Natriuretic peptides and the Framingham Risk score for screening of asymptomatic left ventricular systolic dysfunction in high-risk patients in primary care. The DAVID-BERG study

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Asymptomatic left ventricular systolic dysfunction (ALVSD), or stage B heart failure (HF), is associated with increased cardiovascular (CV) and all-cause mortality, and nonfatal CV events [1,2]. ALVSD is distinctly more common among subjects with stage A HF [3].

ALVSD remains commonly underdiagnosed, particularly in primary care, where diagnostic facilities are limited. Routine echocardiography, the diagnostic gold standard for ALVSD, is not the screening strategy of choice due to lack of accessibility and cost. Alternative approaches using risk scores and biomarkers have been proposed. The Framingham HF risk score (FHFRS) score [4] is a gender-specific risk stratification tool to identify patients at high risk of developing HF within 4 years. Natriuretic peptides (NP) have been evaluated as screening tools for further evaluation in several studies [5–7] and showed prognostic value in stage A/B patients [8].

DAVID-Berg was a prospective cohort study carried out at three primary care group practices in the Northern Italy city of Bergamo to analyse the relative merit of the FHFRS and N-terminal pro-brain natriuretic peptide (NT-proBNP) to screen for ALVSD from a primary care perspective. Each primary care physician reviewed the clinical records of all patients aged ≥55 and <80 years. Patients with known or suspected HF requiring diagnostic validation or severe comorbidity with reduced life expectancy were excluded.

We recruited for screening subjects considered at high risk of ALVSD because of history of any of ischemic heart disease, cerebrovascular or peripheral vessel disease; diabetes; hypertension with evidence of target organ damage (retinopathy; atrial fibrillation, glomerular filtration rate <60 ml/min). Patients gave their written informed consent to participate in study which was approved by the Ethics Committee of the Local Health Authority.

Patients attended the primary care offices to perform measurement of height, weight, and blood pressure, standard 12-lead electrocardiogram (ECG), blood sampling for NT-proBNP, and a Color Doppler echocardiogram, according to American Society of Echocardiography guidelines. Left ventricular ejection fraction (LVEF) was calculated with biplane Simpson rule. ALVSD was defined as LVEF <50%. LV hypertrophy on ECG was blindly coded by Minnesota Code. We calculated the FHFRS using the simplified algorithm [4]. NT-proBNP was measured with competitive enzyme immunoassay (Cardiac Reader Roche Diagnostic). We considered as reference abnormal cutoffs of the 95th percentile of the age- and gender-specific distribution of NT-proBNP in normal blood-donors, reported by the manufacturer.

The association between ALVSD and the FHFRS, NT-proBNP, and their combination were assessed by logistic regression analysis, model calibration by Hosmer–Lemeshow goodness-of fit test and predictive performance by the C statistic. The areas under the ROC curve (AUC) with their 95% confidence interval were compared by the method of De Long et al. [9].

Among a total population of 13,625, GPs reviewed the clinical records of 4047 subjects (50.5% women) aged ≥55 and <80 years. Of these, 623 (15.4%) patients identified as being at high CV risk were screened. ALVSD was found in 33 (5.3%) patients (Table 1). Both FHFRS and NT-proBNP levels were significantly higher in patients with mild ALVSD than in subjects with normal LVEF. Median NT-proBNP were significantly more elevated in higher FHFRS tertiles in both genders, but concentrations overlapped widely (Fig. 1).

By logistic regression, mild ALVSD was significantly associated to stand alone FHFRS (AUC 0.63, 95% CI: 0.53–0.73), stand alone NT-proBNP levels (AUC 0.74, 95% CI: 0.70–0.77, p = 0.011) and their combination (AUC 0.76, 95% CI: 0.67–0.84, p = 0.04).

The Hosmer–Lemeshow demonstrated overall good calibration for all models.

Patient with an abnormal NT-proBNP had a six-fold increase in the risk of mild ALVSD (odds ratio of 6.12 (95% CI 2.85–13.1)), the negative predictive value for ALVSD of a FHFRS ≥15 and of an abnormal NT-proBNP were 96% and 97.7%, respectively.

We found that in an elderly cohort of patients at high CV risk in primary care NT-proBNP levels are better predictors of ALVSD than FHFRS. Since NP offer practical advantages over the ECG in primary care, it may be advocated as first test for screening in these patients.

The optimal strategy to identify ALVSD in a general population is still uncertain. So far direct comparison of HF risk scores to NP was only investigated by Gupta et al. [9]. These authors compared the diagnostic utility of the Health ABC HF risk score, the FHFRS and NP plasma levels in identifying prevalent AHA/ACC stage B HF, in a young (mean age 48 years) multiethnic cohort, in whom ALVSD prevalence was 3%. Among white participants, the Health ABC HF risk score and both NP performed poorly (C-statistic 0.62, 0.63, 0.60, respectively) and the FHFRS was superior to both with moderate discrimination (C-statistic 0.71).

A possible explanation for the modest predictive performance of the FHFRS, confirmed by our findings, is that in the Framingham cohort incident HF diagnosis was based on signs and symptoms and did not include an objective assessment of LV function.
ECG as stand-alone test has been previously shown to have a high negative predictive value for severe or moderate ALVSD, only when interpreted by a cardiologist. Since NP offer distinct practical advantages in the primary care setting with respect to the ECG, NP testing could be the best strategy to “rule out” ALVSD in primary care in the young elderly. Among “oldest old” (>80 years) subjects, prevalence of cardiac dysfunction and HF symptoms increases, the opportunities for prevention shrink and NP and ECG may add little predictive value to a clinical model.

We used the age and gender-specific 95th percentile concentrations for NT-proBNP, as provided by the manufacturer and commonly reported in laboratory test results, rather than testing a particular cut-off. While this method may be less intuitive than a single value for all, it seems to make more sense given the high variance of NP levels according to age and sex.

In an elderly primary care population at high CV risk, measurement of NT-proBNP seems superior to the FHFRS in predicting ALVSD. Because of its practical advantages, NT-proBNP might be routinely used in this setting as an accurate tool to identify patients to be referred for further investigation.

The authors declare that there are no conflicts of interest.

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References


Fig. 1. Box plot of NT-proBNP distribution (median, interquartile range and 95th percentile) according to gender and tertiles of the Framingham Heart Failure Risk Score (FHFRS). p Values are by Kruskal–Wallis test with Bonferroni correction.

Table 1
Baseline characteristics of the study cohort.

<table>
<thead>
<tr>
<th></th>
<th>All cases (n = 619)</th>
<th>No ALVSD (n = 586)</th>
<th>Mild ALVSD (n = 33)</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender</td>
<td>347 (56%)</td>
<td>322 (55%)</td>
<td>25 (76%)</td>
<td>0.019</td>
</tr>
<tr>
<td>Smoking</td>
<td>78 (13%)</td>
<td>75 (13%)</td>
<td>3 (9%)</td>
<td>0.787</td>
</tr>
<tr>
<td>History of hypertension (n = 581)</td>
<td>547 (89%)</td>
<td>522 (90%)</td>
<td>25 (76%)</td>
<td>0.018</td>
</tr>
<tr>
<td>Type 2 Diabetes (n = 582)</td>
<td>196 (33%)</td>
<td>186 (34%)</td>
<td>10 (31%)</td>
<td>0.849</td>
</tr>
<tr>
<td>Chronic kidney dysfunction (n = 587)</td>
<td>11 (18.9%)</td>
<td>107 (19.3%)</td>
<td>4 (12.5%)</td>
<td>0.486</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>205 (33%)</td>
<td>184 (31%)</td>
<td>21 (64%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Valvular heart disease</td>
<td>17 (3%)</td>
<td>13 (2%)</td>
<td>4 (12%)</td>
<td>0.010</td>
</tr>
<tr>
<td>Myocardial infarction (n = 544)</td>
<td>111 (20%)</td>
<td>93 (18%)</td>
<td>18 (58%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cerebrovascular disease (any) (n = 587)</td>
<td>129 (21%)</td>
<td>123 (21%)</td>
<td>6 (18%)</td>
<td>0.828</td>
</tr>
<tr>
<td>Peripheral Vascular Disease (n = 529)</td>
<td>49 (9%)</td>
<td>45 (9%)</td>
<td>4 (14%)</td>
<td>0.316</td>
</tr>
<tr>
<td>Left ventricular hypertrophy on ECG</td>
<td>31 (5%)</td>
<td>27 (5%)</td>
<td>4 (12%)</td>
<td>0.078</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>23 (4%)</td>
<td>19 (3%)</td>
<td>4 (12%)</td>
<td>0.026</td>
</tr>
<tr>
<td>Age, years</td>
<td>70 [64–75]</td>
<td>70 [64–75]</td>
<td>67 [61–73]</td>
<td>0.154</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>151 [134–166]</td>
<td>152 [134–166]</td>
<td>142 [124–166]</td>
<td>0.113</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>84 [76–91]</td>
<td>84 [77–91]</td>
<td>82 [79–92]</td>
<td>0.257</td>
</tr>
<tr>
<td>Glomerular filtration rate, ml/min</td>
<td>77 [64–92]</td>
<td>77 [64–92]</td>
<td>77 [64–91]</td>
<td>0.773</td>
</tr>
<tr>
<td>Total cholesterol, mg/dl</td>
<td>202 [174–228]</td>
<td>202 [175–228]</td>
<td>201 [169–214]</td>
<td>0.294</td>
</tr>
<tr>
<td>LDL cholesterol, mg/dl</td>
<td>120 [95–145]</td>
<td>120 [96–145]</td>
<td>113 [85–133]</td>
<td>0.172</td>
</tr>
<tr>
<td>NT-proBNP, pg/ml</td>
<td>180 [88–355]</td>
<td>170 [87–328]</td>
<td>569 [305–1314]</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Data are expressed as n (%) or median [quartile 1-quartile 3]. * Student’s t-test for continuous variables, chi-square test or Fisher’s exact test for categorical variables and Mann–Whitney test for skewed variables.

ALVSD: Asymptomatic left ventricular systolic dysfunction; LVH: left ventricular hypertrophy; NT-proBNP: N-terminal pro-brain natriuretic peptide.
The relevance of the brain in the diseased heart: Authors' response

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A R T I C L E   I N F O

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To the Editor:

In their comment to our recent paper entitled “Stressed Brain, Diseases Heart: A review on the pathophysiologic mechanisms of neurocardiology,” [1], Domínguez-Rodríguez and Abreu-Gonzalez [2] emphasize the relevance of circadian rhythm in cardiovascular diseases and propose the suprachiasmatic nucleus and melatonin as key mediators in its pathophysiology. We found this a very interesting observation. The incidence of acute myocardial infarction [3] and its extension [4] displays a circadian pattern usually peaking in early morning. Whether this is a consequence of the oscillating levels of circulating hormones or from a direct action of central mechanisms on the heart and vessels themselves is still a matter of dispute.

In addition to melatonin, also cortisol has been implicated in the circadian variation of cardiovascular diseases. Cortisol is produced by the adrenal glands following a circadian pattern with the zenith 1 h before awakening. Interestingly, there is evidence that more relevant than the levels of cortisol at peaks, is the sustained elevation of cortisol (measured in the hair and reflecting the accumulated circulating levels in the previous three months), that has been associated with a significant risk of cardiovascular events [5]. In fact, in a cohort of 4047 patients from the Whitehall II study, Kumari and colleagues showed that flatter slopes in cortisol decline across the day, but not peak morning cortisol levels, were associated with increased risk of all-cause and cardiovascular mortality in a follow-up period of 6 years [6]. In addition, in a recent pilot study, we observed that higher blood cortisol levels at admission to a cardiac care unit were related with a worse outcome during the in-hospital stay regarding left ventricular function and Killip class (Pereira et al., Poster Presentation, Heart Failure 2013). These observations suggest that higher levels of cortisol are associated with worst cardiovascular outcome at the long-term, but fail to demonstrate a direct association between peak levels of cortisol and acute events; this brings to scene the possible role of other mediators in the circadian variation of cardiovascular diseases, which may well include melatonin.

Finally it is interesting to note the relation between stress and the disruption of global circadianism. Chronic stress disturbs the normal circadian rhythm, altering the normal variation of both cortisol [7] and melatonin [8], and directly impairing pineal sympathetic inputs [8], which may well contribute to the increased risk of cardiovascular diseases in patients under chronic psychological stress. The effects of chronic stress in the suprachiasmatic nucleus need to be investigated in greater detail. Highlighting these poorly studied aspects and relating what may seem disperse evidence, will certainly pave the way of neurocardiology and further studies, both at basic and clinical levels, and will be critical to clarify the role of circadian clock regulators in the incidence and natural history of cardiovascular events.

The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology.

References