). Group A was characterized by increased levels of body mass index (32.4± vs 29.2±4.4 kg/m², p = 0.015) and elevated cholesterol plasma levels compared to group B (231± vs 220± mg/dl p < 0.05). Group A compared to group B exhibited significantly increased c-f PWV (8.4± vs 7.2± 0.5 m/sec, p = 0.02) and this difference remained significant after adjustment for confounders (p = 0.03). In the SSRIs treated < hypertensives, c-f PWV was correlated with age (r = +0.35, p = 0.015) and office systolic BP (r = +0.33, p = 0.02), while no significant correlation was demonstrated with cholesterol levels (r = NS).

Conclusions: The administration of SSRIs exerts an incremental effect on arterial stiffness, thus accelerating the vascular aging process.

5D.07 OFFSPRING OF MOTHER RATS EXPOSED TO CIGARETTE SMOKE CONSERNS ARE CHARACTERIZED BY ELEVATED BLOOD PRESSURE AND REDUCED SODIUM URINARY EXCRETION

M. Zarzecki1, M. Adamczak1, A. Wystrychowski1, M-L. Gross1, E. Ritz1, A. Wiecek1, 1Dept of Nephrol., Endocrinol, and Metab. Dis. Med. Univ. of Silesia, Katowice-Poland, 2Department of Pathology, University of Heidelberg, Heidelberg-Germany, 3Department of Internal Medicine, University of Heidelberg, Heidelberg-Germany

Introduction and Aim: It has been suggested that disturbances of fetal development caused by exposure to cigarette smoke as a result of maternal smoking increase the risk of hypertension and chronic kidney disease in the adult life. The aim of the present experimental study was to assess the impact of exposure of pregnant rats to cigarette smoke condensate on blood pressure and natriuresis in their offspring.

Methods: Pregnant Sprague-Dawley rats on day 10 of pregnancy were randomly allocated (5 animals in each group) to twice daily application on oral mucosa cigarette smoke condensate (CSC) containing nicotine or solvent until delivery. Albuminuria, creatinine clearance and sodium, potassium and calcium urinary excretion were measured in 12 weeks old offspring.

Results: After 12 weeks of age significantly elevated systolic blood pressure was found in offspring exposed to CSC during the fetal period (n = 54) compared to controls (n = 51) (122±7 vs. 116±6 mmHg; p < 0.001), respectively. Offspring of mothers exposed to cigarette smoke condensate did not differ from the control offspring with respect to body weight, albuminuria, creatinine clearance and potassium and calcium urinary excretion.
respectively. In contrast, offspring of mother rats exposed to cigarette smoke condensate are characterized both by significantly lower urinary sodium excretion (531 ± 242 vs. 846 ± 384 µmol/24 hours; p < 0.004) and urinary sodium/creatinine ratio (8.1 ± 4.1 vs. 9.6 ± 4.2 mmol/mmol; p = 0.04).

Conclusions: 1. Exposure of pregnant rats to cigarette smoke condensate causes a blood pressure increase and a reduction of sodium urinary excretion in their offspring. 2. Such effect of cigarette smoke condensate on kidney function may have a consequence on development of arterial hypertension and also chronic kidney disease in the adult life.

5D.08 POLYETHYLENE GLYCOL CATALASE REDUCES THE RENAL MEDULLARY EXPRESSION OF NOX4 AND AT1 RECEPTOR BUT MARKEDLY INCREASES SYSTEMIC ANGIOTENSINOGEN LEVELS IN ANGIOTENSIN II-INFUSED RATS

T. Sousa1, S. Oliveira1, J. Afonso1, M. Morato2, D. Patinha1, S. Fraga1, F. Carvalho1, A. Almino-Teixeira1, 2Inst. Pharmacol. & Therapeutics, FAC. Medicine of Porto (FMUP) and IRCM, UNIV. Porto, Porto-Portugal, 3FAC-Pharmacies of Porto, UNIV. Porto, Porto-Portugal

Inappropriate renin-angiotensin system (RAS) activation may lead to hypertension. Through AT1 receptor binding, angiotensin II (Ang II) stimulates NADPH oxidase and enhances the production of reactive oxygen species (ROS) which act as second messengers in the pathogenesis of hypertension. We previously demonstrated that polyethyleneglycol (PEG)-catalase prevents the oxidative stress and improves the renin-angiotensin system activation in Ang II-infused rats, PEG-catalase treatment has a short-term antihypertensive effectiveness that lasted 169.4 ± 22.0 vs 19.6 ± 5.9 ng/kg/24h, p = 0.0259.

PEG-catalase treatment did not significantly change the effect of Ang II on urinary AGT (47.5 ± 11.3 vs 77.0 ± 24.4 ng/kg/24h). Ang II infusion decreased plasma AGT compared to untreated rats (577.3 ± 27.6 ng/mL, p < 0.0001), while PEG-catalase markedly increased plasma AGT of Ang II-infused rats (2644.4 ± 421.3 ng/mL, p = 0.001). These results suggest that the Ang II-induced generation of H2O2 upregulates the expression of AT1 receptor and NOx in the renal medulla: the short-term antihypertensive effectiveness of PEG-catalase is probably due to compensatory mechanisms leading to increased systemic AT1 production.

5D.09 THE RENIN INHIBITOR ALISKIREN IMPROVES VASCULAR REMODELING IN DOUBLE TRANSGENIC RATS

C. Savoia1, E. Arrabito1, R. Parente1, L. Zizza1, L. Sada1, L. Madaro2, C. Nicoletti2, M. D’Agostino1, L. Pucci1, A. Alonso1, C. Rosi1, M. Volpe2, 2Clinical and Molecular Medicine Department, Sapienza University of Rome, Rome-Italy, 3Diem, Sapienza University of Rome, Rome-Italy

Objective: The selective human renin inhibitor aliskiren (ALK) reduces blood pressure and ameliorates cardio-renal organ damage in hypertensive double transgenic rats (dTGRs) which express both human renin and angiotensinogen. Little is known about the effect of ALK on hypertension-related functional and structural alterations of resistance arteries. We tested the hypothesis that chronic treatment with ALK in dTGRs improves resistance arteries’ vascular remodeling which represents the earliest manifestation of target organ damage in hypertensive subjects and has prognostic significance.

Design and Method: dTGRs (5 weeks old) were treated with ALK (3 mg/kg/day, n = 5) or ramipril (RAM, 1 mg/kg/day, n = 5) for 14 days and compared with age-matched untreated dTGRs. Blood pressure (BP) was measured by tail-cuff method. Resistance arteries media-to-lumen ratio (M/L) was evaluated on mesenteric arteries as pressurized preparations. Endothelium-dependent and -independent relaxation responses were assessed by dose-response curves to acetylcholine (Ach, 10-9 to 10-4 mol/L) and sodium nitroprusside (SNP, 10-8 to 10-4 mol/L), respectively, in vessels precontracted with noradrenaline (10-6 mol/L). The expression of AT1 receptor, AT2 receptor, eNOS and the Nadph subunit gp91phox in aorta was evaluated by immunoblotting. The reactive oxygen species (ROS) production was evaluated in aorta by Dihydroethidium (DHE) staining.

Results and Conclusions: BP was similarly reduced in both ALK-treated and RAM-treated rats compared to untreated dTGRs (167 ± 18 mmHg and 169 ± 18 mmHg vs 196 ± 3 mmHg, respectively P < 0.05; reduction of -15% and -14%; P < 0.05). M/L was equally reduced in ALK-treated and RAM-treated dTGRs. AT1 and AT2 receptor expression was similar in all the groups. eNOS expression was increased only in ALK-treated rats (+41.5 ± 6.3 % vs untreated dTGRs, p < 0.05). gp91phox was slightly reduced in both ALK and RAM-treated dTGRs. Both ALK and RAM similarly reduced ROS production in dTGRs compared to untreated rats (14.7 ± 0.2 AU and 13.9 ± 0.3 AU vs 18.1 ± 0.9 AU, respectively; p < 0.05). In conclusion equieffective antihypertensive dose of ALK or RAM improved oxidative stress and reduced M/L of mesenteric arteries. Only ALK increased the eNOS bioavailability. Hence, in dTGRs renin inhibition compares favorably to ACE inhibition in improving vascular remodeling.
ORAL SESSION 6A
BLOOD PRESSURE MEASUREMENT

6A.01 VALIDATION OF THE NON-INVASIVE ASSESSMENT OF CENTRAL BLOOD PRESSURE BY THE SPHYGMOCOR AND OMRON DEVICES AGAINST THE INVASIVE CATHETER MEASUREMENT

F. H. Ding1, Y. Li1, R. Y. Zhang2, Q. Zhang2, W. X. Fan1, J. G. Wang1.

Objective: To investigate the accuracy of the Sphygmocor and Omron devices in the estimation of central blood pressure in comparison with the simultaneous invasive catheter measurement.

Methods: In 33 patients who underwent invasive catheterization, the radial arterial pulse was sequentially recorded by the use of the Omron and Sphygmocor devices, with the calibration of the oscillometrically measured brachial blood pressure, to derive central blood pressures, which were also measured simultaneously with a catheter-based fluid-filled manometer system. The procedure was repeated 3 times to obtain 99 pairs of non-invasive and invasive measurements. The agreement between the non-invasive and invasive measurements was assessed using the intraclass correlation analysis, paired t test and Bland-Altman plots.

Results: The central systolic blood pressures estimated with both non-invasive devices were significantly (P < 0.001) and closely associated with the invasive catheter measurements with an intraclass correlation coefficient of 0.91 and 0.90 for the Sphygmocor and Omron devices, respectively. However, both devices underestimated central aortic systolic blood pressure with a difference of -14.8 mmHg (95% confidence interval [CI], -16.7 to -13.0 mmHg, P < 0.001) for the Sphygmocor and -24.4 mmHg (95% CI, -45.4 to -0.3 mmHg, P = 0.03) for the Omron. The correlation coefficient between the difference between and the mean of the non-invasive and invasive central systolic blood pressure was -0.10 (P = 0.03) and 0.08 (P = 0.09) for the Sphygmocor and Omron devices, respectively. In addition, the oscillometric device significantly underestimated brachial systolic blood pressure in comparison with the invasive measurement by -18.7 mmHg (95% CI, -22.9 to -14.5 mmHg, P < 0.001).

Conclusions: The non-invasively measured central systolic blood pressure by the use of the applation tonometry was closely correlated with the invasive catheter measurement, with a significant underestimation of absolute values by both non-invasive devices. However, the underestimation was larger by Sphygmocor than Omron probably because of the underestimation of brachial systolic blood pressure by the oscillometric device.

6A.02 TRONCO-CONICAL CUFFS CAN PROVIDE MORE ACCURATE BLOOD PRESSURE MEASUREMENTS THAN CYLINDRICAL CUFFS IN PEOPLE WITH LARGE ARMS

E. Benetti1, S. Masiero1, C. Fania1, A. Pizzarnoni1, P. Palatini1. 1University of Padova, Padova-Italy, 2ILMed. Guroda S.r.l., Costermamo-Italy

Objective: Cylindrical cuffs and bladders are currently used for blood pressure (BP) measurement at the upper arm. However, large arms often have a tronco-conical shape. Aim of this study was to ascertain whether cylindrical and tronco-conical cuffs provide different readings according to arm size and shape.

Design and Methods: In 349 subjects (180 men) aged 56±18 years, with arm mid-circumference ranging from 22 to 42.5 cm, proximal, middle, and distal arm circumferences and arm length were measured to calculate the frustum slant angle. Four different cylindrical and four different tronco-conical bladders of appropriate size were constructed, for arm circumferences ranging from 22.0 to 27.0 cm, for circumferences ranging from 27.5 to 32.0 cm, for circumferences ranging from 32.5 to 37.0 cm, and for circumferences ranging from 37.5 to 42.0 cm. Tronco-conical cuff and bladder slant angles for each arm-size group were derived from the anthropometric measures in the 349 subjects and were 87.0°, 86.5°, 86.0°, and 85.0°, respectively, in the four groups. The validation test was conducted in 120 subjects. Sequential same-arm measurements were performed with the subject in the sitting position. In each subject, BP was measured in triplicate by two observers using the two cuffs in a random order.

Results: In all of the subjects upper-arm shape was tronco-conical with slant angles ranging from 89.5° to 82.2° (mean = 86.2°). Conicity was highly correlated to arm mid-circumference (Bonferroni corrected p < 0.001), skinfold thicknesses (p < 0.001), body mass index (BMI, p < 0.001), and was inversely correlated to arm length (p = 0.03). In the 120 subjects who underwent the validation test, similar results to those obtained in the larger population were found. BMI progressively increased on going from the smallest (BMI, 21.5±3.0 kg/m²) to the largest (BMI, 39.2±6.6 kg/m²) arm size group (p < 0.001). Arm slant angle was correlated to the between-cuff systolic BP discrepancy (p < 0.001). Arm size was a significant predictor of the between-cuff systolic BP discrepancy (p = 0.008) and diastolic BP discrepancy (p = 0.018). In comparison with the group with arm circumference between 22 and 27 cm, in the group with circumference 37.5–42 cm the cylindrical cuff overestimated BP measured with the tronco-conical cuff by 2.4±1.8 mmHg (p = 0.004/0.016).

Conclusions: In obese people, the upper arm may have a pronounced tronco-conical shape and cylindrical cuffs may overestimate BP. Tronco-conical cuffs should be preferred for BP measurement in subjects with large arms.

6A.03 PROGNOSTIC VALUE OF WITHIN- AND BETWEEN-VISIT BLOOD PRESSURE VARIABILITY IN A POPULATION STUDY

A. Odili1, T. Kuznetsova2, L. Thijs2, J. Yu2, J. Staessen2. 1College of Health Science, University of Abaja, Abuja-Nigeria, 2Division of Hypertension and Cardiovascular Rehabilitation, University of Leuven, Leuven-Belgium

Objective: To assess the prognostic value of within- and between-visit blood pressure (BP) variability in a random population sample.

Design and Method: We followed health outcomes in a family-based random sample of 2938 subjects (mean age: 44.9 years, 50.8% women) recruited in the framework of the Flemengo study. At baseline BP was measured 5 times consecutively at each of 2 home visits 1 month apart. We assessed within- and between-visit BP variability from the standard deviation (SD), the coefficient of variation (CV), the average real variability (ARV) and the variance independence of the mean index (VIM).

Results: Over 11 years (median) a total of 344 deaths occurred and 309 participants experienced a fatal or non-fatal cardiovascular event. The within-visit systolic BP variability averaged (SD, CV, ARV and VIM, respectively). Older age, higher mean systolic BP, higher pulse rate, lower body mass index and lower serum creatinine were the main correlates of the within-visit systolic blood pressure variability. After adjustments for these covariates, mean systolic BP was a significant predictor of mortality and cardiovascular morbidity. By contrast, there was no relationship between the risk of these endpoints and the within-visit systolic BP variability (standardized adjusted hazard rates for cardiovascular events 1.06, 1.06, 1.04 and 1.06 for SD, CV, ARV and VIM, respectively, P < 0.24). Similarly, the between-visit systolic BP variability and the within- and between-visit diastolic BP variability did not predict mortality or cardiovascular events. The results were consistent in subjects younger and older than median age (43 years) and in subjects whose blood pressure was below and above the median (123/75 mmHg).

Conclusion: In the Flemengo cohort, BP variability did not contribute to risk stratification over and beyond the level of BP.

6A.04 PROGNOSTIC ACCURACY OF AMBULATORY BLOOD PRESSURE VARIABILITY IN TREATED HYPERTENSIVES FOLLOWED-UP FOR 8 YEARS

J. Bastos1, S. Bertoquin1, J. Polonia2. 1Escola Superior de Saúde da Universidade de Aveiro, Aveiro-Portugal, 2Faculdade Psicologia e Ciências da Educação, Porto, Bolsieira FCT, porto-Portugal

Objective: To test and Bland-Altman plots.

invasive measurements. The agreement between the non-invasive and invasive brachial blood pressure, to derive central blood pressures, which were also obtained in the larger population were found. BMI progressively increased on going from the smallest (BMI, 21.5±3.0 kg/m²) to the largest (BMI, 39.2±6.6 kg/m²) arm size group (p < 0.001). Arm slant angle was correlated to the between-cuff systolic BP discrepancy (p < 0.001). Arm size was a significant predictor of the between-cuff systolic BP discrepancy (p for trend = 0.008) and diastolic BP discrepancy (p = 0.018). In comparison with the group with arm circumference between 22 and 27 cm, in the group with circumference 37.5–42 cm the cylindrical cuff overestimated BP measured with the tronco-conical cuff by 2.4±1.8 mmHg (p = 0.004/0.016).

Conclusions: In obese people, the upper arm may have a pronounced tronco-conical shape and cylindrical cuffs may overestimate BP. Tronco-conical cuffs should be preferred for BP measurement in subjects with large arms.
**Aim:** To evaluate the long-term cardiovascular (CV) prognostic significance of 24h ambulatory blood pressure variability.

**Methods:** Casual and ABP were obtained in 1200 hypertensive patients. We used the SD over 24 hours, daytime and nighttime SBP, weighted for the time interval between consecutive readings and the average of the daytime and nighttime SDs weighted for the duration of the daytime and nighttime intervals (SDdn). We analyzed 1200 hypertensive patients, (645 female), ageing 51±12 years, BMI 27.5±5 Kg/m² without previous CV events. The presence of CV events was analyzed by a Cox hazard model adjusted for confounding variables.

**Results:** There were 62 deaths, 152 CV fatal and non-fatal events (79 strokes), 52 coronary events (CE), 22 other CV events) during 8.2±3 years. In a Cox univariate analysis SD of 24h SBP, Daytime SBP, nighttime SBP and SDdn were predictive for global CV events (respectively HR 1.06, 1.08, 1.4, and 1.08 p < 0.001). All, except SD nighttime SBP, were predictive for S (respectively HR 1.78, 1.05, and 1.10, p < 0.001). For CE only SDnn were predictive (HR 1.08, p < 0.05). All lost significance after adjustment other variables (age, BMI, gender, casual BP, antihypertension therapy and diabetes). Probability of event-free of global CV events and S (Kaplan Meyer) was better for SDnn values below vs above median (respectively log rank 7.65 p < 0.006 and log rank 6.54 p < 0.02). Figure shows rate of CV outcome per 1000 patient – years for quintiles of distribution of SDnn for CV events, S and CE. A linear relationship was observed between quintiles of SDnn BP and either CV events and S but not CE (Figure).

**Conclusions:** In patients with treated hypertension, the variability of ABP can predict CV events and stroke solely the median of SDnn.

**6A.05 PROGNOSTIC VALUE OF AMBULATORY BLOOD PRESSURE MONITORING IN VERY ELDERLY PATIENTS’ MORTALITY**


**Hospital Italiano DE Buenos Aires, Buenos Aires-Argentina**

**Introduction:** Studies performed in Europe and Asia have shown that Ambulatory Blood Pressure Monitoring (ABPM) is better than office blood pressure measurements regarding cardiovascular risk assessment and mortality prediction, especially in patients older than 60 years. Objective: to establish whether ambulatory blood pressure registered by ABPM predicts total mortality, cardiovascular mortality and non-cardiovascular mortality in very elderly patients.

**Materials and Methods:** We evaluated a retrospective cohort of patients older than 80 years who belonged to a Health management organization in Buenos Aires, with an ABPM performed between 2003 and 2008. Follow-up was until April 1st., 2010. Death was assessed by retrospective electronic medical records review and classified as: total mortality (TM), cardiovascular mortality (CVM; cardiac mortality, stroke and other vascular causes) and non-cardiovascular mortality (non-CVM; cancer, infectious diseases, etc.). Hazard ratios (HR) for death, were estimated with a Cox proportional hazard model for each ABPM component: 24-h, day-time and night-time systolic (SBP) and diastolic (DBP) blood pressure measurements. We present HR with 95% Confidence Intervals (95% CI) for increments of 10 mm Hg in SBP and 5 mm Hg in DBP.

**Results:** We included 635 patients with a median age of 82 years (SD 1.9), 75% were women, 91% had hypertension and 74% were taking antihypertensive drugs. 45.7% had dyslipidemia; 17.2% coronary heart disease; 10.6% current smoking; 9.1% diabetes; 7.1% stroke; 4.7% chronic kidney disease; 4.4% and heart failure. During a median 3.9 years follow-up, we registered 53 deaths (8.3%), 13 (2%) were cardiovascular, 32 (5%) were non-cardiovascular and 8 (1.3%) were deaths of undetermined cause. TM was associated with: 24-h SBP (HR 1.36; 95% CI 1.10-1.69, p = 0.005), day-time SBP (HR 1.3; 95% CI 1.05-1.61, p = 0.014), and night-time SBP (HR 1.33; 95% CI 1.11-1.60, p = 0.002). After additional adjustment for office BP, the statistical significance for the association remained unchanged: 24-h SBP (HR 1.50; 95% CI 1.19-1.89, p = 0.001), day-time SBP (HR 1.43; 95% CI 1.13-1.81, p = 0.002), and night-time SBP (HR 1.43; 95% CI 1.19-1.73, p < 0.001).CVM was associated with: 24-h SBP (HR 2.03; 95% CI 1.33–3.11, p = 0.001), day-time SBP (HR 1.96; 95% CI 1.30–2.96, p = 0.001), and night-time SBP (HR 1.64; 95% CI 1.16–2.30, p = 0.004). After adjusting for office BP, CVM was associated with: 24-h SBP (HR 2.01; 95% CI 1.31–3.08, p = 0.001), day-time SBP (HR 1.95; 95% CI 1.28–2.97, p = 0.002), and night-time SBP (HR 1.65; 95% CI 1.16–2.33, p = 0.005). In the multivariate analysis only night-time SBP was associated to non-CVM after adjusting for office BP (HR 1.29; 95% CI 1.01-1.67, p = 0.048). 24-h, day-time and night-time DBP were not associated to TM, CVM or non-CVM.

**Conclusion:** In very elderly patients, 24-h, day-time and night-time SBP measured by ABPM predict total and cardiovascular mortality, independently from classical cardiovascular risk factors and office BP. Only night-time SBP predicts non-cardiovascular mortality.

**6A.06 PREDICTIVE VALUE OF ABPM DERIVED VASCULAR INDICES IN DIFFERENT AGE STRATA. RESULTS OF DUBLIN OUTCOME STUDY**

G. Bilo,1, G. Bovish,1, E. Dolan,1, E. O’Brien1, G. Mancia1, G. Parati,1, 1Dept. Cardiology, Ospedale San Luca, Istituto Auxologico Italiano, Milan-Italy, 1InterCare Ltd., Ireland, 1Connolly Hospital, Dublin-Ireland, 1Conway Institute, University College, Dublin-Ireland, 1Dept. Cardiology, Istituto Auxologico Italiano & Dept. of Clin. Med and Prev. Univ. Milano-Bicocca, Milan-Italy

**Background:** Several indices derived from the relationship between systolic (S) and diastolic (D) blood pressure (BP) measured with ambulatory BP monitoring (ABPM) have been shown to have prognostic relevance. The aim of the present study was to assess the prognostic value of the ambulatory arterial stiffness index (AASI), the BP variability ratio (BPVR) and 24 h pulse pressure (PP) in a large cohort of previously untreated subjects stratified by age.

**Methods:** The study included 10,499 untreated subjects (age 54.4±14.5, 47% male) assessed of hypertension in Dublin, Ireland, in whom 24 h ABPM of adequate quality was obtained. AASI was computed as 1-slope of regression of SBP on DBP, BPVR as the ratio of 24 h SBP SD to 24 h DBP SD; 24 h PP as the mean 24 h difference between SBP and DBP. The association of these variables with cardiovascular (CV) mortality was assessed in Cox regression models adjusted for sex, BMI, smoking status, diabetes, previous CV disease, 24 h mean arterial pressure (MAP) and MAP nocturnal fall, and obtained separately for age strata ≤50, 50-65 and >65 years.

**Results:** 498 CV deaths occurred in the study population over the average follow-up period of 5.8 years. Results are shown in the Table.

**Table:** Hazard ratios (HR, per unit change) and Wald statistics for variables of interest in unadjusted and adjusted Cox models in different age strata.

**Conclusions:** BP derived vascular indices differ importantly in terms of predictive power in different age strata. PP is more predictive in elderly subjects, while AASI and BPVR better predict outcome in younger subjects.
The differences in the prognostic power of these indices are probably due to varying underlying pathophysiological characteristics to be identified by future studies.

**6A.07 DIAGNOSTIC ACCURACY OF HOME BLOOD PRESSURE MONITORING: THE MEDIT-HABP STUDY (MEDITERRANEAN HOME VS. AMBULATORY BP)**

G.S. Stergiou¹, E.G. Nasothimiou¹, S. Omboni², A. De La Sierra³, L.M. Ruilope¹, G. Parati⁵. ¹Hypertension Center, Third University Department of Medicine, Sotiria Hospital, Athens- Greece, ²Italian Institute of Telemedicine, Varese-Italy, ³Department of Internal Medicine, Hospital Mutua Terrassa, Terrassa-Spain, ⁴Hypertension Unit, Hospital 12 de Octubre, Madrid- Spain, ⁵University of Milano-Bicocca & Istituto Auxologico Italiano, Milan-Italy

**Objective:** A collaborative dataset from three Mediterranean countries was developed aiming to investigate the diagnostic accuracy of self-home blood pressure (HBP) measurements in hypertension.

**Methods:** A dataset including clinic blood pressure (CBP), HBP and ambulatory blood pressure (ABP) measurements in the same subjects (with elevated blood pressure, untreated or treated) was developed from prospectively collected data from three Mediterranean countries. HBP and ABP measurements were obtained using validated oscillometric devices and CBP with mercury or oscillometric devices. The diagnostic ability of HBP was assessed by taking ABP as reference method. Threshold for hypertension diagnosis was ≥140/90 mmHg (systolic and/or diastolic) for CBP and ≥135/85 mmHg for HBP and daytime ABP.

**Results:** A total of 1,441 subjects from Greece (n = 595), Italy (n = 572) and Spain (n = 274) were analyzed (mean age 56±12 [SD] years, men 55%, treated 59%, BMI 27.9±4.2 kg/m²). When independently considered, ABP detected a high BP condition in 56% and HBP in 61% of subjects (agreement 76%). The two methods allowed identification of sustained hypertension (elevated clinic and out-of-clinic BP) in 46% and 49% (agreement 86%), of white coat hypertension in 19% and 16% (agreement 86%) and of masked hypertension in 11% and 12% (agreement 89%), respectively. The accuracy of HBP in diagnosing hypertension, sustained hypertension, white coat and masked hypertension (ABP taken as reference method) is presented in the table (95% confidence intervals in parentheses).

**Conclusion:** This is the largest study that assessed the diagnostic ability of HBP compared to ABP.

The findings suggest that there is moderate agreement between HBP and ABP in the evaluation of out-of-clinic BP and the detection of the white coat and masked hypertension phenomena, probably because the two methods offer different and complementary information on daily life blood pressure patterns.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Positive predictive value</th>
<th>Negative predictive value</th>
<th>Kappa statistic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>82 (79-85)</td>
<td>67 (63-71)</td>
<td>76 (73-79)</td>
<td>75 (71-78)</td>
<td>0.50 p &lt; 0.001</td>
</tr>
<tr>
<td>Sustained hypertension</td>
<td>88 (85-91)</td>
<td>85 (82-87)</td>
<td>83 (80-85)</td>
<td>90 (87-92)</td>
<td>0.72 p &lt; 0.001</td>
</tr>
<tr>
<td>White coat hypertension</td>
<td>55 (49-61)</td>
<td>93 (92-95)</td>
<td>66 (59-72)</td>
<td>90 (88-92)</td>
<td>0.52 p &lt; 0.001</td>
</tr>
<tr>
<td>Masked hypertension</td>
<td>57 (49-65)</td>
<td>93 (92-95)</td>
<td>50 (43-58)</td>
<td>95 (93-96)</td>
<td>0.48 p &lt; 0.001</td>
</tr>
</tbody>
</table>
ORAL SESSION

ORAL SESSION 6B
HEALTH CARE STRATEGIES

6B.01 EFFECTS OF A MULTIFACETED INTERVENTION ON GPS ON THE CARDIOVASCULAR RISK FACTORS OF HIGH RISK HYPERTENSIVE PATIENTS. ESCAPE TRIAL

D. Pouchain1, D. Huas1, JP Lebeau1, F. Boutite1, M. Lievre1, E. Bruckert1, J. Chapman1, X. Girerd1, 1French National College of Teachers in General Practice, Vincennes-France, 2Hospices Civils DE L’Hôpital Lyon, Lyon-France, 3Unite De Pharmacologie Clinique Hopital Laennec, Lyon-France, 4Hôpital De La Pitie-Salpetriere, Paris-France

Aim: To show that a multifaceted intervention, aimed at general practitioners (GPs), can improve high risk hypertensive patients’ health outcomes, without affecting their quality of life.

Method: Cluster randomized trial. The intervention consisted of one day of medical education, aiming on the therapeutic targets and strategies for achievement featured in the French guidelines, an electronic blood pressure (BP) measurement device, a short leaflet summarizing the guidelines, 4 prevention- dedicated consultations in 2 years, and a feedback on IG patients’ results at baseline and at 1 year follow-up. Patient’s inclusion criteria: hypertensive patients with at least 2 other cardiovascular risk factors in primary prevention. Primary end point: number of patients achieving all the targets featured in the guidelines. Secondary end points: number of patients achieving each target, variation of the value of the targets, and quality of life (SF-8).

Results: 128 GPs were randomized as clusters in the intervention group (IG), and 131 in the control group (CG). GPs have included 1 832 hypertensive patients. 1 047 of them had type 2 diabetes. Wide variations appeared completely. Patient flow was as follows: At T6/T12 120/88 patients in IG-I vs G-II 118/88 patients in IG-II.

Conclusion: A multifaceted intervention aimed at GPs improves high risk hypertensive patients’ health outcomes without affecting their quality of life.

6B.02 PHYSICIAN INERTIA IN RELATION TO ACHIEVEMENT OF BP GOALS IN HYPERTENSIVE PATIENTS WITH COMORBIDITIES IN THE SHARE SURVEY

R. Schmieder1, J. Redon1, 1University Hospital Erlangen, Erlangen-Germany, 2Hypertension Clinic, Valencia-Spain

Objectives: The aim of this analysis was to investigate the levels of blood pressure (BP) that physicians are satisfied with, concerned with, and would take immediate action at in hypertensive patients (pts) with comorbidities.

Design and Methods: The Supporting Hypertension Awareness and Research Europe-wide (SHARE) survey was conducted between May and December 2009, and 2629 European physicians involved in the treatment of hypertension completed questionnaires. Relative frequency density (%/mmHg) curves were calculated which represented the percentages of physicians who selected BP levels (using 1 mmHg increments) within the specified ranges of 110–201 mmHg (SBP) and 70–115 mmHg (DBP).

Results: Physicians would take immediate action, are concerned with or satisfied with over a wide range of BP levels in hypertensive pts with comorbidities (Figure). Half of the physicians would take immediate action only if BP exceeded systolic 160 mmHg and diastolic 90 mmHg and the corresponding values for their general hypertensive pts are 168 and 100 mmHg respectively. Wide variations were also observed in BP levels that would cause concern or trigger immediate action in both groups of hypertensive pts.

Conclusions: The SHARE survey suggests that many physicians would delay immediate action even though BP exceeded the level of 140/90mmHg in hypertensive pts with comorbidities, and that inertia may delay action being taken against hypertension, thereby increasing CV risk.

6B.03 RANDOMIZED EVALUATION OF THE EFFECTS OF A STRUCTURED EDUCATIONAL PROGRAM (HERZ.LEBEN) ON BLOOD PRESSURE IN ESSENTIAL HYPERTENSIVE PATIENTS

R. Zweiker1, S. Perl1, V. Riegleh1, C. Kovi1, P. Mta1, H. Elder2, L. Rakovac1, P. Beck1, G. Klima1, H. Nagy1, T. Pieber1, 1Dept of Cardiology, Dept of Internal Medicine, Medical University of Graz, Graz-Austria, 2Austrian Medical Association, Graz-Austria, 3Joanneum Research, Graz-Austria, 4Styrian Health Insurance Administration, Graz-Austria, 5Dept of Endocrinology, Dept of Internal Medicine, Medical University of Graz, Graz-Austria

Objective: Despite improved awareness and excellent therapeutic options, hypertension remains one of the greatest cardio- and cerebrovascular risk factors. Patient-related aspects like life style and adherence to medical recommendations are generally acknowledged to have a major impact on the course of chronic diseases. As a structured educational program for diabetics proved to be highly effective (Dafne-trial), it was thought that this strategy might provide significant benefits for hypertensives as well. A previously evaluated structured curriculum was followed by doctors and hypertension nurses. Groups of 6-10 patients were instructed on blood-pressure issues including self-measurement, a healthy low salt diet, active life style and pharmacologic antihypertensive therapy. This prospective multicenter randomized controlled study (NCT00453037) was designed to determine the isolated effect of participation in the educational program, neglecting the possible impact of more intense care.

Design and Methods: Between 2007-2010, 256 patients in 13 centers (9 general practitioners’ offices and 4 outpatient departments) were enrolled in the study. After initial evaluation (T0) and written informed consent, all patients were invited to two follow-up visits after 6 (T6) and 12 (T12) months. Patients at each center were randomly assigned to 2 groups (G). G-I (n = 137) underwent the educational program at T0. G-II (n = 119) was designated for participation after T6. The primary endpoint was an apparent difference in office and home blood pressure (BP) at T6. At this point in time, similar conditions of care for all patients could be assumed, but only G-I had undergone the educational program.

Results: Patients’ characteristics and BP at baseline were comparable (office BP G-I: 158±18/88±11 and 161±18/88±14 mmHg, ns/mns). At T6 systolic office and home BP was significantly lower in G-I than in G-II (office BP 142±17/81±11 vs 150±24/84±12; p < 0.01/ns; home BP 134±8/80±2.8 vs 142±16/82±9, p < 0.01/ns). At T12 all patients had undergone the educational program; at this point in time the differences in BP observed at T6 had disappeared completely. Patient flow was as follows: At T6/T12 120/88 patients in G-I and 97/88 patients in G-II had adhered to the scheduled visits.

Conclusion: The results of this multicenter RCT provide significant evidence of a benefit when patients take part in a structured educational program, presumably because of higher levels of information and patient empowerment. Educational strategies so should be considered seriously as standard of care for hypertensive patients.
DISCREPANCY BETWEEN ACCEPTANCE AND IMPLEMENTATION OF BLOOD PRESSURE GUIDELINES (SHARE-BELGIUM)

A. Persu, P. Van der Niepen, on behalf of the Supporting Hypertension Awareness and Research Europe-wide (SHARE) Steering Committee. 1Department of Cardiology, Cliniques Universitaires Saint-Luc, Université Catholique De Louvain, Brussels-Belgium; 2Department of Nephrology and Hypertension, Universitair Ziekenhuis Brussel, Brussels-Belgium

Background: Blood pressure (BP) control rate in Belgium remains low, in the range of 25-30%. As shown in the Supporting Hypertension Awareness and Research Europe-wide (SHARE) survey (N = 2629), this may be due at least in part to hesitation to adapt antihypertensive treatment in hypertensive patients with uncontrolled BP, despite wide acceptance of BP targets defined in the guidelines (Redon J. et al., J. Hypertens. 2010: 28:e210-11). However, whether these findings also apply to Belgium was previously unknown.

Objectives: To assess conceptions and attitudes of Belgian physicians towards BP control.

Results: The questionnaire was filled in by 293 physicians (age: 49.9 ± 11.1 years, 72% men, 68% general practitioners) Eighty-five % of physicians thought that ESH-ESC BP targets were 'about right' (81%) or 'not tight enough' (4%). Furthermore, mean BP levels that would cause concern needing more closely monitoring (SBP: 151 ± mmHg; DBP: 93 ± mmHg) or force physicians to take immediate action (SBP: 169 ± mmHg; DBP: 101 ± mmHg) were significantly higher than guideline BP targets (p < 0.01). Despite this discrepancy between theory and practice, when asked to evaluate the challenges that prevent patients from achieving ESH-ESC BP targets, physicians ranked therapeutic inertia only in fourth position, after patients-related barriers such as low compliance and low awareness of risk. These results were very similar in general practitioners and specialists and are in agreement with the overall data of the Share survey for Europe.

Conclusions: Despite wide acceptance of the ESH-ESC-recommended BP goal (<140/90 mmHg), in daily practice, many physicians are satisfied if patient BP exceeds this target and take immediate action only at much higher values. Furthermore, physicians rate therapeutic inertia as less important than patient-related barriers in preventing patients to reach BP goal. Increased awareness of therapeutic inertia and further insights into its causes could thus contribute to improve BP control rate, both in Belgium and Europe.

NON PHARMACOLOGICAL INTERVENTION TO TREAT HYPERTENSION: INTENSIVE VERSUS REFERRED CARE

L. A. Ferrara, D. Pacioni, B. Russo, L. Staiano, R. Gente, V. Di Fronzo, M.F. Di Rosa, L. Maione. Federico 2nd University of Naples, Naples-Italy

Despite there is evidence in the literature that non pharmacological treatment is useful in the control of elevated blood pressure, its role frequently appears to be of limited importance in the clinical practice because of poor compliance. In the present study we investigated if a more accurate follow-up including meetings of small groups of patients with dietician and medical staff would improve the outcome of the non pharmacological intervention. 165 hypertensive patients with stable BP levels in the last 6 months were, therefore, enrolled. They were randomly divided in the intensive care (IC) and referred care (RC) groups. At baseline both received the best pharmacological and dietary prescription and were thereafter followed at 3-month intervals up to 1 year. In this period patients in the control group were seen by doctors and dietician in the Outpatient Clinic where they received their disease and the control of their BP levels. In the intensive care program received, in addition, information regarding their disease and the importance of the prescribed non pharmacological therapies, according to a previously scheduled protocol of small group meetings, in order to reinforce their motivations. At baseline IC and RC groups were similar for age (50 ± 16 yrs), 56 ± 2.3 yrs), sex (49M, 36 F; 42M, 38F), BMI (28.6 ± 5.5 vs. 29.5 ± 4 kg/m²), BP levels (135/85 ± 18/12 vs. 132/83 ± 15/9 mmHg) as well historical pharmacological treatment and main metabolic parameters. Patients in the IC group significantly reduced total caloric intake (from 2500 ± 680 vs. 2045 ± 490 kcal/day, p < 0.001) as well as total fat (82 ± 23 vs. 62 ± 14 g/day, p < 0.001) and saturated (29 ± 10 vs. 16 ± 13 g/day, p < 0.001) fats and sodium intake (2810 ± 950 vs. 2010 ± 735 mg/day, p < 0.001) whilst no change was detected in the RC group. Level of physical activity significantly increased (p < 0.001) only in the IC group as well. At the end of the 1 year follow-up a significant reduction in SBP, DBP, total and LDL cholesterol was observed only in the IC group and in the 2 way analysis of variance BMI (p < 0.001) and BP (p < 0.001) were significantly lower in the IC group compared to the RC one. Pharmacological treatment during the study was similar for all classes of drugs apart from diuretics whose dose was higher in the RC group at the end of the study (HCTZ 18.75 vs. 12.5 mg/day, p < 0.05). These results indicate that an intensive care program of non pharmacological treatment is able to improve the compliance of hypertensive patients and the control of their BP levels.

REDUCED COMPLIANCE WITH CURRENT GUIDELINES FOR TREATING TOBACCO USE AMONG HYPERTENSIVES


Background: Smoking cessa on is the most effective way to reduce cardiovascular risk but scarce data exist concerning healthcare provider compliance with the guideline for treating tobacco use among hypertensives. We assessed the hypothesis that there is no satisfactory implementation of the current guidelines against tobacco among healthcare providers.

Methods: We examined 162 subjects with newly diagnosed never treated stage I-II essential hypertension (aged = 58 ±13 years, 78 male, office blood pressure = 158/92 mm Hg). Current smokers were defined as persons who reported smoking ≥100 cigarettes in their life and who now smoked some days every day. Based on parents self-reports during their first visit in the outpatient hypertensive unit, we assessed how well providers asked hypertensives about cigarette use, advised users to quit and assisted in their quit a empt in the past year. Providing assistance in quiting was defined as recommending pharmacotherapy; suggesting use of smoking-cessa on class; providing self-help materials; or suggesting the parent set a specific date to stop smoking.

Results: Among participants, 49.5% (42/38 male/female) were current smokers. Of smokers 20.6% reported that they smoked less than 10 cigarettes per day, 31.4% that they smoked up to 20 cigarettes (one packet) and 48% more than 20 cigarettes per day. Similar percentages of heavy smokers (> 20 cigare uses per day) were observed between males and females (52% vs 49%, p = NS). Among current smokers, 81.75% had seen a doctor, nurse or other healthcare professional in the past. Of smokers who were seen by a healthcare provider, 85.2% reported having been asked if they smoked. Overall only 39.5% of smokers who were seen by a healthcare in the past year reported being asked about smoking, advised to quit and assisted in making a quit attempt.

Conclusions: Many smokers are not receiving the brief intervention recommended for smoking cessa on. Given the fact that all smokers should be repeatedly and unambiguously told to permanently quit smoking, reminding and educating health providers to intervene with smokers could be effective in increasing smoking cessa on rates among hypertensives.

FAILURE TO INTENSIFY THERAPY RELATED TO INADEQUATE CONTROL OF HYPERTENSION AND DYSLIPIDEMIA: A COMBINED STITCH AND STITCH2 ANALYSIS


Objective: Management of patients with multiple cardiovascular risk factors remains a global issue for primary care. Aggressive pharmacotherapy is required to reduce risk. However, clinical inertia and/or patient resistance to treatment are barriers to control. To better understand the importance of practitioners failing to advance therapy as a determinant of blood pressure (BP) and LDL cholesterol control, we conducted a post hoc exploratory analysis of antihypertensive and dyslipidemia therapies prescribed for patients from the Stitch and STITCH2 studies.

Design and Methods: The Stitch and STITCH2 studies employed cluster randomized controlled designs to compare simplified hypertension (Stitch, STITCH2) and hyperlipidemia (STITCH2) guidelines-based care in primary care. Intensity of drug therapy was assessed in patients with initially uncontrolled BP and/or LDL cholesterol. Blood
pressure, cholesterol (STITCH2 only) and medication changes were captured over 6 months of follow-up.

**Results:** 2860 patients from the Stitch and STITCH2 study with uncontrolled BP were analyzed. At follow-up, 58% of Stitch patients and 49% of STITCH2 patients achieved BP control. Antihypertensive use in STITCH2 study was lower than in Stitch (Stitch: 1.8±0.03 standard doses, STITCH2: 1.3±0.03, p < 0.001). However, in both studies, patients with BP that remained uncontrolled at follow-up were not prescribed significantly more intensive therapy (Controlled: 1.6±0.03 standard doses, Not controlled: 1.6±0.04) nor more drugs (Controlled: 1.8±0.03 drugs, Uncontrolled: 1.7±0.03), compared to patients that achieved BP control. In the 553 STITCH2 patients with above-target LDL-C at baseline, only 35% achieved LDL targets at follow-up. Of the patients with high LDL cholesterol at baseline, only 68% of those who remained above target were receiving lipid therapy vs. 90% of those who reached their target after 6 months. In multivariate analysis, intensity of therapy and the extent of change in the number of drugs prescribed were predictors of both BP lowering and LDL cholesterol lowering.

**Conclusion:** In a community setting, there appears to be a ceiling on both antihypercholesterolemic and antihypertensive prescription regardless of whether targets are achieved. These data suggest that resistance to advancing therapy remains a significant barrier to achieving BP and LDL cholesterol control.
ORAL SESSION

ORAL SESSION 6C
CLINICAL TRIALS

6C.01 DETAILED ANALYSIS OF VALSARTAN ON STROKE EVENT REDUCTION IN JAPANESE HIGH-RISK HYPERTENSIVE PATIENTS – NEW FINDING FROM KYOTO HEART STUDY–

T. Sawada1, S. Kimura1, J. Shiraishi2, H. Yamada1, H. Matsubara1. 1Kyoto Prefectural University of Medicine, Kyoto-Japan, 2Kyoto First Red Cross Hospital, Kyoto-Japan

Objective: Stroke reduction is known to be highly dependent on blood pressure lowering. Recently, meta-analysis of angiotensin receptor blockers (ARB) trials reported that ARB might reduce the risk of stroke (Eur Heart J 2009;30:2427). However, detailed information of stroke event is still unknown. The Kyoto Heart Study showed that Valsartan exerts an overall cardiovascular (CV) protective effect on the primary endpoint, in which stroke and angina pectoris (AP) were the statistically significant components (Eur Heart J 2009;30:2461). We report a detailed analysis of Valsartan on stroke event reduction.

Method: The Kyoto Heart Study is a multicenter, two-arm parallel treatment group comparison study with response-dependent dose titration scheme. High-risk Japanese patients with uncontrolled hypertension (n = 3031) were randomized to receive either additional Valsartan or conventional non-ARB therapies. The primary endpoint was a composite of defined CV events such as stroke, myocardial infarction, heart failure, and AP. In this sub-analysis, BP control, detailed information of stroke events, and the effectiveness of Valsartan were investigated.

Results: (1) Compared to non-ARB, Valsartan was significantly effective in the stroke prevention (1.6% vs 3.0%, HR 0.55, 95%CI 0.34–0.89, p = 0.015). In the patients with stroke event, BP at the baseline was 165 ± 15 / 90 ± 13 in Valsartan group and 159 ± 11 / 85 ± 12 in Non-ARB group, and mean BP in the study period was 138 ± 8 / 79 ± 4 and 135 ± 10 / 75 ± 7, respectively. (2) In the detailed analysis, 25 stroke events in Valsartan group consisted of 4 TIA, 1 subarachnoid hemorrhage, 2 cerebral bleeding and 18 cerebral infarction, and 46 events in Non-ARB group, 5, 0, 5 and 36, respectively. The only one case in Non-ARB showed cardiogenic infarction and an unquestionable embolic source in the left atrial appendage. Compared to Non-ARB group, Valsartan significantly inhibited cerebral infarction (1.2% vs 2.3%, HR 0.51, 95%CI 0.29–0.90, p = 0.020)

Conclusions: The detailed analysis from The Kyoto Heart Study showed that Valsartan was mainly effective in the prevention of cerebral infarction, but not in cerebral bleeding.

6C.02 USEFULNESS OF THE NUMBER NEEDED TO TREAT (OR TO HARM) IN CLINICAL TRIALS. REVIEW OF THE IMPACT OF ANTIHYPERTENSIVE TREATMENTS ON CORONARY OUTCOME AND MORTALITY REDUCTION

J. Mourad1, K. Kobalava2. 1CHU Avicenne, APHP, Bobigny-France, 2Municipal Hospital No. 64, Moscow-Russia

The number needed to treat (NNT) or to harm (NNH) is a popular measure of the effectiveness of interventions because it is easier to understand than statistical descriptions. NNTs calculated from randomized controlled trials provide the highest level of evidence. As a tool to facilitate clinical decision-making, NNT is also important in pharmacoeconomics. Among major hypertension trials of the last decade, we reviewed published NNTs or calculated them when they were unavailable.

Objective: To calculate NNT (when active treatment decreased the risk) or NNH (when it increased the risk) relative to coronary events, cardiovascular and total mortality outcomes in major 21st century hypertension trials using RAAS inhibitors.

Design and Methods: We analyzed reductions in coronary events and in total and cardiovascular mortality in 21 trials published between 2000 and 2010 in which most patients (at least 2/3) had hypertension. NNT was calculated for the same time exposure (on a 5-year basis) to be comparable, using the following formula: NNT = (D/5)/((Ecg/Ncg)-(Eac/Nac)); D: duration of follow-up (years), Ecg: events in control group, Eac: events in active treatment group, Ncg: patients in control group, Nac: patients in active treatment group. Outcomes with published p values were selected.

Results:
**GC.03 HIGHER CARDIOVASCULAR (CV) RISK OF HYPERTENSIVE PATIENTS REQUIRING ADD-ON THERAPY IN THE FELODIPINE EVENT REDUCTION (FEVER) RANDOMIZED TRIAL**

Y.Q. Zhang, X.Z. Zhang, L.S. Liu, A. Zanchetti, on behalf of FEVER Study Group. 1FU WAI Hospital, CAMS & PUMC, Beijing-China, 2Beijing Hypertension League Institute, Beijing-China, 3Istituto Auxologico Italiano and Centro di Fisiologia Clinica Iperintenzione, University of Milan, Milan-Italy

**Background:** Protocols on antihypertensive treatment trials require that BP be lowered below a given target, and prescribe that, when randomized therapies do not reach that target, additional drugs be administered. Within a given randomized arm, patients requiring or not requiring add-on therapy during follow-up are pooled together, and no consideration is given to the possibility they may be at different CV risk and differently susceptible to the benefits of antihypertensive treatment.

**Methods:** The FEVER study included 9711 Chinese hypertensive patients receiving 12.5 mg/day hydrochlorothiazide and, after 6 weeks, randomized to either felodipine (5 mg/day) or matching placebo. Patients randomized to felodipine had SBP/DBP 4.2/2.1 mmHg lower than placebo patients, and this was accompanied by significant reductions (26 to 35%) of all major types of CV outcomes. During 40 month follow-up, add-on therapy (further diuretic and then other drugs) was required in 3687 patients. The present analyses compare these patients (add-on) with the 5994 who did not require additional therapy (no add-on).

**Results:** Add-on and no-add-on patients did not differ significantly by gender, age, baseline SBP/DBP, smoking, sChol, sCreat, and BMI. ECG-LVH (13% vs 10%), diabetes (14% vs 12%) and prior CV disease (44.5 vs 41%) were slightly more prevalent in add-on than no-add-on patients. Despite more intense treatment on-treatment SBP/DBP was higher in add-on patients (143/84.8 vs 138.7/83.1 mmHg). After adjusting for all major baseline variables and for on-treatment average BP, incidence of all outcomes were about 2.5 times higher in no-add-on patients. Comparing the effects of felodipine vs placebo separately in the two groups showed that a felodipine vs placebo SBP difference of 138.2 vs 142.4 mmHg in no-add-on patients was accompanied by a 32 to 35% reduction in various types of CV outcomes, whereas a SBP/DBP difference of 140.4 vs 145.0 mmHg between felodipine and placebo in add-on patients was never accompanied by significant outcome reduction (>9 to 17%).

**Conclusions:** In the FEVER study patients requiring add-on therapy were at much higher CV risk. This increased risk cannot be ascribed to differences in traditional risk factors or to a slightly higher achieved BP, and may depend on organ damage not usually measured in trial patients. This asymptomatic organ damage may also make these patients much less susceptible to the benefits of drug-induced blood pressure lowering.

**GC.04 EFFECTS OF SINGLE OR MULTIPLE DRUG THERAPIES ON CARDIOVASCULAR OUTCOMES IN HYPERTENSION: ANALYSIS OF DATA FROM THE VALUE TRIAL**

M. Weber, S. Julius, S. Kjeldsen, Y. Jia, H. Brunner, D. Zappe, T. Hua, G. McInnes, A. Schott, G. Marcui, A. Zanchetti, 1SUNY Downstate College of Medicine, Brooklyn-USA, 2University of Michigan, Ann Arbor-USA, 3Ullevaal Hospital, Oslo-Norway, 4Novartis Pharma, East Hanover-USA, 5University of Lausanne, Lausanne-Switzerland, 6University of Graz, Graz-Austria, 7University of Milano-Bicocca, St. Gerardo Hospital, Monza, Milan-Italy, 8Università di Milano and Istituto Auxologico Italiano, Milan-Italy

**Objective:** To further explore the CV outcomes benefits of BP control in hypertension, we have re-analyzed data from the Valsartan Antithypertensive Long-term Use Evaluation (VALUE) trial that originally compared cardiac outcomes during valsartan and amlopidine-based treatments in hypertensive patients at high risk (prior CV events ≥70%) or multiple risk factors, mean age 68.

**Design and Methods:** From the pooled data, we tested whether patients with BP controlled (systolic BP <140 mmHg) by monotherapy have lower event rates than patients controlled by ≥2 drugs [base drug plus hydrochlorothiazide (other classes; polytherapy)]; and if patients controlled with polytherapy have fewer events than those not controlled with polytherapy. Primary endpoint was CV death+non-fatal MI+non-fatal stroke. Baseline risk differences among groups were addressed by covariate adjustments for prior CV events, age, LVH and valsartan/or amlopidine.

**Results:** The Table shows that monotherapy controlled patients had significantly lower event rates (with exception of stroke) than polytherapy controlled patients; but, the primary endpoint in the polytherapy controlled patients did not differ from the non-controlled patients because the lower stroke rate was offset by an unexpected higher CV mortality. University Hospital Erlangen, Erlangen-Germany, 6Clinical and Regulatory Affairs, Novartis Pharma GmbH, Nauenberg-Germany, 7University of Dundee, 8University of Edinburgh, 9University of Hamburg, 10University of Munich, Germany, 11Institut für Herzinfarktforschung Ludwigshafen, Ludwigshafen-Germany

**Background:** Resistant hypertension as a specific subgroup remains understudied. The prevalence of resistant hypertension is unknown. Prospective data on the therapy and blood pressure control in a daily practice setting are rare. We analyzed the blood pressure decrease after 1 year with the direct renin inhibitor aliskiren in the resistant hypertensive population of the 3A registry. Methods – In the non-interventional 3A Registry study conducted in Germany patients were eligible for documentation in which the physician had decided to modify the antihypertensive therapy. This included treatment with the direct renin inhibitor aliskiren or an ACE inhibitor (ACE-I/angiotensin receptor blocker (ARB) or an agent not blocking the renin-angiotensin-system (RAS), alone or on top of an existing drug regimen. Patients were prospectively followed for one year. Here we report the results of a prespecified subgroup with refractory hypertension. Resistant hypertension is defined as blood pressure that remains above goal in spite of the concurrent use of 3 antihypertensive agents of different classes, including a diuretic.

**Results:** 1) Of the 14990 hypertensive patients recruited by 923 physicians in Germany in 2008 and 2009, 5121 (35%) had no adequate blood pressure control of 3 antihypertensive drugs, including a diuretic. In these resistant hypertensive patients, office systolic blood pressure was 157.1±20.1/89.1±11.8 mm Hg and 4.2±1.2 drugs were used at inclusion. At 1 year of follow-up office BP decreased to 139.1±15.7/81.0±9.1 mm Hg, achieving blood pressure control in 47%. The following results in the resistant hypertensive patients treated with different antihypertensive regimen were obtained: Office blood pressure was 158±20/90±12 mm Hg in the Aliskiren containing regimen (N=4000), 152±18/77±11 mm Hg in the ACE-I/ARB containing regimen (N=871) and 153±19/88±11 mm Hg in the No RAS blockade containing regimen (N=244) (p=0.0001/0.0001). At follow-up after 1 year 139±16/81±9 vs 137±15/80±8 8±137±15/81±9, respectively. Mean reduction in office BP was 18.7±22.8±4.14, 14.7±26.0±5.11 and 15.7±19.7±4.12 for the three treatment groups (p ≤0.0001/0.01). Relative BP reduction was 10.8±13.6±2.13 for the Aliskiren group, 8.6±13.6±2.13 for the ACE-I/ARB group and 9.4±12.7±3.13 mm Hg for the non-RAS group (p ≤0.001/0.01)

**Conclusions:** In this large real life registry resistant hypertensive patients (prevalence 34.4%) showed a significant better blood pressure control within one year. Interestingly, patients with an aliskiren-containing regimen showed...
better blood pressure reductions than patients without RAS-blockade, or an ACE-I/ARB-containing regimen.

**BLOOD PRESSURE VARIABILITY IN OLDER THAN 70 OF CHINESE HYPERTENSIVE PATIENTS**

Z. Jin1, Shen Guoying1, Zhao Xiaowei1, Zhong ye1, Fei Pingya1, Wang Jiguang2.

1Songjiang District Central Hospital, Shanghai, China, 2University of Glasgow, UK.

Objective: To investigate whether the intensified antihypertensive treatment (the goal blood pressure ≤140/90 mm Hg), compared with the routine therapy (the goal blood pressure ≤150/90 mm Hg), would further improve cardiovascular outcome in older than 70 of Chinese hypertensive patients, and whether the visit-to-visit variability in blood pressure, was the risk of cardiovascular events.

Methods: In a randomized, open label, blinded end point evaluation, single center study, 723 old hypertensive patients (the average age was 76.6 years) were randomly assigned to either intensified antihypertensive treatment or routine therapy. In both groups, randomized patients started with single drug treatment of an angiotensin-converting enzyme inhibitor, a β-blocker, a calcium-channel blocker, or a diuretic. To achieve the target blood pressure, 1, 2 or 3 oral antihypertensive drugs could be added in patients in both groups. 4 weeks, 3 months, 6 months, and every 6 months thereafter clinic blood pressure was measured in the follow-up period. Primary composite end point consisted of fatal and nonfatal stroke, fatal and nonfatal myocardial infarction, and other cardiovascular death.

Results: At baseline, characteristics of the participants in the 2 groups were similar. During a mean follow-up of 4 years, systolic/diastolic BP (±SD) decreased to (135.7±9.0)/(76.2±6.1) mmHg in the intensified BP control group and (149.7±11.0)/(82.1±7.5) mmHg in the routine therapy group. The between-group differences in systolic and diastolic blood pressures were 14 and 6 mm Hg, respectively. Visit-to-visit variability [expressed as standard deviation (SD)] in SBP and DBP was obviously lower in the intensified BP control group than in the routine therapy group. Intensified antihypertensive treatment, compared with routine therapy, reduced total and cardiovascular mortality by 41.7%(P = 0.001) and 50.2%(P = 0.002), respectively. Furthermore, intensified antihypertensive treatment also reduced the incidence of the primary composite endpoint by 40.2%(P = 0.005), fatal and nonfatal stroke by 41.9%(P = 0.039), and fatal heart failure by 62.7%(P = 0.032). The incidence of acute myocardial infarction was no difference in 2 groups (P = 0.992). Cox regression analysis showed that the average SBP (P = 0.020), 95%CI 1.006-1.069) and SD SBP (P = 0.033, 95%CI 1.006-1.151) were risk factor of endpoint events.

Conclusions: In older than 70 of Chinese hypertensive patients, long-term intensified antihypertensive treatment substantially lowered fatal and nonfatal stroke and fatal heart failure mortality and didn’t increase the incidence of acute myocardial infarction when systolic/diastolic blood pressure approximated to 136/76 mm Hg, and the long-term visit-to-visit variability in systolic blood pressure was associated with the high risk of cardiovascular events.

**INTENSIFIED ANTIHYPERTENSIVE THERAPY AND BLOOD PRESSURE VARIABILITY IN OLDER THAN 70 OF CHINESE HYPERTENSIVE PATIENTS**

Z. Jin1, Shen Guoying1, Zhao Xiaowei1, Zhong ye1, Fei Pingya1, Wang Jiguang2.

1Songjiang District Central Hospital, Shanghai, China, 2University of Glasgow, UK.

Objective: To investigate whether the intensified antihypertensive treatment (the goal blood pressure ≤140/90 mm Hg), compared with the routine therapy (the goal blood pressure ≤150/90 mm Hg), would further improve cardiovascular outcome in older than 70 of Chinese hypertensive patients, and whether the visit-to-visit variability in blood pressure, was the risk of cardiovascular events.

Methods: In a randomized, open label, blinded end point evaluation, single center study, 723 old hypertensive patients (the average age was 76.6 years) were randomly assigned to either intensified antihypertensive treatment or routine therapy. In both groups, randomized patients started with single drug treatment of an angiotensin-converting enzyme inhibitor, a β-blocker, a calcium-channel blocker, or a diuretic. To achieve the target blood pressure, 1, 2 or 3 oral antihypertensive drugs could be added in patients in both groups. 4 weeks, 3 months, 6 months, and every 6 months thereafter clinic blood pressure was measured in the follow-up period. Primary composite end point consisted of fatal and nonfatal stroke, fatal and nonfatal myocardial infarction, and other cardiovascular death.

Results: At baseline, characteristics of the participants in the 2 groups were similar. During a mean follow-up of 4 years, systolic/diastolic BP (±SD) decreased to (135.7±9.0)/(76.2±6.1) mmHg in the intensified BP control group and (149.7±11.0)/(82.1±7.5) mmHg in the routine therapy group. The between-group differences in systolic and diastolic blood pressures were 14 and 6 mm Hg, respectively. Visit-to-visit variability [expressed as standard deviation (SD)] in SBP and DBP was obviously lower in the intensified BP control group than in the routine therapy group. Intensified antihypertensive treatment, compared with routine therapy, reduced total and cardiovascular mortality by 41.7%(P = 0.001) and 50.2%(P = 0.002), respectively. Furthermore, intensified antihypertensive treatment also reduced the incidence of the primary composite endpoint by 40.2%(P = 0.005), fatal and nonfatal stroke by 41.9%(P = 0.039), and fatal heart failure by 62.7%(P = 0.032). The incidence of acute myocardial infarction was no difference in 2 groups (P = 0.992). Cox regression analysis showed that the average SBP (P = 0.020), 95%CI 1.006-1.069) and SD SBP (P = 0.033, 95%CI 1.006-1.151) were risk factor of endpoint events.

Conclusions: In older than 70 of Chinese hypertensive patients, long-term intensified antihypertensive treatment substantially lowered fatal and nonfatal stroke and fatal heart failure mortality and didn’t increase the incidence of acute myocardial infarction when systolic/diastolic blood pressure approximated to 136/76 mm Hg, and the long-term visit-to-visit variability in systolic blood pressure was associated with the high risk of cardiovascular events.

**CLINIC AND 24 H LONG-TERM BLOOD PRESSURE (BP) VARIABILITY IN NON BETA-BLOCKER AND BETA-BLOCKER-TREATED HYPERTENSIVE PATIENTS. DATA FROM ELSA TRIAL**

G. Mancia1, R. Facchetti1, G. Parati1, A. Zanchetti1. 1University of Milano Bicocca - SAN Gerardo Hospital, Milano-Italy, 2Istituto Auxologico Italiano, Milano-Italy

Background: Recent studies suggest that in patients under antihypertensive treatment between-visit BP variability has prognostic significance, independently on the mean BP value throughout the observation period. They further suggest that this long-term BP variability is greater for beta-blocker than for other types of treatment. To measure long-term variability of BP in hypertensive patients treated for 4 years with atenolol or lacidipine (ELSA trial). To further examine in all patients pooled the relationship of long-term BP variability with end-of-study carotid artery, wall thickness (CAWT) and cardiovascular events. To examine, for the first time, the long-term variability and clinical significance of 24h BP, taking advantage of the availability of multiple 24h BP measurements in all treated patients of the ELSA trial.

Methods: Long-term BP variability was defined as the coefficient of variation (CV) of the average systolic (S) or diastolic (D) BP throughout the treatment period, only considering patients in whom ≥7 clinic (6 months interval) or ≥3 (yearly interval) 24h values were available from the end of the drug titration phase to the end of the study. 1650 patients fit these requirements.

Results: Atenolol reduced clinic and 24h BP to a somewhat greater degree than lacidipine. CV was lower for 24 h than for clinic SBP or DBP (6.3 vs 5.0 and 6.3 vs 5.1, P < 0.01). The CV of clinic BP was slightly greater (4.5%) in atenolol than in lacidipine-treated patients whereas the CV of 24h BP showed no significant between-group difference. In all patients pooled CAWT increased progressively with an increase in clinic or 24h in-treatment SBP mean (quartiles), the increase remaining significant (P < 0.01) after adjustment for multiple confounders. CAWT increased progressively also with an increase of CV of SBP (quartiles), but the increase became not significant after adjustment for in-treatment SBP mean. There was never a relationship between in-treatment DBP mean or CV and CAWT. In-treatment BP mean was greater in patients experiencing than in those non-experiencing a CV event whereas the CV of BP was similar in the two groups.

Conclusion: The ELSA trial data show that in-treatment 24h BP is more stable than clinic BP, and that no substantial difference existed in long-term BP variability between beta-blocker and calcium antagonist treatment. No evidence was found of an independent relationship of long-term clinic or 24h variability with vascular damage or CV events.

**CHANGES IN VISIT-TO-VISIT BP VARIABILITY WITH betablokker, diuretic and calcium antagonist**

H. Charvat1, T. Bejan-Angoulvant1, V. Musini1, F. Boutitie1, M. Perez2, J.A. Staessen1, S.J. Pocock1, J.M. Wurtz1, H. Gaeyffier1.

1Interuniversity Research Centre for Epidemiological Studies and Clinical Trials, Brussels, Belgium, 2London School of Hygiene and Tropical Medicine, London-United Kingdom

Rationale: The variability of blood pressure (BP) from visit to visit has recently been shown to have a prognostic impact, independent of BP level, essentially for stroke. Based on the assumption that the between-individual variability of BP measures at one visit reflects the within-patient visit-to-visit variability, Rodwell et al. showed that the impact of treatment on BP variability depends on the class of the drug used to lower BP. We explored the impact of three drug
classes used as first line BP lowering therapies directly on within patient visit-to-visit variability, as compared to placebo.

Methods: Based on individual patient data, we explored the visit-to-visit changes in systolic BP measures taken in sitting position, in the different treatment groups over the complete follow-up period, expressed as standard deviation (SD) and coefficient of variation (CV). SystEur, a double blind randomized trial, compared nitrendipine as first-line therapy to placebo. MRC35–64, a single blind randomized trial, compared both propranolol as well as bendrofluazide to placebo as first line drugs. The comparisons are based on Kruskal Wallis’ and Wilcoxon’s tests.

Results: Compared to placebo, the within patient visit-to-visit SD and CV were significantly increased in the beta-blocker group (p = 0.01 for SD, <0.0001 for CV). In contrast, the diuretic group displayed a significant reduction, both on SD (p < 0.0001) and on CV (p < 0.05). SD was decreased with calcium antagonist (p < 0.0001) but CV was increased (p = 0.003).

Conclusions: Based on SD and CV of BP computed for all follow-up measures in two large trials, visit-to-visit BP variability was reduced only with a first-line diuretic therapy. Both measures were increased with beta-blocker, and coefficient of variation increased with calcium antagonist.
In this study, we investigated whether the novel selective AT2 receptor agonist, Compound 21 (C21), modulates basal cardiovascular parameters and baroreflex control of heart rate (HR) in normotensive Wistar (WT) or spontaneously hypertensive rats (SHR). Reflex bradycardia and tachycardia were induced by alteration of graded doses of phenylephrine (0.2-2μg) or sodium nitroprusside (0.5-4μg), respectively. Recordings of blood-pressure (BP) and heart rate (HR) were made with C21 at concentrations of 1 μmol/L and higher, decreased the constrictor effects could be blocked by irbesartan or PD123319. An identical biphasic effect was observed in the coronary circulation of AT2R-/y mice. Neither NALP3-KO nor ASC-KO 2K1C treated mice developed hypertension. Neither NALP3-KO nor ASC-KO 2K1C treated mice developed hypertension. Ne
increased compared to tap water groups. However, the heart and kidney index in DOCA/salt treated NALP3-KO mice was significantly lower than that in DOCA/salt WT mice.

Conclusion: The results suggest that NALP3 inflammasome has an impact on blood pressure and renin secretion during renal hyperfusion induced by a renal clip and contributes to renin-dependent renovascular hypertension. Our results also suggest that NALP3 inflammasome contributes to the development of cardiac and renal hypertrophy independently of blood pressure in the DOCA/salt model.

**6D.04** (PRO)REIN RECEPTOR BLOCKADE COUNTERACTS THE BENEFICIAL VASCULAR EFFECTS OF RENIN INHIBITION IN DIABETIC TRANSGENIC MREN2 RATS (TGR (MREN2)27)


**Objective:** Elevated prorenin levels associate with microvascular complications in patients with diabetes mellitus. Prorenin may generate angiotensin (Ang) I at tissue sites, possibly by binding to the (pro)renin receptor (r(PRR)). Here we evaluated this possibility in diabetic TGR(MREN2)27 rats.

**Design and Methods:** Rats made diabetic with streptozotocin were treated for 3 weeks with vehicle or the renin inhibitor aliskiren with or without the (P)RR antagonist HRP. Telemetry transmitters were implanted to monitor blood pressure and heart rate. After 3 weeks, rats were sacrificed, and mesenteric arteries (MA) were removed to evaluate vascular reactivity.

**Results:** Aliskiren lowered blood pressure by maximally 40 mm Hg, without altering heart rate. HRP did not alter this. Acetylcholine (ACH) fully relaxed preconstricted MA of vehicle-treated rats. The NO synthase inhibitor L-NAME partially blocked the effect of ACH, whereas adding Tram34 and apamin (inhibitors of intermediate and small conductance Ca2+-dependent K+ channels) on top of L-NAME relaxed the relaxed ACH response into a contractile effect. Aliskiren did not alter the relaxant effect of ACH, nor the degree of blockade by L-NAME, but prevented the contractile response to ACH in the presence of L-NAME, Tram34 and apamin. Yet, following co-treatment with HRP, the latter response returned, suggesting that HRP counteracts the aliskiren-induced downregulation of ACH-induced constriction, either by upregulating contractile muscarinic receptors and/or by enhancing the release of endothelium-derived contractile factor(s). Treatment did not alter the NOresponsiveness of the vascular smooth muscle cells, evaluated with the NO donor SNAP. Endothelin-1 constricted MA identically with and without treatment. Yet, the ETA receptor antagonist BQ123 inhibited this effect in aliskiren+HRP-treated rats only, suggesting selective upregulation of ETA receptors by HRP.

**Conclusions:** HRP upregulates ETA receptors and the contractile response to ACH, thereby counteracting the beneficial vascular effects of aliskiren. This occurs in a blood pressure-independent manner, and argues against detrimental effects of (P)RR-prorenin interaction.

**6D.05** QUANTITATIVE ANALYSIS OF (PRO)REIN RECEPTOR IN THE MEDIUM OF HUMAN UMBILICAL VEIN ENDOTHELIAL CELLS, HUVEC

K. B. Biswas1, A.H.M.N. Nabi2, Y. Arai3, N. Nakagawa2, A. Ebihara2, A. Ichihara1, T. Inagami4, F. Suzuki1. 1Graduate School of Agricultural Science, Gifu University, Gifu-Japan, 2Faculty of Applied Biological Sciences, Gifu University, Gifu-Japan, 3Keio University School of Medicine, Tokyo-Japan, 4Vanderbilt University School of Medicine, Nashville-USA

**Objective:** Soluble form of shedded (pro)renin receptor [s(P)RR] is reported to be secreted in human plasma and in the conditioned medium of cultured cells. In this study, a sandwich enzyme-linked immunosorbent assay (ELISA) was established for measuring the concentration of s(P)RR in the cultured medium of Huvec to elucidate its binding properties to prorenin.

**Design and Method:** The recombinant (P)RR (with 292 residues from N17-) was secreted in human plasma and in the conditioned medium of cultured cells. In this study, a sandwich enzyme-linked immunosorbent assay (ELISA) was established for measuring the concentration of s(P)RR in the cultured medium of human umbilical vein endothelial cells (Huvec). Prorenin binding with soluble (P)RR was determined using surface plasmon resonance via immobilized anti-(P)RR antibodies.

**Results:** The standard curve constructed using recombinant (P)RR showed a validated quantitative range of 0-300 pM. The assay system had a good linearity (r2 = 0.99) with intra-day (5.8-97.6%) and inter-day (2.1-7.0%) precision. In the cultured medium of Huvec, the concentration of s(P)RR was 32 pM. Human recombinant prorenin binds to s(P)RR and the KD was estimated at 4.0 nM which was four-fold higher compared to that of native recombinant (P)RR.

**Conclusion:** This established ELisa could be useful to evaluate the functional properties of the (pro)renin receptors in the medium levels of cultured cells.

**6D.06** URINARY REIN, BUT NOT ANGIOTENSINOGEN, REFLECTS RENIN-ANGIOTENSIN SYSTEM (RAS) ACTIVITY AND THE EFFICACY OF RAS BLOCKADE IN THE KIDNEY


**Objective:** Urinary angiotensinogen (Ao) has been reported to reflect renal RAS activity. Here we studied whether this is also true for urinary renin and/or prorenin (R, PR).

**Design and Method:** Urinary and plasma R, PR, Ao, aldosterone, albumin, total protein and creatinine were measured in hypertensive patients without (HT: 31 M, 27 F, age 51±12 yrs) or with (DM: 24 M, 19 F, age 59±8 yrs) diabetes mellitus. The majority of these patients took RAS blockers (44 HT, 28 DM).

**Results:** Plasma PR, but not plasma R, Ao, aldosterone, creatinine, albumin or total protein, was elevated in DM vs HT (P<0.05). Urinary PR was below detection limit under all conditions, and urinary Ao, aldosterone, creatinine and total protein were similar in HT and DM. Yet, urinary albumin (P<0.05) and renin (P<0.01) were higher in DM. Plasma RAS components displayed a sexual dimorphism, men having >50% higher plasma R and PR levels, and >15% lower plasma Ao levels (P<0.05). Plasma creatinine and albumin were also higher in men (P<0.01). No sex-related difference was observed for plasma total protein. Urinary RAS components showed no significant differences between men and women, while urinary creatinine, total protein and albumin were increased in men (P<0.05). RAS blocker treatment increased plasma R (P=0.08) and decreased plasma Ao (P<0.05), without altering plasma aldosterone. In contrast, in urine, RAS blockers decreased R and aldosterone (P<0.05) without affecting Ao. Finally, when analyzing all patients together, urinary Ao excretion closely mimicked that of albumin, while urinary Ao and albumin levels were <0.1% of their concomitant plasma levels. This most likely reflects the identical glomerular filtration and tubular handling of both proteins, which have a comparable molecular weight (MW). In contrast, urinary R excretion did not correlate with that of albumin, and the urinary/ plasma concentration ratio of R was >200x the ratio of albumin, despite its comparable MW. This is suggestive for R release from renal tissue sites into urine.

**Conclusions:** The increased urinary R levels in DM and the decreased urinary R levels following RAS blockade, occurring independently of changes in plasma R, reflect the activated renal RAS in DM and the success of RAS blockade, respectively. Urinary R therefore more closely reflects renal RAS activity than urinary Ao.

**6D.07** EFFECT OF OLMESARTAN ON OXIDATIVE STRESS IN HYPERTENSIVE PATIENTS, MECHANISTIC SUPPORT TO CLINICAL TRIALS DERIVED EVIDENCE

L. Cali, L. Dal Maso, P. Caelii, E. Pagini, M. Pengo, A.C. Pessina. University Of Padova, Padova-Italy

**Objective:** The role of oxidative stress in the pathophysiology of hypertension and target organ damage is widely recognized. Using a molecular biology approach, we report, in essential hypertensive patients, the effect of the Angiotensin II type 1 receptor blocker olmesartan on the mononuclear cell (PBMC) protein expression of major elements in the oxidative stress and vascular remodeling-related pathways, p22phox and HO-1, along with the phosphorylation state of ERK1/2 and plasma oxidized LDL (oxLDL).

**Design and Methods:** Twenty untreated uncomplicated essential hypertensive patients, 14 males and 6 females (range blood pressure: 142-156/94-98 mmHg) were treated with olmesartan medoxomil (20 mg/day for 6 months) and blood samples collected at baseline, 3 and 6 months for PBMC p22phox and total protein, was elevated in DM vs HT (P<0.05).
and HO-1 protein expression, phosphorylation state of ERK1/2 (western blot) and oxLDL level (ELISA) evaluations.

Results: Olmesartan normalized blood pressure since the third month (149±4.7 mmHg vs 137.89±2.08 at 3 months, p < 0.001 and 135.44 at 6 months p < 0.001 and p = 0.016 vs 3 months (systolic blood pressure) and 94.88±1.9 vs 88.44±2.0 at 3 months, p < 0.001 and 85.78±1.2 at 6 months, p < 0.001 and p = 0.004 vs 3 months (diastolic blood pressure), Anova: p < 0.001.

Compared to baseline, p22phox protein level declined (Anova: p < 0.001) at 3 months: 7.10±2.61 vs 9.32±2.43 densitometric units (d.u.), p < 0.001, and further declined at 6 months both compared to baseline: 4.55±1.26, p < 0.001 and to 3 months p < 0.02. HO-1 levels increased at 3 months: 10.87±1.92 vs 7.70±0.71 d.u., p = 0.001, and further increased at 6 months (11.11±1.89, p = 0.001) with no significant increment compared to 3 months (Anova: p < 0.001). Phosphorylated ERK1/2 declined at 3 months, further declining at 6 months: 3.94±1.44 vs 5.62±1.11, p = 0.001 and was further significantly reduced at 6 months both compared to baseline (1.94±0.87, p < 0.001) and compared to 3 months (p = 0.001). Plasma oxLDL level reduction approaching statistical significance at 3 months: 270.06±100.34 vs 300.84±109.13 ng/ml, p = 0.06), while it was significant at 6 months both compared to baseline (171.92±61.83, p < 0.001 and to 3 months, p = 0.002, Anova:p < 0.001.

Conclusions: These results demonstrate that olmesartan inhibits oxidative stress. Given the involvement of oxidative stress and its signaling in atherogenesis and the available evidence of olmesartan’s vasoprotective, anti-inflammatory and anti-atherosclerotic effects derived from clinical trials in humans such as the Eutopia, VIOS, MORE and Oliverus clinical trials, the results of our study provide a mechanistic rationale for the olmesartan’s antioxidant and anti-inflammatory potential translation, in the long term, toward the antiatherosclerotic and antiremodeling effects reported on the clinical ground.

6D.08 VTP-27999: A NOVEL RENIN INHIBITOR WITH POTENTIAL FOR SUPERIOR NEPHROPROTECTION

R. Gregg1, G. McGeehan1, C. Bryson1, A. Danser2, D. Claremon1, J. Stegbauer1, S.B. Gurley2, M.A. Sparks2, L.C. Rump1, T.M. Coffman2. 1Department of Nephrology, Heinrich-Heine University Düsseldorf, Düsseldorf-Germany; 2Division of Nephrology, Duke University Medical Center, Durham-USA

Diabetic and hypertensive nephropathy (DN/HTN) are the leading causes of chronic kidney disease (CKD) which frequently progresses to end-stage renal disease (ESRD). Inhibitors of the RAAS pathway (ACE inhibitors and ARBs) have been demonstrated to slow the progression of DN/HTN. However, the specific cell lineages within the kidney responsible for BP control have not been identified. Because of the importance of the collecting duct (CD) for determining final adjustments of salt and water excretion, we hypothesized that AT1 receptors in the CD would have a significant impact on BP regulation. Therefore, we generated mice lacking AT1A receptors only in the collecting duct (CD-KOs) using Cre-Loxp technology with a Hoxb7-cre transgene on 129Sv/EV background. AT1A receptor mRNA expression was reduced by 43% in inner medulla (IM) dissected from CD-KO mice compared to controls (p < 0.01). On a normal salt diet, BPs measured by radiotelemetry were similar in CD-KO and controls (121±2 vs 119±1 mmHg). To test whether the absence of AT1A receptors in CD modifies hypertensive responses to angiotensin (Ang) II, mice were chronically infused with AngII (1000ng/kg/min) for 2 weeks. Unexpectedly, AngII infusion caused a significantly greater increase in BP in CD-KO mice compared to controls (MAP: 163±3 vs 151±3 mmHg, p < 0.01). We tested several possible mechanisms for the enhanced hypertensive response. Urinary aldosterone, NOx levels, and eNOS expression were similar, and treatment with L-NAME during AngII infusion enhanced the BP differences between CD-KOs and controls suggesting that alterations in the NO pathway did not explain this effect. While mRNA levels for cyclooxygenase (COX) -1 and COX-2 did not differ in the IM between CD-KO and controls at baseline, the increase in COX-2 expression caused by AngII infusion was significantly attenuated in the CD-KOs (5.5±0.5 vs. 10.6±1.8; p < 0.01). Likewise, inner medullary COX-2 protein levels were almost 2-fold greater in control compared to CD-KO mice. Interestingly, immunohistochemistry revealed COX-2 expression in intercalated and not in principal cells of the collecting duct. AngII-stimulated urinary excretion of the vasodilator prostanooids PGE2 and 6-keto-PGF1α were reduced in CD-KOs compared to controls (4305±910 vs. 9303±1881 pg/mg creatinine; p < 0.05, and 7457±1509 vs. 15991±3314 pg/mg creatinine; p < 0.05), whereas urinary TxB2 levels was unaffected. During AngII infusion, treatment with a specific COX-2 inhibitor abolished the blood pressure difference between CD-KO and control mice. These results suggest that AT1A receptors in the CD do not have a major impact on BP regulation under basal conditions but, in AngII-dependent hypertension, they act to attenuate BP increases by stimulating COX-2 in intercalated cells and promoting the synthesis of vasodilator prostanoiods. Thus, AT1 receptors in the kidney play a complex role in the pathogenesis of hypertension.

6D.09 CELL-SPECIFIC DELETION OF THE TYPE 1A (AT1A) ANGIOTENSIN RECEPTOR FROM COLLECTING DUCT EXAGGERATES ANGIOTENSIN II-DEPENDENT HYPERTENSION

J. Stegbauer1, S.B. Gurley2, M.A. Sparks2, L.C. Rump1, T.M. Coffman2. 1Department of Nephrology, Heinrich-Heine University Düsseldorf, Düsseldorf-Germany; 2Division of Nephrology, Duke University Medical Center, Durham-USA

Our group has recently shown that AT1 receptors inside the kidney play a key role in blood pressure (BP) regulation. However, as AT1 receptors are expressed throughout the kidney, the specific cell lineages within the kidney responsible for BP control have not been identified. Because of the importance of the collecting duct (CD) for determining final adjustments of salt and water excretion, we hypothesized that AT1A receptors in the CD would have a significant impact on BP regulation. Therefore, we generated mice lacking AT1A receptors only in the collecting duct (CD-KOs) using Cre-Loxp technology with a Hoxb7-cre transgene on 129Sv/EV background. AT1A receptor mRNA expression was reduced by 43% in inner medulla (IM) dissected from CD-KO mice compared to controls (p < 0.01). On a normal salt diet, BPs measured by radiotelemetry were similar in CD-KO and controls (121±2 vs 119±1 mmHg). To test whether the absence of AT1A receptors in CD modifies hypertensive responses to angiotensin (Ang) II, mice were chronically infused with AngII (1000ng/kg/min) for 2 weeks. Unexpectedly, AngII infusion caused a significantly greater increase in BP in CD-KO mice compared to controls (MAP: 163±3 vs 151±3 mmHg, p < 0.01). We tested several possible mechanisms for the enhanced hypertensive response. Urinary aldosterone, NOx levels, and eNOS expression were similar, and treatment with L-NAME during AngII infusion enhanced the BP differences between CD-KOs and controls suggesting that alterations in the NO pathway did not explain this effect. While mRNA levels for cyclooxygenase (COX) -1 and COX-2 did not differ in the IM between CD-KO and controls at baseline, the increase in COX-2 expression caused by AngII infusion was significantly attenuated in the CD-KOs (5.5±0.5 vs. 10.6±1.8; p < 0.01). Likewise, inner medullary COX-2 protein levels were almost 2-fold greater in control compared to CD-KO mice. Interestingly, immunohistochemistry revealed COX-2 expression in intercalated and not in principal cells of the collecting duct. AngII-stimulated urinary excretion of the vasodilator prostanooids PGE2 and 6-keto-PGF1α were reduced in CD-KOs compared to controls (4305±910 vs. 9303±1881 pg/mg creatinine; p < 0.05, and 7457±1509 vs. 15991±3314 pg/mg creatinine; p < 0.05), whereas urinary TxB2 levels was unaffected. During AngII infusion, treatment with a specific COX-2 inhibitor abolished the blood pressure difference between CD-KO and control mice. These results suggest that AT1A receptors in the CD do not have a major impact on BP regulation under basal conditions but, in AngII-dependent hypertension, they act to attenuate BP increases by stimulating COX-2 in intercalated cells and promoting the synthesis of vasodilator prostanoiods. Thus, AT1 receptors in the kidney play a complex role in the pathogenesis of hypertension.
ORAL SESSION

ORAL SESSION 7A

THERAPEUTIC ASPECTS

7A.01 DOSE-RESPONSE RELATIONSHIP OF AMLODIPINE / LOSARTAN COMBINATION IN HYPERTENSION

C. Park1, H. Youn2, S. Chae3, J. Yang4, M. Kim5, T Hong6, C. Kim7, J. Kim8

Purpose: To determine the dose-response relationship and assess the efficacy and safety of amiodipine or losartan monotherapy and amiodipine/losartan combination therapy in patients with essential hypertension.

Methods: At screening, adult patients 18-75 years old with essential hypertension received placebo for 2-4 weeks. Eligible patients (N=320) were randomized to one of eight treatment groups for 8 weeks: amiodipine 5 mg or 10 mg, losartan 50 mg or 100 mg, amiodipine/losartan 50/50 mg, 50/100 mg, 100/50 mg or 10/100 mg. The assumption of strict superiority was estimated using the mean change in sitting diastolic blood pressure (DBP) at 8 weeks. Safety was monitored through physical exams, vital signs and adverse events.

Results: The reduction in DBP at 8 weeks was significantly greater in patients treated with the combination therapies compared with the monotherapies for all specified comparisons except amiodipine/losartan 10/100 vs amiodipine 10 mg. The incidence of adverse events in the group of patients treated with the amiodipine/losartan 10/50 mg combination tended to be higher than for any other group (27.9%, 12/43); however, the effect was not statistically significant.

Conclusion: Combination amiodipine/losartan (5/50 mg, 5/100 mg and 10/50 mg) resulted in significantly greater blood pressure lowering compared with amiodipine or losartan monotherapy, and was determined to be generally safe and tolerable in patients with essential hypertension.

7A.02 RELATIONSHIP BETWEEN BLOOD PRESSURE AND LIPID PROFILE IN EUROPE. THE EURIKA STUDY

C. Borghi - Department of Internal Medicine, Aging and Clinical Nephrology, University of Bologna, Bologna-Italy

Purpose: Hypertension and lipid abnormalities are the most prevalent risk factors. A relationship between lipid profile and blood pressure (BP) has been previously described in single-population surveys (e.g. Tromso Study, Brisighella Heart Study). The relationship between lipid and BP levels across Europe has been investigated in the EURIKA (The European Study on Cardiovascular Risk Prevention and Management in Daily Practice (NCT00882336) study).

Methods: EURIKA was a cross-sectional study conducted in 12 countries. We collected information on risk factors from 806 randomly selected physicians enrolling 7641 patients 50 years, free of clinical CVD, and with a last one major CVD risk factor. A linear regression was performed to analyze individual BP values (in mmHg) with lipid parameters including: Total (TC), LDL (LDL-C), non-HDL (non-HDL-C) and HDL-Cholesterol (HDL-C). We also analyzed the plasma levels of both Apo-A1 and Apo-B lipoproteins. Pearson’s correlation coefficient with correspondent p-value has been calculated.

Results: In the whole EURIKA population 68.6% and 42.9% were treated with antihypertensive and lipid lowering drugs and is less evident in those receiving statin treatment. This might reflect a pathogenic link between lipid profile and blood pressure raising the question of whether early management of dyslipidemia may also prevent the progression of hypertension and associated arterial disease.

7A.03 ALDOSTERONE-RECEPTOR ANTAGONISTS LEAD TO PROLONGED BLOOD PRESSURE REDUCTION IN UNCONTROLLED HYPERTENSION: A RETROSPECTIVE ANALYSIS

P.M. Jansen1, K. Verdonk1, B.P. Imholz1, A.H.J. Danser1, A.H. van den Meiracker1, 1Erasmus Medical Center, Rotterdam-the Netherlands, 2Twee Steden Hospital, Waalwijk-The Netherlands

Introduction: Aldosterone-receptor antagonists (ARAs) have been shown to effectively reduce blood pressure (BP) in patients with uncontrolled hypertension. However, the long-term efficacy of ARAs as add-on treatment in uncontrolled hypertension has not yet been reported.

Methods: Data from 123 patients (21 with primary aldosteronism, 102 with essential hypertension) with difficult-to-treat hypertension who received an ARA between May 2005 and September 2009 were analyzed retrospectively for their effect on blood pressure (BP) and biochemistry at first follow-up after start with ARA and the last follow-up available. Possible predictors for a better BP response were subsequently tested in a multivariate regression model.

Results: Systolic BP decreased by 22 ± 20 and diastolic BP by 9.4 ± 12 mmHg after a median treatment duration of 25 months. In patients that received treatment ≥ 5 years, SBP was 33 ± 20 and DBP 16 ± 13 mmHg lower than at baseline. Changes in BP were not significantly different for PA and EH patients. Serum potassium increased from 4.0 to 4.4 mmol/L (p < 0.001) in EH and from 3.4 to 4.3 mmol/L (p = 0.001) in PA. In addition, serum creatinine showed a significant rise upon ARA treatment (85 to 94 μmol/L (p < 0.001) in EH, and 86 to 96 μmol/L (p = 0.01) in PA). The total defined daily dose (DDD) of antihypertensive drugs remained unchanged (5 at baseline versus 4.5 at end of follow-up, p = 0.459). Multivariate analysis revealed that baseline BP and follow-up duration were positively correlated with BP response.

Conclusion: Add-on ARA treatment in difficult-to-treat hypertension results in a profound and sustained BP reduction.

7A.04 THERAPEUTIC INFLUENCE OF COMBINATION THERAPY ON LEFT VENTRICULAR MASS INDEX (LVMI) IN ESSENTIAL HYPERTEENSIVE (EAH) PATIENTS IS RELATED TO POLYMORPHISMS OF ACE, AGTR1, ENOS, PPARGAMMA2, AND ARDRBETA1 GENES

L. Sydorchuk1, K. Amosova2, A. Sydorchuk3, R. Sydorchuk1, J. Ursuljak1, I. Sydorchuk1, 1Bucovinian State Medical University, Chernivtsi-Ukraine, 2National State Medical University, Kyiv-Ukraine

Objective: To evaluate LVMI changes in EAH patients under the combo treatment depending on D/D polymorphism in ACE gene, A1166G in AGTR1 gene, T894G in eNOS gene, Pro12Ala in Ppar-γ2, Arg389Gly in ADRB1 gene.

Design/Methods: 249 patients (EAH I – 26.5%; EAH 22 – 45.8%; EAH 222 – 27.7%; women – 48.2%, men – 51.8%, mean age 50.5 ± 10.4 yrs) under-
went 9-12 months combination therapy depending on genes' polymorphism (hydrochlorothiazide (HCTZ)-angiotensin II receptor (ARB) blocker), HCTZ=BB-blockers (BB), HCTZ=ACE inhibitor (Acel), calcium antagonists (CA=ARB, CA+BB, CA+ACE), LVMi and wall thickness/radius ratio (T/R) were detected with EchoCG. Efficacy criteria: LVMi in male/female ≤125/110 g/m², wall T/R ratio <0.42 (ESC/ESH 2007).

Results: Target LVMi and T/R patients' number increased by 8.0% and 6.0% (p<0.05). HCTZ=ARB lead to target LVMi and T/R patients' increasing by 6.7% (p = 0.08) and 11.6% (p<0.05) accordingly: reliably only in II (ACE) carriers (δ = 0.34). HCTZ=BB caused normal LVMi patients' increase by 8.8% (p = 0.05) reliably only in ID-genotype (ACE), target T/R ratio increased by 5.6%: significantly in DD (ACE) (p = 0.003). HCTZ was well tolerated, and AE-related AEs, n/N (%)†

Conclusions: Pharmacogenetically determined treatment of EAH patients with CA combinations in DD-genotype (ACE gene) carriers caused more effective decrease of LVMi and T/R ratio, than treatment of I-allele carriers (ACE) with HCTZ combo (p < 0.05), without reliable differences (after drug combination) on pprospective G Tri (A166C), eNOS (T894G), Pparγ2 (Pro12Ala) and ADRβ1 (Arg98Gly) genes.

7A.05 LONG-TERM EFFICACY AND SAFETY OF COMBINATION OLMESARTAN MEDOXOMIL/AMLODIPINE BY SYLestyne + HYDROCHLOROTHIAZIDE BASED ON HYPERTENSION SEVERITY: THE TRIUNITY STUDY

D. Kereiakes1, S. Chrysant2, J. Izzo2, S. Oparil1, M. Melino1, J. Lee6, V. Fernandez6, R. Heyrman1.

1University of Alabama AT Birmingham, Birmingham-USA, 2State University of New York at Buffalo, Buffalo-USA, 3Oklahoma Cardiovascular and Hypertension Center and University of Oklahoma College of Medicine, Oklahoma City-USA, 4State University of New York at Buffalo, Buffalo-USA, 5Piedmont Medical Research Associates, Winston-Salem-USA, 6Daiichi Sankyo, INC, Parsippany-USA

Objective: To evaluate the long-term efficacy and safety of olmesartan (OM)/amlodipine (AML)-hydrochlorothiazide (HCTZ) in a prespecified subgroup analyses of the TRIUNITY study, study participants (pts) were administered OM 40/AML 5 HCTZ 12.5 mg in 40-week open-label extension. Those not achieving BP goal (<140/90 or <130/80 mmHg for pts with diabetes, chronic renal disease, or chronic cardiovascular disease; safety population ET: early termination).

Table: Efficacy and Safety at week 52 ET by Hypertension Severity

<table>
<thead>
<tr>
<th></th>
<th>OM 40/AML 5 + HCTZ 12.5 mg</th>
<th>OM 40/AML 5 + HCTZ 25 mg</th>
<th>OM 40/AML 10 + HCTZ 12.5 mg</th>
<th>OM 40/AML 10 + HCTZ 22.5 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>BP goal, n/%</td>
<td>Moderate HTN</td>
<td>712</td>
<td>175</td>
<td>176</td>
</tr>
<tr>
<td></td>
<td>Severe HTN</td>
<td>112</td>
<td>68</td>
<td>57</td>
</tr>
<tr>
<td>Drug-related AEs, n/N (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI&lt;30</td>
<td>OM 40/AML 5 + HCTZ 12.5 mg</td>
<td>125 (71.0)</td>
<td>214 (33.2)</td>
<td>194 (20.0)</td>
</tr>
<tr>
<td>BMI&lt;30</td>
<td>OM 40/AML 5 + HCTZ 22.5 mg</td>
<td>140.2 (16.0)</td>
<td>147 (39.6)</td>
<td>140.2 (18.5)</td>
</tr>
</tbody>
</table>

*All throughfulness was based on criteria for state 2 HTN, 11.0% of the randomized population has stage 1 HTN this was due to the fact the baseline BP was not the same as the BP measurement used to determine eligibility; therefore the moderate HTN group includes a small subset of pts with mild HTN. BP goal is defined as <140/90 or <130/80 mmHg for pts with diabetes, chronic renal disease, or chronic cardiovascular disease.

7A.06 LONG-TERM EFFICACY AND SAFETY OF COMBINATION OLMESARTAN MEDOXOMIL/AMLODIPINE BY SYLestyne + HYDROCHLOROTHIAZIDE STRATIFIED BY DIABETES STATUS AND BODY MASS INDEX: SUBGROUP ANALYSES OF THE TRIUNITY STUDY

S. Oparil1, J. Izzo2, S. Chrysant3, D. Kereiakes4, T. Littlejohn5, M. Melino6, J. Lee6, V. Fernandez6, R. Heyrman1.

1University of Alabama AT Birmingham, Birmingham-USA, 2State University of New York at Buffalo, Buffalo-USA, 3Oklahoma Cardiovascular and Hypertension Center and University of Oklahoma College of Medicine, Oklahoma City-USA, 4The Christ Hospital Heart and Vascular Center and the Carl and Edyth Lindner Center, Cincinnati, OH, USA, 5Piedmont Medical Research Associates, Winston-Salem-USA, 6Daiichi Sankyo, INC, Parsippany-USA

Objective: In prespecified subgroup analyses, the long-term efficacy and safety of olmesartan (OM)/amlodipine (AML)-hydrochlorothiazide (HCTZ) were evaluated by diabetes status (diabetes mellitus [DM; 15.8 %] or non-DM [84.2 %]) and body mass index (BMI; <30 kg/m² [36.9 %] or ≥30 kg/m² [63.1 %]).

Design and Method: After completing the 12-week double-blind TRIUNITY study, study participants (pts) were administered OM 40/AML 5 HCTZ 12.5 mg in a 40-week open-label extension. Those not achieving BP goal (<140/90 or <130/80 mmHg for pts with diabetes, chronic renal disease, or chronic cardiovascular disease) after 2 weeks were randomly titrated to OM 40/AML 5 HCTZ 25 mg or OM 40/AML 10 HCTZ 12.5 mg. At week 16, those not achieving BP goals were further titrated to OM 40/AML 10 HCTZ 25 mg. Back-titration to a lower dose of triple therapy was allowed at the investigator’s discretion. The study objectives were SeSBp at each open-label visit (weeks 12-52), percentage (%) of pts reaching BP goal, and safety assessments.

Table: Efficacy and Safety at week 52 ET by Diabetes Status and BMI

<table>
<thead>
<tr>
<th></th>
<th>OM 40/AML 5 + HCTZ 12.5 mg</th>
<th>OM 40/AML 5 + HCTZ 25 mg</th>
<th>OM 40/AML 10 + HCTZ 12.5 mg</th>
<th>OM 40/AML 10 + HCTZ 22.5 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI&lt;30</td>
<td>OM 40/AML 5 + HCTZ 12.5 mg</td>
<td>124 (73.6)</td>
<td>127 (68.1)</td>
<td>124 (73.6)</td>
</tr>
<tr>
<td>BMI&lt;30</td>
<td>OM 40/AML 5 + HCTZ 25 mg</td>
<td>128 (77.0)</td>
<td>129 (73.9)</td>
<td>128 (77.0)</td>
</tr>
<tr>
<td>BMI≥30</td>
<td>OM 40/AML 5 + HCTZ 12.5 mg</td>
<td>131 (78.3)</td>
<td>130 (72.2)</td>
<td>131 (78.3)</td>
</tr>
<tr>
<td>BMI≥30</td>
<td>OM 40/AML 5 + HCTZ 25 mg</td>
<td>135 (82.1)</td>
<td>135 (76.1)</td>
<td>135 (82.1)</td>
</tr>
</tbody>
</table>

*All throughfulness was based on criteria for state 2 HTN, 11.0% of the randomized population has stage 1 HTN this was due to the fact the baseline BP was not the same as the BP measurement used to determine eligibility; therefore the moderate HTN group includes a small subset of pts with mild HTN. BP goal is defined as <140/90 or <130/80 mmHg for pts with diabetes, chronic renal disease, or chronic cardiovascular disease; safety population ET: early termination.
Results: Mean BP (mmHg; on treatment) at week 12 (open-label start): 138.9/81.2 (DM); 134.1/82.5 (non-DM); 133.3/80.7 (BMI <30); and 135.7/83.2 (BMI ≥30). Efficacy and safety results are presented in the Table. The % of pts reaching BP goal ranged from 24.4% to 64.5% (DM), 51.6% to 81.0% (non-DM), 46.5% to 79.2% (BMI <30), and from 43.7% to 80.3% (BMI ≥30) at week 52/ET. Most drug-related AEs were mild or moderate and not different between subgroups.

Conclusions: Long-term treatment with OM/AML+HCTZ was both effective and well tolerated regardless of diabetes status or body mass index.

### 7A.07 LONG-TERM EFFICACY AND SAFETY OF COMBINATION OLMESARTAN MEDOXOMIL/AMLODIPINE BESYLATE + HYDROCHLOROTHIAZIDE STRATIFIED BY RACE: A TRINITY STUDY SUBGROUP ANALYSIS


**Objective:** The long-term efficacy and safety of olmesartan (OM)/amlodipine (AML) + hydrochlorothiazide (HCTZ) were evaluated in black (B, 29.5%) and non-black (NB, 70.5%) study participants (pts) in a prespecified subgroup analysis of the TRINITY study.

**Design and Method:** After completing the 12-week double-blind TRINITY study, pts were administered OM 40/AML 5+HCTZ 12.5 mg in a 40-week open-label extension. Pts not achieving BP goal (<140/90 or <130/80 mmHg for pts with diabetes, chronic renal disease, or chronic cardiovascular disease) after 2 weeks were randomly titrated to OM 40/AML 5+HCTZ 25 mg or OM 40/AML 10+HCTZ 12.5 mg. At week 16, pts not achieving BP goal were further titrated to OM 40/AML 10+HCTZ 25 mg. Back-titration to a lower dose of triple therapy was allowed at the investigator's discretion. Study objectives were to evaluate tolerability and safety at each open-label visit (weeks 12-52), percentage (%) of pts reaching BP goal, and safety assessments.

**Results:** At wk 12 (open-label start), mean BP (on treatment) was 135.7/84.0 mmHg (B) and 134.5/81.6 mmHg (NB). Efficacy and safety results are presented in the Table. In B and NB pts, the incidence of AEs was 30.2% to 56.6% and 39.3% to 60.5% and the incidence of drug-related AEs was 5.4% to 16.8% in B and 12.8% to 21.3%, respectively. Most AEs were mild or moderate in severity.

**Conclusions:** Long-term treatment with OM/AML+HCTZ appeared to have similar efficacy and safety regardless of race.

### Table: Efficacy and Safety at week 52/ET by Race

<table>
<thead>
<tr>
<th>BP goal*, n (%)</th>
<th>B (n=518)</th>
<th>NB (n=184)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-black</td>
<td>77.2 (8.7)</td>
<td>78.2 (9.6)</td>
</tr>
<tr>
<td>Black</td>
<td>81.8 (9.8)</td>
<td>82.0 (9.6)</td>
</tr>
<tr>
<td>n (%)</td>
<td>Black</td>
<td>NB</td>
</tr>
<tr>
<td>OM 40/AML 5 + HCTZ 12.5 mg</td>
<td>153 (74.6)</td>
<td>531 (81.4)</td>
</tr>
<tr>
<td>OM 40/AML 5 + HCTZ 25 mg</td>
<td>60 (63.5)</td>
<td>119 (64.7)</td>
</tr>
<tr>
<td>OM 40/AML 10 + HCTZ 12.5 mg</td>
<td>60 (63.5)</td>
<td>119 (64.7)</td>
</tr>
<tr>
<td>OM 40/AML 10 + HCTZ 25 mg</td>
<td>60 (63.5)</td>
<td>119 (64.7)</td>
</tr>
</tbody>
</table>

### 7A.08 DISTRIBUTION OF SYSTOLIC BLOOD PRESSURE REDUCTIONS FROM THE TRINITY STUDY: EFFICACY OF COMBINATION OLMESARTAN MEDOXOMIL-AMLODIPINE BESYLATE-HYDROCHLOROTHIAZIDE

T. Littlejohn1, D. Kereiakes1, S. Chrysant1, J. Izzo1, S. Oparil1, M. Melino1, J. Lee2, V. Fernandez3, R. Heyrman2.

**Objective:** To investigate the efficacy and safety of the single-pill combination (SPC) of telmisartan 80 mg/amlodipine 10 mg (T80/A10) compared with amlodipine 10 mg (A10) in patients with diabetes and hypertension.

**Design and Method:** An 8-week, double-blind, parallel-group study, in 706 patients aged ≥18 years with type 2 diabetes and stage 1 or 2 hypertension (systolic blood pressure [SBP] ≥140 mmHg) randomized to T80/A10 (n = 352) or A10 (n = 354); patients receiving T80/A5 or A5 for the first 2 weeks. The primary endpoint was change from baseline in mean seated trough cuff SBP.

**Results:** Patient baseline characteristics were comparable between the treatment groups (SBP 160.8 mmHg; mean BMI 32.1 kg/m²). After 8 weeks’ treatment, significantly greater reductions in SBP were observed with T80/A10 vs A10 alone (-29.0 vs -22.9 mmHg; p < 0.0001), with superior reductions already seen after 1 week (-17.5 vs -12.6 mmHg; p < 0.0001). T80/A10 SPC resulted in higher SBP goal rate (73.2% vs 56.8%), BP goal rate (71.4% vs 53.8%) and
SBP response rate (93.1% vs 87.5%). Greater 24-h SBP reduction (<16.5 vs -11.1 mmHg; p = 0.0044) and consistently higher 24-h BP goal rates (<130/80 mmHg; 52.9% vs 39.1%) were seen with T80/A10 SPC. Overall, the most common adverse events (AEs) were peripheral edema (18.8%) and headache (2.2%). Treatment-related AEs were less frequent with T80/A10 with less peripheral edema (17.6% vs 20.1%) and a lower rate of treatment discontinuation (2.8% vs 5.4%).

Conclusions: In added risk hypertensives such as patients with diabetes, obesity and metabolic syndrome, T80/A10 SPC resulted in significantly greater SBP reductions than A10 monotherapy (~29.0 vs -22.9 mmHg; p < 0.0001). Patients treated with T80/A10 SPC experienced greater 24-h SBP reduction and a higher proportion reached 24-h goal than with A10. The safety profile of T80/A10 SPC was comparable to previous trials with T/A.

**7A.10 SUPERIOR PERIPHERAL AND CENTRAL BLOOD PRESSURE CONTROL AFTER SWITCHING TYPE 2 DIABETIC PATIENTS WITH UNCONTROLLED HYPERTENSION FROM RAMIPRIL/HYDROCHLOROTHIAZIDE TO PERINDOPRIL/INDAPAMIDE**

T Mengden1, W Schmert1, 1Kerkhoff Rehabilitation Clinic, Bad Nauheim-Germany, 2Cardiovascular Research Institute, Dortmund-Germany

Objective: The specific pharmacological properties of perindopril/indapamide (Per/Ind) result in superior outcomes as shown in the ADVANCE trial. Both perindopril and indapamide have specific effects on small and large arteries, reducing total peripheral resistance and central blood pressure (BP). Whereas ACE inhibitors have beneficial effects on central BP, the effects of diuretics are unclear. The aim of this study was to compare the change from baseline BP (office, 24-h ambulatory BP measurement [ABPM], central BP) in uncontrolled hypertensive type 2 diabetic (T2D) patients after switch of therapy from ramipril/hydrochlorothiazide (Ram/HCTZ) to a dose-equal fixed combination of Per/Ind.

Design and Methods: Investigator-initiated, non-randomized, one-arm study. Male and female T2D patients ≥18 years, with uncontrolled hypertension as defined by a sitting office BP >130/80 mmHg. TriPLICATE office BP was measured with a validated, automatic, oscillometric upper arm device (Microlife watch) according to ESH guidelines. 24-h ABPM (central and peripheral BP) was measured with the validated device Mobilograph (IEM, Germany). Central BP in the clinic was measured with the validated device Sphygmocor (Atcor) as recommended by the ESH Working Group on Large Arteries. Measurements were performed at baseline and after 8 weeks of treatment with Per/Ind.

Results: Eighteen patients with a mean age of 61+10 years and a BMI of 27+6 kg/m² were included. Mean daily dosage was 5.3 mg/22.2 mg for Ram/HCTZ and after the switch 9.7 mg/1.9 mg for Per/Ind.

Conclusions: Switching T2D patients with uncontrolled hypertension from Ram/HCTZ to Per/Ind resulted mainly in superior systolic BP control. This effect was persistent for central BP as well as for 24-h ABPM. Due to the NO-dependent vasodilatory effect of indapamide it may be assumed that peripheral as well as central hemodynamics are controlled better with indapamide than with HCTZ. This effect should translate into better BP control within a short period (8 weeks) and potentially also after prolonged therapy. This effect should translate into better BP control within a short period (8 weeks) and potentially also after prolonged therapy. Due to the antihypertensive effect of perindopril, peripheral as well as central hemodynamics are controlled better with indapamide than with HCTZ. This effect should translate into better BP control within a short period (8 weeks) and potentially also after prolonged therapy.

**7A.11 THE EFFECT OF A COMBINATION OF ANGIOTENSIN RECEPTOR BLOCKER AND DIURETIC ON LEFT VENTRICULAR DIASTOLIC FUNCTION IN HYPERTENSIVE PATIENTS: A MULTICENTRAL TRIAL**

H. Kihara1, H. Ito1, K. Ishii1, H. Watanabe1, K. Shimada1, J. Yoshikawa1, on behalf of Eden Investigators. 1Kihara Cardiovascular Clinic, Asahikawa-Japan, 2Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama-Japan, 3Kansai Denryoku Hospital, Osaka-Japan, 4Sakakibara Memorial Hospital, Tokyo-Japan, 5Osaka City University Hospital, Osaka-Japan, 6Nishinomiya Watanabe Hospital, Nishinomiya-Japan

Objective: Antihypertensive therapy plays a major role in the treatment of heart failure with preserved ejection fraction (HFP EF). A combination of angiotensin receptor blocker (ARB) and diuretics has higher blood-pressure-lowering effects than ARB alone. However, diuretic treatment could activate the renin–angiotensin system, which is involved in left ventricular (LV) remodeling processes. We investigated the effects of ARB/diuretics combination on LV diastolic function in patients with hypertension in a prospective, multicenter trial (Effect of ARB/Diuretics on diastolic function in patients with hypertension, EDEN trial).

Design and Method: We enrolled 371 patients with hypertension who had LV diastolic dysfunction and had not achieved appropriate blood pressure lowering after a standard dose of ARBs or angiotensin-converting enzyme inhibitors (ACE-I) (236 men, mean age 68 ± 10 year old). We switched the treatment from ARBs/ACE-I to a combination of losartan 50mg and hydrochlorothiazide (HCTZ) 12.5mg. We followed the study patients for 24 weeks to assess the changes in diastolic parameters on echocardiography such as mitral annular velocity (e’), E/e’, left atrial volume (LAV) and LV mass (LVM).

Results: ARB/HCTZ treatment significantly decreased systolic/diastolic blood pressure after 24 weeks ([154.6 ± 15.0 to 132.2 ± 12.4 mmHg; p < 0.0001; 87.1 ± 11.3 ± 76.3 ± 10.1 mmHg, p < .0001]. It significantly reduced LVM (171.5 ± 42.0 to 161.2 ± 41.7 mm, p < .0001), improved diastolic function (e’: 5.5 ± 1.4 to 6.5 ± 1.8 cm/s, p < .0001; E/e’: 12.1 ± 3.8 to 10.6 ± 3.7, p < .0001) and reduced LAV (42.2 ± 15.5 to 39.2 ± 14.5 mL, p < .0001). We measured BNP and hs-CRP in the study group, and found that they were also reduced after 24 week treatment (BNP: 48.6 ± 73.2 to 36.5 ± 55.7 µg/mL; p = .0006, hs-CRP: 0.5 ± 0.6 to 0.3 ± 0.7 mg/dL, p < .0001). A multivariate regression analysis demonstrated that changes in hs-CRP was an independent predictor of changes in e’ velocity (p = 0.001) along with systolic blood pressure, serum total cholesterol and BNP among clinical and biochemical parameters.

Conclusions: The present multicenter trial demonstrated that intensive treatment by a combination of ARB/HCTZ reduced LV hypertrophy and improved LV diastolic function in hypertensive patients who had not achieved optimal blood pressure after ARB/ACE-1 alone. Anti-inflammatory effect of ARB/HCTZ treatment might be involved in the improvement of LV diastolic function.

**7A.12 BETA-BLOCKERS ARE RELATIVELY OVERUSED IN FINLAND. WHY ARE WE NOT FOLLOWING THE GUIDELINES? RESULTS FROM A LARGE NATIONAL DATABASE BETWEEN 2000 AND 2006**

T. Ahola1, A. Jula1, I. Kantola1, P. Puukka2, A. Reunanen3. 1Turku University Hospital, Turku-Finland, 2National Institute for Health and Welfare, Turku-Finland, 3National Institute for Health and Welfare, Helsinkis-Finland

Objective: To uncover changes and differences in the utilization of antihypertensive drugs and drug combinations for various treated hypertensive patients between late 2000 and late 2006 and, in addition, to determine whether evidence-based recommendations of hypertension management and/or new onset diseases during the follow-up time have been guiding in the selection of drugs.

Design and Method: From the databases of the Social Insurance Institution of Finland, 274791 severe hypertensives and 70185 uncomplicated hypertensives who had purchased prescribed antihypertensive drugs in late 2000 and in late 2006 were identified. Changes in concomitant diseases and pharmacotherapy (including triple combinations), were analyzed on individual level. In addition, the prevalence of drugs and chronic diseases and their relative differences in 2006, between 274791 formerly treated hypertensives and 91843 newly treated hypertensives, were assessed after adjustment with age, sex, and district of living.

Results: Among severe hypertensives, utilization of antihypertensive drugs became more frequent and multiple, mainly because of aging and new-onset of diseases, especially diabetes and coronary heart disease. However, among uncomplicated hypertensives, utilization of antihypertensive drugs increased without changes in the disease profiles of the patients. The triple combination used most frequently became a BB and a diuretic combined with either a CCB or an ARB. RAS blockers were used more frequently in monotherapy and in 2-drug combinations among newly treated hypertensives than among those treated formerly. Still, RAS blockers were prescribed, on the average, as a second-line or third-line drug after BBs, which were used in monotherapy more frequently than other antihypertensive agents, even among newly treated hypertensives, without compelling indication for their use.

Conclusions: BBs are relatively overused in Finland, especially in monotherapy. Treatment guidelines of hypertension are insufficiently followed, particularly among those with a longer history of antihypertensive pharmacotherapy, indicating that clinicians do not easily change their prescribing patterns.
**EVALUATION OF BLOOD PRESSURE BEFORE AND AFTER PERCUTANEOUS TRANSLUMINAL RENAL ANGIOPLASTY IN FIBROMUSCULAR DYSPLASIA**

J. Smit1, T. Wierema2, P. De Leeuw1.  
1Maastricht University Medical Centre, Maastricht-The Netherlands, 2Tweedesteden Ziekenhuis, Tilburg-The Netherlands

**Objective:** The objective of this study was to evaluate the effects of percutaneous transluminal renal angioplasty (PTRA) on blood pressure control and renal function in fibromuscular dysplasia (FMD).

**Design and Method:** 51 patients with treatment-resistant hypertension in whom FMD was diagnosed after renal angiography were compared with 51 essential hypertensive patients who had a negative angiography for the same indication. Patients in the target group were matched for gender and age. Blood pressure, count of antihypertensive medication according to WHO/DDD method and renal function (serum creatinine) were assessed at 0, 1, 6 and 12 months of follow-up. Patients were also assessed for cure (RR equal or higher with more medication) 1 year after angiography. Complications of angiography were also registered.

**Results:** Groups did not differ significantly with regard to baseline characteristics. In the FMD group, average blood pressure levels decreased from 172.9/97.0 mmHg to 155.9/90.9 mmHg (p < 0.001) at 12 months follow-up, without an increase in medication (p = 0.61). Blood pressure in the control group decreased from 168.9/96.2 mmHg to 157.3/89.4 mmHg (p = 0.01). In the FMD group 4.5% was cured at 12 months, 47.7% improved and 47.8% failed. In the control group 2.4% cured, 56.1% improved and 41.5% failed. Serum creatinine values increased from 77.4 ± 9.2 μmol/L to 81.9 ± 11.5 μmol/L (p = 0.022) in the FMD group and from 76.8 ± 8.8 μmol/L to 78.3 ± 9.1 μmol/L (p = 0.023) in the control group. Complications of angiography were seen in 6.9% (n = 7); 5 in the FMD group and 2 in the control group.

**Conclusions:** PTRA did result in better blood pressure control in patients with FMD as compared to treatment-resistant essential hypertension. Although there was little cure, FMD patients needed less antihypertensive medication. Also renal function may be better preserved after PTRA. However, PTRA resulted in more complications.
handling of the NO synthase inhibitor ADMA in subjects with unilateral low-grade ARAS.

**Design and Methods:** From our angiography cohort, we selected 20 subjects with unilateral low-grade (30-50%) ARAS and 20 subjects with unilateral significant ARAS (>50%). In addition, 20 matched (age, gender, BMI, renal function, cholesterol, smoking, cardiovascular events and DM) hypertensives (HT) with patent renal arteries were included for both groups. All underwent, selective mean renal blood flow (MRBF) measurements ([123Xenon washout] and selective blood sampling from the aorta and both renal veins, and renal angiography. Plasma [ADMA] were determined and the renal plasma clearance (CL) was calculated.

**Results:** [Arterial] ADMA did not differ between subjects with 30-50% ARAS and matched HT1, whereas ADMA was higher in subjects with >50% ARAS compared to matched HT2 (Fig A, p < 0.01). Subjects with 50% ARAS showed a difference in MRBF between the stenotic and non-stenotic kidney (157 vs. 199 ml/min/100g kidney, p = 0.02), subjects with 30-50% ARAS did not (186 vs. 194, p = 0.62). However, plasma CL of ADMA was already disturbed in the 30-50% ARAS kidneys compared to the contra-lateral non-stenotic kidneys (Fig B, p = 0.02). This difference was even more apparent in subjects with >50% ARAS (p < 0.01).

**Conclusion:** Subjects with low-grade stenosis show a disturbed renal elimination of ADMA despite obvious changes in [arterial] ADMA and renal blood flow. This may contribute to long-term renal NO-inhibition, hemodynamic changes and consequently early renal damage.

---

**7B.05 IMPAIRED RENAL FUNCTION IS ASSOCIATED WITH VASCULAR STIFFNESS AND INFLAMMATION IN PATIENTS WITH SEVERE CORONARY ARTERY DISEASE**

S.H. Rossi¹, E.P. McQuarrie², R.M. Mackenzie³, W.H. Miller¹, J.A. Dyment¹, M.U. Moreno⁴, C. Taurino⁵, A.M. Miller¹, U. Neisius⁴, G.A. Bergi⁶, Z. Burneikaitë⁷, J. Hoyle⁸, J.A. Hanna⁹, A.F. Dominiczak¹, C. Delles¹. ¹University of Glasgow, Glasgow-United Kingdom, ²Golden Jubilee National Hospital, Clydebank-United Kingdom, ³Gartnavel General Hospital, Glasgow-United Kingdom

**Objective:** In a previous pilot study we reported an inverse relationship between renal excretory function and vascular stiffness in patients with severe coronary artery disease (CAD). Inflammation and oxidative stress have been proposed as mediators of vascular stiffening in chronic kidney disease (CKD), but their role in patients with co-existing CAD and only mild-to-moderate impairment of renal function remains unclear.

**Design and Method:** We studied 119 patients with CAD prior to surgical coronary revascularisation and 81 subjects without CAD. Creatinine clearance (CLcr) and glomerular filtration rate (eGFR) were estimated using the Cockcroft-Gault and 4-variable MDRD formulas, respectively. Impaired renal function was defined as CKD stage 3 or 4. Vascular stiffness was assessed by measuring pulse wave velocity (PWV; SphygmoCor®). Circulating biomarkers were assessed in plasma using multiplexing technique (Lumex®).

**Results:** In the whole cohort, PWV was inversely correlated with CLcr (r = -0.386 p < 0.001). In patients with CAD, PWV was determined by CLcr (b = -0.322, p = 0.022) even after adjustment for blood pressure, diabetes, body mass index and LDL-cholesterol. Patients with CAD and impaired renal function had greater PWV (9.9 [4.0] vs 8.2 [2.9] m/s; p = 0.015) compared to those with CAD alone. Patients with CAD and impaired renal function were characterised by increased levels of intercellular adhesion molecule 1 (33.1 ± 11.6 vs 26.5 ± 5.8 ng/ml), E-selectin (16.6 [7.4] vs 10.4 [9.8] ng/ml), osteopontin (1.2 [2.4] vs 0.4 [1.2] ng/ml), leptin (12.6 [20.1] vs 7.8 [10.4] ng/ml) and adiponectin (7.8 [5.4] vs 4.6 [4.3] μg/mL; all P < 0.05) compared to those with CAD alone. Mononuclear cell superoxide production was not different (baseline: 66.8 [45.8] vs 51.6 [37.7], PMA stimulated, 813 ± 390 vs 820 ± 390 M Ui/min/106 cell; all P = n.s.) between patients with or without renal impairment.

**Conclusions:** Renal function is a strong determinant of vascular stiffness even in patients with severe atherosclerotic disease. This was paralleled by differences in markers of cell adhesion and adipokines. A greater number of adherent mononuclear cells could trigger inflammation and thereby accelerate vascular stiffening in patients with concomitant CKD, even if the superoxide release from individual cells appears not to be affected by renal impairment.

---

**7B.06 ARTERIAL STIFFNESS IS AN INDEPENDENT DETERMINANT OF COMPENSATORY HYPERFILTRATION AFTER KIDNEY DONATION**

P. Lesjer, J. Ribstein, G. du Callar, G. Mourad, A. Mimran. Lapeyronie Hospital, Montpellier-France

After kidney donation, the remaining kidney tends to hypertrophy thus limiting the initial loss of renal function. However, the potential determinants of this compensatory hyperfiltration (CHF) and the possible influence of arterial function are not known. In 26 normotensive healthy kidney donors (51 ± 9 yrs [mean ± SD], 22 females), glomerular filtration rate (GFR) was measured by the clearance of continuously infused [125I]DTPA and timed urine collections at baseline -i.e. before donation- and 1 year after donation. CHF was computed as post-donation GFR minus half of baseline GFR. Arterial function was assessed at baseline through carotid-femoral pulse wave velocity (PWV) and carotid augmentation index (AIx). After kidney donation, there were no significant changes in blood pressure (BP), but 2 subjects became hypertensive. GFR decreased from 104 ± 17 to 71 ± 11 ml/min/1.73m² [mean ± SD] and mean CHF was 19 ± 9 ml/min/1.73m². In univariate analysis, CHF was inversely correlated to baseline age (r = 0.15, p = 0.049) and PWV (r = 0.23, p = 0.012), but not mean BP or Alx. In multivariate analysis, CHF remained inversely correlated to PWV (p = 0.020), independently of baseline age and mean BP (model r² = 0.54, p = 0.002).

In conclusion, in healthy subjects, increased arterial stiffness seems to be associated with a limited magnitude of post-donation hyperfiltration. This could reflect an influence of arterial function on renal reserve, providing further insights into the relationship between macrocirculation and renal microcirculation.

---

**7B.07 SHORT-TERM EFFECTS OF INTRARENAL EPROSARTAN INFUSION ON THE RENAL HANDLING OF ASYMMETRIC DIMETHYLARGININE (ADMA)**


**Objective:** Studies with angiotensin II receptor blockers (ARBs) have shown a positive effect on vascular nitric oxide (NO) synthesis. Moreover, they possibly improve endothelial function by reducing asymmetric dimethylarginine (ADMA), a NO synthase inhibitor. However, the effects of ARBs on the renal NO-system and inhibition have not been totally clarified yet. Therefore, we investigated the short-term effects of intrarenal eprosartan infusion on the renal handling of ADMA in hypertensive subjects.

**Design and Methods:** In 84 hypertensive subjects, scheduled for renal angiography [plasma] of ADMA were assessed. Selective blood samples were drawn from the aorta [A] and both renal veins [V], before and after intrarenal eprosartan infusion (n = 71, doses 3 and 10 μg/kg/min, each for 15 minutes) or before and after intrarenal saline infusion (n = 15). Furthermore, selective mean renal blood flow (MRBF) was measured [133Xenon washout] before and directly after infusion of eprosartan. Plasma clearance (CL) of ADMA was calculated as (mean renal plasma flow * [(A-V)/A]).

**Results (Table):** [A] ADMA decreased after eprosartan infusion, whereas [V] increased. Consequently, the calculated plasma CL changed from net uptake in net production. MRBF increased (231 to 266 ml/min/100g kidney, p < 0.001), whereas intrarenal systolic and diastolic blood pressure decreased (132 to 124 mmHg, p < 0.05). We did not observe an eprosartan dose relation. Subjects treated with saline infusion did not show significant changes in [A], [V] or plasma CL of ADMA.
RENAL DOPAMINERGIC ACTIVITY IS INCREASED IN THE RENALASE KNOCKOUT MOUSE MODEL

Janete Queilhas-Santos, Paula Serrão, Cátia Fernandes-Cerqueira, Liliana Silva, Isabel Soares-Silva, Daria Sizova, Benedita Sampaio-Maia, Gary Desir, Manuel Pestana, Nephrology Research and Development Unit, Faculty of Medicine, Hospital S. João, Porto-Portugal, 2Institute of Pharmacology and Therapeutics, Faculty of Medicine, University of Porto, Porto-Portugal, 3Department of Medicine, Yale University School of Medicine, New Haven-USA, 4Faculty of Dental Medicine, University of Porto, Porto-Portugal

Renalase or MAO-C is a recently discovered oxidase produced mainly by the kidney and secreted into blood and urine where it can metabolize catecholamines, with preference for dopamine (DA). Renalase deficiency in a mouse knockout (KO) model causes increased plasma catecholamine levels, increased blood pressure, increased sensitivity to adrenergic stimulation and enhanced susceptibility to ischemic myocardial damage. DA of renal origin reduces tubular sodium reabsorption and controls blood pressure. The present study examined renal DA system activity in the renalase KO mouse model. Renal function as assessed by plasma creatinine, blood urea nitrogen and daily urinary excretion of sodium was reduced in KO mice (p < 0.05) without changes in renal tubular AADC activity (Vmax 472.0±97.2 nmol/mg prot/h; p = ns). In summary, renalase deficiency alone, in the absence of measurable changes in renal function, is associated with increased renal DA system activity. This occurs in spite of enhanced methylated of renal DA in KO mice. The increased renal DA system activity in COX mice appears to be mediated not only by deficient renalase or MAO-C activity (Vmax 10.45±0.55 vs. 12.09±0.87 nmol/mg prot/h; p = ns), but also by enhanced uptake of L-DOPA in renal proximal tubules. These data support the notion that the renal DA system activity may contribute to maintain sodium balance and control blood pressure in KO mice. Project supported by grant PIC/28/2029/2007 from FCT/FEERED. Queilhas-Santos J. supported by the fellowship SFRH/BD/39066/2007.

CONCLUSIONS: Acute intrarenal administration of eprosartan results in a decrease of systemic [A] ADMA. However, renal plasma CL of ADMA showed an inversion. This may be the result of eprosartan-related changes in ADMA transporters. Long-term effects of eprosartan on the renal handling of ADMA need further investigation.

7B.08 SUSTAINED REDUCTION OF CENTRAL SYMPATHETIC OUTFLOW AFTER RENAL DENERVATION IN END STAGE RENAL DISEASE

M. Schlaich1, G. Lambert1, E. Lambert1, H. Krum1, T. Walton1, P. Sobota1, M. Eister1, Baker IDI Heart and Diabetes Institute, Melbourne-Australia, 2Monash University and Alfred Hospital, Melbourne-Australia, 3Ardian Inc, Mountain View-USA

Objective: Sympathetic activation is a cardinal feature of end stage renal disease (ESRD) and contributes to the poor cardiovascular outcome in this patient cohort. Both efferent renal sympathetic nerve activity and afferent signaling via renal sensory nerves from the diseased kidneys play a crucial role in blood pressure regulation and hypertension commonly associated with ESRD. Here we report on the long term effect of renal denervation on central sympathetic outflow and blood pressure in a patient with ESRD.

Methods: Percutaneous endovascular radiofrequency ablation was performed in a 37 year old patient with ESRD and hypertension. To assess physiologic short and long terms responses to the intervention systemic blood pressure, whole body and renal noradrenaline spillover (radioisotrace dilution methodology at baseline and 3 months), and muscle sympathetic nerve activity (microneurography at baseline, 3, 12, and 33 months) were measured after treatment of both kidneys.

RESULTS: The patient underwent treatment of both kidneys in one session. Serial angiographic evaluation before, directly after and 3 months post procedure confirmed the absence of pathologic findings in the treated renal arteries. Compared to baseline we observed a reduction in renal (from 130 to 101 ng/min) and whole body noradrenaline spillover (from 761 to 646 ng/min) at 3 months post procedure. Serial assessment of central sympathetic outflow revealed a gradual normalization of muscle sympathetic nerve activity from 46 bursts/min at baseline to 33, 21, and 19 bursts/min at 3, 12, and 33 months follow up, respectively. These changes were accompanied by a reduction in clinic blood pressure from 155/95 mmHg at baseline to 131/81 mmHg at 33 months follow up despite reduction of the antihypertensive treatment regimen from initially five to one drug at 33 months follow up.

CONCLUSIONS: Selective denervation of the kidney in ESRD is associated with a reduction in renal sympathetic nerve activity and gradual normalization of central sympathetic outflow over the course of ~12 months. This normalization of central sympathetic outflow is sustained over at least 33 months and associated with improved blood pressure control and reduced requirement of antihypertensive drug therapy. These findings corroborate the importance of efferent sympathetic and afferent sensory activity of renal nerves in ESRD and indicate that selective renal denervation has a sustained effect on sympathetic nerve activity and blood pressure.
ORAL SESSION 7C
RISK FACTORS

7C.01 MOST IMPORTANT CONSTITUENTS OF QUALITY OF LIFE OF ELDERLY PEOPLE WITH ARTERIAL HYPERTENSION

L. Yankovskaya. Grodno State Medical University, Grodno-Belarus

Objective: The aim of the study was to assess the quality of life (QL) of elderly people with arterial hypertension (AH) in Belarus.

Design and Methods: A single screening study in representative sample of 820 elderly individuals was performed. AH was detected by patients history according to ESHT0 criteria. The patients were divided into two groups: group I included 468 patients aged 65-69 years, group II included 352 patients of 70-74 years. QL was estimated by means of the computerised NAIF method. The integral QL index (IQLI) including six constituents - physical mobility (PM), emotional state (ES), sexual function (SF), social status (SS), cognitive function (CF) and economic status (EcS) - was calculated in percents. QL was considered to be good if IQLI made up 75-100%, moderately reduced if IQLI averaged 74.9-82.0, strongly reduced if IQLI was 49.9% and below.

Results: QL was determined to be good only in 7% of respondents from group I and 3% of respondents from group II. QL was determined to be moderately reduced in 66.5% of respondents from group I and 54% of respondents from group II. QL was determined to be markedly reduced in 26.5% of respondents from group I and 43% of respondents from group II. A single-factor analysis of variance showed age to be an independent factor lowering QL in elderly people with AH (F = 23.5; p < 0.0001). The IQLI in the second group (51 ± 12%) was lower (p < 0.05), than in the first group (56 ± 14%). Reduction of mean values of QL constituents with age (p < 0.05) was demonstrated on: PhM in group I – 50 ± 16%, group II – 45 ± 16%; SS in group I – 54 ± 16%; in group II – 49 ± 12%; CF in group I – 0.65 ± 0.14, in group II – 0.57 ± 0.12. Factor analysis revealed key factors defining QL of elderly people with AH. In group I QL is 40% dependent on ES (0.79), CF (0.77), PhM (0.71) and 16% on SF (0.74). In group II QL is 44% dependent on ES (0.77), CF (0.79), PhM (0.74), SS (0.74). Analysis of correlation coefficients demonstrated that QL of elderly people with AH is most strongly and statistically significantly (p < 0.05) influenced by PhM (R = 0.80), CF (R = 0.75), ES (R = 0.74), SS (R = 0.73). EcS does not significantly influence QL of elderly people with AH.

Conclusions: QL of elderly people with AH is reduced. QL reduction depends on age. The most significant correlating factors leading to the reduction of QL of elderly people with AH are ES (irritability, sensation of neglect), CF (memory deterioration) and reduced PhM. An additional factor influencing significantly QL of elderly people (group II) is SS (people don’t leave their homes, rarely meet their relatives and friends, often stay alone), which requires special attention.

7C.02 DAIRY CONSUMPTION AND INCIDENCE OF HYPERTENSION: DOSE-RESPONSE META-ANALYSIS OF PROSPECTIVE COHORT STUDIES

L.D.M. Verberne1, S.S. Soedamah-Muthu1, E.L. Ding2, F.B. Hu2, J.M. Geleijnse1. 1Wageningen University, Wageningen-The Netherlands, 2Harvard School of Public Health, Boston-USA

Objective: To examine dose-response associations between the intakes of total dairy, low-fat dairy, high-fat dairy, and different types of dairy products with hypertension risk by means of a meta-analysis of prospective cohort studies.

Design and Method: A systematic literature search was conducted until November 2010, using PubMed, Embase, Scopus, and hand search, to identify eligible studies. The generalized least squares for trend estimation method was used to calculate a relative risk for a certain unit of exposure. Random effects models were used to pool the data in forest plots. Between study heterogeneity was assessed via the F statistic. Ding’s Spaghetti plot was used to illustrate the direction of the association.

Results: A total of 1709 articles were screened from which nine prospective cohort studies were selected. The nine studies comprised 57,256 individuals and 15,367 cases of incident hypertension with a mean follow-up time of 2-15 years. Consumption of total dairy (9 studies), low-fat dairy (6 studies) and milk products (8 studies) was associated with a lower risk of hypertension. The pooled relative risks per intake of 200 g/d were 0.97 (95% CI:0.95-0.99) for total dairy, 0.96 (95% CI:0.93-0.99) for low-fat dairy, and 0.97 (95% CI:0.95-0.99) for milk products. In none of the analyses statistical heterogeneity was present. No significant dose-response associations were found for the intake of high-fat dairy (6 studies), fermented dairy (4 studies), yogurt (5 studies), and cheese (8 studies), with pooled relative risks of approximately 1.

Conclusions: This meta-analysis indicates that the intake of dairy, and in particular low-fat dairy and milk products, may reduce the risk of hypertension.

7C.03 HYPERTENSION MANAGEMENT IN A LOW-INCOME NEIGHBOURHOOD: A COMMUNITY-BASED CASE-CONTROL STUDY IN SINGAPORE

L. E. Wee, G.C.H. Koh, W.Y. Xeo, B. Seow, R.T. Chin. Yong Loo Lin School of Medicine, National University of Singapore, Singapore-Singapore

Aims: Factors influencing hypertension management in low-income settings are largely unknown in urban Asian communities. We determined hypertension awareness, treatment, and control in a multi-ethnic urban low-income Asian community in Singapore; comparing these estimates against a better-off community in the same geographic location.

Methods: We studied a neighborhood of 3 blocks of rented public flats (poorer community) and 3 adjacent blocks of owner-occupied public flats (better-off community) in Taman Jurong, Singapore. Blood pressure (BP) was measured at baseline; information on demographic details and reasons for irregular BP screening, monitoring and treatment were collected from 2000-2010. In 2004, newly diagnosed hypertensives and known hypertensives from the poorer community non-compliant with treatment/with non-optimal BP control were recruited into a 1-year free followup program in which patients were visited monthly by medical volunteers to encourage good hypertension management.

Results: The participation rate was 90.0% (359/400) for the rental-flat community and 70.2% (351/500) for the owner-occupied flats. Prevalence, awareness, treatment and control in the low-income community (rental flats) was 63.9% (228/357), 61.8% (141/228), 69.5% (98/141) and 43.9% (43/98); adjusting for sociodemographic variables, awareness, treatment, and control were poorer in the low-income community compared to the better-off community. In the low-income community, awareness of hypertension was higher amongst diabetics, dyslipidemics, those = 60yrs and those with regular access to doctors. Treatment was more likely amongst those = 60yrs, but less likely amongst those needing financial aid. Controlled BP was less likely in the employed. The high cost of screening and further treatment, if diagnosed with hypertension, was the most frequently cited barrier amongst the low-income group. 209 patients from the low-income community were included in the study. After followup, treatment amongst known hypertensives increased significantly [63.4% (52/82) to 92.7% (76/82), p < 0.001]; and amongst the known hypertensives on treatment, blood pressure control improved from 42.3% (22/52) to 78.9% (60/76) (p < 0.001).

Conclusion: Hypertension management in lower-income is poorer than the higher-income. While improved finances might lead to increased treatment, employment can lead to poorer control. Misperceptions and cost need to be addressed. In the lower-income community, free followup improved hypertension management in known hypertensives, but not in newly diagnosed hypertensives.

7C.04 C-REACTIVE PROTEIN IS ASSOCIATED WITH DETERIORATED HEALTH RELATED QUALITY OF LIFE IN HYPERTENSIVE SUBJECTS

V. Katsi1, G. Sourvetis1, K. Kontouangelos1, S. Veioglou1, K. Koundi2, I. Vlasseros1, P. Sakkas1, C.H. Stefanadis1, G.N. Papadimitriou1, I. Kalikazaros1. 1Hippokration Hospital, Athens-Greece, 2Eginitio Hospital, Athens-Greece

Abstracts e105
Background: The association between essential hypertension (EH) and low scores of health-related quality of life (HRQoL) is well established, while inflammation is emerging as a precursor and predictor of cardiovascular disease. We assessed the hypothesis that there might be a possible association between high sensitivity C-reactive protein (hs-CRP), a time-honored marker of inflammation and HRQoL, in the setting of EH.

Methods: We studied 154 consecutive subjects (aged = 58 ± 17 years, male = 78 ), with stage I-II untreated uncomplicated EH (office blood pressure = 150/98 mm Hg). In all participants venous blood samples were drawn for evaluation of hs-CRP levels. To assess the HRQoL, the widely validated Short Form 36 (SF-36) General Health Survey questionnaire was administered. The SF-36 is a generic HRQoL instrument that includes eight subscales. These subscales were further grouped into two summary scales: the physical component summary (PCS) and the mental component summary (MCS).

Results: There was a significant negative correlation between hs-CRP levels and scores in six dimensions of SF-36, thus with the total score. (Table).

Conclusions: In conclusion, there is an intriguing link between inflammation and low scores of health-related quality of life in the setting of essential hypertension. The pathophysiologic substrate of these interrelationships needs further investigation through large scale prospective studies.

Correlations of SF-36 scales with hs-CRP

<table>
<thead>
<tr>
<th>SF-36 SCALES</th>
<th>SPEARMAN'S RHO</th>
<th>P-VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical Functioning</td>
<td>-0.484</td>
<td>0.003</td>
</tr>
<tr>
<td>Role Physical</td>
<td>-0.314</td>
<td>0.005</td>
</tr>
<tr>
<td>Bodily Pain</td>
<td>-0.517</td>
<td>0.001</td>
</tr>
<tr>
<td>General Health</td>
<td>-0.383</td>
<td>0.027</td>
</tr>
<tr>
<td>Vitality</td>
<td>-0.378</td>
<td>0.032</td>
</tr>
<tr>
<td>Role Emotional</td>
<td>-0.274</td>
<td>0.047</td>
</tr>
<tr>
<td>PCS</td>
<td>-0.477</td>
<td>0.005</td>
</tr>
<tr>
<td>MCS</td>
<td>-0.182</td>
<td>0.377</td>
</tr>
<tr>
<td>Total SF-36 score</td>
<td>-0.432</td>
<td>0.004</td>
</tr>
</tbody>
</table>

Design and Methods: The data presented here were obtained from random samples of adult population recruited in 9 Italian regions in the framework of the National Health Institute Cardiovascular Epidemiology Observatory/Health Examination Survey 2008-2011 and composed overall by 784 men and 800 women aged 35-79 yrs. Sodium and potassium intakes were estimated from 24-hour urine collections using standardized procedures. Urinary creatinine excretion was used to estimate the accuracy of urine collection. Nutritional habits, anthropometrics and metabolic risk factors was obtained through standardized questionnaires, clinical examination and serum biochemistry.

Results: The average urinary sodium excretion was 191mmol(or 11.2g of salt/day) among men and 147mmol(or 8.7g of salt/day) among women(range 53-549 and 32-532mmol, respectively), suggesting that 97% of men and 88% of women had a consumption higher than the WHO recommended of 9g/day. The average urinary potassium excretion was 61mmol for men and 52mmol for women(range 21-137mmol and 17-121mmol), thus 95% of men and 98% of women having an intake lower than 100 mmol/day, the amount recommended by the ESH/ESC guidelines for prevention of hypertension. The mean urinary Na/K ratio was 3.1 for men and 2.8 for women, i.e. threefold greater than the desirable level of 0.85. The highest levels of sodium intake were observed in Southern regions, while no geographical differences were seen for potassium intake. There was a direct relationship between sodium and potassium excretion with body weight, in both women and men. Sodium and potassium excretion were 133 ± 53 (Mean ± SD: mmol/24hours) and 50 ± 17 in normal weight women;139 ± 44 and 52 ± 16 in overweight women;177 ± 69 and 56 ± 18 in obese women (p for trend <0.05 for both). Sodium and potassium excretion were 172 ± 67 and 56 ± 18 in normal weight men;190 ± 66 and 61 ± 19 in overweight men;215 ± 75 and 66 ± 21 in obese men (pc<0.01 for both).

Conclusions: These preliminary results indicate that in all the Italian regions thus far surveyed, in both men and women, dietary sodium intake was largely higher and potassium intake definitely lower than the recommended intakes. These findings further highlight the critical direct association between overweight/obesity and excess habitual salt intake.

References:

7C.05 ABO AND RHESUS BLOOD GROUPS AND CARDIOVASCULAR RISK IN ESSENTIAL HYPERTENSIVE PATIENTS

S. M. Kyvelou1, G. Vysous1, E. Karpanou1, V. Tzamou1, T. Gialerinos1, C Stefanadis2, 11st Cardiology Clinic University of Athens Hippokration Hospital, Athens-Greece, 21st Cardiology Clinic Onassis Cardiosurgery Center, Athens-Greece

Objective: Many studies have suggested an association between blood groups and various manifestations of heart disease. We have conducted the present study, in a large cohort of essential hypertensive patients, in order to assess any possible relations of different blood groups and the possible effect of the Rhesus system to total cardiovascular risk.

Design and Methods: The study finally comprised 6533 essential hypertensive, non-diabetic patients who were subjected to physical examination, medical history, anthropometric measurements, repeated clinical BP measurements, blood sampling for routine laboratory examinations and 24-hour ABPM and echocardiographic study. Furthermore patients were divided according to the ABO and the Rhesus D antigen. Total 10-years cardiovascular risk was estimated after calculation of the Framingham Risk Score (FRS) and Heart Score (HS).

Results: Patients were divided in two groups, Rhesus positive (n = 5462) and Rhesus negative (n = 1071). Furthermore, patients were divided in eight subgroups according to ABO group and Rhesus blood group systems. Patients with B Rhesus negative blood group presented with the highest Framingham and Heart risk score while patients with AB Rhesus negative blood group with lowest. There are differences remained significant even after adjustment for age and gender.

Conclusions: AB Rhesus negative phenotype offers protection against cardiovascular risk of essential hypertensive Greek patients with Rhesus blood type does not affect risk profile per se.

7C.06 SODIUM AND POTASSIUM INTAKE OF THE ITALIAN ADULT POPULATION: PRELIMINARY RESULTS OF THE MINISAL-GIRCSI STUDY

R. Ippolito1, C. Donfrancesco1, C. L.O. Noce1, G. Russo1, L. Palmieri2, D. Yanuzzi1, F. Galli1, S. Giampaoli3, P. Strazzullo4, 1Dept. of Clin and Exp Medicine Federico II University OF Naples, Napoli-Italy, 2National Institute of Health, Roma-Italy, 3Center for Cardiovascular Prevention, ASS `, Udine-Italy

Objective: Excess sodium and inadequate potassium dietary intakes are both causally related to risk of hypertension and cardiovascular disease. However, scanty and largely inaccurate information is available about sodium and potassium intake in Italy. The MINISAL-GIRCSI program was promoted and implemented by the Interdisciplinary Working Group for Reduction of Salt Intake in Italy (GIRCSI) with the support of the Ministry of Health to provide a reliable estimate of the dietary sodium and potassium intake of the Italian population.

Design and Methods: The population sample included 430 initially normotensive adult men recruited in 9 Italian regions in the framework of the National Health Institute Cardiovascular Epidemiology Observatory/Health Examination Survey 2008-2011 and composed in total by 784 men and 800 women aged 35-79 yrs. Sodium and potassium intakes were estimated from 24-hour urine collections using standardized procedures. Urinary creatinine excretion was used to estimate the accuracy of urine collection. Nutritional habits, anthropometrics and metabolic risk factors was obtained through standardized questionnaires, clinical examination and serum biochemistry.

Results: The average urinary sodium excretion was 191mmol(or 11.2g of salt/day) among men and 147mmol(or 8.7g of salt/day) among women(range 53-549 and 32-532mmol, respectively), suggesting that 97% of men and 88% of women had a consumption higher than the WHO recommended of 9g/day. The average urinary potassium excretion was 61mmol for men and 52mmol for women(range 21-137mmol and 17-121mmol), thus 95% of men and 98% of women having an intake lower than 100 mmol/day, the amount recommended by the ESH/ESC guidelines for prevention of hypertension. The mean urinary Na/K ratio was 3.1 for men and 2.8 for women, i.e. threefold greater than the desirable level of 0.85. The highest levels of sodium intake were observed in Southern regions, while no geographical differences were seen for potassium intake. There was a direct relationship between sodium and potassium excretion with body weight, in both women and men. Sodium and potassium excretion were 133 ± 53 (Mean ± SD: mmol/24hours) and 50 ± 17 in normal weight women;139 ± 44 and 52 ± 16 in overweight women;177 ± 69 and 56 ± 18 in obese women (p for trend <0.05 for both). Sodium and potassium excretion were 172 ± 67 and 56 ± 18 in normal weight men;190 ± 66 and 61 ± 19 in overweight men;215 ± 75 and 66 ± 21 in obese men (pc<0.01 for both).

Conclusions: These preliminary results indicate that in all the Italian regions thus far surveyed, in both men and women, dietary sodium intake was largely higher and potassium intake definitely lower than the recommended intakes. These findings further highlight the critical direct association between overweight/obesity and excess habitual salt intake.

7C.07 OLIVETTI HEART STUDY: CYCAREETTE SMOKING PREVENTS THE CHANGES IN BLOOD PRESSURE LEVELS AND THE RISK OF HYPERTENSION

L. D’Elia, D. De Palma, G. Rossi, R. Ippolito, P. Strazzullo, F. Gallletti, Dept. of Clin and Exp Medicine Federico II University of Naples, Napoli-Italy

Objective: Few studies evaluated the role of cigarette smoking on future incidence of hypertension (HPT) and their results were not conclusive. Therefore, the aim of this study was to assess the effect of cigarette smoking on changes in blood pressure over time and on the risk to develop hypertension in an 8 year-follow-up investigation of a sample of adult male population (The Olivetti Heart Study).

Design and Methods: The population sample included 430 initially normotensive men, with normal renal function and without diabetes, who were examined in 1994-95 (baseline) and after 8 years (2002-04).

Results: Baseline prevalence of cigarette smoking was 49%. BMI, diastolic blood pressure (BP) and mean arterial pressure, at baseline, were lower in smokers (S, n = 212) than in non-smokers (NS, n = 218). After 8 years, the changes (Δ) in BP values were significantly higher in S than in NS (Δ systolic BP: +16.0 ± 1.02 vs +12.4 ± 0.87 mmHg, p = 0.007; Δ Diastolic BP: +10.3 ± 0.69 vs +8.1 ± 0.56 mmHg, p = 0.015; Δ mean Δ, despite the influence of drug therapy meanwhile prescribed to most of the hypertensive participants. The overall incidence of hypertension was 33% in 8 years, 56% among smokers.
and 47% in non-smokers (p = 0.04). Multivariate analysis showed that smoking status significantly predicted the development of HPT, upon accounting for basal age, BMI, physical activity, alcohol use, GFR, Home index and Systolic BP (OR: 1.83, 95%CI: 1.19–2.82, p = 0.006). Furthermore, the number of years of smoking was positively associated with the pulse pressure levels after 8-year (r = 0.21, p = 0.003).

**Conclusions:** In this sample of initially normotensive men, smoking status predicted: i) the increments in BP during follow-up in the population overall, and ii) the risk to develop HPT, independently of the main confounders. Moreover, the duration of smoking habit was directly related to higher BP levels over 8 years.

**Results:**

In this sample of initially normotensive men, smoking status predicted: i) the increments in BP during follow-up in the population overall, and ii) the risk to develop HPT, independently of the main confounders. Moreover, the duration of smoking habit was directly related to higher BP levels over 8 years.

**Conclusion:** Higher caffeine intake is associated with reduced risk of hypertension in the general adult population. Smoking seems to modify the effects of caffeine intake on blood pressure and hypertension remains controversial. In addition, the effect modification of smoking on the relation between caffeine intake and hypertension has not been previously considered in population-based studies.

**Design and Methods:** Population-based cross-sectional study (CoLaus) including adults in Switzerland. Blood pressure was measured thrice (oscillometric method) and the average of the last two blood pressure readings was used for analyses. Hypertension was defined as mean systolic blood pressure ≥140 mmHg or mean diastolic blood pressure ≥90 mmHg or presence of anti-hypertensive medication. Multiple regression analysis was used to test the association between reported caffeine beverages intake and hypertension, while adjusting for major confounding factors (age, sex, BMI, contraceptive use, total cholesterol, triglycerides, diabetes, alcohol, CKD-EPI). Model adjusted p value for multiple comparisons was 0.019. Interactions between smoking and reported caffeine intake were tested. We conducted additional analyses in participants without any medication and participants not aware of having hypertension. We replicated our findings using food frequency questionnaire data on coffee consumption from another independent population-based study (Bus Santé, N = 7573).

**Objectives:**

- To determine the prevalence of cardiovascular risk factors in the population attending the primary care centers of the Region of Madrid.
- To analyze the prevalence of cardiovascular risk factors and the population attending the primary care centers of the Region of Madrid.
- To assess the effect of self-administered risk assessment and educational intervention on cardiovascular risk profile.

**Design and Method:** An observational study including all the population 24 year and older registered in one of the primary care centers of 6 Health Areas of the Region of Madrid who had at least one visit to a primary care center during 2006. The source of information was the electronic medical record. Variables assessed were: prevalence of hypertension, dyslipidemia, diabetes and obesity, stratified by age, sex and income.

**Results:** The population was composed by 1,318,020 individuals. The prevalence of hypertension was 27.2%, of dyslipidemia 20.7%, of obesity 12.4% and 9% of diabetes. All those prevalences increased with age. Hypertension and obesity were more frequent among women (28.1% vs 26.1%, and 14.1% vs 10.3%, respectively). People with low income levels showed a higher prevalence than high income levels of hypertension (30.5%); dyslipidemia (21.9%); obesity (15.1%); and diabetes (10.6%).

**Conclusions:** Cardiovascular risk factors represent a significant public health problem. This population assessment using information extracted from electronic medical records in primary care in Spain indicates and increased prevalence in advanced ages, the existence of differences in the prevalence of those factors between man and women, and the existence of differences in low socio-economic groups. A prospective analysis will follow up this population to assess the long term evolution of those cardiovascular risk factors.
and glucose level (present in lower educated population), should be differentiated with described seasonal shift in autumn and winter period. Interventional educational program based on medical Avatar system seem to be efficient tool for modification of CV risk factors. Our data indicate that the interventional approach should be individualized to the target population, considering differences related with education level.

<table>
<thead>
<tr>
<th>Table: Change in CV profile 6 months after Avatar session</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline vs 6 months after intervention; (Women/Men); *p&lt;0.05, **p&lt;0.01</td>
</tr>
<tr>
<td>All (290/55)</td>
</tr>
<tr>
<td>Age (years)</td>
</tr>
<tr>
<td>SBP [mmHg]</td>
</tr>
<tr>
<td>DBP [mmHg]</td>
</tr>
<tr>
<td>TC (mg/dL)</td>
</tr>
<tr>
<td>FPG [mg/dL]</td>
</tr>
</tbody>
</table>

---

**7C.12 THE ROLE OF MATERNAL MALARIA IN THE RISE OF BLOOD PRESSURE IN NIGERIAN INFANTS**

Omolola Ayoola (Univ Ibadan), I Gemmell, PE Clayton, J. K. Cruickshank. University of Manchester, Manchester-United Kingdom

**Objective:** We established a birth cohort in Nigeria, where hypertension and its complications are increasingly common, to assess the impact of maternal malaria on blood pressure (BP) in Nigerian infants at one year, adjusting for early growth.

**Methods:** Healthy pregnant women were followed to delivery at Adeoyo Maternity Hospital, Ibadan with blood films for malaria parasites throughout delivery. Anthropometric and BP measures were carried out on 318 babies, all followed from birth to 3 and 12 months. Analysis used multiple regression on longitudinal data.

**Results:** Babies whose mothers had malaria in pregnancy (52%) were shorter, smaller and thinner at birth and remained smaller at 1 year, most marked in boys, whose BP adjusted for weight at 3 and 12 months was higher if exposed to maternal malaria (p < 0.05). Change in SBP over the first year was greater in boys than girls (20.9 vs 15.7mmHg p = 0.002) and in those exposed to maternal malaria, this effect being most significant in girls (18.7 vs 12.7mmHg, p = 0.02). After exposure to maternal malaria boys' first year growth was poor and associated with a large SBP change while such girls' first year growth was better than in boys, but also associated with a large increase in SBP.

**Conclusions:** Intrauterine exposure to malaria appears to have important gender-dependent effects on growth and changes in infant BP and may contribue to the global burden of hypertension.
ORAL SESSION

ORAL SESSION 7D

EPILOGOLOGY

7D.01 EFFECTS OF PREHYPERTENSION AND HYPERTENSION SUBTYPE ON CORONARY HEART DISEASE IN THE ASIA-PACIFIC REGION

H. Arima Y. Murakami M. Woodward, on behalf of the Asia Pacific Cohort Studies Collaboration. The George Institute for Global Health, Sydney-Australia

Objective: The Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC7) defined blood pressure (BP) levels of 120-139/80-89 mmHg as prehypertension and those of ≥140/90 mmHg as hypertension. Hypertension is logically divided into three main categories: isolated diastolic (IDH: systolic BP <140 mmHg and diastolic BP ≥90 mmHg), isolated systolic (ISH: systolic BP ≥140 mmHg and diastolic BP <90 mmHg) and systolic-diastolic hypertension (SDH: systolic BP ≥140 mmHg and diastolic BP ≥90 mmHg). While there is clear evidence that ISH and SDH increase the risks of future coronary events, there remains uncertainty about the effects of IDH. The objective was to determine the effects of prehypertension and hypertension subtypes (IDH, ISH and SDH) on the risks of coronary heart disease in the Asia-Pacific Region.

Design and Method: The Asia Pacific Cohort Studies Collaboration is an individual participant data overview conducted by the principal investigators of cohort studies in the region. This analysis included a total of 3,46570 participants from 36 cohort studies. Outcome was coronary heart disease. The relationship between BP categories and stroke were explored using Cox proportional hazards models adjusted for age, sex, cholesterol and smoking.

Results: Compared with normal BP (<120/80mmHg), hazard ratios (95% confidence intervals [CI]) of coronary heart disease were 1.31 (1.14–1.50) for prehypertension, 1.74 (1.43–2.12) for IDH, 1.76 (1.54–2.01) for ISH and 2.47 (2.16–2.82) for SDH.

Conclusions: In the Asia-Pacific region, prehypertension and all hypertension subtypes including IDH were clearly associated with increased risks of coronary heart disease.

7D.02 RELATIONSHIP BETWEEN SALT INTAKE AND CENTRAL AORTIC HEMODYNAMICS IN A COHORT OF UNTREATED HYPERTENSIVE PATIENTS

J. Polonia, J.A. Silva, S. Bertoquini, L. Barbosa. BP Unit Hospital Pedro Hispano, Matosinhos-Portugal

Introduction: Central pulse pressure (PPc) predicts cardiovascular (CV) outcomes. High salt intake has been related with blood pressure (BP) rise as well as with increased CV risk particularly with stroke.

Aim & Methods: The aim of the present study was to examine in untreated hypertensive subjects the relationship between salt intake and central aortic hemodynamics and PPc (radial and carotid applanation tonometry, Sphygmocor) and pulse wave velocity (PWV, Compilor).

Results: We evaluate 232 untreated nondiabetic hypertensive patients (64% female) aged 51+13 years, BMI 29.5±Kg/m2, PWV 11.1±2.3 m/s, office pulse pressure (PPo) 64±17 mm Hg, 24h pulse pressure (PP24h) 53±10 mm Hg, nighttime systolic BP fall 9.4 ± 6.9%, central pulse pressure (cPP) 48±10 mm Hg, central augmentation pressure (Aug P) 144±29 mm Hg and central augmentation index (Alx) 27.6±15.6%, 24h urinary sodium excretion (NaUr) 202±71 mEq/day, potassium (KUr) 49±16 mmol/dL. After adjustment for age, BMI, gender, smoking, PWV and MAPc, the 24h urinary sodium excretion (but not urinary Na/K+ ratio) was independently associated with central PP (P < 0.02) and 24h PP and central Alx (both P < 0.05).

Conclusion: Our data suggest that in these untreated hypertensive patients high salt intake is associated with abnormal central hemodynamics and increased central BP independently of peripheral BP. It is plausible that by these effects high salt intake may aggravate CV prognosis whereas reduction in salt intake is prone to improve central pressures and CV prognosis.

7D.03 BLOOD PRESSURE CONTROL IN A SPANISH HYPERTENSIVE POPULATION AGED 80 YEARS OR OLDER ATTENDED IN PRIMARY CARE SETTINGS (THE PRESCAP 2010 STUDY)

G.C. Rodríguez Roca1, J.J. Listerri Caro2, F.J. Alonso Moreno3, L.M. Artigao Rodenas4, V. Barrios Alonson5, J. Polo Garcia6, C. Escobar Cervantes7, J.A. Santos Rodriguez3, J.M. Fernandez Toro8, D. Asensio Torres9, on behalf of the working group of arterial hypertension of the Spanish Society of Primary Care physicians (Group HTA / Semergen) and the PreScap 2010 investigators. 1Centro de Salud La Puebla de Montalbán, Toledo-Spain, 2Centro de Salud Ingeniero Joaquín Benlloch, Valencia-Spain, 3Centro de Salud Sillería, Toledo-Spain, 4Centro de Salud Zona III, Albacete-Spain, 5Servicio de Cardiología Hospital Ramón y Cajal, Madrid-Spain, 6Centro de Salud Cañar de Cáceres, Cáceres-Spain, 7Hospital Infanta Sofia, Madrid-Spain, 8Centro de Salud de Riancho, Coruña-Spain, 9Centro de Salud Zona Centro, Cáceres-Spain, 10Departamento Médico. Almirall S.A., Barcelona-Spain

Objective: To analyze the degree of blood pressure (BP) control in a Spanish hypertensive population aged 80 years or older, attended in a Primary Care (PC) setting.

Design and Method: Epidemiological, observational, cross-sectional and multicentric study carried out in the 17 Autonomous Regions of Spain. Patients aged ≥ 80 years, with an established clinical diagnosis of hypertension and with antihypertensive treatment, were included in this analysis. BP was measured following European Guidelines (ESH/ESC 2007), and BP control was regarded as optimum when SBP/DBP was <140/90 mmHg (Reappraisal ESH 2009). Statistical analysis was performed using the SAS 9.2 package.

Results: A total of 1,540 hypertensive patients (mean age 83.5 ± 3.1 years; 61.9% women) were included. 63.0% of patients had a sedentary lifestyle, 53.2% dyslipidaemia and 46.6% abdominal obesity. Left ventricular hypertrophy was present in 12.1% of patients, diabetes mellitus in 53.2%, heart disease in 27.5% (48.7% ischemic cardiopathy, 39.2% heart failure and 12.1% ischemic cardiopathy and heart failure), and 13.7% nephropathy. A total of 72.3% of patients were treated with combination therapy (47.4% 2 drugs, 19.2% 3 drugs and 5.7% more than 3 drugs). Mean SBP was 156.7 ± 15.2 mmHg and the mean DBP was 75.2 ± 9.8 mmHg. 59.9% (95% CI: 57.4-62.3%) showed good SBP and DBP control, 61.3% (95%CI: 58.9-63.7) only SBP control and 91.4% (95%CI: 90.0-92.8) only DBP control.

Conclusion: The results of PreScap 2010 study show that 6 out of 10 Spanish hypertensive patients attended in PC and aged 80 years or older have an optimum BP control according to ESH 2009 criteria. The use of Reappraisal ESH 2009 criteria and the high use of antihypertensive therapy may have determined these results.

7D.04 ADVERSE EFFECT OF VARIOUS CLINICAL AND GEOGRAPHICAL FACTORS ON BLOOD PRESSURE OUTCOMES IN PATIENTS WITH CORONARY HEART DISEASE

V. Heazlewood1, K. Kotsve2, E.L. Turner3, D. Wood1. 1Caboolture Hospital Queensland Health, Caboolture-Australia, 2Imperial College, London-United Kingdom, 3London School of Hygiene and Tropical Medicine, London-United Kingdom

Objective: Our aim was to determine if there was an association between various clinical or geographical factors on adverse blood pressure outcomes in coronary heart disease (CHD) patients.

Design and Method: The cluster randomised controlled intervention Euroaction trial performed in 6 European countries involved a multidisciplinary cardiovascular disease prevention programme addressing lifestyle and medical risk factor
management in patients with CHD or at high risk for such. Post-hoc analyses were performed in 942 intervention patients with CHD; examining the degree of blood pressure target achievement (e100% for those with diabetes) over 12 months with respect to age, CHD diagnostic category, self-reported and documented diabetes, body weight and waist and study centres.

Results: Patients 65 years or older (OR 0.79, CI 0.66–0.94, p = 0.007), clinical diagnosis of stable angina (OR 0.75, CI 0.64–0.87, p < 0.001) compared to acute coronary syndromes, self-reported (OR 0.22, CI 0.10–0.31, p < 0.001) or documented diabetes (OR 0.33, CI 0.23–0.45, p < 0.001), highest waist category (OR 0.69, CI 0.58–0.83, p < 0.001), obesity (OR 0.55, CI 0.41–0.74, p < 0.001) or being overweight (OR 0.68, CI 0.50–0.93, p = 0.014) were all associated with suboptimal categorized blood pressure outcomes. Achievement of blood pressure target was similar (mean 72%, sd 2.5%) for the countries of Italy, Spain, Sweden, France and United Kingdom but was only 41% for Poland (OR 0.23, CI 0.15–0.35, p < 0.001). Blood pressure as a continuous variable showed similar findings, except for diastolic pressure in the elderly where it was lower than in that younger age groups.

Conclusions: Though increased age and weight are well documented in the literature to be associated with impaired blood pressure control, the other data concerning clinical diagnoses and study centre location is expository and hypothesis-generating in nature, deserving further study.

PREVALENT AND DETERMINANTS OF RESISTANT HYPERTENSION IN A HYPERTENSION UNIT

R. M. Bruno, I. Del Irate, V. Mazzi, E. Daghini, L. Ghiadoni, S. Taddei. University of Pisa, Pisa-Italy

Background: The diagnosis of resistant hypertension allows to identify patients with higher cardiovascular risk and in which different diagnostic and therapeutic options should be considered. However the prevalence of this condition is still a matter of debate. The aim of the study is to investigate the prevalence of resistant hypertension, using ESC/ESH definition, in a Outpatient Hypertension Unit, and to identify clinical parameters characterizing this condition.

Methods: 541 consecutive hypertensive patients were enrolled. Medical history, anthropometric parameters, and routine blood exams were collected. Resistant hypertension was identified according to the following criteria: office blood pressure that remains above goal in spite of the concurrent use of 3 antihypertensive medications the level of control remains poor.

Results: 93 patients (17.2%) resulted be resistant to antihypertensive treatment. Among resistant hypertensive patients the following conditions were significantly more represented: older age (62.3 ± 10.5 vs 55.9 ± 13.1 years, p < 0.001), sedentary status (91.1 vs 81.5% p < 0.05), previous cardiovascular events (31.8 vs 15.2%, p < 0.001), diabetes (36.9 vs 14.5%, p < 0.001), hypercholesterolemia (22.7 vs 14.5%, p < 0.05), obesity (27.2 vs 14.3%, p < 0.001), chronic kidney disease (28.3 vs 16.0%, p < 0.05). In a logistic regression model adjusted for confounders, only obesity (p = 0.02) and diabetes mellitus (p = 0.002) were associated to an increased probability to have resistant hypertension.

Conclusions: Resistant hypertension affects about 1 out of 6 patients seen by a Hypertension Specialist. Through all classical cardiovascular risk factors were more frequent in resistant hypertensive patients, only obesity and diabetes mellitus were independently associated with this condition.

EPIDEMIOLOGY OF ARTERIAL HYPERTENSION IN NORTH AFRICA: THE ETHNA STUDY

C. Nejari1, M. Ararbi2, M-T. Chentir1, R. Boujnah4, O. Kemmou5, H. Megdiche6, F. Boulahrouf7, K. Messoussi7, V. Bulatov5.

Background: It has recently been suggested that only systolic blood pressure (SBP) should be measured in subjects older than 50 years since it carries all the cardiovascular risk associated with elevated blood pressure. It is likely that the age, at which the prognostic importance of SBP exceeds diastolic blood pressure (DBP), is influenced by other cardiovascular risk factors known to promote atherosclerosis.

Methods: We examined data from 12 European countries within the Morgam (Monica Risk, Genetics, Archiving and Monograph) database. Traditional cardiovascular risk factors were measured in 1982-1997 in 68,894 subjects aged 19-77 years, without cardiovascular disease, and not receiving any antihypertensive treatment. After a mean of 13.2 years of follow-up, fatal and non-fatal stroke were assessed in 1998-2007.

Results: The incidence of fatal and nonfatal stroke was 2.8%. With both SBP and DBP in the same adjusted multiple Cox-regression model, the association between SBP (per 10 mmHg) and stroke was greater for all ages (HR 1.16 [1.13–1.19], p < 0.0001) than that between DBP (per 5 mmHg) and stroke (HR 1.02 [0.99–1.05], NS). Due to a significant interaction between age and blood pressure (p < 0.01), we divided the population into five age classes: 19-39, 40-49, 50-59 and 60-77 years, with 181, 340, 773 and 608 strokes with an incidence of 0.84%, 2.1%, 3.3% and 7.6%, respectively. The risk of stroke was lower related to DBP than to SBP in subjects aged 19-39 years (HR = 1.17 [1.07–1.27], p = 0.004 vs. HR = 1.06 [0.94–1.20], NS), whereas it was lower related to SBP than to DBP in subjects aged 40-49 years (HR = 1.23 [1.13–1.32], p < 0.0001 vs. HR = 1.03 [0.96–1.11], NS), 50-59 years (HR = 1.19 [1.14–1.24], p < 0.0001 vs. HR = 1.01 [0.97–1.05], NS), and 60-77 years (HR = 1.18 [1.13–1.23], p < 0.0001 vs. HR = 0.97 [0.93–1.02], NS). Neither smoking, diabetes nor serum cholesterol influenced the interaction between blood pressure and age on outcome significantly.

Conclusion: The study shows that the prevalence of HTN in North Africa general practice is high. It confirms in this population the known link between age, gender, smoking, obesity and HTN. The study uncovers high numbers of undiagnosed cases and shows that despite high usage of antihypertensive medications the level of control remains poor.
Conclusion: In subjects older than 39 years stroke was predicted more strongly by SBP than by DBP and vice versa in subjects younger than 40 years. This influence of age on the ability of SBP and DBP to predict later stroke was unaffected by smoking, diabetes and serum cholesterol supporting the idea of measuring only SBP in subjects older than 50 years in order to simplify identification and treatment of patients with hypertension.

**7D.08** THE IMPACT OF FETAL SIZE AND MATERNAL FACTORS IN NEWBORN BLOOD PRESSURE

C. Garcia-Vicent*, I. Torro*, F. Aguilar†, J. Alvarez*, F. Ponce*, E. Lucbe*, †Cardiovascular Risk Unit Hospital General Universitario University of Valencia, Valencia-Spain, ‡Ciberobn, Health Institute Carlos III, Madrid-Spain

Tracking of blood pressure (BP) from childhood to adulthood is well known. It is therefore important to determine predictors of BP as early as at birth.

**Objectives:** The present research was undertaken to analyze the association between maternal and neonatal factors on BP at birth.

**Subjects and Methods:** Four hundred and fifty-eight Caucasians of both sexes, of European origin, born at term and after a normal pregnancy and in the absence of diabetes were included. Birth weight (BW) was obtained from obstetrical records and low BW was qualified as BW lower than the 10th percentile for gestational age. Each newborn’s BP was measured at the absence of diabetes before 5.5% for day and 6.1% for night (P < 0.001). Median FEUA was 7.7% and 5.5% for day and night in women (P < 0.001), and, 4.3% and 3.4% for day and night, in men (P < 0.001), respectively. In multiple median regression, sex, overweight, urine flow rate (ml/min) and Na excretion rate (mmol/min) were significant determinants of day FEUA and night FEUA.

**Conclusions:** The lower SUA in women is due to increased renal excretion and not to reduced urate production. FEUA is higher during the day than at night, in both men and women. About 70% of the 24-h urinary urate excretion occurs during the day. Day and night SUA have similar determinants, with lower levels in men and overweight people. There is a clear circadian rhythm of renal urate handling in adult men and women.

**7D.10** CARDIOVASCULAR RISK FACTORS BY BLOOD PRESSURE CATEGORIES IN A CZECH POPULATION RANDOM SAMPLE. CROSS-SECTIONAL DATA AND LONGITUDINAL TRENDS


**Objectives:** Population-based studies have shown that both hypertension and high-normal BP cluster with other CV risk factors. The aim of our study was to compare CV risk factors by BP categories in 3 cross-sectional surveys of a representative sample of the Czech population.

**Design and Methods:** In 2006-09, a cross-sectional survey for CV risk factors was performed in 9 districts of the Czech Republic (1% population sample aged 25-64 years; mean age 47 years; response rate 62.8%). Complete data were obtained in 3,610 individuals. The following BP categories were assessed: optimal (<120/80 mmHg), normal (120-129/80-84 mmHg), high-normal (130-139/85-89 mmHg), untreated hypertension (140/90 mmHg), and drug-treated hypertension. Similar surveys were conducted in 1997/98 and 2000/01.

**Results:** In males, BMI, lipid parameters, and prevalence of diabetes rose continuously with BP category. Untreated male hypertensive patients experienced the worst lipid profile. Similar trends were obtained for females showing a smaller difference in the CV risk profile between the high-normal BP group and both hypertensive groups.

Longitudinal trends within each BP category showed a significant BP decrease over the 10-year period only in drug-treated hypertensives; BMI rose within each BP category only in males. There was a significant improvement in lipid parameters over time, being the greatest in drug-treated hypertensives. Prevalence of diabetes did not change over time.

**Abstracts e111**

M. Bochud*, M. Maillard**, T. Lyngdahl†, P. Vollenweider*, F. Paccaud*, M. Burnier†, *Institute of Social and Preventive Medicine, Lausanne-Switzerland, †Nephrology Division, University Hospital of Lausanne (CHUV), Lausanne-Switzerland, ‡Department of Internal Medicine, University Hospital of Lausanne (CHUV), Lausanne-Switzerland

**Background:** Women have lower serum uric acid (SUA) levels and higher fractional excretion of urate (FEUA) than men. Yet little is known about the circadian rhythm of renal urate handling in women. The study shows that childhood urate handling is different among sex, overweight, urine flow rate (ml/min). Women have lower serum uric acid (SUA) levels and higher fractional excretion of urate (FEUA) than men. Yet little is known about the circadian rhythm of renal urate handling in women. The study shows that childhood urate handling is different among sex, overweight, urine flow rate (ml/min).

**Results:** Median FEUA was 7.7% and 5.5% for day and night in women (P < 0.001), and, 4.3% and 3.4% for day and night, in men (P < 0.001), respectively. In multiple median regression, sex, overweight, urine flow rate (ml/min) and Na excretion rate (mmol/min) were significant determinants of day FEUA and night FEUA.
**Conclusions:** There is a continuous deterioration of the CV risk profile with BP category in a representative population sample in the Czech Republic. The greatest improvement over the 10-year period was achieved in drug-treated hypertensives whereas untreated hypertensives still have the worst risk profile.

**7D.11 INCOME FACTORS IN POPULATION BLOOD PRESSURE AND HYPERTENSION. RESULTS FROM THE COPENHAGEN CITY HEART STUDY**

U. O. Andersen, G.B. Jensen. Copenhagen City Heart Study, Copenhagen-Denmark

**Objective:** The aim of this study is to investigate any role of income factors on the population BP, prevalence of hypertension and on hypertension treatment.

**Design:** Copenhagen City Heart Study is a prospective longitudinal epidemiological study. The study population is the subjects examined in survey 4 (N = 6119).

**Methods:** The BP measurement was fully standardised and measurement method was unchanged throughout the observation period. A questionnaire concerning income, drinking habits, smoking, medical therapy and physical exercise was completed by the participants and double-checked by the technicians.

**Results:** After adjusting for cardiovascular risk factors there are no significant differences in SBP by income group among men. However, SBP among women decreased significantly by increasing income group (p < 0.0001). A significantly greater fraction of subjects in the lower income groups are hypertensive compared to the richer income groups. A significantly greater fraction of poor hypertensives are treated with antihypertensive therapy as compared to rich hypertensives. The risk index was also unevenly distributed with a large part of high risk subjects in the lower income classes. The treated hypertensives are treated equally without treatment differences across the income groups.

**Conclusion:** Income factors have a role in SBP and hypertension independently from the known risk factors. The exact nature of the social factors is not known. There are gender differences in the effect of social factors. These results may indicate that a subdivision of the population into socioeconomic classes separately for the two genders may be necessary to find the minor determinant factors for SBP. More poor hypertensives are treated with antihypertensive medicine than rich hypertensives probably because of more high-risk hypertensives among the poor. The treatment success did not differ between the income groups.

**7D.12 PREVALENCE OF ABNORMAL URINARY ALBUMIN EXCRETION IN A GENERAL POPULATION SAMPLE IN SPAIN**


**Objectives:** Hermex is an observational, longitudinal, population based study which try to evaluate the relative weight of classic, as well as, non classic cardiovascular risk factors in the population of Extremadura. This report provides the prevalence obtained about microalbuminuria in a large Spanish population.

**Design and Methods:** Cross-sectional, population based study. 3,402 were randomly selected from the Health Care System of Extremadura. For every subject age, gender, anthropometric measures, blood pressure and cardiovascular risk factors were recorded. Total cholesterol, LDL and HDL fractions, fasting glucose and urinary albumin excretion rate (UAER) in a first morning urine sample were analyzed. Microalbuminuria was diagnosed when UAER was higher than 22 in men or 31 mg/g in women.

**Results:**

The final sample included 2,813 subjects (mean age 51.2 years, 53.5% female). Prevalence of abnormal UAER in general population was 5.2% (microalbuminuria: 4.6%; proteinuria 0.6%). Microalbuminuria grew slightly in patients between 65 and 74 y and showed a dramatic increase in subject older than 75 y (p < 0.001, X² test). Men showed a high prevalence of microalbuminuria (5.8% vs. women 3.6%; p = 0.006. Microalbuminuria was more common in obese subjects (6.7% vs. 3.6%, p < 0.001), hypertensive patients (8.3% vs. 2.3%, p < 0.001) and diabetic ones (10.9% vs. 3.7%, p < 0.001). The multivariate analysis showed a positive correlation of microalbuminuria only with body mass index, systolic blood pressure, plasma creatinine and triglyceride levels.

**Conclusions:** A low frequency of microalbuminuria was detected in a randomly selected sample of Spanish general population. This finding agreed with the low rates of cardiovascular mortality and morbidity observed in Spain in spite of a high prevalence of classic cardiovascular risk factors.
ORAL SESSION

7E.01 GENETIC VARIANTS IN THE SIRT1 GENE MAY AFFECT DIABETES RISK IN INTERACTION WITH PRENATAL EXPOSURE TO FAMINE

I.P.G. Bodden, M.C. Zillikken, S.R. De Rooij, J.G. Langendonk, A.H.J. Danser, E.J.G. Sijbrands, T.J. Roseboom. - Erasmus University Medical Center, Department of Internal Medicine, Rotterdam, The Netherlands, 2Academic Medical Center of the University of Amsterdam, Department of Clinical Epidemiology, Amsterdam, The Netherlands

Objective: Fetal malnutrition predisposes to type 2 diabetes. This is thought to reflect fetal programming, and may be due to epigenetic modifications. Activation of SIRT1 (NAD-dependent deacetylase sirtuin-1) leads to epigenetic alterations by deacetylation of histones, but also controls cell metabolism by direct deacetylation of non-histion targets. It is involved in the glucose metabolism by regulating various transcription factors, like PGC-1α, a transcriptional coactivator that controls glucose metabolism in the liver and muscle. It has been suggested that SIRT1 genetic variation might have an association with type 2 diabetes. We hypothesized that genetic variants in the SIRT1 gene might interact with fetal malnutrition to influence the risk of type 2 diabetes.

Design and Method: Three SIRT1 tagging single nucleotide polymorphisms (SNPs) that covered most of the common variations of the SIRT1 gene were selected. Next, four common multimarker haplotypes with a frequency >10% were selected from these SNPs. Analyses were performed in the Dutch Famine Birth Cohort Study, which consists of term singletons born before the time of the famine in the Netherlands during World War II (793 participants; 337 exposed to famine, 456 unexposed). We analyzed the interaction between these SNPs or haplotypes and prenatal exposure to famine on type 2 diabetes risk by using interaction terms (genetic variant (coded 0 or 1) x exposure group (coded 0 or 1)).

Results: In the total population (exposed and unexposed), SIRT1 variants and diabetes were not associated. A significant interaction was found between two SIRT1 SNPs and exposure to famine in utero on diabetes risk (OR for rs7895833 0.35, 95% CI 0.14–0.89, p = 0.03; OR for rs1467568 0.32, 95% CI 0.14–0.78, p = 0.01). The minor alleles of these SNPs were associated with a lower prevalence of type 2 diabetes, but only in individuals with prenatal exposure to famine (OR for rs7895833 0.50, 95% CI 0.24–1.03, p = 0.06; OR for rs1467568 0.32, 95% CI 0.21–0.91, p = 0.02).

Conclusions: Carriers of two common genetic SIRT1 variants who were exposed to famine in utero, had about a 50% reduced risk to develop diabetes compared to noncarriers. SIRT1 may be an important genetic factor which is involved in fetal programming during malnutrition and associated with type 2 diabetes risk later in life.

7E.02 SAFETY AND EFFICACY OF LOW BLOOD PRESSURE AMONG PATIENTS WITH DIABETES: SUB-GROUP ANALYSES FROM THE ONTARGET TRIAL

J. Redon, G. Manca, P. Sleight, H. Schumacher, P. Gao, J. Pogue, R. Danser, E. J. G. Sijbrands, T. J. Roseboom. - Erasmus University Medical Center, Department of Internal Medicine, Rotterdam, The Netherlands

Objectives: To determine if the BP target values at which CV protection is achieved differ between diabetics and non-diabetics in patients from the OnTARGET trial.

Methods: 25584 patients (9,603 diabetics), older than 55 years, with very high CV risk were randomized to ramipril, telmisartan or both over 4.6 years. We pooled all subjects in order to examine the BP-risk relating the primary composite outcome and its components to baseline systolic BP (SBP), SBP changes from baseline to event, average in-trial SBP and in-trial DBP for each in-trial SBP level.

Results: The primary outcome occurred in 1938 (20.2%) diabetics and in 2276 (14.2%) non-diabetics. Compared to non-diabetics, diabetics had a significantly higher risk for the main outcome (Hazard ratio [HR] 1.48; 95% confidence intervals [CI] 1.38–1.57) and cause-specific events: CV death (HR 1.56; 95% CI 1.42–1.71); myocardial infarction (HR 1.30 (95% CI 1.17–1.46); stroke (HR 1.39, 95% CI 1.29–1.51). Treatment of the famine in the Netherlands during World War II (793 participants; 337 exposed to famine, 456 unexposed). We analyzed the interaction between these SNPs or haplotypes and prenatal exposure to famine on type 2 diabetes risk by using interaction terms (genetic variant (coded 0 or 1) x exposure group (coded 0 or 1)).

Results: In the total population (exposed and unexposed), SIRT1 variants and diabetes were not associated. A significant interaction was found between two SIRT1 SNPs and exposure to famine in utero on diabetes risk (OR for rs7895833 0.35, 95% CI 0.14–0.89, p = 0.03; OR for rs1467568 0.32, 95% CI 0.14–0.78, p = 0.01). The minor alleles of these SNPs were associated with a lower prevalence of type 2 diabetes, but only in individuals with prenatal exposure to famine (OR for rs7895833 0.50, 95% CI 0.24–1.03, p = 0.06; OR for rs1467568 0.32, 95% CI 0.21–0.91, p = 0.02).

Conclusions: Carriers of two common genetic SIRT1 variants who were exposed to famine in utero, had about a 50% reduced risk to develop diabetes compared to noncarriers. SIRT1 may be an important genetic factor which is involved in fetal programming during malnutrition and associated with type 2 diabetes risk later in life.

7E.03 RESTING HEART RATE AND THE RISK OF DEATH AND CARDIOVASCULAR COMPLICATIONS IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

J. Chalmers, M. Woodward, A. Rodgers, C. Chow, A. Patel, R. Webster, D. Batty, Q. Li, T. Nanniyiya, S. Zoungas, G. Hiliis. - The George Institute and the University of Sydney, Sydney-Australia, 9Universitätskliniken des Saarland, Homburg-Saar, Germany, 10Department of Cardiovascular Sciences, University of Leicester, London, United Kingdom, 11Universiti Institut Technologi Malaysia, Shah Alam-Malaysia

Objective: An association between resting heart rate (RHR) and mortality has been described both in the general population and in patients with cardiovascular disease (CVD). There are, however, few data exploring the relationship between RHR and CVD in patients with diabetes mellitus. The aim of the current study is, therefore, to explore any relationship between RHR and all cause mortality and cardiovascular events in a large cohort of patients with type 2 diabetes mellitus.

Design and Methods: The Action in Diabetes and Vascular Disease: Preterax and Diamoncr Modified Release Controlled Evaluation (Advance) study made two randomised comparisons: a double-blind assessment of the efficacy of a fixed combination perindopril-indapamide versus placebo and an open-label evaluation of intensive glucose lowering using modified release gliclazide (target HbA1c ≤ 6.5%) versus standard guidelines based therapy. We assessed the association between RHR and all cause mortality, cardiovascular death, and major cardiovascular events (a composite of cardiovascular death, non-fatal myocardial infarction and non-fatal stroke) over the duration of the trial (median 4.4 years). Baseline RHR was considered both as a continuous variable and in quintiles, using unadjusted and adjusted Cox regression analyses.

Results: The Advance study randomised 11,140 patients of whom 11,138 had baseline RHR recorded (mean 74 bpm). A higher RHR was associated with a significantly increased risk of all cause mortality, cardiovascular death, and major cardiovascular outcomes without adjustment and after adjusting for age and sex and multiple co-variates (fully adjusted hazard ratio [HR] for death 1.13 per 10 bpm, 95% confidence intervals [CI] 1.07–1.19, p < 0.001). The increased risk associated with a higher RHR is most obvious in patients with previous cardiovascular complications (fully adjusted HR for death 1.70 for upper [mean 91 bpm] v lowest [mean 57 bpm] quintile of RHR in this subgroup, 95% CI 1.23–2.36, p = 0.001) and is evident in both genders.
Conclusions: Among patients with diabetes a higher heart rate is associated with increased risk of death and cardiovascular complications. Whether a higher HR is directly mediates the increased risk or is merely a marker for other characteristics that determine a poor outcome merits further investigation.

**7E.04 PRESERVED CAPILLARY DENSITY IN TREATED HYPERTENSIVE PATIENTS WITH OR WITHOUT TYPE 2 DIABETES**

F. Feihl1, J. Aellen1, A. Dabiri1, A. Heim1, L. Liaudet2, M. Burnier3, J. Ruiz4, B. F. Heim1, A. Dabiri1, A. Heim1, L. Liaudet2, M. Burnier3, J. Ruiz4, B. F. Nystrom.

Objective: To evaluate capillary density in diabetic hypertensive patients as compared with non-diabetic hypertensive patients.

Methods: Capillary density was assessed by two methods, first with videomicroscopy to visualize and count capillary loops in dorsal finger skin, and second with laser Doppler imaging to measure the maximum blood flow elicited in forearm skin by local heating to a temperature of 43°C. Data were summarized as means ± SD, with simple Anova used to assess differences between groups. In both hypertensive groups, no significant difference was found concerning capillary density between nondiabetics and diabetics.

Results: In patients with diabetes, protection from stroke increases with the magnitude of BP reduction. We were unable to detect such a relation for MI.

**7E.05 EFFECTS OF INTRAVENOUS BLOOD PRESSURE REDUCTION ON MYOCARDIAL INFARCTION AND STROKE IN DIABETES: A META-ANALYSIS IN 73,913 PATIENTS**

G. Reboli1, G. Gentile1, F. Angeli1, G. Ambrosio1, G. Mancia1, P. Verdecchia1, 1University of Perugia, Perugia-Italy, 2Hospital Santa Maria della Misericordia, Perugia-Italy, 3University of Milano-Bicocca, Milan-Italy, 4Hospital of Asstai, Assisi-Italy

Objective: Guidelines generally recommend intensive lowering of blood pressure (BP) in patients with type 2 diabetes. There is uncertainty about the impact of this strategy on case-specific events. Thus, we generated estimates of the effects of BP reduction on the risk of myocardial infarction (MI) and stroke in diabetic patients.

Methods: We selected studies which compared different BP-lowering agents and different BP intervention strategies in patients with diabetes. Outcome measures were MI and stroke. We abstracted information about study design, intervention, population, outcomes, and methodological quality for a total of 73,913 patients with diabetes (295,652 patient-years of exposure) randomised in 31 intervention trials.

Results: Overall, experimental treatment reduced the risk of stroke by 9% (p = 0.0059), and that of MI by 11% (p = 0.0015). Allocation to more-tight, compared with less-tight, BP control reduced the risk of stroke by 31% (RR 0.69, 95% CI 0.61-0.79), while the reduction in the risk of MI approached, but did not achieve, significance (OR 0.87, 95% CI 0.74-1.02). In a meta-regression analysis, the risk of stroke decreased by 13% (95% CI 5-20, p = 0.002) for each 5-mmHg reduction in systolic BP, and by 11.5% (95% CI 5-17, p < 0.001) for each 2 mmHg reduction in diastolic BP. In contrast, the risk of MI did not show any association with the extent of BP reduction (systolic BP: p = 0.793; diastolic BP: p = 0.832).

Conclusions: In patients with diabetes, protection from stroke increases with the magnitude of BP reduction. We were unable to detect such a relation for MI.

**7E.06 HIGH CENTRAL PULSE PRESSURE IS COMMON IN TYPE 2 DIABETES DESPITE CLINICAL NORMOTENSION, AND IS ASSOCIATED WITH MARKERS OF ATHEROSCLEROSIS**


Objective: Central pulse pressure (CPP) is a new and potentially useful marker of increased cardiovascular risk. Adverse cardiovascular outcomes have been reported with CPP ≥ 50 mmHg. However, it is currently not known how common elevated CPP levels are in clinically normotensive patients with type 2 diabetes, or whether this cut-off value can be used to identify patients with more advanced atherosclerosis.

Methods: We investigated patients with type 2 diabetes with or without previously known hypertension, who participated in the community-based observational study Cardipp (Cardiovascular Risk Factors in Patients with Diabetes – A Prospective study in Primary care). Conventional office blood pressure (mean of three consecutive readings) and non-invasive central blood pressure (SphygmoCor®) were measured. Carotid intima-media thickness (IMT) was assessed with ultrasonography, and aortic pulse wave velocity (PWV) was assessed with applanation tonometry.

Results: Among 690 study participants who had completed the base-line analysis, we identified 168 patients with clinical normotension (office BP < 130/80 mmHg). Among these, CPP ≥ 50 mmHg was found in 32 patients (19.0%). Clinically normotensive patients with CPP ≥ 50 mmHg had significantly higher carotid intima-media thickness (0.76 mm vs 0.70 mm, p < 0.05) and significantly higher pulse wave velocity (10.9 m/s vs 9.5 m/s, p < 0.01) compared with clinically normotensive patients with CPP < 50 mmHg. There was no significant inter-group difference concerning office systolic blood pressure or diastolic blood pressure (120.7/70.0 mmHg vs 118.7/71.3 mmHg). Office pulse pressure was significantly higher in clinically normotensive patients with CPP ≥ 50 mmHg than in clinically normotensive patients with CPP < 50 mmHg (50.7 mm Hg vs 47.4 mm Hg, p < 0.05) but clinically normotensive patients with office pulse pressure ≥ 50 mmHg did not have higher PWV or higher IMT than clinically normotensive patients with office pulse pressure < 50 mmHg.

Conclusion: In normotensive patients with type 2 diabetes, central but not office pulse pressure levels ≥ 50 mmHg identifies a subgroup of patients with more advanced atherosclerosis. Future prospective studies will be needed to find out whether these patients would benefit from intensified risk factor management.

**7E.07 MICROVASCULAR DYSFUNCTION INCREASES THE RISK OF TYPE 2 DIABETES MELLITUS. A META-ANALYSIS**

D. Murs, A. Houben, M. Schram, C. Stehouwer. Dept. of Internal Medicine, Maastricht University, Maastricht-The Netherlands

Objective: Type 2 diabetes mellitus (DM2) is characterized by microvascular dysfunction. Recent data support the hypothesis that impairment of microvascular function may cause insulin resistance and thus contribute to the development of DM2. The aim of this meta-analysis was, therefore, to investigate whether microvascular dysfunctions contribute to the development of impaired glucose tolerance.

Design and Method: We searched Medline and Embase for studies published from inception (1989) to April 15th 2010. Prospective studies were included if they focused on microvascular measurements (retinal diameters, skin microvascular endothelium (independent reactivity, capillary density, peripheral vascular reactivity, or plasma biomarkers of endothelial dysfunction) in a population-based sample without DM2 at baseline. We conducted a meta-analysis by use of RevMan5 to determine the effects of microvascular function on glucose tolerance status, using the generic inverse variance method. The pooled relative risk and 95% confidence interval (95%CI) of the fully adjusted models were estimated by use of the random effects model.

Results: 15 studies met our pre-specified inclusion criteria. One standard deviation (1SD) increase in retinal venular diameter resulted in a 15% higher IGF risk (95%CI [1.01, 1.31], p = 0.03), and 1SD decrease in retinal arteriolar/venular-ratio (AVRatio) increased this risk by 14% (95%CI [0.98, 1.32], p =
Conclusion: These data indicate that microvascular dysfunction, and in particular endothelial dysfunction, increase the risk of IFG and DM2. This suggests a role of the microcirculation in the (early) pathogenesis of DM2.

Methods: We studied 4,447 subjects with type 2 diabetes and at least one additional cardiovascular risk factor in a randomized, double-blind, multicentre, controlled, and event driven (MAU) trial. They received either 40 mg olmesartan medoxomil (OM) or placebo (Pb) od. for a median duration of 3.2 years. In both groups, additional antihypertensive treatment (except ACE inhibitors or ARBs) was used to reach the target BP of <130/80 mmHg.

Results: The SBP/DBP control was excellent during the entire study with an average of 125.77±4.3 mmHg in the olmesartan group and 128.77±2.2 mmHg in the placebo group. During the double blind period, 178 (8.2%) subjects in the OM group and 210 (9.8%) subjects in the Pb group developed MAU (time-to-onset: HR: 0.77; 95.1% CI: 0.63 to 0.94, p = 0.01). In 1389 patients with an urine albumin creatinine ratio (UACR) >3 mg/g, 4.1% vs. 3.4% (HR: 1.19; 95% CI: 0.69 to 2.06) in the olmesartan and placebo group developed MAU. In 1572 patients with an UACR of 3-5 mg/g vs. 7.2% (HR: 0.80; 95% CI: 0.53 to 1.18) and in 1737 patients with an UACR >5 mg/g vs. 20.0% (HR 0.69; 95% CI: 0.53-0.89, p = 0.004). As we observed a reduction of the eGFR in the olmesartan treated group, we analysed if the change in eGFR within the first 6 months of treatment would predict the future occurrence of microalbuminuria in our population. We were unable to find such an association. Patient who developed MAU after month 6 had a slight increase of the eGFR by 0.17 ml/min/1.73m² from baseline to month 6, whereas patients who developed no MAU had no change in eGFR. The change of eGFR was also comparable in patients who developed MAU and in patients who remained normoalbuminuric in the subgroups of patients treated with olmesartan or placebo. These data suggest that the effect of olmesartan on GFR is dissociated from its effect on UACR.

Conclusions: In subjects with type 2 diabetes treatment with olmesartan reduced the incidence of MAU in patients with an UACR >3 mg/g. The benefit on UACR was not attributable to an initial reduction of eGFR in the olmesartan group.

Clinical Trials. gov ID no.: NCT00185159.

7E.09 PREVENTION OF MICROALBUMINURIA: EFFECT OF BASAL UAER AND CHANGES IN THE EGF ON OUTCOME (ROADMAP TRIAL)

Background:

H. Haller1, S. Ito1, L. Jurinjak, University of Zagreb, Zagreb-Croatia

Objective: Several studies have shown that a sympathovagal imbalance (manifested by depression of the parasympathetic nervous activity) associates with insulin resistance. Resting heart rate reflects autonomic activity, and higher resting heart rate reflects increased sympathetic and/or reduced parasympathetic activity. We investigated the hypothesis that in type 1 diabetes higher heart rate, as an early sign of sympathovagal imbalance, is associated with insulin resistance.

Patients and Methods:

To investigate the interplay between insulin resistance and heart rate in type 1 diabetes we divided 304 patients (age 37.9 ± 11.3 years, 166M/138F, BMI 24.2 ± 3.1 kg/m², waist-to-hip ratio (WHR) 0.82 ± 0.8, HbAlc 7.22 ± 1.6%, duration of diabetes 15.9 ± 10 years, heart rate 73 ± 13 beats/min, systolic blood pressure 126 mmHg (90-180), diastolic blood pressure 79 mmHg (50-110)) according to median estimated glucose disposal rate (eGDR) = 9.72 mg/kg⋅min⁻¹ into lower (n = 153) and higher-insulin sensitivity (n = 151) group. None showed signs of adrenal, thyroid, renal or cardiovascular disease and received drugs, apart from insulin, that could attenuate glucose metabolism or insulin sensitivity. Estimated glucose disposal rate was calculated using the equation: eGDR = 24.31⋅(12.22×WHR)⁻¹⋅(3.29×HTT)⁻¹·(0.57×HbAlc). Patients with lower insulin sensitivity (eGDR = 7.67 ± 1.39 mg/kg⋅min⁻¹) in comparison to patients with higher insulin sensitivity (eGDR = 11.01 ± 0.80 mg/kg⋅min⁻¹) showed significantly higher heart rate (77.3 compared to 73.0 beats/min, t-test = -2.955, p = 0.003). Multivariate logistic regression models have found significant association between heart rate and progression to insulin resistance in type 1 diabetes (odds ratio 1.02, 95% CI 1.00-1.04, p = 0.004).

Conclusion: In this study of a large cohort of patients with type 1 diabetes we provided the evidence that reduced insulin sensitivity is associated with higher heart rate in type 1 diabetic patients, and that heart rate is risk predictor of insulin resistance. In type 1 diabetes sympathovagal imbalance and insulin resistance has been shown to confer an increased risk of cardiovascular disease. Higher heart rate, associated with sympathovagal imbalance and insulin resistance has been shown to confer an increased risk of cardiovascular disease. Higher heart rate, associated with sympathovagal imbalance and insulin resistance, increase the risk of cardiovascular events and mortality in type 1 diabetes.
Conclusions: Despite many patients taking more than one treatment for hypertension, control of SBP was suboptimal. The OPTIMISE results provide evidence from a randomised controlled trial that BM exerts a positive effect on such an unmet need as SBP target attainment and was significantly improved in European type 2 diabetic patients.

### 7E.11 PREDICTIVE VALUE OF BLOOD BACTERIAL DNA ON THE ONSET OF TYPE 2 DIABETES FROM GENERAL POPULATION


Methods: The incidence of diabetes both has reached epidemic proportions. Experimental evidence suggests that the presence of bacterial components in blood could be an initial step leading to diabetes and obesity. To test this hypothesis, the relations between the concentration of a bacterial component that is highly conserved between different species of bacteria, the 16S rDNA gene, and the onset of diabetes and obesity, were studied in blood DNA from a general population. The overall metagenomic population is also reported.

Background: The incidence of diabetes both has reached epidemic proportions. Experimental evidence suggests that the presence of bacterial components in blood could be an initial step leading to diabetes and obesity. To test this hypothesis, the relations between the concentration of a bacterial component that is highly conserved between different species of bacteria, the 16S rDNA gene, and the onset of diabetes and obesity, were studied in blood DNA from a general population. The overall metagenomic population is also reported.

Methods: D.E.S.I.R. is a longitudinal cohort study with the primary aim of describing the natural history of the metabolic syndrome. Participants were evaluated at inclusion and at 3-, 6-, and 9-yearly follow-up visits. Blood bacterial gene concentration was measured at baseline. A nested case control study, where cases had incident diabetes, identified bacterial phylotypes present in blood, and the onset of diabetes and obesity, were studied in blood DNA from a general population. The overall metagenomic population is also reported.

Conclusions: The presence of abdominal adiposity at the end of nine years, after adjustment for confounders, with a standardized odds ratio 1.18 (1.03 to1.34), p = 0.01. Furthermore, pyrosequencing analyses showed that subjects destined later to become diabetic and controls shared a core blood microbiota, mostly composed of the Proteobacteria phylum (85-90%).

### 7E.12 NIGHTTIME SYSTOLIC BLOOD PRESSURE IN DIABETIC PATIENTS: DUBLIN OUTCOME STUDY

L. Van Der Poel1, E. Dolan1, O. O’Brien1. 1Connolly Hospital, Dublin-Ireland, 2Conway Institute of Biomolecular and Biomedical Research, University College Dublin, Dublin-Ireland

Background: Cardiovascular disease is the major cause of mortality and morbidity in diabetic patients. Diabetic patients with hypertension exhibit a higher cardiovascular risk than hypertensive patients without diabetes. There is a lack of data on the value of ambulatory blood pressure monitoring (ABPM) in patients with diabetes. Nighttime systolic blood pressure (SBP) has consistently been shown to be a potent predictor of cardiovascular risk. We studied the predictive value of nighttime ABPM in a cohort of diabetic patients.

Design and Methods: At baseline, when not on antihypertensive medication, 11,291 patients (5326 male, mean age 54.6 years) underwent ABPM. Using a computerised national registry of death, mortality outcome was ascertained. Over a mean follow up of 5.3 years there were 566 cardiovascular deaths with 74 deaths among 857 diabetic patients.

Results: In a Cox proportional-hazard model, nighttime SBP was an independent predictor of cardiovascular and in particular stroke mortality in diabetic patients. After adjustment for sex, age, smoking history, previous cardiovascular events, body mass index (BMI), and daytime SBP, a 10mmHg increase in nighttime SBP resulted in hazard ratios of 1.32(1.12–1.69), 1.95(1.18–3.20) and 1.24(0.99–1.56) for total cardiovascular, stroke and cardiac mortality respectively.

Conclusion: Nighttime SBP is a significant predictor of cardiovascular mortality independent of other risk factors in patients with diabetes and nighttime blood pressure predicted mortality independent of daytime blood pressure. Future research into the mortality benefits of nighttime dosing of antihypertensives in patients with diabetes is warranted
Systolic inter-arm BP difference in hypertension is associated with increased cardiovascular and all-cause mortality for a difference ≥ 15mmHg, and increased cardiovascular mortality for a ≥ 10mmHg difference. This supports suggestions that inter-arm difference is due to peripheral vascular disease. An inter-arm difference should be considered a marker of elevated cardiovascular risk, and its detection should prompt aggressive lifestyle and risk factor intervention.

Methods: observational cross-sectional study. CVR and CVRF were assessed in a sample of 930,404 workers who underwent a routine occupational health checkup. The sample consisted of 1,488 physicians (0.2%), 481,880 blue-collar workers and 25.5% white-collar workers. Bivariate analyses were performed to compare CVR and CVRF among groups. Because sex and age significantly differed among occupational groups (p < 0.001), all analyses were adjusted for these variables. Chi-square test (categorical data), t-test and ANOVA (quantitative data) were used. All analyses were performed with SPSS 17.0.

Results: Prevalence of high CVR (SCORE criteria) among physicians was 3.4%. Dyslipidemia (TC > 200 or LDL-C = 160 mg/dl) and tobacco consumption were the most prevalent CVRF. The prevalence of CVRF among physicians was: dyslipidemia 43.1%; tobacco consumption 29.6%; hypertension (PAS = 140 or PAD = 90 mmHg or treatment) 17.4%; obesity (BMI > 30) 9.0%; central obesity 13.3%; and metabolic syndrome (ATPIII) 6.6%. Differences between occupational groups were smaller than expected. Neither diagnosis of dyslipidemia nor any of its components were significantly less prevalent among physicians. However, prevalence of dyslipidemia among < 40-years-old male physicians was even higher than in other occupations. On the other hand, tobacco consumption was significantly lower among physicians (29.6% vs. 40.5%; p < 0.001). When physicians were compared only to workers in other scientific and intellectual professionals, i.e. a group with similar socioeconomic and educational level, we still found very few significant differences: tobacco consumption lower among women physicians < 40 years-old; lower prevalence of obesity among women physicians 40 years-old; and lower prevalence of high CVR among male physicians 40 years old. Among workers treated for CVRF, achieved SBP was significantly lower in physicians than in other workers (136.5 vs. 146.6 mmHg; p < 0.001), but TC (220.4 vs. 216.9) and TG (209.2 vs. 162.7 mg/dl) were higher.

Conclusions: Physicians appear not to be at a lower CVR than other workers. While they are less prone to the habit of smoking and, when hypertensive, achieve a significantly better control of SBP, dyslipidemia is no less common, and even more prevalent among young male physicians, and, when treated for dyslipidemia, their TC and TG are less controlled.

Objective: To compare overall cardiovascular risk (CVR) and individual cardiovascular risk factors (CVRF) among physicians, other scientific and intellectual professionals, and workers with different occupations in a large database of working people in Spain.

Methods: Observational cross-sectional study. CVR and CVRF were assessed in a sample of 930,404 workers who underwent a routine occupational health checkup. The sample consisted of 1,488 physicians (0.2%), 83,075 other scientific and intellectual professionals (9.2%) and 821,580 workers with different occupations. This last group was composed of 74.5% blue-collar workers and 25.5% white-collar workers. Bivariate analyses were performed to compare CVR and CVRF among groups. Because sex and age significantly differed among occupational groups (p < 0.001), all analyses were adjusted for these variables. Chi-square test (categorical data), t-test and ANOVA (quantitative data) were used. All analyses were performed with SPSS 17.0.

Results: Prevalence of high CVR (SCORE criteria) among physicians was 3.4%. Dyslipidemia (TC > 200 or LDL-C = 160 mg/dl) and tobacco consumption were the most prevalent CVRF. The prevalence of CVRF among physicians was: dyslipidemia 43.1%; tobacco consumption 29.6%; hypertension (PAS = 140 or PAD = 90 mmHg or treatment) 17.4%; obesity (BMI > 30) 9.0%; central obesity 13.3%; and metabolic syndrome (ATPIII) 6.6%. Differences between occupational groups were smaller than expected. Neither diagnosis of dyslipidemia nor any of its components were significantly less prevalent among physicians. However, prevalence of dyslipidemia among < 40-years-old male physicians was even higher than in other occupations. On the other hand, tobacco consumption was significantly lower among physicians (29.6% vs. 40.5%; p < 0.001). When physicians were compared only to workers in other scientific and intellectual professionals, i.e. a group with similar socioeconomic and educational level, we still found very few significant differences: tobacco consumption lower among women physicians < 40 years-old; lower prevalence of obesity among women physicians 40 years-old; and lower prevalence of high CVR among male physicians 40 years old. Among workers treated for CVRF, achieved SBP was significantly lower in physicians than in other workers (136.5 vs. 146.6 mmHg; p < 0.001), but TC (220.4 vs. 216.9) and TG (209.2 vs. 162.7 mg/dl) were higher.

Conclusions: Physicians appear not to be at a lower CVR than other workers. While they are less prone to the habit of smoking and, when hypertensive, achieve a significantly better control of SBP, dyslipidemia is no less common, and even more prevalent among young male physicians, and, when treated for dyslipidemia, their TC and TG are less controlled.
Azilsartan Medoxomil/Chlorthalidone Fixed-Dose Combination Lowers BP More Than Olmesartan/Hydrochlorothiazide Fixed-Dose Combination in Stage 2 Systolic Hypertension


1University of Tennessee College of Medicine, Memphis-USA, 2University of Chicago Pritzker School of Medicine, Chicago-USA, 3Virginia Commonwealth University Health System, Richmond-USA, 4Takeda Global Research & Development Center, Deerfield-USA

Background: Azilsartan medoxomil (AZL-M) is a newly approved, highly effective, long-acting angiotensin II receptor blocker (ARB). Chlorthalidone (CLD) is a potent, long-acting thiazide-like diuretic.

Methods: We compared fixed-dose combinations (FDCs) of AZL-M/CLD 20/12.5 mg QD force titrated to 40/25 or 40/12.5 mg QD force titrated to 80/25 mg with an FDC of olmesartan medoxomil (OLM), another ARB, plus the thiazide diuretic hydrochlorothiazide (HCTZ) 20/12.5 mg QD then force titrated to 40/25 mg (its highest approved dose). This randomized, double-blind, 12-wk study included 1071 subjects with mean clinic systolic BP (SBP) 160–190 mm Hg and diastolic BP ≤ 119 mm Hg. The primary endpoint was change from baseline to wk 12 in trough seated clinic SBP. Secondary endpoints were changes in 24-hr ambulatory BP. We also assessed safety and tolerability.

Results: At baseline, patients were 57 yrs old (mean), 41% were women, and 22% were black, with a clinic BP of 165/96 mm Hg and 24-hr mean BP of 151/88 mm Hg. Trough seated clinic SBP changed significantly more with both AZL-M/CLD doses than with olmesartan/HCTZ at 4, 8, and 12 wks (Table). At 12 wks, both AZL-M/CLD doses reduced 24-hr mean SBP more than OLM/HCTZ (−33.9 and −32.7 vs −27.5 mm Hg; both P < 0.001). Adverse events leading to permanent drug discontinuation occurred in 7.9%, 14.5%, and 7.1% of the groups given AZL-M/CLD 40/25 mg, AZL-M/CLD 80/25 mg, and OLM/HCTZ 40/25 mg, respectively.

Conclusions: This first large, forced-titration study of an ARB-CLD combination demonstrated superior efficacy of AZL-M/CLD FDCs versus OLM/HCTZ. Tolerability was relatively similar for the lower dose of AZL-M/CLD, with a moderately higher adverse-event discontinuation rate for the higher dose.

BLOOD PRESSURE REDUCTION FOLLOWING INTERVENTION ON PSYCHOSOCIAL WORK FACTORS

X. Trudel1, M. Gilbert-Ouimet1, C. Brisson1, A. Milot2, M. Vezina2, B. Massé1.

1URESPP Centre hospitalier affilié universitaire de Quebec, Quebec-Canada, 2Centre Hospitalier Universitaire De Quebec, Quebec-Canada, 3Fred Hutchinson Cancer Research Center, Seattle-USA

Background: Adverse psychosocial work factors have been shown to contribute to the development of chronic health problems, such as hypertension. Preventive interventions aimed at reducing psychosocial work factors have been conducted in workplaces. However, few studies have rigorously evaluated their effectiveness in reducing psychosocial work factors and improving blood pressure (BP).

Methods: An intervention was conducted in a large public insurance company to reduce adverse psychosocial work factors. These factors and ambulatory BP were measured at baseline, 6- and 30-month post-intervention. Ambulatory BP measurements were taken every 15 minutes during a working day. Psychosocial work factors were measured using validated scales. Associations between exposure to psychosocial work factors and BP were also examined, using generalized estimating equations (GEE). The study sample consisted of 2132 workers and 4263 observations.

Results: During the entire study period, workers exposed to high psychological demands, job strain and reward imbalance had mean blood pressure approximately 2 mmHg higher than workers not exposed to these factors. By the 6- and 30-month follow-up, three of the targeted factors had significantly decreased (high psychological demands, low reward and effort-reward imbalance). The 30-month follow-up also showed significant reductions in the prevalence of hypertension (16.4% to 12.5%), mean systolic BP (126.1 to 123.9 mmHg) and mean diastolic BP (80.6 to 78.8 mmHg).

Conclusion: These results suggest that interventions that aim to reduce adverse psychosocial work factors may lead to improvements in BP.

Hypertension Phenotypes Defined by Office and Ambulatory Blood Pressure in 9,153 Subjects Referred to Hypertension Clinics in Four Continents: The ARTEMIS International Registry

G. Parati1, S. Omamb1i, G. Stergiou1, A. de la Sierra1, E. Dolan2, G. Head3, T. Kahan7, I. Kantola8, K. Kawecka-Jaszcz9, K. Narkiewicz10, T. Ohkubo11, J. Siegalová12, E. Silva13, Y. Zhang14, G. Mancia1, On Behalf of ARTEMIS International Ambulatory Blood Pressure Registry; TeleMonitoring of Hypertension and Cardiovascular Risk project Investigators. 1Department
Background: Ambulatory blood pressure monitoring (ABPM) is a particularly useful technique that improves the management of hypertensive patients. The ARTEMIS Project has been designed to setup an international registry of subjects from Hypertension (HT) Clinics in different countries, in whom clinical information and 24 h ABPM is available, aiming to assess the prevalence of daily life HT phenotypes and cardiovascular risk factors.

Methods: Data have been provided by existing databases of HT Clinics worldwide. Treated or untreated subjects performing an ABPM for clinical or research purposes were included in the analysis if fulfilling inclusion criteria. Demographic data, medical history and major cardiovascular risk factors were assessed. Sitting clinic blood pressure (CBP) was measured in all subjects before being submitted to 24 h ABPM using validated automated devices. The prevalence of HT was assessed in the clinic (CBP ≥ 140/90 mmHg) and by average 24 h ABP (≥ 130/80 mmHg).

Results: Overall 9,189 subjects were included in Europe (16 countries, n = 7,522, 82% of the sample: Belarus, Bosnia Herzegovina, Croatia, Czech Republic, Finland, Greece, Ireland, Italy, Poland, Portugal, Romania, Russia, Serbia, Slovakia, Spain, Sweden), South America (2 countries, n = 266, 3%: Colombia, Venezuela), Asia (2 countries, n = 1,190, 13%: China, Japan) and Oceania (1 country, n = 211, 2%: Australia). Mean participants’ age was 56 ± 14 years (range 17–92 years), 51% males, 48% treated for HT, 13% with cardiovascular disease, 16% with diabetes, 32% with dyslipidemia, 19% smokers. The prevalence of uncontrolled HT was higher when based on CBP (n = 6,371; 69%) than ABPM (n = 5,295, 58%, p < 0.001) and sustained uncontrolled HT (elevated CBP and ABP) was detected in 47% of subjects (treated 44%, untreated 52%). The HT phenotypes are presented in the table. Overall, the prevalence of sustained HT tended to be higher in samples from South America and Europe than Asia and Oceania (p < 0.001). Isolated clinic HT was more common in untreated subjects (p < 0.001) and masked uncontrolled HT in treated subjects (p < 0.001).

Conclusions: Preliminary analysis of the ARTEMIS International Registry, in spite of a yet unbalanced sample size among the different continents in this early project stage, provides interesting comparative information on HT phenotypes in treated and untreated subjects attending HT clinics worldwide. Significantly higher prevalence of sustained HT was observed in clinics in Europe and South America than in Asia and Oceania.
ORAL SESSION

ORAL SESSION 8A

CLINICAL ASPECTS

8A.01 CLINICAL SIGNIFICANCE OF BAROREFLEX SENSITIVITY IN HYPERTENSIVE PATIENTS AFTER ACUTE ISCHEMIC STROKE

D. Celovská1, J. Staskó1, J. Gonsorcik1, A. Dukál1, 2Comenius University, Faculty of Medicine, Bratislava-Slovak Republic, 2Institute of Cardiology, Presov-Slovak Republic

Objective: Examination of baroreflex sensitivity (BRS) is a noninvasive marker of autonomic dysfunction. The aim of the present study was to evaluate the clinical significance of baroreflex sensitivity in hypertensives after acute ischemic stroke.

Design: A total of 26 patients (66 ± 10 years of age, 11 female/15 male) with a history of the first ever ischemic stroke (6 month and more after stroke onset), which was neuroradiologically confirmed, were studied. These were compared to 30 hypertensive patients without history of any cardiovascular event, being of similar age and sex. The relationship between baroreflex sensitivity (BRS) and blood pressure in hypertensives with stroke in comparison with a group of stroke-free control patients was evaluated. Method: BRS was determined by the sequence and spectral method: a five-minute non-invasive heart-to-beat record-

Results: Nearly half of the uncontrolled hypertensive pts are treated with only a single-drug therapy. The most frequent therapeutic decision for these uncontrolled pts is to maintain the same TS. On the contrary another therapeutic class is added for only one third of the pts. This study demonstrated that clinical therapeutic inertia is important in the GPs management of uncontrolled hypertensive pts.

8A.02 QUANTIFICATION OF CLINICAL INERTIA DURING GENERAL PRACTITIONER’S MANAGEMENT OF UNCONTROLLED HYPERTENSIVE PATIENTS – CLEPSYDRE STUDY

X. Girerd1, B. Fiquet2, S. Quere2, A. Francillon2, 1Pitié Salpêtrière Hospital, Paris-France, 2Novartis Pharma SAS, Rueil-Malmaison-France

To assess therapeutic inertia during the management of uncontrolled hypertensive patients (pts) (blood pressure (BP) > 140/90 for non diabetic (DB) and BP> 135/80mmHg for DB pts).

Method: French cross sectional study conducted with 1419 GPs in 2010. Each physician included the first 5 consecutive hypertensive pts according to above inclusion criteria. The therapeutic score (TS) was defined for each pt according to the number of antihypertensive classes prescribed before and after the inclusion criteria. The therapeutic score (TS) was defined for each pt accord-

Results: Nearly half of the uncontrolled hypertensive pts are treated with only a single-drug therapy. The most frequent therapeutic decision for these uncontrolled pts is to maintain the same TS. On the contrary another therapeutic class is added for only one third of the pts. This study demonstrated that clinical therapeutic inertia is important in the GPs management of uncontrolled hypertensive pts.

8A.03 OPTIMAL CUT-OFF AMBULATORY BLOOD PRESSURE LEVEL FOR DIAGNOSIS OF TRUE RESISTANT HYPERTENSION AND EFFECT OF SPIRONOLACTONE

J.A. Garcia-Donaire, J. Segura, C. Cerezo, V. Mottiva, L. Fernandez, L. Guererro, L.M. Ruilope. Hypertension Unit. Department of Nephrology, Hospital 12 De Octubre, Madrid-Spain

Aim: To describe the prevalence of white coat resistant hypertension (RH) in a cohort of patients with RH diagnosis according to office measurements, to evaluate the value of two cut-off ambulatory BP levels to identify those popula-

Results: 143 patients with RH were included, with a mean age of 65 ± 10 years old, 51.0% female, and 39.2% diabetic. The percentage of patients with white coat RH was 30.8% (n = 44) according to the dayWCRRH, and 24.5% (n = 35), according to the 24hWCRRH cut-off level. A 67.1% (n = 96) of the sample can be classified as true RH according to both cut-off points and 22.4% (n = 32) can be classified as white coat RH (coincidence percentage of 89.5%, kappa concor-

Conclusion: Nearly half of the uncontrolled hypertensive pts are treated with only a single-drug therapy. The most frequent therapeutic decision for these uncontrolled pts is to maintain the same TS. On the contrary another therapeutic class is added for only one third of the pts. This study demonstrated that clinical therapeutic inertia is important in the GPs management of uncontrolled hypertensive pts.

8A.04 TRENDS IN ALBUMINURIA UNDER RAS SUPPRESSION AND RELATIONSHIP WITH CARDIOVASCULAR DISEASE

C. Cerezo1, J. Segura2, J.R. Banegas3, J.I. De La Cruz2, J.A. Garcia Donaire1, T.J. Rabellino1, L.M. Ruilope1, 1Hypertension Unit. Department of Nephrology, Hospital 12 De Octubre, Madrid-Spain, 2Department of Preventive Medicine & Public Health, Universidad Autonoma, Madrid-Spain, 3Department of

Abstracts e121
Conclusions: Fulfillment compliance with antihypertensive drug therapy and outcome adjusting for several covarates.

Results: During a mean of 6 years of follow-up, 12,016 members of the cohort experienced the outcome. Compared with patients who experienced at least one episode of treatment discontinuation, those who continued treatment had a 37% reduced risk of cardiovascular outcomes (95% confidence interval: 34%–40%). Compared with patients who had very low drug coverage (proportion of days covered, ≤25%), those at intermediate (from 51 to 75%) and high coverage (>75%) had risk reductions of 20% (16%–24%) and 25% (20%–29%), respectively. Similar effects were observed when controlling for other covariates.

Conclusion: Compliance with antihypertensive drug therapy is effective in the primary prevention of cardiovascular outcomes.
in our patients cortisol levels appeared unexpectedly to be negatively related to stress profiles, suggesting a possible primary defect in coping with emotional stress and anxiety in arterial hypertension.

**Conclusions:** Admission to the ED for hypertensive emergencies and urgencies is still high. Our results underline the need for a correct diagnosis and classification of these clinical conditions.

**8A.08 PREVALENCE AND CLINICAL CHARACTERISTICS OF PATIENTS ADMITTED TO AN EMERGENCY DEPARTMENT FOR HYPERTENSIVE EMERGENCIES AND URGENCIES**

A. Paini, M. Salvetti, S. Cobelli, L. Torazzi, C. Agabiti Rosei, C. Aggiusti, D. Zotti, A. Bazzà, F. Bertacchini, F. Beschi, D. Stassaldi, C. Concoreggi, E. Agabiti Rosei, M.L. Muiesan, 1Internal Medicine, University of Brescia, Brescia-Italy, 2Emergency Department, Spedali Civili, Brescia-Italy

**Background:** Few data are available on the prevalence of hypertensive emergencies and urgencies and on clinical characteristics of patients admitted to Emergency Departments (ED). Aim of our study was to provide data on the prevalence of hypertensive emergencies and urgencies in an ED in Northern Italy, over a period of 12 months.

**Methods:** Between January and December 2008, medical records of patients aged > 18 yrs, admitted to the ED of the Spedali Civili di Brescia with blood pressure values ≥180 mmHg (SBP) and/or ≥120 mmHg (DBP) were collected and analysed.

**Results:** Out of 77,154 patients admitted to the ED, BP was found ≥180 mmHg (SAP) and/or ≥120 mmHg (DAP) in 2.2%. Medical records were obtained and analysed in 95% of these patients (16,36 pts, 44% males, mean age 70 ± 14 yrs, range 18-102). According to the clinical presentation and the presence of acute organ damage 328 pts (20%) were classified as “hypertensive emergency” (HE, BP 193 ± 15/102 ± 15 mmHg) and 1308 pts (80%) as “hypertensive urgency” (HU). Among urgencies we identify 3 subgroups: 890 pts with “hypertensive urgency” (BP 188 ± 11/94 ± 12 mmHg), 38 with “pseudo-hypertensive urgency” and 38 pts with “hypertensive urgency and a first diagnosis of hypertensive crisis” (BP 193 ± 18/103 ± 14 mmHg). The most frequent symptoms or signs were: chest pain (20%), dyspnoea (18%), neurological changes (17%), headache (11%), arrhythmias (6%), changes in mental status (3%). Among hypertensive emergencies the different forms of organ damage were distributed as follows: 25% acute coronary syndromes, 25% acute pulmonary oedema, 10% atrial and ventricular arrhythmias, 1% aortic dissection, 32% ischemic stroke, 7% hemorrhagic stroke. Patients with HE were more frequently male and patients with “hypertensive urgency and a first diagnosis of hypertension” were younger as compared with all other groups.

**Conclusions:** Admission to the ED for hypertensive emergencies and urgencies is still high. Our results underline the need for a correct diagnosis and classification of these clinical conditions.

**8A.09 HYPERTENSIVE EMERGENCIES AND URGENCIES IN AN EMERGENCY DEPARTMENT. ASSOCIATION WITH SUBSEQUENT CARDIOVASCULAR EVENTS DURING 2 YEARS FOLLOW-UP**

M. Salvetti, A. Paini, L. Torazzi, S. Cobelli, C. Agabiti Rosei, C. Aggiusti, A. Bazzà, D. Zotti, F. Bertacchini, D. Stassaldi, C. Concoreggi, E. Agabiti Rosei, M.L. Muiesan, 1Internal Medicine, University of Brescia, Brescia-Italy, 2Emergency Department, Spedali Civili, Brescia-Italy

**Background:** At present, few data are available on the prognostic significance of hypertensive emergencies and urgencies admitted to Emergency Departments (ED). The aim of our study was to evaluate the incidence of total and cardiovascular events (CV) during follow-up in hypertensive patients admitted to an ED of the Brescia Hospital (Northern Italy) with hypertensive emergencies (HE) or urgencies (HU).

**Methods:** Between January and December 2008, medical records of patients aged > 18 yrs, admitted to the ED of the Spedali Civili di Brescia with blood pressure values ≥180 mmHg (SBP) and/or ≥120 mmHg (DBP) were collected and analysed (328 pts were classified as “hypertensive emergency”, 890 pts as “hypertensive urgency”, 380 pts as “pseudo hypertensive urgency” and 38 pts with “hypertensive urgency and a first diagnosis of hypertension”). Data on 947 patients were analysed; the mean duration of follow-up after admission to the ED was 2 years.

**Results:** A first fatal or non fatal CV event occurred in 226 patients (62 cardiovascular events, 45 cerebrovascular events, 42 hospital admissions for heart failure, 46 cases of new onset renal failure and 31 cases of new-onset diabetes). Patients with CV events were older, more frequently males, with a higher prevalence of diabetes mellitus and previous CV disease, and a greater proportion of inadequate BP control. During the follow-up a new episode of “hypertensive crisis” was recorded in 203 pts (24%). The incidence of hypertensive crises was significantly higher in patients with hypertensive emergency in comparison with hypertensive urgency (p = 0.03). The incidence of fatal and non fatal events was 14.8, 5.1, 5.3, 2.5 per 100 patient-years in patients with hypertensive emergency, urgency, pseudo-urgency and first diagnosis of hypertension, respectively (p < 0.001 emergency vs others, by the log-rank test). Similar results were obtained when we considered separately the occurrence of cardiovascular, cerebrovascular or renal events.

**Conclusions:** Admission to the ED for hypertensive emergencies identifies hypertensive patients at increased risk for fatal and non fatal cardiovascular events. Our results underline the need for a strict and accurate follow-up in patients with hypertensive crises.
Methods and Results: This study is a sub-analysis of the Ediva project, which is a prospective, multicenter and observational cohort study involving 2200 individuals of Portuguese nationality (1290 men) aged between 18 and 91 years (mean 46.33 ± 13.76 years), with annual measurements of PWV (Complior). All incident major cardiovascular events (MACE) - death, cerebrovascular accident (CVA), coronary accidents (CHD), peripheral arterial disease and renal failure - were recorded.

During a mean follow-up period of 21.42 ± 10.76 months, there were 47 non-fatal MACE (2.1% of the sample). Cardiovascular risk was estimated in all patients based on the HeartSCORE algorithm. The average value of HeartSCORE was 5.98 ± 8.02, and PWV was 10.05 ± 2.03m/s. For the analysis, the Z-scored HeartSCORE and PWV were divided into tertiles. The event-free survival at 2 years was 98.6%, 98.0% and 96.1% respectively in the 1st, 2nd and 3rd tertiles of HeartSCORE (log-rank p < 0.001). The hazard ratio (HR) per 1-SD for MACE was 1.474 (95CI:1.150–1.890, p = 0.002) for HeartSCORE, and 2.265 (95CI:1.791–2.864, p < 0.0001) for PWV. HR (Cox deviation coding) for HeartSCORE risk classes was 0.582 (95CI:0.378–0.895, p = 0.014), 1.017 (95CI:0.574–1.804, p = 0.953) and 1.689 (95CI:0.378–0.895, p = 0.014), respectively for 1st, 2nd and 3rd tertile, suggesting a curvilinear relationship with the risk of MACE. The ROC area under the curve (AUC) for HeartSCORE was 0.619 (95CI:0.536–0.702, p = 0.005), shifting to an AUC of 0.701 (95CI:0.630–0.772, p < 0.001) with the addition of PWV, with similar results for stroke and coronary events. The risk of MACE by tertiles of PWV and HeartSCORE increased curvilinearly, and the risk was particularly more pronounced in the highest tertile of PWV for any category of the HeartSCORE, demonstrating an interaction in the prediction of cardiovascular risk. It was clearly depicted a high discriminative capacity of PWV even in groups of apparent low cardiovascular risk (tertile 1 and 2 of HeartSCORE).

Conclusion: The results clearly illustrate benefits of integrating PWV in the risk assessment strategies, as advocated by HeartSCORE, insofar as it contributes to a better discriminative capacity of global cardiovascular risk, particularly in individuals with low or moderate cardiovascular risk.

**8B.03 COMPARISON OF TWO RADIO-FREQUENCY BASED ULTRASOUND SYSTEMS FOR ASSESSMENT OF CAROTID STIFFNESS**

C. Palombo1, M. Kozakova2, C. Morizzo1, G. Bini3, N. Gurasci1, V. Di Bello1, A. Balbarini1.

1University of Pisa, Department of Surgery, Pisa-Italy, 2Esaote, Genova-Italy, 3Department of Internal Medicine, University of Pisa, Pisa-Italy, 4University of Pisa, Cardiac and Thoracic Department, Pisa-Italy

Objective: Measurement of arterial stiffness is becoming widely used for assessing cardiovascular risk and target organ damage. Two commercially available ultrasound systems (QAS, Esaote, Italy and eTracking, Aloka, Japan) provide radio-frequency (RF)-based tracking of carotid wall, thus allowing automatic accurate real-time determination of vessel diameter and distension, and subsequent calculation of indices of carotid stiffness. The measurement is performed in a single line by eTracking and in 16 equidistant lines within the region of interest by QAS. Aim of the present study was to evaluate whether the measures of carotid stiffness obtained by the two systems are interchangeable, and to assess the intra- and inter-operator variability of acquisitions.

Design and Methods: In the same session, MyLab 70 (Esaote, Italy) and Alpha 7 (Aloka, Japan) were used in random order to measure (2 cm before the flow divider) right common carotid artery (CCA) diameter and distension, and to calculate beta-index (Beta) in 104 subjects divided into 4 groups: 24 healthy controls (NL, age 32 ± 7 yy), 24 prehypertensive subjects (PHBP, age 50 ± 10 yy), 26 hypertensive patients (HBP, age 57 ± 10 yy) and 27 type 2 diabetic patients (DM, age 62 ± 6 yy). In 30 subjects, the second acquisition was performed after a 60-minute interval, both by the same operator and by a second operator. The reported values represent a mean of 3 measurements.

Results: Brachial BP was similar during the acquisition with QAS and eTracking (p = 0.94), and the correlation between the two systems for CCA distension and Beta was high (r = 0.94 and 0.90, respectively, p < 0.0001 for both). In the entire study population, the values of distension and Beta obtained with QAS were systematically lower and higher, respectively, than those obtained with


**BB.04 CENTRAL PRESSURES AND PRESSURE AMPLIFICATION AS PREDICTORS OF CAROTID DISEASE AND MORTALITY. THE ROTTERDAM STUDY**

F. Mattace Raso1, B. Westerhof2, G. Verwoert1, W.J. Bos3, I. Guelen2, A. Hofman1, J.C.M. Witteman1, 2Erasmus University Medical Center, Rotterdam-Netherlands Antilles, 2Bemetery, Amsterdam-The Netherlands, 3St. Antonius Ziekenhuis, Nieuwegein-The Netherlands

**Objective:** We investigated the value of central pressures in predicting cardiovascular disease and all-cause mortality in the population.

**Design and Methods:** We included 2102 subjects participating the third examination phase of the Rotterdam Study, a large ongoing population-based study. Finger blood pressure was measured (Finapres) and central pulse pressure was calculated using upper arm level correction and a generalized transfer function. Information on smoking habits and previous cardiovascular disease were obtained. Body mass index was calculated. Serum total cholesterol and HDL cholesterol values were determined and diabetes mellitus was defined. Subjects with previous cardiovascular events were excluded from the analyses. Cox’s proportional hazard multivariate regression analyses were carried out.

**Results:** The mean age of the participants was 71.4 years, 39.5% were men. During a mean follow-up time of 6.1 years, 162 subjects had CHD, 241 subjects developed cardiovascular events (coronary heart disease + stroke) and 414 subjects died. HR’s and 95% CI of CHD were 1.12 (1.01–1.26) for the central PP, and 1.06 (1.01–1.11) for the PP amplification (bPP-cPP). HR’s and 95% CI of cardiovascular disease were 1.13 (1.04–1.23) for central PP and 1.16 (1.01–1.13) for the PP amplification (bPP-cPP). HR’s and 95% CI of all-cause mortality were 1.01 (0.94–1.08) for central pulse pressure, and 1.02 (0.99–1.05) for the PP amplification (bPP-cPP).

**Conclusion:** In a large population of older adults, central pressures were predictive of cardiovascular events and borderline predictive of all cause mortality. A high amplification was also predictive of cardiovascular events and borderline predictive of all cause mortality. A high amplification was also predictive of cardiovascular events. This counterintuitive result is most likely the related to impaired cardiac ejection patterns.

**BB.05 INSULIN, FATTY ACID SYNTHASE, HOMOCYSTEINE LEVELS AND MEASURE OF ARTERIAL PROPERTIES. THE ROTTERDAM STUDY**

G. Verwoert1, F. Mattace-Raso1, A. Hofman1, B. Westerhof2, W. Bos3, E. Sijbrands3, J. Witteman1, 1Erasmus MC, Rotterdam-The Netherlands, 2Academic Medical Center, Amsterdam-The Netherlands, 3St Antonius Hospital, Nieuwegein-The Netherlands

**Objective:** To investigate whether serum levels of insulin, fatty acid synthase and homocysteine are associated with measure of arterial properties.

**Methods:** This study has been performed within the framework of the Rotterdam Study, a population based cohort study. More than 2500 participants and measures of arterial properties including, aortic pulse wave velocity (aPWV), cardio-ankle pulse wave velocity (CA-PWV), serum insulin levels, homocysteine (Hcy) levels and central blood pressure. Furthermore, homocysteine levels play a role in the development of carotid atherosclerosis, but not central blood pressure or arterial stiffness.

**Results:** There was a significant association between insulin and aPWV (0.43 m/s; 95% CI 0.29–0.57 m/s), carotid distensibility (−0.56 mPa; 95% CI −0.76–−0.36 mPa), carotid intima media thickness (0.020 mm; 95% CI 0.013–0.027 mm), and central blood pressure (cSBP 3.20 mmHg; 95% CI 1.91 – 4.50 mmHg; cDBP 2.11 mmHg; 95% CI 1.40–2.83 mmHg; cMAP 2.80 mmHg; 95% CI 1.91–3.69 mmHg; cPP 1.09 mmHg; 95% CI 0.11–2.06 mmHg). Homocysteine is significantly associated with carotid intima media thickness (0.005 mm; 95% CI 0.004 – 0.006 mm). Fatty acid synthase levels are not associated with measures of arterial properties.

**Conclusion:** Our findings suggest that serum insulin levels play a pathophysiological role in the development of increased arterial stiffness, atherosclerosis and central blood pressure. Furthermore, homocysteine levels play a role in the development of carotid atherosclerosis, but not in central blood pressure or arterial stiffness.

**BB.06 NORMAL VALUES FOR AORTIC PULSE WAVE VELOCITY IN A PEDIATRIC POPULATION**

D. Krach1, A. Doyon1, C. Jacob1, F. Schaefer1, S. Sorrentino1, B. Schmidt1, E. Wuehl1, A. Melk1, 1Hannover Medical School, Hannover-Germany, 2University Hospital Heidelberg, Heidelberg-Germany

**Study aim:** Aortic pulse wave velocity (aPWV) predicts cardiovascular mortality in adults. Arterial stiffening advances with age and is accelerated in specific diseases. In childhood aPWV has not been investigated in larger cohorts. The aim of this study is to provide normal values and prove the suspected increase with age.

**Methods:** Pulse waves were captured by oscilometry simultaneously on the right carotid and femoral artery (Vicorcor®) in 405 healthy school children aged 6 to 18 years. Intima-media thickness (IMT) and elasticity on both carotid arteries by B- and M-mode ultrasound were measured.

**Results:** aPWV significantly increased with age: 6-8 year olds (n = 97): 4.2 ± 0.4 m/s; 9-11 year olds (n = 135): 4.5 ± 0.4 m/s; 12-14 year olds (n = 97): 4.9 ± 0.5 m/s; 15-18 year olds (n = 66): 5.2 ± 0.5 m/s (p < 0.0001). aPWV significantly correlated with age (r = 0.63, p < 0.0001). Further significant correlations existed for weight, height, mean systolic and diastolic blood pressure. We found no correlation of aPWV with IMT, but significant correlations with elasticity markers: distensibility coefficient (r = –0.42, p < 0.0001) and incremental elastic modulus (r = 0.43, p < 0.0001). Independent predictors for aPWV in multiple regression analysis were found for age, gender, diastolic blood pressure and elasticity parameters.

**Conclusions:** This study defines aPWV normal values in children and adolescents using a new non-invasive oscillometric method. Even in healthy children correlations to cardiovascular risk factors can be seen. Interestingly, a connection of aPWV to functional parameters of arterial elasticity was observed.

**BB.07 RELATIONSHIP BETWEEN CAROTID ARTERY PROPERTIES, MUSCLE SYMPATHETIC NERVE ACTIVITY AND CARdiovascular VARIABILITY**

D. Hering1, R. Nowak1, K. Czeczenowicz1, W. Kucharska1, P. Brands2, P. Boutouyrie1, S. Lauren1, K. Narkiewicz1, 1Department of Hypertension and Diabetology, Medical University of Gdańsk, Gdańsk-Poland, 2Exaese Europe BV, Maastricht-The Netherlands, 3Department of Clinical Pharmacology, HEGP, APHP, Université Paris Descartes, Inserm U970, Paris-France

**Objective:** The relationship between direct measures of sympathetic traffic and common carotid artery (CCA) properties has not been previously studied. We therefore tested the hypothesis that muscle sympathetic nerve activity (MSNA) and cardiovascular variability are independently linked to CCA intima-media thickness and distensibility.

**Design and Methods:** We measured MSNA (microneurography), heart rate (ecg), arterial pressure (Finapres system), and CCA intima-media thickness (IMT) and distensibility (AnLab system) in 20 subjects with high normal blood pressure and newly detected stage 1 hypertension (18 males, age 36 ± 2 years, BMI 27 ± 1 kg/m², mean ± SEM). SBP and RR-interval variabilities were defined as the standard deviation of the means.

**Results:** MSNA averaged 27 ± 3 bursts/min, mean CCA intima-media thickness was 0.46 ± 0.03 mm, and carotid distensibility was 26 ± 3 kPa 1/2. CCA IMT was related to MSNA (r = 0.54; P < 0.01), but not to variability of SBP (r = 0.27; P = NS) or RR-interval (r = 0.26; P = NS). CCA distensibility was positively associated with RR-variability (r = 0.48; P < 0.05), but not with MSNA (r = 0.22; P = NS) or with SBP variability (r = 0.13; P = NS). The correlations between MSNA and CCA IMT, and between CCA distensibility and RR-interval variability remained significant after adjustment for age, body mass index and blood pressure.

**Conclusions:** Common carotid artery properties are related to muscle sympathetic nerve activity and cardiovascular variability. While increased intima-media thickness is associated with higher neural sympathetic traffic, higher carotid artery distensibility is linked to greater heart rate variability.
**ORAL SESSION**

**ORAL SESSION 6C**

**HEART**

**8C.01 HERITABILITY OF LEFT VENTRICULAR STRUCTURE AND FUNCTION IN CAUCASIAN FAMILIES**

Y. Jin1, T. Kuznetsova1, M. Bochud2, T. Richart3, L. Thijs1, D. Cusi4, R. Fagard1, J. Staessen1. 1University of Leuven, Leuven-Belgium; 2University of Lausanne, Lausanne-Switzerland; 3Maastricht University, Maastricht-The Netherlands; 4University of Milan, Milano-Italy

**Objective:** To investigate the heritability as well as genetic and environmental correlations between left ventricular structural and functional traits in complex pedigrees of a Caucasian population.

**Design and Methods:** We randomly recruited 459 white European subjects from 52 families (50% women; mean age 45 years). Left ventricular structure was measured by M-mode and 2D echocardiography and diastolic function was measured by conventional Doppler and Tissue Doppler Imaging. Other measurements included blood pressure, anthropometric and biochemical measurements. We estimated the heritability of left ventricular traits while adjusting for covariables, including sex, age, body height and weight, systolic and diastolic blood pressures, and heart rate.

**Results:** With full adjustment, heritability of left ventricular mass was 0.23 (p = 0.025). The Tissue Doppler derived mitral annular velocities Ea and Aa showed moderate heritability (h² = 0.36 and 0.53, respectively), whereas the mitral inflow A peak had weak heritability (h² = 0.25) and the E peak was not heritable (h² = 0.11). We partitioned the total phenotypic correlation when it reached significance, into a genetic and environmental component. The genetic correlations were 0.61 between the E and Ea peaks and 0.90 between the A and Aa peaks.

**Conclusions:** Our study demonstrated moderate heritability for left ventricular mass as well as the mitral annular Ea and Aa peaks. We also found significant genetic correlations between the mitral valve left ventricular E and Ea peaks and between the A and Aa peaks. Our current findings support the goal to map and detect genetic variants that might contribute to the variation in left ventricular mass and other cardiac structural and functional phenotypes.

**8C.02 BLOOD PRESSURE CONTROL AND ANTIHYPERTENSIVE MEDICATION POST MYOCARDIAL INFARCTION – THE FARIM REGISTRY**

J. Spinat, J. Vitovec, L. Spinarova. University Hospital, Brno-Czech Republic

**Aims:** The FARIM registry (FARmakotherapy after Myocardial Infarction) is a web side based database. Included were patients who visited a polyclinic in a stable condition and had a history of myocardial infarction more than 30 days before the inclusion visit. Medication was recorded, patient’s history was controlled, blood pressure (BP) and heart rate were measured and basic metabolic measurements included blood pressure, anthropometric and biochemical measurements. We estimated the heritability of left ventricular traits while adjusting for covariables, including sex, age, body height and weight, systolic and diastolic blood pressures, and heart rate.

**Results:** With full adjustment, heritability of left ventricular mass was 0.23 (p = 0.025). The Tissue Doppler derived mitral annular velocities Ea and Aa showed moderate heritability (h² = 0.36 and 0.53, respectively), whereas the mitral inflow A peak had weak heritability (h² = 0.25) and the E peak was not heritable (h² = 0.11). We partitioned the total phenotypic correlation when it reached significance, into a genetic and environmental component. The genetic correlations were 0.61 between the E and Ea peaks and 0.90 between the A and Aa peaks.

**Conclusions:** Our study demonstrated moderate heritability for left ventricular mass as well as the mitral annular Ea and Aa peaks. We also found significant genetic correlations between the mitral valve left ventricular E and Ea peaks and between the A and Aa peaks. Our current findings support the goal to map and detect genetic variants that might contribute to the variation in left ventricular mass and other cardiac structural and functional phenotypes.

**8C.03 MICROVASCULAR BUT NOT MACROVASCULAR FEATURES SUPPORT DIAGNOSIS OF CORONARY ARTERY DISEASE**

U. N. Neisius1, E. Olson1, S. Rossi2, H. Ibrahim1, A. Dominiczak1, C. Delles1. 1University of Glasgow, Institute of Cardiovascular and Medical Sciences, Glasgow-United Kingdom; 2University of Glasgow, Faculty of Medicine, Glasgow-United Kingdom

**Objective:** Endothelial dysfunction is one of the early stages of the cardiovascular continuum. In contrast, macrovascular features such as increased carotid intima media thickness (cIMT), accelerated pulse wave velocity (PWV) and reduced carotid distensibility coefficient (DC) reflect on disease progression. We examined in patients with angina pectoris whether microvascular and macrovascular characteristics differ between subjects with significant coronary artery disease (CAD) and those with normal arteries.

**Methods:** Seventy-one patients (age, 56 ± 6 years) who underwent coronary angiography for assessment of stable angina pectoris were invited to 15 months after the procedure. We measured reactive hyperaemia index (RHI), a marker of endothelial function, using digital arterial tonometry (Endo-PAT2000). PWV was measured with the SphygmoCor device. To determine cIMT and DC, ultrasonography was performed with an 8 MHz linear-array transducer. cIMT was measured on B-mode and DC on M-mode picture of the common carotid artery.

**Results:** Thirty-six patients had obstructive CAD. RHI was significantly lower in patients with CAD compared to those with normal coronary arteries (1.80 ± 0.99) vs. 2.08 ± 1.39; P = 0.017). In contrast there were no differences between patients with obstructive CAD and those without in cIMT (0.73 ± 0.10 vs. 0.74 ± 0.10 mm; p = 0.46), in PWV (8.1 ± 1.3 vs. 8.3 ± 1.8 mm/s; p = 0.62) and in DC (5.0 ± 1.5 vs. 4.7 ± 1.2 m/s²/p; p = 0.27).

**Conclusion:** Endothelial function differed between subjects with obstructive CAD and those with normal coronary arteries whereas macrovascular markers were not different between these groups. Assessment of RHI could be a useful tool in the diagnostic work-up of patients with chest pain.

**8C.04 LEFT VENTRICULAR HYPERTROPHY IN HYPERTENSIVE PATIENTS WITH NORMAL ELECTROCARDIOGRAM**


**Objective:** In hypertensive patients the presence of left ventricular hypertrophy (LHV) is associated with increased cardiovascular (CV) morbidity and mortality. Unfortunately electrocardiogram (ECG) has a low sensitivity in detecting LHV, while echocardiography cannot be routinely and extensively performed in all hypertensive patients. In this study we evaluated the prevalence of LHV and of anomalies of diastolic function in a group of hypertensive patients with normal ECG, and free of diabetes and CV diseases.

**Design and Methods:** Patients with CV diseases, diabetes, chronic kidney disease (CKD), electrocardiographic LHV ( Sokolow-Lyon’s or Cornell criterion) or “strain” were excluded. We enrolled 196 middle-aged hypertensive patients (M/F: 124/72). All the enrolled subjects underwent an echocardiographic examination (Acuson Sequoia 512). Left ventricular mass (LVM) was indexed by body surface area (LVM/BSA), and by height² (LVM²/H,²). LVM was defined as LVM >125g/m² in men and >110 g/m² in women, or as LVM²/H,² >51 g/m² in both sexes. Diastolic function was principally assessed by Tissue Doppler Imaging (TDI).

**Results:** With regard to LVM, 20/196 patients (10.2%) had LHV (2 eccentric and 18 concentric, 12 women and 8 men). In this subgroup of 20 subjects, the value of LVM had a percentage difference from the cut-off value for LHV of 15.1 ± 11.4%. Among the 196 patients, only 6 out of the 20 with LHV had

was used in less than 10% of the patients. Better BP and cholesterol control was in patients treated by cardiologists than by general practitioners.

**Conclusion:** We have confirmed a high adherence to ESH and ESC guidelines in the treat-ment of blood pressure and cholesterol in patients post myocardial infarction. We did not find gender differences; older people are more frequently undertreated. Lower than recommended doses of ACE-I and statins are used.
alterations of diastolic function, defined as early diastolic myocardial velocity (Em) < 0.08 m/sec. The same evaluation was repeated with regard to LVMi\(^1\). In this case 52/196 patients (26.5%) had LHV (22 eccentric and 30 concentric, 18 women and 34 men). In the subgroup with LHV, the value of LVMi\(^1\) had a percentage difference from the cut-off value for LVH of 19.6 ± 15.9%. Among the 196 patients, only 12 out of the 52 with LHV had Em < 0.08 m/sec.

Conclusions: The prevalence of LVH among hypertensive patients with normal ECG, free of diabetes, CKD, and CV diseases, is not high if LVM is indexed by body surface area, while is higher than 25% if LVM is indexed by height\(^1\). Hypertensive patients with normal ECG and LHV evidenced by echocardiography had LVM values which generally identified mild LVH, which only in few cases was accompanied by alterations of LV diastolic function.

THE PARADOX OF DIASTOLIC BLOOD PRESSURE IN HYPERTENSIVE PATIENTS WITH ACUTE MYOCARDIAL INFARCTION AND LONG TERM EVENT FREE SURVIVAL

G. Bertone, R. Cordiano, R. Palmieri, GJ. Guarnieri, L. Collot, S. Pianca, P. Mornino, R. De Toni, P. Palatini, C. Congeliani General Hospital, Congeliani-Italy, A. Adria General Hospital, Adria-Italy, University Hospital, Padova-Italy.

Objective: Even if presence of hypertension (HT) is well demonstrated to be associated to unfavorable prognosis, much less is known on the role and long event free survival (EFS) long after acute myocardial infarction (AMI). Our aim was to ascertain whether HT and blood pressure (BP) have a prognostic role on ten-year EFS after AMI.

Design and Method: This is a prospective study including 504 consecutive unselected patients admitted with definite AMI at 3 intensive care units in 1995-1998. BP was considered as the mean of 3 measurements between 7 and 8 a.m. of the 3rd day after admission. History of hypertension (HT) was documented in 47% patients (mean duration 11.9 ± 9.4 years). Mean age was 69.6 ± 11.4 years among HT and 63.7 ± 11.9 among normotensives (NT) (p < 0.0001); females were 41% and 18% respectively (p < 0.0001). Mean BP was 126 ± 19/77 ± 10 mmHg among HT and 115 ± 14/72 ± 9 mmHg among NT (p < 0.0001 for both). The endpoint was EFS for 10 years after AMI. Absence of any of the following was considered EFS: death from all causes, nonfatal reinfarction and stroke, angina at rest with electrocardiographic changes, hospitalization for congestive heart failure, revascularization (coronary artery bypass graft surgery or percutaneous coronary angioplasty), and heart transplantation. Risk estimates were made using logistic regression models and expressed as odds ratio (OR) powered to –1.

Results: At the end of follow-up, the EFS patients were 95 (19%): 24% among NT and 13% among HT (p = 0.002). At logistic regression analysis, HT was negatively associated to EFS [OR = 2.0 (95%CI 1.3–3.3)]. HT showed no interaction with systolic BP, and the rate of EFS was similar through quartiles of SBP both in NT and HT. At variance, a positive interaction was found between action with systolic BP, and the rate of EFS was similar through quartiles of diastolic BP. Logistic regression models and expressed as odds ratio (OR) powered to –1.

Conclusions: The prevalence of LVH among hypertensive patients with normal ECG, free of diabetes, CKD, and CV diseases, is not high if LVM is indexed by body surface area, while is higher than 25% if LVM is indexed by height\(^1\). Hypertensive patients with normal ECG and LHV evidenced by echocardiography had LVM values which generally identified mild LVH, which only in few cases was accompanied by alterations of LV diastolic function.

AORTIC ENLARGEMENT IS ASSOCIATED TO CENTRAL BLOOD PRESSURE IN ESSENTIAL HYPERTENSION


Background: Arterial hypertension is a leading cause of aortic root dilatation (ARD). Mechanical stress in the aortic wall is proportional to blood pressure (BP) and vessel diameter, thus hypertension and aortic dilatation are risk factors for aortic dissection. Objective of this study was to evaluate the association between brachial and central blood pressure (bBP and cBP) levels and aortic root dilatation (ARD) in essential hypertensive patients.

Methods: A total of 190 untreated and treated essential hypertensive patients (mean age, 55 ± 11 years) were considered for this analysis. We measured pulsatile hemodynamics and proximal aortic diameter directly using tonometry, ultrasound imaging (echocardiography), and Doppler.

Results: 11 hypertensive patients had an ARD (defined as Aortic Size Index (ASI) > 2 cm/m²). Central haemodynamic variables were significantly associated to ASI. Patients with increased ASI, were significantly older (50 ± 10 vs. 50 ± 11 years; p < 0.0001), had higher levels of Augmentation Index (AIx; 28 ± 10 vs. 21 ± 10 p < 0.0001), Augmentation Pressure (AP; 13 ± 6 vs 8 ± 5 mmHg, p < 0.0001), and central Pulse Pressure (CPP; 44 ± 10 vs 39 ± 8 mmHg, p < 0.001) compared to patients with normal ASI. In a logistic regression analysis AIX resulted the only significant predictor of ASI.

Figure 1A and 1B: A) Association between Central Pressure (cPP) and aortic size index (ASI). B) Association between AIx and ASI

Conclusions: In hypertensive patients Augmentation Index and central Blood Pressure were associated to Aortic Root Dilatation, whereas brachial Pulse Pressure was not. Patients with increased Aortic Size index may loose part of the elastic properties of the aorta, demonstrating a more strict correlation between ASI and central haemodynamic indexes, in particular central Pulse Pressure and Augmentation Index.
**BC.08** PREVALENCE OF SYSTOLIC DYSFUNCTION DESPITE NORMAL OR SUPERNORMAL EJECTION FRACTION IN AFRICAN-AMERICANS WITH HYPERTENSIVE KIDNEY DISEASE: THE AASK STUDY


**Background:** Left ventricular hypertrophy (LVH), highly prevalent in pts with chronic renal insufficiency (CRI), is thought to maintain ejection fraction (EF) despite adverse loading conditions. However, LVH can be associated with LV myocardial dysfunction (reduced midwall shortening—FSmW) and high cardiovascular risk, despite normal EF. We sought to investigate this discrepancy between EF and FSmW among African-Americans enrolled in AASK a group with high prevalence of concentric LVH—high relative wall thickness (RWT).

**Methods:** Data from 594 pts (age 60.1±10.1yrs, 38% women, GFR 44.2±16 mL/min/1.73 m²) with hypertensive CRI and normal EF were analysed. We repeated the analysis in those with supranormal EF (>75%). Subclinical LV dysfunction was defined as FSmw<14.7% (a prognostically validated partition value).

**Results:** 220 of 594 pts (37%) had low FSmw. Compared with normal FSmw pts, they had larger LA (4.2±1 vs 3.9±1 cm), LV mass (293±81 vs 221±105 g) and RWT (0.62±0.7 vs 0.46±0.14; all p<0.001). However, when limiting the analysis to pts with supranormal EF (n=229) a peculiar cardiac phenotype was found in pts with low FSmw (n=60 or 26%): low tissue Doppler velocity (e'; 8.5±3 cm/s vs 10.3±4 cm/s), paired with a higher Doppler E/e’ ratio (7.9±3 vs 8.7±4; both p<0.05), indicative of higher LV filling pressures.

**Conclusions:** Impaired myocardial systolic dysfunction (low FSmw) is common in African Americans with CRI likely due to the advanced abnormalities in cardiac geometry. Moreover, one in four CRI patients with supranormal EF also had low FSmw, as well as associated significant abnormalities in diastolic function, increased filling pressure. This phenotype highlights the dissociation between myocardial function and EF and argues that FSmw is the preferred systolic function index among hypertensive African-Americans, especially with CRI. In these pts, moreover, diastolic dysfunction and low FSmw appear to be coupled.

**BC.09** METABOLIC SYNDROME RELATIONSHIP WITH LEFT VENTRICULAR HYPERTROPHY IN OVERWEIGHT/OBESE HYPERTENSIVES IS DEPENDENT ON BODY MASS INDEX

F. Guerra, L. Mancinelli, L. Angelini, A. Buglioni, V. Pierini, P. Dessì-Fulgheri, R. Sarzani. Internal Medicine Department, University Politecnica Delle Marche, Ancona-Italy

It is unclear whether the presence of metabolic syndrome (MetS) in hypertensive patients affects left ventricular mass (LVM) and hypertrophy (LVH) more than the sum of its single components. The main aim of this study was to evaluate whether MetS has an independent relationship with LVH in overweight (ow)/obese (ob), non-elderly, hypertensive patients. Our primary hypothesis was to verify whether the relationship between MetS and LVH could be independent from BMI. Three hundred and eighty non elderly ow/ob patients under chronic stable treatment for essential hypertension were studied. LVH was defined as LVM/h² 49.2 g/m².7 in males and 46.7 g/m².7 in females. MetS was defined according to NCEP III/ATP with AHA modifications. Hypertensive patients with MetS had significantly higher BMI, systolic and mean BP, interventricular septum and relative wall thickness, and lower ejection fraction than those without MetS. LVM/h² was significantly higher in MetS patients (59.1±14.9 vs 55.3±14.6 g/m².7; p=0.022). Hypertensive patients with MetS had a 2.3-fold higher risk to have LVH/h² after adjustment for age, SBP, and therapy (OR 2.28; 95% CI 1.43-3.62; p=0.001), but MetS lost its independent relationship with LVH when BMI was included in the model. Moreover, patients with MetS had a 2.8-fold higher relative risk to have CR (OR 2.81; 95% CI 1.41–5.62; p=0.002). In the subgroup of patients (n=184, 48%) in which 24-hour ambulatory blood pressure measurements were available, the use of 24-hour SBP instead of office SBP confirmed the results, and the overall fit of the models actually improved. In ow/ob hypertensive patients, MetS maintains its relationship with LVH independently of age, SBP, and therapy, resulting in a useful predictor of target organ damage in clinical practice. However, MetS loses its independent relationship with LVH when BMI is taken into account, suggesting that the effects on LV parameters are mainly driven by the degree of adiposity.
8D.01 SERUM ANDROGENS IN PRE-ECLAMPTIC AND NORMOTENSIVE PREGNANT WOMEN
M. Kashanian, F. Shariatradef, F. Fatemi. Tehran University of Medical Sciences, Tehran-Iran

Introduction: Pre-eclampsia and its complications is one of the major causes of maternal and fetal mortality and morbidity. Because of its great importance, it is necessary to determine the factors that make pregnant women at risk.

Objective: The purpose of the present study is to compare the serum androgens level during the third trimester of pregnancy between normotensive and pre-eclamptic women.

Method: A case- control study was performed on 64 pregnant women with the gestational age of 28-34 weeks. 32 women were pre-eclamptic (case group), and 32 women were normotensive till gestation (control group). The serum level of androgens including sex hormone binding globulin (SHBG), total and free testosterone, androstendion (ADD), and dihydroepiandrostron sulfate (DHAS), were compared between the two groups.

Results: The women of the two groups had no statistically significant difference according to age, gestational age, BMI (Body Mass Index), parity and free sexual. Serum level of SHBG (90.86 ± 9.30 VS 55.86 ± 8.02 nmol/ml, p = 0.02), total testosterone (3.70 ± 0.57 VS 2.06 ± 0.24 ng/ml, p = 0.01), free testosterone (1.28 ± 0. 17 VS 0. 74 ± 0.07 pg/ml, p = 0.01), and ADD (2.47 ± 0.10 VS 2.17 ± 0.10 ng/ml, p = 0.04), was higher in the pre- eclamptic women. However, there was no difference between the 2 groups for DHAS (0.75 ± 0.18 VS 0.51 ± 0.08 µg/ml, p = 0.19).

Conclusion: Serum androgen levels during third trimester of pregnancy are higher in pre-eclamptic women and this may propose an effect of androgens in the pathogenesis of pre-eclampsia.

8D.02 BENEFITS OF MONITORING PATIENTS OPERATED ON FOR PHEOCHROMOCYTOMA OR FUNCTIONAL PARAGANGLIOMA
J.P. Baguet1, C. Dalliet1, N. Wion-Barbot1, F. Chaffanjon1, O. Chabre2, 1Cardiology Department, University Hospital, Grenoble-France, 2Endocrinology Department, Grenoble-France, 1Vascular, Thoracic and Endocrinology Surgery Department, Grenoble-France

Objective: Pheochromocytomas (PH) and functional paragangliomas (FPGL) represent a potentially curable cause of hypertension HT. Monitoring of patients operated on for PH or FPGL should, however, be extended so as not to overlook any recurrence, new lesions or lesions associated with a genetic form.

Methods and Results: The records of 59 patients (27 male subjects, mean age during surgery 44.9±16.9 years, 5 FPGL) operated on for PH or FPGL at Grenoble University Hospital since January 1991, were studied. Eleven patients have died since surgery (3 from metastatic PH, 4 from neurological events, 2 from myocardial infarction, 1 from colorectal cancer, and 1 from AIDS). Contact was made with the 48 surviving patients, and 39 agreed to take part in the study which included a medical visit, ABPM over 24 hours, assay of plasma metanephrines and a genetic study (VHL, SDH-B, -C and -D, and RET in patients not tested previously). Two plasma normetadrenaline assays were pathological. The first (x34) in a 29-year-old patient with progressive metastatic malignant FPGL, and the other (x2.5) in a 52-year-old female patient operated on 16 years previously for right PH (hypertensive peaks during 24-hours ambulatory blood pressure monitoring, left adrenal tumour with likely left suprarenal and subrenal adenopathy evidenced by computed tomography/MIBG scintigraphy). The female patient underwent surgery with a histological diagnosis of PH associated with 2 FPGL. Before the start of the study, 23 patients (39%) had already undergone genetic screening due to family history or associated lesions (12 patients suffered from genetic disease: 7 NF1, 4 NEM and 1 VHL disease). The 3 patients with bilateral PH showed gene mutation. During our study, 13 additional patients underwent genetic screening, and no additional mutations were discovered, including the female patient presenting new sites.

Conclusions: Monitoring (both clinical and hormonal) of patients operated on for PH or FPGL should be extended so as not to overlook any recurrence or other sites, irrespective of their genetic status.

8D.03 PERIPHERAL ARTERIAL STIFFNESS IN PRIMARY ALDOSTERONISM
J. Rosa, O. Petrak, B. Strauch, Z. Somloova, T. Indra, T. Zelinka, R. Holaj. J. Widimsky Jr. General University Hospital, Prague-Czech Republic

Objective: Arterial stiffness assessed by central (aortic) pulse wave velocity (PWV) is considered to be an independent cardiovascular risk factor. Only few data are, however, available on the potential impact on the deterioration of peripheral arterial stiffness. We found in our previous study higher aortic PWV in patients with primary aldosteronism (PA). The current study was aimed at investigating the effect of aldosterone overproduction on peripheral arterial stiffness as assessed by femoral-tibial PWV in PA patients in comparison to essential hypertension patients.

Design and Methods: 37 patients with confirmed PA (saline suppression test) and 42 patients with essential hypertension were assessed. Patients were matched for age, blood pressure, body mass index, lipid profile and fasting glucose. PWV was obtained using the Sphygmocor application tonometer (AtCor Medical, West Ryde, Australia).

Results: Both, peripheral (11.47 vs. 10.46 m/s, p = 0.004) and central (8.78 vs. 7.96 m/s, p = 0.021) PWV were significantly higher in PA patients in comparison to essential hypertensive patients, while blood pressure was comparable (154/91 vs. 150/88 mmHg, p > 0.05). Aldosterone levels seem to be the main predictor of peripheral PWV in PA (β = 0.50, p < 0.005).

Conclusions: Our data indicate, that aldosterone overproduction in PA does not preferentially affect central arterial system. Fibroproliferative effects of higher aldosterone levels lead to alteration of central-elastic as well as peripheral-muscular arteries with subsequent increase in its stiffness.

8D.04 DIFFERENCES IN PULSE WAVE VELOCITY BETWEEN MAIN TYPES OF PRIMARY ALDOSTERONISM
Z. Somloova, J. Rosa, T. Indra, O. Petrak, B. Strauch, T. Zelinka, R. Holaj. J. Widimsky Jr. 3rd Internal Medicine Dept., 1st Faculty of Medicine, Charles University and General Teaching Hospital, Prague-Czech Republic

Introduction: Primary aldosteronism (PA) is a common form of secondary hypertension. In our former study we showed higher prevalence of metabolic syndrome in patients with idiopathic hyperaldosteronism (IHA) compared to aldosterone producing adenoma (APA). We showed previously that patients with primary aldosteronism have higher pulse wave velocity than patients with essential hypertension (EH). In this study we focused on the potential differences in aortic stiffness between two main types of primary aldosteronism- APA and IHA. The distinction between both types of PA was based on adrenal venous sampling and/or successful surgery with histopathological examination.

Methods: We analyzed data in 80 patients with PA (40 patients with IHA and 40 patients with APA). Groups were matched by age, duration of hypertension and systolic and diastolic blood pressure and there were no significant differences in gender.

Results: The pulse wave velocity was significantly higher (p < 0.05) in patients with IHA than in APA (9.71 ± 2.21 vs. 8.31 ± 1.87 m/s). Clinic and 24-h blood pressure levels were comparable (148.58 ± 15.73 vs. 146.54 ± 12.69 mmHg). The prevalence of the metabolic syndrome (70 vs. 43%), the body mass index value (30 ± 3.7 vs. 28 ± 4.8 kg/m²) and triglycerides levels (1.9 ± 0.9 vs. 1.3 ± 0.8 mmol/l) were all significantly (p < 0.05) higher in IHA compared to APA patients. Aldosterone levels were significantly higher in patients with APA.
Compared to APA. Lower pulse wave velocity correlated with lower level of metabolic syndrome, higher BMI and triglycerides and higher aortic stiffness main forms of PA. Patients with IHA have significantly higher prevalence of Adrenalectomy led to significant increase in BMI (25 ± 5 vs. 25 ± 3 kg/m²; p = 0.004) and percentage of body fat (25 ± 5 vs 30 ± 7%; p = 0.001). We have found significant decrease in BMI after adrenalectomy (173 ± 314 vs. 1539 ± 215; p = 0.002) even after adjustment to anthropometric measurements – body surface (926 ± 88 vs. 820 ± 59 m²; p < 0.0001) and body weight (23 ± 2 vs 21 ± 3 kg/Kg; p < 0.0001). Measured values were comparable to predictive values (1539 ± 215 vs 1577 ± 290 kcal/day; NS). Respiratory Quotient did not differ between groups (0.80 ± 0.08 vs 0.83 ± 0.09; NS). No significant correlation among indirect calorimetry parameters, catecholamines and metabolic features was found.

Conclusion: Chronic catecholamines overproduction leads to hyper metabolic state characterized by increase in resting energy expenditure in patients with pheochromocytoma. Adrenalectomy is accompanied by normalization of energetic metabolism followed by increase in BMI and body fat percentage.

Support: MSM-0021620808 a MSM-0021620807.

The Adrenal Vein Sampling International Study (AVIS) on Use and Interpretation of Adrenal Vein Sampling for Differentiating the Major Subtypes of Primary Aldosteronism

G. P. Rossi1, M. Barisic2, B. Allolio3, R. Autsch4, G. Klime4, A. Lacroix5, J.W.M. Lenders5, S.B. Magill6, M. Naruse7, T. Nishikawa7, P.F. Plouin8, M. Reincke9, L.C. Rump7, F. Satoh10, M. Stowasser11, ‘Department of Clinical and Experimental Medicine - Internal Medicine 4, University of Padova, Padova-Italy, 2University hospital Wuerzburg, Wuerzburg-Germany, 3University of Texas Southwestern Medical Center at Dallas, Dallas-USA, 4Foothills Medical Centre, University of Calgary, Calgary-Canada, 5Centre Hospitalier de l’Université de Montréal, Montréal-Canada, 6Radboud University Nijmegen Medical Center, Nijmegen-The Netherlands, 7Endocrinology Clinic Community Memorial Medical Commons Medical College of Wisconsin, Menomonee Falls-USA, 8National Hospital Organization, Kyoto Medical Center, Kyoto-Japan, 9Department of Endocrinology & Metabolism, Yokohama Rosai Hospital, Yokohama City-Japan, European Hospital Georges. P. Pompidou, Paris-France, 10Medizinische Klinik Innenstadt, Department of Endocrinology, Munich-Germany, 11Heinrich Heine University Duesseldorf, Duesseldorf-Germany, 12Yokohama University Hospital, Sendai-Japan, 13Endocrine Hypertension Research Centre, University of Queensland School of Medicine, Greenslopes Hos, Brisbane-Australia

Objective: The differentiation between lateralised and non-lateralised causes of aldosterone excess is crucial for the choice of medical or surgical treatment of primary aldosteronism (PA) and requires adrenal venous sampling (AVS). Since because of the lack of accepted criteria use and interpretation of AVS remains challenging we performed a large international multicenter study involving referral centres to determine how AVS is being performed and interpreted and at what complication rate.

Design and Method: The centres were identified through database search and invited to participate to the AVS Study, which entailed 2 phases. In the first phase summary data were collected while in the second, which is ongoing, individual data will be gathered. The first phase was concluded in November 2010. Data on percent of use of AVS in PA patients, modalities of performance and interpretation of the test and rate of adrenal vein rupture were analysed.

Results: Nineteen of the 23 (82.6%) centres that were invited agreed to participate. They are scattered all over Asia, Europe, North America, and Australia. They furnished data on a total of 2955 AVS studies performed over the last 5 years. The percentage of PA patients systematically submitted to AVS was extremely variable across these centres ranging from 40% to 100% (median 77.5). The sequential catheterization technique was used at 63.2% of centres and 36.8% of the bilateral simultaneous technique. AVS was performed with ACTH stimulation at 52.6% of the centres. A wide variability of cut-off values for the selectivity, lateralization and contralateral suppression index existed. Moreover, some centres used absolute hormonal values, instead of these indexes for diagnosis. Overall the major complication rate was 0.57%, but it showed a significant heterogeneity across centres. A significant correlation between complication rate and the number of radiologists performing AVS at each center was found (r = 0.543; p < 0.05).

Conclusions: The AVS study, the largest survey ever performed on AVS, showed that: 1) AVS is being performed at a very low complication rate at most referral centres worldwide; 2) most centres continue to use ACTH stimulation even though it was shown to confound the assessment of lateralization; 3) notwithstanding the lack of any theoretical basis some centres continue to use absolute hormonal values instead of the appropriate indexes. Hence, these results emphasize the need for a consensus conference in order to optimize the clinical use of AVS.

Under-expression of the Twik-related Acid-sensitive K+/Channel 2 (TASK-2) Gene is a Hallmark of Aldosterone Producing Adenoma Causing Human Primary Aldosteronism


Changes of Energy Metabolism in Pheochromocytoma

O. Petrá1, T. Zelinka1, D. Haluzíková1, P. Pávkálová1, B. Brausch1, J. Rosa1, R. Holaj1, Ž. Šomlóová2, T. Indra3, A. Vránková1, D. Michalskú1, M. Haluzík1, J. Widimská1, General Faculty Hospital and IST Faculty of Medicine Charles University, Prague-Czech Republic

The aim of the study was to evaluate changes in resting energy metabolism expressed as resting energy expenditure (REE) in patients with pheochromocytoma measured by indirect calorimetry. Methods: We have investigated 17 patients (8 women/9 men) with benign pheochromocytoma by indirect calorimetry device (Deltatrac, Datex-Engström, Helsinki, Finland). Body fat percentage was measured by Bodystat (Bodystat Ltd, UK). All patients were examined before and one year after adrenalectomy and underwent anthropometric measurements and routine biochemical screening. Diagnosis of pheochromocytoma was based on measurement of plasma metanephrines and urine catecholamines and confirmed by histology.

Results: REE in pheochromocytoma was about 10% higher in comparison to predictive value (1731 ± 314 vs 1581 ± 271 kcal/day, p = 0.004). Adrenalectomy led to significant increase in BMI (25 ± 4 vs 26 ± 4 kg/m²; p = 0.004) and percentage of body fat (25 ± 5 vs 30 ± 7%; p = 0.01). We have found significant decrease in REE after adrenalectomy (1731 ± 314 vs. 1539 ± 215; p = 0.002) even after adjustment to anthropometric measurements – body surface (926 ± 88 vs. 820 ± 59 m²; p < 0.0001) and body weight (23 ± 2 vs 21 ± 3 kg/Kg; p < 0.0001). Measured values were comparable to predictive values (1539 ± 215 vs 1577 ± 290 kcal/day; NS). Respiratory Quotient did not differ between groups (0.80 ± 0.08 vs 0.83 ± 0.09; NS). No significant correlation among indirect calorimetry parameters, catecholamines and metabolic features was found.

Conclusion: Chronic catecholamines overproduction leads to hyper metabolic state characterized by increase in resting energy expenditure in patients with
**Objective:** Primary aldosteronism is highly prevalent cause of arterial hypertension, but its underlying molecular mechanisms are unknown. K+ is a key regulator of aldosterone secretion and interacts with physiological secretagogues of aldosterone as angiotensin II (Ang II). The Tsk-related Acid-Sensitive K+ (TASK) channels are a widely distributed class of channels that generate background or “leak” potassium (K+) currents. Noteworthy, in vivo genetic manipulation of two such channels created a phenotype that closely mimics human primary aldosteronism.

**Design and Method:** We therefore investigated the gene expression of K+ channels, including those of the TASK family, and the microRNA profiles of a large series (n = 32) of aldosterone-producing adenoma (APA).

**Results:** A whole transcriptome analysis and quantitative real time RT-PCR showed that in both normal zona glomerulosa (ZG) and APAs the most expressed TASK channel gene was TASK-1, followed by TASK-2 and TASK-3. Moreover, as compared to the normal adrenal cortex there was a marked under-expression of TASK-2 channel in all APA, while TASK-1 and TASK-3 were heterogeneously expressed. Immuno-cytometry, confocal microscopy, and co-immunoprecipitation experiments disclosed the subcellular localization of TASK-2 and its heterodimerization with TASK-1 and TASK-3. Moreover, with a regression analysis we identified hsa-miR-34 and hsa-miR-455 as the strongest predictors of TASK-2 under-expression. Finally, with a promoter analysis of the TASK-2 gene in 101 patients with primary aldosteronism we identified three novel mutations, two of which were germline and one somatic, which can predispose to blunting the TASK-2 expression.

**Conclusions:** Thus, a reduced expression of TASK-2 channels is a feature of APA that can be important pathophysiologically as a blunted activity of TASK-2 through cell depolarization increases the opening state probability of voltage-gated T-type calcium channels, thus rendering adrenocortical cells more sensitive to aldosterone secretagogues.

**8D.09 TARGETED CLINICAL FOLLOW-UP FOR PHEOCHROMOCYTOMA/PARAGANGLIOMA IN A POPULATION OF SUSCEPTIBLE SUBJECTS IDENTIFIED BY GENETIC ANALYSIS**

M. Giacche, L. Mori, M.C. Tacchetti, A. Panarotto, L. Daffini, C. Cappelli, E. Agabiti Rosei, M. Castellano. *University of Brescia/Spedali Civili, Brescia-Italy*

**Background:** Over the last few years, wider adoption of genetic screening in patients with pheochromocytoma/paraganglioma (PHEO/PGL) and/or associated syndromes (such as patients with multiple endocrine neoplasia type 2, von Hippel–Lindau disease or neurofibromatosis), is allowing the identification of mutation-carrier index cases, as well as of their relatives with susceptibility to develop the same disease.

**Aim of the study:** To evaluate the impact of a targeted clinical follow-up in the early detection of PHEO/PGL in carriers of known predisposing mutations.

**Design and Methods:** Study population involved 193 subjects (59 index cases and 134 relatives): 52 subjects had mutation in SDHB/SDHD genes (11/1 index and 41/0 relatives), 10 in VHL (9 index, 1 relative), 7 in NF1, 123 RET (31 index, 92 relatives). At the time of recognition of the genetic predisposition all subjects were submitted to a clinical protocol, including biochemical and imaging investigation, aimed to detect any manifestation of disease, and in particular PHEO/PGL; in addition, they were submitted to extended, usually biennial, follow-up reassessment.

**Results:** PHEO/PGL was present at the first evaluation in 25/59 index cases (100% of SDHB/SDHD; 100% of VHL; 29% of NF1; 6.5% of RET) and in 3/134 mutation carrier relatives (2.5% of SDHB, 100% of VHL; 1% of RET. Average duration of follow-up was 65.4 months for index cases and 59.6 months for relatives; over this period of time six new cases of PHEO/PGL (3 occurring in RET mutation carriers and 3 in NF1 subjects) and two recidivisms (1 SDHB and 1 RET) were observed (overall, 8 cases per 1000 subject-years at risk). Penetrance of PHEO/PGL was rather different according to the involved gene and individual mutation: in this series, the highest rate was observed for VHL, followed by NF1, SDHB and RET mutations. Noteworthy, seven subjects were completely asymptomatic for PHEO/PGL despite a significant increase of urinary metanephrines excretion and were identified only through targeted clinical screening and follow-up: 3 of them were affected by NF1, 2 by RET, one by SDHB mutation and finally one patient-relative carrying VHL mutation resulted affected by bilateral PHEO.

**Conclusion:** Hereditary PHEOs/PGLs differ in penetrance and clinical expression and are most likely underdiagnosed diseases. Their genetic recognition and subsequent targeted clinical follow-up enable early and even preclinical diagnosis, which is of great value both to prevent the high clinical risks associated with secreting PHEO/PGL and to allow less aggressive and adrenal sparing surgical treatment.
ORAL SESSION

ORAL SESSION 9A

CLINICAL TRIALS

9A.01 EFFECTS OF VALSARTAN FOR HIGH-RISK HYPERTENSIVE PATIENTS WITH NEW-ONSET DIABETES: NEW FINDING FROM KYOTO HEART STUDY

T. Sawada1, S. Kimura1, J. Shiraishi2, H. Yamada1, H. Matsubara1. 1Kyoto Prefectural University of Medicine, Kyoto-Japan, 2Kyoto First Red Cross Hospital, Kyoto-Japan

Objective: Some clinical trials in patients with high-risk hypertension indicate that ACE inhibitors and ARBs significantly lowered the incidence of newly diagnosed diabetes. However, most of the data was not a primary endpoint, and detailed information for new-onset diabetes and cardiovascular (CV) events are still unknown. The Kyoto Heart Study showed that Valsartan exerts a overall CV protective effect on the primary endpoint and in patients of new-onset diabetes in Japanese high-risk hypertensive patients (Eur Heart J 2009;30: 2461). We report new findings of the effects of Valsartan for high-risk hypertensive patients with new-onset diabetes.

Method: The Kyoto Heart Study is a multicenter, two-arm parallel treatment group comparison study with response-dependent dose titration scheme. High-risk Japanese patients with uncontrolled hypertension (n = 3031) were randomized to receive either additional Valsartan or conventional non-ARB therapies. The primary endpoint was a composite of defined CV events such as stroke, myocardial infarction, heart failure, and angina pectoris. In this sub-analysis, detailed information of new-onset diabetes and the effectiveness of Valsartan were investigated.

Results: (1) The patients with diabetes at baseline (n = 807) showed a significantly higher primary endpoint events compared with the patients without diabetes at baseline (n = 2224), (10.3% vs 7.1%, HR 1.48, 95%CI 1.13–1.93). In diabetes group, valsartan add-on treatment (n = 401) showed less prevalence of primary endpoints than non-ARB treatment (n = 406) (7% vs 13.5%, HR 0.52, 95%CI 0.38–0.80). (2) In the patients without diabetes at baseline, Valsartan add-on treatment (n = 1161) significantly decreased new-onset diabetes compared to non-ARB treatment (n = 1108) (58 vs 86, P = 0.0282). (3) During the follow-up, the primary event was much higher in patients with new-onset diabetes than without new-onset diabetes (12.5% vs 6.5%, HR 1.91, 95%CI 1.20–3.03). In the patients with new-onset diabetes, Valsartan add-on treatment showed less prevalence of primary endpoints than non-ARB treatment (5% vs 17%, HR 0.30, 95%CI 0.09–0.98). Patient characteristics and mean blood pressure during follow-up showed no significant differences among the groups.

Conclusion: CV event risk in the patients with new-onset diabetes was relatively equivalent to the patients with diabetes at baseline. In patients with high risk hypertensive patients, Valsartan add-on treatment was effective not only for the incidence of new-onset diabetes but also for reduction of CV events in patients with new-onset diabetes.

9A.02 EFFECT OF ATORVASTATIN TREATMENT ON ARTERIAL STIFFNESS AND CENTRAL AORTIC BLOOD PRESSURE IN PATIENTS WITH MILD HYPERTENSION AND HYPERCHOLESTEROLEMIA: A DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED STUDY

A. Kanaki1, P. Georgiannos1, P. Saradits2, I. Tziolos1, E. Zairi1, L. Hadjistavri1, V. Liakopoulos1, S. Iliadis2, V. Tyradelli1, A. Lasaridis1. 11st Department of Medicine, Ahepa University Hospital, Thessaloniki-Greece, 2Laboratory of Biological Chemistry, School of Medicine, Aristotle University of Thessaloniki, Thessaloniki-Greece

Background: Animal and human studies have shown statins to exert beneficial actions on endothelial function in different vascular beds; the vascular benefits of statin treatment may be also translated into a beneficial impact of these agents on large artery elastic properties. However, clinical studies investigating this hypothesis are very few and their results are considered inconclusive. Therefore, aim of this study was to explore the potential effects of atorvastatin on arterial stiffness and central hemodynamics in patients with mild hypertension and hypercholesterolemia.

Methods: A total of 50 patients with mild hypertension of recent onset or mild uncontrolled hypertension and hypercholesterolemia participated in this double-blind, randomized, placebo-controlled study. Patients were randomized to either 10mg atorvastatin or placebo for 26 weeks (6 months). Concurrent antihypertensive treatment, if any, remained unchanged during follow-up. At baseline and study-end arterial stiffness was assessed by measuring pulse wave velocity (PWV) in the carotid–femoral arterial segment using a SphygmoCor system. Heart rate–adjusted aortic augmentation index (AIx(75)), a measure of wave reflections, and central aortic blood pressure (BP) were estimated by radial artery application tonometry.

Results: Atorvastatin significantly reduced c-f PWV and AIx(75) as compared to placebo after 6 months of treatment (-2.03 ± 0.9 vs +0.4 ± 0.8 mmHg, p < 0.001 and -7.2 ± 3.5 vs +1.0 ± 3.1, p < 0.001). In addition, significant reductions in central aortic systolic BP (134.0 ± 6.2 vs 130.0 ± 7.8 mmHg, p < 0.001) and pulse pressure (49.9 ± 6.6 vs 48.2 ± 6.8 mmHg, p < 0.05) levels between baseline and study-end were evident in the atorvastatin group, whereas central homodynamic parameters remained unchanged during the follow-up in the placebo group.

Conclusion: The present study shows that low dose atorvastatin treatment improves elastic properties of large arteries and reduces central BP in patients with mild hypertension and hypercholesterolemia.

9A.03 BLOOD PRESSURE VARIABILITY IN RELATION TO AUTONOMIC NERVOUS DYSREGULATION: THE X-CELLENT TRAIL

Y. Zhang1, D. Agnoletti2, J. Blacher2, M.E. Safar2. 1Shanghai Institute of Hypertension, Shanghai-China, 2Diagnosis and Therapeutic Center; Hôtel-Dieu Hospital, AP-HP, Paris Descartes University, Paris-France

Objective: To investigate the association of autonomic nervous dysregulation with blood pressure variability (BPV).

Methods: Of 2370 participants in the X-CELLENT study, 579 patients (59.0 ± 10.2 years) were randomly selected to participate in an ambulatory blood pressure monitoring (ABPM) ancillary study. We proposed a novel autonomic nervous regulation index termed as dSBP/dHR, which was defined as the absolute value of the slope of regression equation between 24h systolic blood pressure (SBP) and heart rate (HR) for each participant. Within-subject standard deviation (SD) of SBP, weighted for the time interval between consecutive validated readings from 24h ABPM, was used to evaluate BPV.

Results: Men, compared with women, had higher dSBP/dHR (0.71 ± 0.44 vs 0.63 ± 0.37, mmHg/beat/min, P = 0.01). As dSBP/dHR was studied by tertiles, we noted a progressive increase in daytime SBP, a progressive decrease in nighttime SBP, and a progressive decrease in daytime SBP gradient, form tertile 1 to tertile 3 (p < 0.001). On the contrary, both daytime and nighttime SBP SD were consistently and significantly increased from tertile 1 to tertile 3 (p ≤ 0.002). Both before and after adjustment for age, gender and mean SBP, all of these increasing or decreasing trends reached statistical significance (p ≤ 0.007). Furthermore, in our sensitivity analysis when men and women were studied separately, the present findings were confirmatory.
Conclusion: Autonomic nervous dysfunction was associated with the increased day-night SBP gradient and increased systolic blood pressure variability in patients with essential hypertension.

9A.04 PREDICTIVE FACTORS OF BLOOD PRESSURE CONTROL IN RESISTANT HYPERTENSION TREATED BY SEQUENTIAL NEPHRON BLOCKADE VS SEQUENTIAL RENIN ANGIOTENSIN SYSTEM BLOCKADE

G. Bobrie1, M. Franck2, M. Azizi3, S. Peyrat3, P. Boutouyrie1, G. Chatellier1, S. Laurent1, J. Menard1, P-F. Plouin1, 1Hypertension Unit - HEGP - APHP, Paris-France, 2CIC - HEGP - APHP, Paris-France, 3URC - HEGP - APHP, Paris-France, 4Department of Pharmacology - HEGP - APHP, Paris-France

Background: In 167 patients resistant to a standardized 4-week 3-drug regimen (irbesartan 300mg/d, hydrochlorothiazide 12.5mg/d, amlopidine 5mg/d), we have demonstrated in a PROBE study that add-on treatment with sequential nephron blockade (SNB, spironolactone 25 mg/d + furosemide 20 to 40 mg/d + amlopidine 5mg/d) reduced more blood pressure (BP), than sequential renin angiotensin system blockade (SARB, ramipril 5 to 10mg + bisoprolol 5 to 10mg/d). The mean difference between the two groups in changes from baseline in day-time ambulatory BP (dABP) was 10 mmHg [95% CI: 7-14] / 4 mmHg [2-7]; (p = 0.0001/0.001) in favour of the SARB-group.

Objective: To identify predictive factors of dABP control (<135 and 85 mmHg).

Methods: Multiple-variable logistic regression was performed to identify a combination of baseline (under 3-drug regimen) characteristics (age, sex, ethnicity, baseline systolic dABP, body mass index, eGFR, plasma sodium, potassium and protein concentrations, log-transformed plasma renin [by immuno-radiometric assay] and aldosterone [by radioimmunoassay] concentrations) that made statistically independent contributions to the prediction of BP control. Only the variables significant at the 5% level in the univariate analyses were included in the multivariate analyses.

Results: The covariates associated with dABP control were baseline systolic dABP in both groups (odds ratio, 95% CI: 1.23 [1.08; 1.35], p = 0.004 in the SNB group and 1.25 [1.03; 1.42], p = 0.03 in the SARB group for each 5 mmHg lower baseline systolic dABP), plasma sodium concentration in the SNB-group (odds ratio, 95% CI: 1.25 [1.02; 1.53], p = 0.03 for each 1 mmol/L increase in plasma sodium concentration) and log-transformed plasma renin concentration in the SRASB-group (odds ratio, 95% CI: 1.85 [1.20; 2.87], p = 0.0057 for each doubling of plasma renin concentration). The efficacy of the both strategies to control BP was independent of age, sex, body mass index, ethnicity, and baseline plasma aldosterone concentration.

Conclusions: Besides baseline BP, predictive factors of BP control are plasma sodium concentration in the SNB group and log-transformed plasma renin concentration in the SRASB-group in patients with RH to a standardized 4-week 3-drug regimen.

9A.06 BLOOD PRESSURE LOWERING DRUGS DO NOT DECREASE THE RISK OF SUDDEN DEATH

Y. Mimouni1, A. Le Digarcher2, M. Armanet2, R. Quarta Colosso3, T. Bejan4, A. Le Digarcher1, J.M. Wright1, F. Gueryfiller1, Z. Jarai1, J. Nemcsik1, A. Tabak1, T. Oltmman1, P. Salvi1, A. Tischer3, 1Omnipharma University, University Hospitals, Bron Cedex-France, 2University of British Columbia, Vancouver-Canada

Introduction: Many studies have shown that BPLDs reduce the risk of stroke, with a lesser reduction of the risk of myocardial infarction (MI). MI is a composite outcome that includes three different events: non-fatal MI, fatal MI and sudden death (SD), with potentially different risk reductions. Our objective was to assess the effect of BPLDs in reducing the risk of non-fatal MI, fatal MI and SD in patients with hypertension.

Methods: Systematic review of all randomized controlled trials (RCTs) involving BPLDs used in the prevention of cardiovascular diseases in hypertensive patients, comparing these drugs to placebo or no treatment, or comparing intensive treatment regimen versus less intensive regimen, and providing separated data on the three types of coronary events. We searched PubMed and Cochrane library. Two reviewers assessed trials quality and extracted data independently. If detailed data were missing, authors were contacted. Sensitivity analyses were performed according to the type of comparator, the Jadad quality.

Results: We identified 33 studies with 97,582 patients. Separated outcome data were available for 17 trials including 45,463 patients. The sensitivity analysis of the nine highest quality trials (i.e. placebo as comparator, high Jadad-score and ITT analysis) gathered 21,118 patients. Its results showed a significant reduction of non-fatal MI risk by 22% (46% of the events, Relative Risk (RR) = 0.78, 95% CI 0.65, 0.93) and a decrease of fatal MI risk by 42% (24% of the events, RR = 0.58, 95% CI 0.43, 0.77). There was no significant effect on SD (30% of the events, RR = 0.94, 95% CI 0.76, 1.15). The inclusion of lesser quality trials did not change significantly the direction of the results.

Conclusion: The benefit of BPLD in preventing fatal MI was of the same magnitude as that observed for stroke, of less magnitude in preventing non-fatal MI, and there was no apparent effect on SD. We hypothesise that these drugs could induce some sudden deaths while preventing others. This could be tested in further analyses on individual patients’ data, and extended to comparison of drug classes.

9A.07 THE EFFECT OF CARVEDILOL, NEBIVOLOL AND METOPROLOL ON CENTRAL ARTERIAL PRESSURE AND ITS DETERMINANTS: A RANDOMIZED CLINICAL TRIAL

P. Studinger1, P. Torza2, B. Fekete1, J. Kapocsi1, A. Tabak1, T. Oltmman1, P. Salvi1, A. Tischer3, 1Semmelweis University, Budapest-Hungary, 2University of Nancy, Nancy-France

Objective: Classical beta blockers seem to elicit a smaller decrease in central arterial pressure than other types of antihypertensive agents. Only few data are available about the effects of the newer beta blockers with vasodilator properties on central pressure and its determinants. Our objective was to assess the effects of carvedilol, nebivolol, and metoprolol on central arterial pressure, augmentation index (AIx) and carotid-femoral pulse wave velocity (PWV).

Design and Method: In this prospective, open label trial with blind end-point determination a total of 60 hypertensive patients (18-70 yrs) were randomised to carvedilol 1.25/2.5mg or metoprolol 50/100mg or nebivolol 2.5/5mg o.d. and followed for 3-month. Central arterial pressure, AIx and PWV were measured with applanation tonometry (Pulse Pen, Diacsense, Milan) at baseline and at the end of follow up. Changes in these parameters for the whole group and in each group were analysed.

Results: The three beta blockers as a group decreased heart rate (-8 ± 9 beats/min), brachial systolic and diastolic pressures (-11 ± 4 and -7 ± 8 mmHg, respectively) and central systolic pressure (-8 ± 11 mmHg) significantly without
any difference between the three groups. PWV did not change significantly. AIx, adjusted for changes in heart rate, decreased by 3.6 ± 13.7% for the whole group, which decrease was significant only for nebivolol (−5.4 ± 11.1%). In linear regression models, changes in heart rate and in brachial systolic pressure were strong predictors of changes in AIx elicited by carvedilol and metoprolol (r² = 0.41, and r² = 0.46 for carvedilol and metoprolol, respectively), but did not explain changes in AIx caused by nebivolol (r² = 0.09).

Conclusion: The “classical” beta-blocker metoprolol and the newer beta blockers carvedilol and nebivolol decrease central blood pressure equally. Their impact on pressure augmentation seems to be different, however, with nebivolol having the largest potential of decreasing heart rate-adjusted AIx. While AIx changes associated with carvedilol and metoprolol treatment are strongly driven by peripheral blood pressure and heart rate changes, those associated with nebivolol treatment seem to be the result of other mechanisms.

9A.08 BLOOD PRESSURE TARGETS RECOMMENDED BY GUIDELINES AND INCIDENCE OF CARDIOVASCULAR AND REINAL EVENTS IN THE ONTARGET TRIAL

G. Mancia1, H. Schumacher2, J. Redon1, P. Verdecchia1, R. Schmieder2, G. Jennings3, K. Yusuf4, L. Ryder5, G.L. Liu6, R. Fagard7, K. Teo8, P. Sleight1, S. Yusuf1. 1University of Milano Bicocca·San Gerardo Hospital, Milano-Italy, 2Boehringer-Ingelheim, Ingelheim-Germany, 3Carlos III, Hospital Clinico de Madrid, Madrid-Spain, 4Erlangen-Germany, 5Baker Medical Research Institute, Melbourne-Australia, 6Baker Medical Research Institute, McMaster University, Hamilton-Canada, 12CV Medicine, John Radcliffe Hospital, Oxford-United Kingdom

Background: Hypertension treatment guidelines recommend to lower blood pressure (BP) to <140/90 mmHg in all hypertensive patients but to be more aggressive, i.e. to reach <130/80 mmHg in patients with a high cardiovascular risk (CV) profile. We investigated the cardiovascular and renal benefits associated with these BP targets in the high cardiovascular risk population of the ONTARGET trial.

Methods and Results: We analyzed ‘post hoc’ 14,490 patients with a baseline BP >140/90 mmHg (systolic/diastolic) who were divided into 4 groups according to the proportion of in-treatment visits in which BP was reduced to <140/90 mmHg: <25%, 25% to 49%, 50% to 74%, >75%. The same analysis was carried out in patients with a baseline BP >130/80 mmHg (n = 19631) the target BP value being <130/80 mmHg. A progressive increase in the proportion of visits in which BP was controlled either to <140/90 mmHg and to <130/80 mmHg was associated with a progressive reduction in the incidence and the risk of stroke and renal events (endstage renal disease or doubling of serum creatinine). Compared to the group in which BP control to <140/90 mmHg was rarest in the group in which it was most frequent BP fell from 155/84 to 125/73 mmHg and stroke and renal events reduction being 49% and 66%. There were also in the same groups marked beneficial effects on proteinuria. Similar findings were observed when data were adjusted for baseline demographic and clinical variables involved in CV risk. In contrast, an increased frequency of BP control to either <140/90 mmHg or <130/80 mmHg did not have any effect on incidence and adjusted risk of myocardial infarction and heart failure. A more frequent BP control reduced the incidence of the primary outcome (combined fatal and non fatal CV events) only for the <140/90 target.

Conclusion: In patients at high CV risk achieving the target BP values recommended by guidelines may lead to cerebral and renal protection but not to cardiac protection, the relative prevalence of these events determining the overall effect on cardiovascular events combined. Thus, the appropriateness of these recommendations and the clinical conditions in which they should be implemented need to be further clarified.

9A.09 BENEFITS AND PSYCHOLOGICAL RISKS OF M-HEALTH REMOTE PATIENT MONITORING OF HYPERTENSION IN DIABETES: A 1-YEAR RANDOMIZED CONTROLLED TRIAL

A. Tisler1, J. Irvine2, W. McIsaac2, D. Feig1, J. Cafazzo1, A. Logan1. 1Semmelweis University, Budapest-Hungary, 2University of Toronto, Toronto-Canada

Objectives and Design: Home blood pressure (BP) monitoring actively engages patients in their own care, but the psychological consequences of enhancing self-care are unknown. We undertook a 1-year RCT to test the effectiveness of a mobile BP telemonitoring (TM) system in reducing BP and assess its effect on several psychological variables.

Methods: Adult diabetic patients with uncontrolled systolic hypertension were randomly assigned to monitor their BP at home in the standard manner (n = 55, control group) or using a fully automated TM system (n = 55, TM group). After each reading, TM patients automatically received progress and coaching messages, and if necessary, alerts and reminders. Physicians were sent summary reports and critical alerts. All patients had two different BP measures (24-h ambulatory BP monitoring and 7-days of home BP readings) and completed a set of psychological questionnaires at entry and exit. Primary care physicians made all treatment decisions.

Results: There was a significant decrease in daytime, nighttime, and 24-h systolic BP of 9.1 ± 15.6, 6.7 ± 15.9, and 8.7 ± 14.7 mm Hg (mean ± SD), respectively (p < 0.003 for all) in the TM group and no significant changes in the control group. Mean between-group differences in daytime and 24-h systolic BP of 7.1 ± 2.3 and 6.8 ± 2.4 mm Hg (mean ± SE) respectively were also significant (p < 0.005 for both) and in 7-day home readings, systolic 9.0 ± 2.4 (p = 0.002). Mean between-group differences in diastolic BP also were highly significant (data not shown). In the Anxiety Sensitivity Index, there was a significant decrease in the control group (p = 0.034) and no change in the TM group, although there was no time by group interaction effect. In the Hospital Anxiety and Depression Scale, depression worsened significantly in the TM group (p = 0.016) and remained unchanged in the control group, and there was a borderline time by group interaction effect (p = 0.061). Both groups demonstrated a significant decrease in comfort with self-measurement of BP (p < 0.003) with no between-group difference. There was no significant between-group differences in the number of antihypertensive drug classes prescribed or number of doctor visits in the study year.

Conclusions: The highly beneficial effects of a mobile phone-based TM system on reducing BP in diabetic patients with uncontrolled systolic hypertension were obtained at a possible cost of psychological well-being and comfort.
ORAL SESSION 9B

HAEMODYNAMICS

9B.01 AORTIC ROOT DILATATION IN HYPERTENSIVE PATIENTS: A MULTICENTER SURVEY IN ECCOGRADICOGRAPHIC PRACTICE


Background and Aim: The prevalence of aortic root dilatation (ARD), a cardiovascular phenotype of adverse prognostic value, has been mostly investigated in population-based samples and selected hypertensive cohorts. Rather scanty data are available from clinical practice. Thus, we examined the prevalence and correlates of ARD in a large sample of hypertensive patients referred by general practitioners for a routine echocardiographic examination.

Methods: A total of 2229 untreated and treated hypertensive subjects (mean age 62±7 years) referred to 17 out-patient echocardiographic laboratories across Italy for detection of hypertensive subclinical cardiac damage were included in the study. ARD was defined by an aortic diameter exceeding 5.3 cm in women and 5.9 cm in men.

Results: ARD was found in 263 patients out of 2229, with an overall prevalence of 11.8% (16.9% in men and 6.2% in women p=0.05). In multivariate regression analyses, body surface area (BSA), left ventricular (LV) mass and age were in ranking order the most important correlates of AR size in the whole population study as well as in men. In women, LV mass and its derivative indexes were the most important independent variables associated to AR size.

Conclusions: This multicenter nation-wide survey indicates that ARD is a frequent cardiovascular phenotype in treated hypertensives referred to echo-labs for detection of hypertensive organ damage. BSA, LV mass and age but not BP status are the most important correlates of AR size in the whole population study as well as in men. In women, LV mass and its derivative indexes were the most important independent variables associated to AR size.

9B.02 RENAL FLOW RESERVE IS ASSOCIATED WITH ADMA LEVELS IN HYPERTENSION. AN INVASIVE APPROACH OF RENAL MICROCIRCULATION

C. Tsitsoufis, D. Tsiachris, G. Latias, K. Dimitriadis, I. Tatsis, D. Syrseloudis, D. Roussos, C. Stefanadis. First Cardioiology Clinic, University of Athens, Hippokration Hospital, Athens-Greece

Background: Renal flow reserve (RFR) expresses the ability of the kidneys to augment their perfusion from baseline to a maximal value and is defined as the quotient of renal blood flow (RBF) at maximal hyperemia divided by RBF at baseline. Asymmetric dimethylarginine (ADMA), an endogenous inhibitor of nitric oxide synthase is a marker of endothelial dysfunction. In this study we examined the possible relationship between RFR with ADMA levels in essential hypertensive patients.

Design and Methods: For this purpose, we studied 12 hypertensive patients (aged 58 years, 5 males, office BP 150/95mmHg) with not significant stenoses in the renal angiography. In order to assess RFR, a 0.014 in. Doppler flow wire (Flowline, Volcano) was introduced into the renal artery for the measurement of average peak velocity under baseline and maximal hyperemic conditions. RFR was calculated in response to bolus intrarenal administration of dopamine (50μg/kg) as the ratio of hyperemic to baseline average peak velocity of the distal vessel. Serum creatinine levels (sCr), glomerular filtration rate (eGFR according to MDRD formula) and ADMA were assessed from a morning blood sample.

Results: Based on the mean value of RFR (1.73), hypertensives were classified into those with high (n = 6) and low RFR values (n = 6). Hypertensives with low RFR values compared to those with high values did not differ with respect to age, sex, office BP values and anthropometric characteristics. Although sCr and eGFR were similar between hypertensives with low and high RFR values (0.88 ± 0.11 vs. 0.78 ± 0.11 mg/dl and 82 ± 9 vs. 91 ± 15 ml/min/1.73m², p = NS for both), patients with low RFR exhibited higher levels of ADMA compared to those without (0.62 ± 0.1 vs. 0.42 ± 0.17 μmol/l, p = 0.042). In the entire study population RFR was negatively correlated with ADMA (r = −0.645, p = 0.032).

Conclusions: Hypertensives with normal renal arteries and impaired renal microcirculation, based on invasively assessed decreased RFR values, are characterized by endothelial dysfunction as reflected by higher ADMA levels.

9B.03 THE ISOLATED AND ASSOCIATED EFFECTS OF AEROBIC EXERCISE AND LOW-DOSE ESTROGEN THERAPY ON BLOOD PRESSURE, SYMPATHETIC NERVE ACTIVITY AND FOREARM BLOOD FLOW IN HEALTHY POSTMENOPAUSAL WOMEN


Objective: To evaluate the isolated and associated effects of aerobic exercise and low-dose estrogen therapy on blood pressure, sympathetic nerve activity and forearm blood flow in healthy postmenopausal women.

Design and Method: Forty five postmenopausal women (51 ± 3 years) participated in an initial session of the study. They were randomly divided into 4 different groups: SED-PLA (n = 11), SED-HRT (n = 14), PT-PLA (n = 12) and PT-HRT (n = 8). The HRT group received 1 mg / day of Estradiol Valerate while the PLA group received placebo. The PT group performed aerobic exercise on a cycle ergometer for 50 minutes, 3 times a week during 6 months while the SED group remained sedentary for the same period of time. All of the participant individuals joined in a second experimental session 6 months after the initial session of the study being completed. At the experimental session, muscle sympathetic nerve activity (MSNA, microneurography), forearm blood flow (FBF, plethysmography), blood pressure (BP, oscillometry), heart rate (HR), were measured during 10 minutes, after 30 minutes of rest. Collected data was analyzed by a three-way ANOVA.

Results: Estrogen administration alone did not change any of the variables analyzed. Physical training was proven to significantly reduce systolic blood pressure (155 ± 15 to 145 ± 13mm Hg, p = 0.03) and MSNA (40 ± 7 to 34 ± 4 bursts/min, p = 0.01). Exercise increased FBF (1.92 ± 0.26 to 2.65 ± 1.34 ml/min/100ml, p = 0.03) and improved aerobic capacity of the subjects. The association of physical training and estrogen administration was shown to reduce HR (65 ± 8 to 62 ± 7 bpm, p = 0.01).

Conclusion: Physical training has proven to be more effective than estrogen administration, reducing blood pressure and muscle sympathetic nerve activity. It also increased forearm blood flow and improved aerobic capacity of the subjects. The association of physical training and estrogen administration reduced heart rate in health post menopausal women.

9B.04 PULSE PROPAGATION AND WAVE REFLECTION IN ARTERIES: NEW INSIGHTS USING ADVANCED MODELING METHODS

L. Taelman$, J. Degroote$, A. Swijme$, J. Vierendeels$, P. Segers$. 1Ghent University, IBiTech-bioMMeda, Gent-Belgium, 1Ghent University, Flow, Heat and Combustion Mechanics, Gent-Belgium

Objective: Non-invasive diagnostic devices for arterial stiffness often synthesizes information related to the propagation and reflection of pressure pulses throughout the arterial system. These phenomena are, however, complex and still not fully understood.

Methods: We return to the basics by studying the propagation and reflection of a short, isolated pressure pulse in a straight and tapered aorta (see Figure 1) mimicking the foot of the physiological pressure wave. Theoretical pulse wave velocity (PWV), in the straight model was 4.88 ms. It increased from 4.38 to 5.35 m/s (average 4.88 m/s) in the tapered model. Additional simulations included a local stiffening (– a non-obstructing repaired aortic coarctation). Full 3D numerical fluid-structure interaction simulations with a short time step (1ms) were used. Reflective waves at the distal end were suppressed, thus isolating the effects of reflection due to aortic tapering and the presence of the rigid segment.
Results: In both control models, PWV$_V$ was higher than PWV$_V$ (5.50 and 5.60 m/s, respectively). Interestingly, a so-called "precursor wave" appeared in the simulations (e.g. at t=0.025s at the outlet), traveling back and forth within the arterial wall at a speed approximately 3 times higher than PWV$_V$ (16.5 m/s). Figure 1. Tapering amplifies the forward wave (Figure 1C). In the tapered model, the backward wave shows the same pattern induced by the precursor waves, but with an offset indicating continuous wave reflections. The stiff segment induced backward waves proximal to the rigid zone; distally, the forward traveling wave was reduced by approximately 9%. 

Conclusions: PWV$_V$ does not match the theoretical PWV and aortic tapering complicates the unequivocal interpretation of wave reflections. The appearance of a fast-traveling wave in the arterial wall warrants further investigation, but may open new perspectives for more direct characterization of the mechanical properties of arterial tissue.

9B.05 THE SHORT TERM EFFECT OF BARIATRIC SURGERY ON HAEMODYNAMICS

B. Van Den Bogaard, B.A. De Weijer, M.J. Serlie, B.J. Van Den Born. Academic Medical Center; Amsterdam-The Netherlands

Background: Hypertension and obesity are closely linked. Bariatric surgery induced weight loss has shown to decrease blood pressure. How haemodynamics are affected by bariatric surgery induced weight loss has been less well established. We aimed to assess changes in haemodynamics before and after bariatric surgery.

Methods: We examined 11 obese women (mean age 39 ± 8, BMI 46.4 ± 6 kg/m$^2$) before and 6 weeks after Roux-en-Y gastric bypass surgery. Brachial blood pressure was measured with an automatic oscillometric device and mean arterial pressure (MAP), heart rate (HR), stroke volume (SV), cardiac output (CO) and systemic vascular resistance (SVR) were calculated from continuous finger arterial blood pressure measurements (Nexfin, Bmeye, Amsterdam, The Netherlands).

Results: Surgery led to a mean weight loss of 14.2 ± 5 kg after six weeks. Brachial systolic blood pressure decreased significantly from 133.8 ± 10 mmHg at baseline to 124.7 ± 11 mmHg (p < 0.01), while diastolic blood pressure decreased from 84.5 ± 5 to 79.4 ± 8 mmHg (p = 0.04). HR (66.6 ± 9 to 56.1 ± 10 bpm), MAP (101.4 ± 9 vs. 93.0 ± 10 mmHg) and CO (8.5 ± 6.6 ± 6.6 ± 1/min) were significantly lower at 6 weeks compared to baseline (p < 0.01), while SVR increased (972 ± 127 vs. 1149 ± 142 dyn/s/cm$^5$, p = 0.02).

Conclusions: Roux-en-Y gastric bypass surgery led to a significant decrease in blood pressure in young obese women after 6 weeks with marked decreases in heart rate and cardiac output. Surprisingly, systemic vascular resistance slightly increased. These haemodynamic changes may point towards a decrease in sympathetic activity (HR and MAP). We hypothesize that the paradoxical increase in SVR may be caused by a decreased metabolic demand.

9B.06 PULSE WAVE VELOCITY IN YOUNG PEOPLE: ROLE OF BIRTH WEIGHT, POSTNATAL GROWTH, LIFESTYLE, ANTHROPOMETRIC AND HEMODYNAMIC PARAMETERS

P. Salvi$^1$, M. Temmar$^1$, L. Joly$^1$, M. Iaia$^1$, C. Borghi$^1$, A. Benetos$^1$. $^1$University of Bologna, Bologna-Italy; $^1$Telomere Cardiology Center, Ghardaia-Algeria.

Abstract 9B.07

**DIFFERENT CALIBRATION METHODS FOR ESTIMATION OF CENTRAL BLOOD PRESSURE PROVIDES CLINICALLY DIFFERENT RESULTS**


Objective: To examine whether using different calibration methods results in important differences in estimation of central blood pressures.

Methods: We included 127 patients with type-II diabetes mellitus and hypertension. On basis of ambulatory blood pressure measurement patients were characterized as having controlled (CH) or resistant (RH) hypertension. Estimation of central blood pressure (BP) was performed under standardized conditions. For comparison we used a validated method and a commercially available algorithm. The device was recommended by the manufacturer using brachial systolic and diastolic blood pressures and measured the pressure waveform over the radial artery using the generalized transfer function. Afterwards we recalibrated the device using diastolic blood pressure and mean arterial pressure. Analysis of the data was done offline in customized software.

Results: When using the recommended calibration method peripheral and central systolic BP and pulse pressure differed significantly in patients with CH (p = 0.001 and p = 0.0004). In patients with RH only systolic BP differed significantly (p = 0.006). When using the alternative calibration method there was no significant difference between peripheral and central systolic BP and pulse pressure. After six months intensified antihypertensive treatment we found that the changes in peripheral systolic BP for patients with RH was significant (p = 0.003) whereas the changes in pulse pressure was not. Using the recommended calibration method changes in central systolic BP in patients with RH was significant (p = 0.005) which was not the case when using the alternative calibration method (p = 0.09). None of the changes in central pulse pressure were significant. We also found that using the alternative calibration method produced higher estimates of central systolic BP.

Conclusion: It is important to take the role of pulse pressure amplification into account when interpreting different estimates of central BP as the method of calibration can change the results markedly. Using the recommended calibration method, from our data we could conclude that central BP change in patients with RH, whereas when using the alternative calibration method only the peripheral blood pressure changes significantly. As diastolic blood pressure and mean arterial pressure are fairly constant throughout the arterial system we find that these are to be used for calibration when estimating central pressures using the radial pressure wave.
ORAL SESSION

ORAL SESSION 9C

NEURAL MECHANISMS

9C.01 SUSTAINED VOLTAGE-DEPENDENT RESPONSE OF BLOOD PRESSURE WITH CAROTID BAROREFLEX ACTIVATION IN RESISTANT HYPERTENSION

T. Alnima1, I. Scheffers1, P.W. De Leeuw1, B. Winkens2, H.A. Jongen

1Department of Hypertension and Diabetology, Medical University of Gdansk, Gdansk-Poland, 2Divisions of Hypertension and Cardiorenal Medicine, Mayo Clinic, Rochester-USA, 3Department of Maastricht Medical Center, Maastricht-The Netherlands, 4University of Maastricht, Maastricht-The Netherlands

Objective: Graded increase in stimulation voltage in patients with a carotid baroreflex stimulator (Rheos® system) causes a greater short-term drop in blood pressure and heart rate. Aim of this study is to evaluate whether this voltage-dependent blood pressure and heart rate response changes in patients with long-term activated carotid baroreflex stimulator.

Design and Methods: 17 patients with a carotid baroreflex stimulator underwent a Dose Response Test (DRT) before start of carotid baroreflex activation therapy (baseline), and after 3, and 12 months of chronic stimulation. After switching off the device temporarily, DRT started by increasing voltage from 0 to 6 volts, by 1-volt step every 5 minutes. Blood pressure and heart rate were measured at the end of every step.

Results: At baseline mean blood pressure was 172/98 mmHg at 0 volt and fell to 139/79 mmHg at 6 volts. Heart rate fell from 76 to 66 beats/min. After 3 months and 12 months of chronic therapy mean blood pressure was significantly decreased when DRT started at 0 volt (158.9/91 and 155.5/90 mmHg, respectively). Pattern of blood pressure decrease during DRT was comparable with baseline and did not differ significantly. Maximum systolic blood pressure decrease reduction during DRT did not change with long-term therapy.

Conclusions: Voltage-dependent blood pressure decrease with electrical carotid baroreflex stimulation is sustained for at least a year of chronic stimulation in patients with resistant hypertension. There is no evidence of baroreflex adaptation, reduced responsiveness or nerve fatigue with long-term carotid baroreflex stimulator.

9C.02 MUSCLE SYMPATHETIC NERVE ACTIVITY IS NOT INFLUENCED BY LONG-TERM SLOW BREATHING TRAINING IN HYPERTENSION

D. Hering1, W. Kucharska1, T. Kara2, V.K. Somers2, G. Parati3, K. Narkiewicz1, 1Department of Hypertension and Diabetology, Medical University of Gdansk, Gdansk-Poland, 2Divisions of Hypertension and Cardiorenal Medicine, Mayo Clinic, Rochester-USA, 3Department of Cardiology, University of Milano-Bicocca, Monza-Italy

Objective: Sympathetic cardiovascular regulation has been shown also to be affected by respiratory activity. Evidence is available that slow breathing exercise (SLOWB) may acutely reduce sympathetic activity (SA). Aim of our study was to assess the effects of both acute and long-term SLOWb on blood pressure (BP), heart rate (HR) and direct measurements of SA in humans, an issue yet largely unexplored.

Design and Methods: Using device-guided respiratory pacing, we examined the effects of acute and long-term SLOWb on BP, HR and muscle sympathetic nerve activity (MSNA) in 10 hypertensive males (age 37 ± 4 years; body mass index 26.0 ± 0.9 kg/m², and waist circumference 91 ± 2 cm) at rest and during laboratory stressors. Hypertensive patients were newly diagnosed, never treated for hypertension and free of any other diseases. All subjects were studied before and after acute SLOWb and 8 weeks of SLOWb home training.

Results: Acute SLOWb (from 12.7 ± 1.9 to 5.8 ± 0.5 breaths/min.) had no influence on BP or HR, but decreased MSNA (29.4 ± 4.3 vs. 19.3 ± 3.5 bursts/min.; p < 0.01). BP, HR and MSNA responses to handgrip test were similar before and after shorter SLOWb. Short-term SLOWb tended to reduce Sympathetic (SDBP (21 ± 3 vs. 12.4 ± 2.8 mmHg; p = 0.09) and HR interval (-176 ± 48 vs. -123 ± 35 ms) responses, but had no influence on MSNA changes during mental stress (13 ± 8 vs. -4 ± 8 %; p = NS). Long-term SLOWb training reduced significantly office SBP (154.9 ± 3.1 vs. 137.2 ± 2.5 mmHg; p = 0.001), diastolic (DBP) (91.2 ± 1.8 vs. 84.5 ± 2.3 mmHg; p < 0.01), and HR (73.8 ± 3.9 vs. 66.2 ± 3.3; p = 0.001), but had no effect on 24h ambulatory BP or HR. MSNA was not influenced by long-term SLOWb training (26 ± 3 at baseline vs. 25 ± 4 bursts/min. on the final visit; p = NS). Long-term SLOWb training did not influence the magnitude of BP, HR or MSNA responses to handgrip and cold pressor test, but reduced BP and HR responses to mental stress (21 ± 3 vs 9.2 ± 2 mmHg; p = 0.05; –176 ± 48 vs. –106 ± 43 ms; p = 0.05); sympathetic responses remained unchanged.

Conclusions: (1) MSNA is reduced during acute SLOWb, but is not influenced by long-term SLOWb training in hypertensives. (2) Long-term SLOWb reduces office, but not ambulatory BP and HR. (3) SLOWb attenuates cardiovascular effects of mental but not of physical stressors.

9C.03 NEUROADRENERGIC PROFILE IN PATIENTS WITH RESISTANT HYPERTENSION

G. L. Seravalle1, M. Volpe2, F. Ganz1, L. Magni1, G. Brambilla1, R. Dell’oro1, M. Bombelli1, G. Manci3, G. Grassi4, 1Osp. San Luca, Istituto Auxologico Italiano, Milano-Italy, 2Clinica Medica, Osp. S. Gerardo, UNIV. Milano-Bicocca, Monza-Italy

Introduction: Resistant hypertension is characterized by profound abnormalities in neurohumoral homeostatic control of circulation. Whether these include also adrenergic cardiovascular influences is largely unknown.

Methods: In 8 patients (6 males, 2 females) with documented resistant hypertension (RHT, defined by blood pressure values not at goal and a systolic blood pressure ≥ 160 mmHg) and direct measurements of SA in humans, an issue yet largely unexplored.

Results: An 8.8 vs. -4 mmHg; p = 0.09) and RR interval (-176 ± 48 vs. –106 ± 43 ms; p = 0.05); sympathetic responses remained unchanged.

Conclusions: (1) MSNA is reduced during acute SLOWb, but is not influenced by long-term SLOWb training in hypertensives. (2) Long-term SLOWb reduces office, but not ambulatory BP and HR. (3) SLOWb attenuates cardiovascular effects of mental but not of physical stressors.

Results: In 8 patients (6 males, 2 females) with documented resistant hypertension (RHT, defined by blood pressure values not at goal and a systolic blood pressure ≥ 160 mmHg) and direct measurements of SA in humans, an issue yet largely unexplored.

Results: The two hypertensive groups displayed, as expected, blood pressure and MSNA values significantly greater than C. For similar age (61.8 ± 2.9 vs. 59.7 ± 2.5 years), body mass index (25.2 ± 1.1 vs. 24.1 ± 0.9 Kg/m²) and clinic systolic and diastolic blood pressure (171.2 ± 2.9/98.4 ± 2.0 vs.169.7 ± 2.9/97.4 ± 1.9 mmHg), RHT showed MSNA values significantly greater than HT both when expressed as bursts incidence over time and as bursts incidence corrected for heart rate (60.5 ± 2.9 vs. 44.8 ± 2.2 bs/min.86.1 ± 5.1 vs. 70.3 ± 3.9 bs/100 hrs, P< 0.05 for both). Plasma aldosterone and HOMA index values were also significantly greater in RHT than in HT (13.8 ± 1.4 vs 9.1 ± 0.8 ng/dl and 2.31 ± 0.3 vs 1.5 ± 0.2; p < 0.05 for both), whereas plasma renin activity significantly lower (0.8 ± 0.2 vs 1.5 ± 0.3 ng/ml/h, P < 0.05). In RHT, but not in HT, plasma aldosterone and HOMA index values were significantly and directly correlated with MSNA.

Conclusions: These data provide the first evidence that resistant hypertension is a state of marked sympathetic activation, greater for magnitude than that seen in non-resistant essential hypertension. They also suggest that in resistant hypertension the adrenergic overdrive is independent on sleep apnea and is likely related to metabolic (insulin resistance) and/or humoral (elevated aldosterone levels) factors with documented central sympathoexcitatory influences.

9C.04 CHANGES IN SYMPATHETIC TONE CORRELATE WITH REGIONAL CHANGES IN BRAIN ACTIVATION

J. Coulson, K. Murphy, A. Harris, M. Fjodorova, J. Cockcroft, R. Wise, Cardiff University, Cardiff-United Kingdom

Objective: The aetiology of hypertension, in the majority of cases, remains unclear. Increased sympathetic nervous system (SNS) activity has been observed in young adults with hypertension. The neuro-anatomical location of this apparent increase in SNS activity is unknown. We used blood oxygenation level dependent functional magnetic resonance imaging (BOLD fMRI) to identify areas of the brainstem and
higher brain structures whose activity correlate with the SNS-mediated, pressor response to voluntary isometric forearm contraction (IFC) in young adults.

Methods: 6 adults (2 female) without a history of hypertension, aged 24 - 37 years, performed 3 experimental runs in which voluntary IFC was performed at -40% of their maximum grip strength for periods of time ranging from 11 to 180 seconds whilst acquiring fMRI images. A 3 T scanner with an 8-channel receive coil (General Electric, US) was used, 170 image volumes (scan time = 12m 39s) were collected for each of the 3 repetitions. Each volume covered the entire brain and brainstem (57 slices, 2.3 mm slice thickness, field of view = 19.2 cm², 128x128 TR = 4385 ms, TE = 25 ms, flip = 90°). Structural images were collected using a T1-weighted sequence in order to facilitate visualisation. Analysis was performed using FLAT (Fmrib). Blood pressure changes were modelled with a 2nd order ARMAX model and its coefficients might correlate non-linearly to the blood pressure. Therefore, we used an out-of-scanner recording.

Results: IFC was associated with an increase in mean arterial blood pressure of 22% ± 7 % SD from the baseline. Group analyses showed increased activation in the right subgenual anterior cingulate cortex in response to linear increases in blood pressure at a rate of 0.3 mmHg.s⁻¹. The contralateral motor cortex, right anterior insular cortex, left insular cortex, thalamus, cerebellum and medulla also showed activation during IFC.

Conclusion: We have identified areas of regional brain activity that correlate with the pressor response to IFC. These areas have also been associated with the initiation of a pressor response in studies that used electrode stimulation studies or other imaging modalities. We now intend to use this technique to investigate potential differences between young hypertensives and healthy controls.

**9C.05** LONGITUDINAL TRACKING OF MUSCLE SYMPATHETIC NERVE ACTIVITY AND ITS RELATIONSHIP WITH BLOOD PRESSURE IN NORMOTENSIVE SUBJECTS

D. Hering, K. Czechowicz, R. Nowak, W. Kucharska, K. Narkiewicz. Department of Hypertension and Diabetology, Medical University of Gdansk, Gdansk-Poland

Objective: The “tracking phenomenon” is an important longitudinal characteristic of blood pressure. It is unclear whether muscle sympathetic nerve activity (MSNA) and its changes might contribute to this phenomenon. Therefore, we investigated the association of blood pressure (BP) with longitudinal MSNA tracking in normotensive subjects over an 8-year period.

Design and Methods: We measured BP and MSNA (microneurography) in 13 normotensive males (age 39 ± 2 years, BMI 27 ± 2 kg/m², mean ± SEM). All subjects were studied at baseline and after 8 years of follow-up.

Results: At baseline, BP averaged 128 ± 2.81 ± 2 mmHg, and mean MSNA was 24 ± 3 bursts/min. On follow-up, BP increased by 7 ± 2.5 ± 2 mmHg (p < 0.01), and MSNA by 11 ± 3 bursts/min. (p < 0.001). Both SBP and DBP had high tracking coefficients (r = 0.88; p < 0.001 and r = 0.82; p = 0.004). The tracking of MSNA (r = 0.85; p = 0.002) was similar to that of BP. The correlations between MSNA and BP were stronger for DBP than for SBP. MSNA was strongly related to DBP at baseline (r = 0.87; p < 0.001) and on follow-up (r = 0.76; p < 0.001). MSNA change was positively associated with change in DBP (r = 0.72; p < 0.05). The correlations remained significant after adjustment for baseline body mass index and its changes.

Conclusions: Our results indicate that the tracking of muscle sympathetic nerve activity contributes to tracking of blood pressure.

**9C.06** IMPACT OF ELEVATED PERIPHERAL CHEMOSENSITIVITY ON SPONTANEOUS BAROREFLEX FUNCTION IN CHRONIC HEART FAILURE PATIENTS WITH CARDIONEUROPATHY SYNDROME

N. Franchineau, P. Desplan, M. Labruyere, M. Galier, J.M. Senard, A. Pathak,1 University Hospital of Rangueil, Toulouse-France, 1Institut National DE LA Sante ET DE LA Recherche Mедицине, U 858, Toulouse-France, 3Institut DE Мedecine Moléculaire, IFR 31, Toulouse-France

Objective: Cardiorenal syndrome is known to increase mortality and morbidity in patients with CHF. The role of the sympathetic nervous system and related-reflexes in the pathophysiology remains unknown.

Design and Methods: The prospective study was conducted at the Intensive Cardiac Care Unit, Rangueil University Hospital, Toulouse, France. We studied 15 patients with CRA syndrome (age: 60.2 ± 3.2 years; mean BMI: 24.12 ± 0.9 kg/m²) and 15 control patients with CHF alone matched for age, gender distribution, type of cardiomyopathy, left ventricular ejection fraction (LVEF) and BMI. We compared sympathetic nerve activity (MSNA), sympathetic baroreflex function (assessed by the slope of the relationship between muscle sympathetic nerve activity (MSNA) and diastolic blood pressure) and its modulation by peripheral chemoreflexes, in both groups.

Results: Baseline MSNA was significantly elevated in CHF patients with CRA syndrome compared with patients with CHF alone (83.0 ± 4.63 versus 64.9 ± 2.9; p = 0.0039) and sympathetic baroreflex function impaired (r = 2.2 ± 0.5 versus −5.4 ± 0.6; p = 0.0002). In comparison with control, chemoreflex deactivation with administration of 100% oxygen led to a significant decrease in muscle sympathetic nerve activity and an increase in arterial baroreflex sensitivity in patients with CRA syndrome.

Conclusion: CRA syndrome is associated with elevated sympathetic activity mediated by both baroreflex impairment and tonic activation of peripheral chemoreflex. The latter, through direct interaction with sympathetic baroreflex function subsequently contributes to further activation of the SNS tone. Altogether, mechanisms described in this study could partly explain how CRAS contributes to the progression of CHF and increases morbidity and mortality in these patients.

**9C.07** ASSOCIATION OF BETA-1 ADRENERGIC RECEPTOR SER49GLY POLYMORPHISM WITH BEAT-TO-BEAT CARDIAC DYNAMICS IN LATINS

J.C. Ochoa, M.M. Correa, J.A. Gallo, J.G. Mewers, G. Bilo, D. Arstizabal, G. Parati. 1University of Milano-Bicocca & Istituto Axsologico Italiano, Milan-Italy, 2Centro Clinico Y De Investigacion, Sicor, Medellin- Colombia, 3School of Medicine, University of Antioquia, Medellin-Colombia, 4Corporacion Para Investigaciones Biologicas, Medellin-Colombia, 5Dept. Cardiology, Ospedale San Luca, Istituto Axsologico Italiano, Milan-Italy, 6Dept. Cardiology, Ist. Axsologico Italiano & Dept. of Clin. Med and Prev. Univ. Milano-Bicocca, Milan-Italy

Objective: Beta-1 adrenergic receptor (ADRB1) plays a key role in acutely modulating beat-to-beat cardiac function. Although Gly46 variant of the Ser49Gly polymorphism has been reported to be associated with constitutive ADRB1 activation and higher long-term rates of survival in patients with heart failure, evidence on its pathophysiological relevance is preliminary. Aim of our study was to explore the association between this SNP and indices of cardiac performance.

Methods: 800 individuals from the general population participating in the Medellin’s Heart Study (M-46%, aged 30-65 years) were recruited. Polymorphism Ser49Gly was genotyped by competitive allele-specific PCR SNP genotyping system (KASP chemistry). Quality control was done through blind duplicates and Hardy-Weinberg equilibrium (HWE) tests. In 500 subjects, stroke volume (SV) and R-R interval (RRI) were recorded beat-to-beat by impedance cardiography and ECG (Biopac Systems, Inc.). Conventional supine blood pressure (BP) measurements were repeated over 5 minutes. Beat-to-beat cardiac and hemodynamic indices were computed and averaged: RRI, heart rate (HR), pre-ejection period (PEP), left ventricular ejection time (LVET), SV, SBP index (SI), cardiac output (CO), CI index (CI) and left cardiac work (LCW).

Results: Ser49Gly polymorphism was in HWE. In a co-dominant model, analysis of variance adjusting for age, sex, smoking, diabetes, and BMI showed significant differences between genotype categories for CO, CI and LCW. In a dominant model, carriers of one or two copies of the Gly allele, showed significantly higher SV, SI, CO, CI and LCW when compared to Ser/Ser homozygotes. See table.

<table>
<thead>
<tr>
<th>Model</th>
<th>Genotype</th>
<th>SV (ml/beat)</th>
<th>SI (ml/beat/beat)</th>
<th>CO (l/min/m²)</th>
<th>CI (l/min/m²)</th>
<th>LCW (l/min/m²)</th>
<th>LVET (ms)</th>
<th>PEP (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ser/Gly co-dominant</td>
<td>Ser/Ser (n=377)</td>
<td>80.6±1.2</td>
<td>46.7±0.6</td>
<td>5.2±0.1</td>
<td>3.0±0.4</td>
<td>6.5±0.1</td>
<td>931±8.0</td>
<td>296±3.0</td>
</tr>
<tr>
<td>Ser/Gly (n=53)</td>
<td>84.4±1.7</td>
<td>49.4±0.9</td>
<td>5.6±0.1</td>
<td>3.3±0.7</td>
<td>7.0±0.1</td>
<td>921±12</td>
<td>298±4.0</td>
<td>112.2±2.0</td>
</tr>
<tr>
<td>Gly/Gly (n=27)</td>
<td>89.6±6.0</td>
<td>51.7±3.4</td>
<td>6.3±0.4</td>
<td>3.6±0.2</td>
<td>7.8±0.6</td>
<td>855±4.2</td>
<td>296±13</td>
<td>95.3±2.0</td>
</tr>
</tbody>
</table>

P-value** | 0.06 | 0.05 | 0.008 | 0.001 | 0.008 | 0.1 | 0.2 | 0.08 |

P-value** | 0.02 | 0.01 | 0.01 | 0.007 | 0.008 | 0.4 | 0.1 | 0.5 |

*Values are expressed as margin means a standard error; **P values were adjusted for age, sex, diabetes, cigarette smoking, and BMI (ANCOVA).

Conclusion: Our findings show that the Gly allele of the Ser49Gly polymorphism is associated with an enhanced systolic performance. This finding could be relevant to explain the association between β1 adrenoceptor gene polymorphisms and cardiovascular disorders such as hypertension and congestive heart failure.
LONGITUDINAL CHANGE IN BLOOD PRESSURE IN RELATION TO 5 CANDIDATE GENES AND URINARY SODIUM EXCRETION IN 1405 SUBJECTS FROM 5 EUROPEAN POPULATIONS

K. Stolarz-Skrzypek1, T. Kuznetsova2, L. Thijs3, W. Wojciechowska1, V. Tikhomirov4, J. Seidlerova4, E. Brand4, G. Bianchi5, S. Maloyutina1, E. Casiglia1, J. Filipovsky4, K. Kawecka-Jaszcz2, Y. Nikitin5, J. Staessen3, on behalf of the European Project on Genes in Hypertension (Epogh) Investigators. 1First Department of Cardiology and Hypertension, Jagiellonian University Medical College, Krakow-Poland, 2Studies Coordinating Centre, Division of Hypertension, University of Leuven, Leuven-Belgium, 3Department of Clinical and Experimental Medicine, University of Padova, Padova-Italy, 4Faculty of Medicine in Pilsen, Charles University, Pilsen-Czech Republic, 5Department of Internal Medicine D, University of Munster, Munster-Germany. 

Objective: The genes encoding angiotensin converting enzyme (ACE), adducin subunits (ADD1, ADD2 and ADD3) and aldosterone synthase (CYP11B2) share the potential of influencing blood pressure (BP) via sodium homeostasis. In this analysis we aimed to investigate longitudinal changes in BP in relation to polymorphisms in aforementioned genes (ACE I/D, ADD1 Gly460Trp, ADD2 C1797T, ADD3 A386G, and CYP11B2 C-344T) in White Europeans recruited from 5 populations.

Design and Methods: At baseline and after median (IQR) 6.3 (5.2–8.3) years of follow-up, we measured conventional BP and 24-h urinary sodium excretion (24-h UVNa) as index of salt intake, in 1,405 never treated subjects recruited using a family-based random sampling frame from Hechtel-Eksel (Belgium, n = 1038), Krakow (Poland, n = 106), Novosibirsk (Russian Federation, n = 64), Padova (Italy, n = 138) and Pilsen (Czech Republic, n = 59). The analyses of genotype-phenotype relations were adjusted for covariables and relatedness of study participants.

Results: In analyses not accounting for urinary sodium, ACE DD homozygosity was associated with a greater increase in diastolic BP during follow-up (DD vs D+D: adjusted mean ± SE): 5.40 ± 0.50 vs 4.40 ± 0.39 mmHg; p = 0.036), but not in systolic BP (5.72 ± 0.69 vs 4.72 ± 0.54 mmHg; p = 0.14) as compared to D alleles carriers. We have not observed any association between polymorphisms in CYP11B2 and 3 adducin subunits and follow-up changes in blood pressure. The relation between ACE genotype and change in BP depended on baseline sodium excretion (P for interaction between baseline 24-h UVNa and change in systolic BP = 0.059). In subjects with higher then sex- and country-specific median of baseline 24hUVNa (167 mmol/24h), carriers of D allele had higher increase in systolic (4.36 ± 0.72 vs 2.34 ± 1.10 mmHg; p = 0.049) and diastolic BP (4.53 ± 0.52 vs 3.08 ± 0.78 mmHg; p = 0.044) as compared to II homozygotes. Such relation was not observed in subjects with lower than median baseline 24hUVNa (P = 0.37). We did not observe any gene–gene interactions among polymorphisms under study.

Conclusions: The I/D polymorphisms of the ACE gene influences longitudinal BP change. However, sodium intake seems to modulate this genetic effect.

TRANSCRIPTIONAL REGULATION OF SOLUBLE ADENYLYL CYCLASE (SAC) AND SAC BINDING TO CAMP RESPONSE ELEMENT (CRE) BINDING SITES

M. Herrmann1, K. Giske1, B. Schmitz2, A. Salomon3, S.-M. Brand1, E. Brand1.
1University Hospital Munster, Internal Medicine D, Munster-Germany, 2Medical Faculty of the Westfalian Wilhelms-University, Münster-Germany, 3Leibniz-Institute for Atherosclerosis Research, Münster-Germany.

Objective: The soluble adenylyl cyclase (sAC) activates the Na+/K+-ATPase in renal epithelial collecting duct cells and is involved in the regulation of blood pressure. sAC is induced by HCO3- and exists in microdomains in close proximity to targets of the cAMP pathway, by constituting a functional complex in the nucleus with cAMP response element binding protein (CREB). Consequently, we analysed the chromatin binding of sAC and CREB to determine the effect of sAC on gene expression. Furthermore, we functionally characterised expression relevant promoter portions and the influence of nucleotide variations on sAC gene regulation.

Design and Methods: We performed Chromatin Immunoprecipitation (ChiP) to detect the binding pattern of sAC and CREB to regulatory regions. We screened ~4.000 bp of the sAC 5’-flanking region in 60 patients with cardiovascular disease to characterize its variant structure. Molecular haplotypes (MolHaps) and promoter deletion constructs were transfected into the Human Embryonal Kidney (HEK 293T) cell line, the Immortalized Human Kidney Epithelial (HIKE) cell line and the human vascular endothelial cell line Ea.hy926. Cells were kept under basal conditions or stimulated with 8-Br-cAMP (0.5 mM) for 4 hrs.

Results: In vivo binding of sAC with CRE motifs was shown using CRE consensus sequences in ChiP experiments. We identified seven variants in the 5’-flanking region of sAC, three of which newly described by our group (G-3568A, A-2560T, G-2211A). Three of the seven variants are in linkage disequilibrium (r2=0.99, D=1). We compared two MolHaps: A [Ins2356Del, C-2181T, T-2092G] and B [Ile211Val, T-2109G, T-2092G].
A. Salomon1, B. Schmitz2, A. Rötrige1, E. Brand3, P.E. Morange4, F. Cambien5,

tation factors linking differential sAC function to blood pressure phenotypes and

and stimulation-specific. Lef1 could account for the increased transcription by

5´-flanking region is polymorphic and genetic variants reside within transcrip-

in complex with CREB will be determined in further studies. 2) The

Conclusions: 

5´-flanking region between positions -1112 and -991 to harbour a potential lymphoid enhancer binding factor 1 (Lef1) binding site.

Objective: HIVEP1 binds to NF-κb consensus sequences and is therefore sug-

gested to regulate the expression of genes involved in inflammatory processes. We recently identified rs169713 positioned 90 kb upstream of the HIVEP1 gene to be replicatively associated with venous thrombosis (Morange et al., AJHG 2010). Thus, we molecular functionally characterized HIVEP1 promoter por-

tions and the putative enhancer region adjacent to rs169713.

Design and Methods: A 332 bp potential enhancer fragment, harbouring rs169713CT was cloned into the pGL3-Promoter vector, serial HIVEP1 promoter deletion constructs were introduced into the pGL3-Basic vector. Sequencing the 5´-flanking region (5 kb) in 60 CVD patients revealed 10 genetic variants. Individual subcloning and resequencing of positions -1060 to -935 generated 4 molecular haplotypes. Reporter gene assays were performed by transient trans-

fection in vascular endothelial cells (EA.hy926) and monocytes (THP1).

Results: In EA.hy926 cells, the construct harbouring rs169713T showed signifi-

cant higher transcriptional activity (TA) over the empty pGL3-Promoter vector (p < 0.001). Basic TA was located between positions -469 and -1099, strongest TA between positions -1241 and -1650 (p < 0.001); similar results were found in THP1 cells. Endogenous HIVEP1 expression was stimulated by cAMP, TNFα, IL1β and IL4. Cotransfection of transcription factor (TF) SP1 led to an overall increase of TA. A portion of intron 1 displayed a regulatory effect on TA medi-

ed by a TF module comprising WT1-family members in EA.hy926 cells. The rs169713 T-allele harbours potential activational capacity

OF THE HUMAN IMMUNODEFICIENCY VIRUS TYPE I ENHANCER BINDING PROTEIN 1 (HIVEPI)

HIVEP1 expression was stimulated by cAMP, TNF

and IL4. Cotransfection of transcription factor (TF) SP1 led to an overall increase of TA. A portion of intron 1 displayed a regulatory effect on TA medi-

ed by a TF module comprising WT1-family members in EA.hy926 cells. The rs169713 T-allele harbours potential activational capacity

OF THE HUMAN IMMUNODEFICIENCY VIRUS TYPE I ENHANCER BINDING PROTEIN 1 (HIVEPI)

HIVEP1 expression was stimulated by cAMP, TNF

and IL4. Cotransfection of transcription factor (TF) SP1 led to an overall increase of TA. A portion of intron 1 displayed a regulatory effect on TA medi-

ed by a TF module comprising WT1-family members in EA.hy926 cells. The rs169713 T-allele harbours potential activational capacity

RESULTS 9E. Koenigshaufen, M. Ruetze, U. Zierhut, S.A. Potthoff, M. Woznowski,

Department of Nephrology, University Hospital, Duesseldorf-Germany

Introduction: Microalbuminuria serves as an early marker for glomerular injury in hypertensive and diabetic patients. Inhibitors of the renin-angiotensin-

sin-aldosterone system but not calcium channel blockers reduce albuminuria in these patients. Albuminuria results from a defect in the glomerular filter that is composed of fenestrated endothelium, glomerular basal membrane and podocytes with slit diaphragms. A major component of the glomerular slit diaphragm is nephrin, that is endocytosed upon binding to the adaptor protein β-arestin2.

Methods: Cells expressing the AT1-receptor or its mutant D125AR126L, nephrin and β-arestin2 were stimulated with Angiotensin II (Ang II). After cell lysis, co-immunoprecipitation with subsequent westernblot analysis was performed. For the inhibitor studies, cells were pretreated with the inhibitor 60 min before stimulation with Ang II(100nM, 1μM). For siRNA experi-

ments cells were transfected with Gag siRNA and lysed three days thereafter. siRNA expression was confirmed by western blot. The effect of Ang II on the β-arestin2 binding motif was studied by using two nephrin mutants. For the endocytosis assay, cells were stimulated with Ang II and incubated with biotin before cell lysis.

Results: Ang II stimulation increases the protein interaction between nephrin and β-arestin2. This Ang II effect is dependent on the AT1-receptor and can be inhibited by AT1-receptor blockers. The G-protein signalling is essential for the Ang II effect, as the AT1-receptor mutant D125AR126L abolishes all G-protein signalling and inhibits the Ang II mediated increase of the nephrin β-arestin2 interaction. SiRNA against the Gag subunit as well as an inhibitor of phospholipase C (PLC) blocks the Ang II effect. Phosphorylation of T1120 and T1125 of the nephrin C-terminus is essential for the binding of β-arestin2 even after stimulation with Ang II. Stimulation with Ang II increases endocy-

tosis of nephrin, which can be inhibited with AT1-receptor and PLC-blockers. The Ang II effect on nephrin-β-arestin2 interaction is also found in isolated glomeruli from mouse kidneys.

Conclusion: Ang II weakens the integrity of the slit diaphragm through increase of nephrin endocytosis and is perceived to promote proteinuria. This novel molecular effect of Ang II helps to understand the molecular mechanism of Ang II induced proteinuria beyond hemodynamic effects.
Objective: Smoking and obesity associated BDNF gene has been implicated in psychiatric and substance related disorders. Furthermore, recent genome wide association studies (GWAS) have shown strong associations between genetic BDNF variation, smoking behavior and BMI. Our aim was to test if the smoking and obesity associated BDNF polymorphism rs4923461 (A/G) alters the risk of smoking related complications among smokers in the Malmö Diet and Cancer Study (MDCS), a population based prospective cohort study.

Methods: At the MDCS baseline exam 1991–1996, subjects were classified as current smokers (n = 6507) and as non-smokers (n = 18 564), the latter including 8 791 previous smokers. Association between the rs4923461 and smoking behavior was tested with logistic regression. Cox proportional-hazards models were used to relate the BDNF rs4923461 polymorphism to total, cancer and cardiovascular mortality and incidence of CVD (myocardial infarction or stroke) during 12 ± 2.6 years of follow-up.

Results: In an additive model adjusted for sex, age and BMI, the major allele (A) was significantly associated with ever having smoked (current smokers + previous smokers) (OR = 1.05, 95% CI 1.01–1.10, p = 0.03). Among current smokers, there were 1049 deaths, 346 CVD deaths, 492 cancer deaths and 802 incident first CVD events during follow-up. After adjustment for age, sex, BMI and smoking quantity, the A-allele gradually increased the risk of all cause mortality (HR = 1.12, 95% CI 1.00–1.25, p = 0.04). As well as smoking, in the adjusted model the A-allele was significantly associated with all cause mortality (HR = 1.23, 95% CI 1.01–1.49, p = 0.04). There was no significant association between the A-allele and cancer mortality (p = 0.15) or CVD incidence (p = 0.29) but AA- homozygotes had an increased risk of cancer mortality compared to GG-homozygotes (HR = 1.87, 95% CI 1.03–3.42, p = 0.04). As expected, rs4923461 was not associated with mortality or CVD incidence in non-smokers.

Conclusion: Our data suggests that genetic BDNF variation affects the propensity to quit smoking, resulting in an increased mortality rate independently of BMI and smoking quantity. Determination of BDNF genotype in smokers may guide the intensity of smoke cessation interventions needed.

Objective: Smoking and obesity associated BDNF gene has been implicated in psychiatric and substance related disorders. Furthermore, recent genome wide association studies (GWAS) have shown strong associations between genetic BDNF variation, smoking behavior and BMI. Our aim was to test if the smoking and obesity associated BDNF polymorphism rs4923461 (A/G) alters the risk of smoking related complications among smokers in the Malmö Diet and Cancer Study (MDCS), a population based prospective cohort study.

Methods: At the MDCS baseline exam 1991–1996, subjects were classified as current smokers (n = 6507) and as non-smokers (n = 18 564), the latter including 8 791 previous smokers. Association between the rs4923461 and smoking behavior was tested with logistic regression. Cox proportional-hazards models were used to relate the BDNF rs4923461 polymorphism to total, cancer and cardiovascular mortality and incidence of CVD (myocardial infarction or stroke) during 12 ± 2.6 years of follow-up.

Results: In an additive model adjusted for sex, age and BMI, the major allele (A) was significantly associated with ever having smoked (current smokers + previous smokers) (OR = 1.05, 95% CI 1.01–1.10, p = 0.03). Among current smokers, there were 1049 deaths, 346 CVD deaths, 492 cancer deaths and 802 incident first CVD events during follow-up. After adjustment for age, sex, BMI and smoking quantity, the A-allele gradually increased the risk of all cause mortality (HR = 1.12, 95% CI 1.00–1.25, p = 0.04). As well as smoking, in the adjusted model the A-allele was significantly associated with all cause mortality (HR = 1.23, 95% CI 1.01–1.49, p = 0.04). There was no significant association between the A-allele and cancer mortality (p = 0.15) or CVD incidence (p = 0.29) but AA- homozygotes had an increased risk of cancer mortality compared to GG-homozygotes (HR = 1.87, 95% CI 1.03–3.42, p = 0.04). As expected, rs4923461 was not associated with mortality or CVD incidence in non-smokers.

Conclusion: Our data suggests that genetic BDNF variation affects the propensity to quit smoking, resulting in an increased mortality rate independently of BMI and smoking quantity. Determination of BDNF genotype in smokers may guide the intensity of smoke cessation interventions needed.