ANP did not result in significant changes. These favorable renal effects were associated increases in both plasma cGMP and urinary cGMP excretion, which were similar with BNP and Uro, however was unchanged with ANP. This study demonstrates the superiority of BNP to Uro and ANP in enhancing renal function in severe experimental CHF. These studies also support the conclusion that with CHF, renal resistance to natriuretic peptides in increasing rank order is BNP < Uro < ANP. These results may have clinical implications when considering the therapeutic efficacy of these peptides in the management of overt CHF.

582 Plasma levels of adrenomedullin, big-endothelin-1 and osteopontin in chronic heart failure
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Chronic heart failure (CHF) is characterized both by ventricular and vascular remodeling. Osteopontin (OP) is an extracellular matrix protein, that might have a role as a marker of ventricular remodelling, its expression being increased in myocardial tissue of CHF patients from biopsies. Adrenomedullin (AM), a potent vasodilator peptide secreted by endothelial cells, and endothelin (ET), a substance with long-acting vasocostrictor action, might express the paracrine vasomotor response to CHF progression. In the present study, we measured plasma levels of AM, OP and of big-endothelin-1 (Big-ET-1), the ET-1 precursor, whose circulating levels may reflect ET-1 overproduction more accurately than ET-1 itself. We studied 125 patients affected by CHF of idiopathic or post-ischemic origin, (ejection fraction: 33.6 ± 0.87%, mean ± SEM), 82 in NYHA class I-II and 43 in III-IV class and 20 healthy subjects, as control group. Plasma AM levels were determined by a radioimmunoassay while Big-ET-1 and OP plasma levels were determined with ELISA methods. The mean (± SEM) plasma levels of AM in control subjects were 13.8±1.05 pmol/l and in patients with CHF showed tendency to be increased in those in functional class I-II (18.8±1.12 pmol/l) and were significantly increased in those in NYHA class III-IV (21.4±2.3 pmol/l, p<0.015). Plasma levels of Big-ET-1 in control subjects were 1.4±0.12 fmol/l, in patients with CHF were unaffected in those in functional class I-II (1.4±0.08 fmol/l) but significantly increased in those in NYHA class III-IV (2.0±0.22 fmol/l, p<0.047). Plasma levels of OP in normal subjects were 238.0±16.0 mg/ml and were significantly increased in those in NYHA classes I-II (366.2±21.9 mg/ml, p<0.0001) and III-IV(485.6±70.5 mg/ml, p<0.0001). A significant correlation between plasma levels of AM and Big-ET-1 (r=0.5, p<0.001) was observed. These results indicate that plasma levels of AM, OP and Big-ET-1 are elevated in CHF, with an increase proportional with the severity of disease, suggesting a role of these substances as markers of endothelial vasomotor response to CHF progression and of myocardial remodeling, respectively.

583 Cardiac BNP mRNA reflects fibrosis and is blood pressure-independent in mice
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Since first reports demonstrated interactions between the natriuretic peptide (NPs) and renin-angiotensin system (RAS), our experiments should clarify whether cardiac BNP is regulated in mice genetically altered for components of the RAS. The study was carried out in hypertensive AT1- and angiotensinogen (ANG)-, in normotensive AT2-knockout mice, and in hypertensive animals overexpressing ANG and their own wildtypes. Ventricular BNP expression was analyzed by RNase protection assay (n=6). Cardiac fibrosis was visualized by Sirius red staining. While ANG overexpression increases cardiac BNP-mRNA expression (1035±210 vs. wildtype: 405±95 in PSL/mm2, P<0.01), its deficiency had no influence. Both AT1- and AT2-knockouts showed significantly decreased BNP-mRNA concentrations (AT1: 21±6 vs. wildtype: 139±28 in PSL/mm2, P<0.001; AT2: 8±2 vs. 19±3 in PSL/mm2, P<0.05). These alterations correlate to reduced cardiac fibrosis in AT2-deficient animals, but not in ANG knockouts. Increased BNP-mRNA levels in hypertensive ANG-overexpressing mice and decreased BNP in hypotensive AT1-deficient animals indicate that this mRNA expression is blood pressure dependent. However, the observed alterations of fibrosis and the unchanged BNP in hypertensive ANG knockouts and impaired BNP-mRNA expression in normotensive AT2-deficient mice demonstrate a direct interaction of the RAS and NPs that is fibrosis but not blood pressure dependent.

584 Circulating adrenomedullin levels and Doppler-derived dP/dt in idopathic cardiomyopathy
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Increased circulating adrenomedullin (AM) concentration has been reported in human congestive heart failure (HF) suggesting that plasma AM, as other circulating peptides, is a marker for cardiac dysfunction. It was suggested that the dysfunctioning myocardium secretes AM contributing to its elevation, as a probable compensatory mechanism. However, no significant relation has been demonstrated so far between left ventricular (LV) systolic function and circulating AM in patients (pts). Aim of the present study was to assess, in pts with idiopathic cardiomyopathy (ICM), the possible relationship between circulating AM concentration and LV contractile state as non-invasively assessed by the rate of pressure rise (RPR) from a mitral regurgitation velocity curve at Echocardiography. This parameter correlates with invasively derived peak LV dP/dt and is an independent prognostic indicator in HF. Forty-four ICM pts (31 males, mean age 63 years, LVEF 32.0±6.0, mean ± SD, angiographically normal coronary arteries in all) underwent a complete Echo-Doppler examination within 1 week of circulating AM measurement. Five pts were in NYHA Class I, 23 in NYHA Class II, 16 in NYHA Class III. RPR was calculated by measuring the mean rate of pressure rise of the mitral regurgitation jet between 1 and 3 m/s on 5 consecutive beats. LVEF was obtained by the modified Simpson’s rule. Plasma AM levels were measured in HF pts and in 20 control subjects by radioimmunoassay after solid phase extraction on Sep-pak C18 columns. The extraction recovery was evaluated by adding 125-I-AM to plasma samples. In 39/44 pts a clearly defined mitral regurgitation Doppler spectrum was obtained. RPR was reduced (r=-0.60 mmHg/s) in 23/39 pts. A negative relation was found between RPR and circulating AM levels (r = 0.48 p = 0.02); on the contrary, no relation was found between LVEF and circulating AM (r = 0.13, p = NS). Thus, in pts with ICM, circulating AM levels are elevated in proportion of depressed RPR and increased BNP-mRNA levels in patients with CHF were unaffected in those in functional class I-II (1.4±0.08 fmol/l) but significantly increased in those in NYHA class III-IV (2.0±0.22 fmol/l, p<0.047). Plasma levels of OP in normal subjects were 238.0±16.0 mg/ml and were significantly increased in those in NYHA classes I-II (366.2±21.9 mg/ml, p<0.0001) and III-IV(485.6±70.5 mg/ml, p<0.0001). A significant correlation between plasma levels of AM and Big-ET-1 (r=0.5, p<0.001) was observed. These results indicate that plasma levels of AM, OP and Big-ET-1 are elevated in CHF, with an increase proportional with the severity of disease, suggesting a role of these substances as markers of endothelial vasomotor response to CHF progression and of myocardial remodeling, respectively.

585 Autoantibodies against the thrombin (PAR-1) and the tryptase (PAR-2) receptor in the sera of patients with Raynaud’s-syndrome
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Raynaud’s-syndrome is a disease of the small arteries, most commonly in the fingers and toes. The symptoms are caused by vasospasm and occur