SCIENTIFIC LETTER

Plasma concentrations of N-terminal atrial natriuretic peptide are raised in asymptomatic relatives of dilated cardiomyopathy patients with left ventricular enlargement

J Grzybowski, Z T Bilinska, J Janas, E Michalak, W Ruzyllo

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The prognosis among patients with dilated cardiomyopathy (DCM) who present to a referral centre for heart failure management is poor, as the disease is usually well advanced by the time it is diagnosed.[1] There is established evidence of the favourable effects of angiotensin converting enzyme (ACE) inhibitors in patients with asymptomatic left ventricular (LV) dysfunction; therefore, identification of patients at an earlier stage of the disease would hopefully have a positive impact on prognosis.

Prospective family screening has identified a subset of asymptomatic relatives with LV enlargement (LVE) that may represent early disease.[2] A recent study found that overt DCM developed in 27% of patients with LVE during a three year follow up.[3] Nevertheless we do not know which relatives are at highest risk of developing overt DCM.

N-terminal atrial natriuretic peptide (N-ANP) is known to be a sensitive marker of LV dysfunction in the general population.[4] These findings strongly support a possible role for N-ANP as an important additional marker for the diagnosis of patients with symptomless LV dysfunction in the setting of possible early disease in familial DCM. We hypothesised that asymptomatic LVE in the relatives of DCM patients would be accompanied by signs of early neurohumoral activation—namely, raised N-ANP concentrations.

Our study therefore aimed to determine plasma N-ANP concentrations in asymptomatic relatives with LVE, and to compare them with relatives without LVE and with normal controls.

METHODS

The study protocol included: clinical examination, 12 lead ECG, two dimensional echocardiogram, and determination of plasma N-ANP concentration. The diagnosis of DCM was made according to World Health Organization criteria. LVE was defined according to the method of Henry (percentage LV end diastolic diameter > 112%). This cut-off value is used in our studies in relatives of DCM patients, as well as by others.[2 3 5] Blood samples were drawn from an antecubital vein in the supine position after 30 minutes rest. Serum was stored and frozen at –20°C from all patients and controls before analysis. N-ANP concentrations were evaluated by radioimmunoassay using a commercial kit (Peninsula Laboratories, San Carlos, California, USA), performed according to the manufacturer's instructions.

Baseline characteristics are presented as mean (SD). Student *t* test was used to compare numerical data. The relation between analysed variables was estimated using Pearson correlation coefficients. The receiver operator characteristic (ROC) curve was evaluated using the logistic function in order to select the best cut-off value for plasma N-ANP concentration above which LV dilation is likely. All statistical analyses were performed using the SAS system. A probability value of $p < 0.05$ was regarded as significant.

This study was approved by the hospital's ethics committee. Written informed consent was obtained from all participants.

RESULTS

Sixty six asymptomatic relatives of DCM patients were assessed (48 male, 18 female, mean age 27.4 (12.8) years). Their mean fractional shortening was 30.0 (4.6)%, and their mean percentage LVE was 112.5 (9.6)%. Thirty two relatives were found to have LVE (mean 119.9 (7.6)%), while the remaining 34 relatives had an LV end diastolic diameter within the normal range (mean 105.6 (5.0)%). N-ANP concentrations were significantly raised in patients with LVE compared to controls (351 (201) pg/ml *v* 230 (49) pg/ml, $p < 0.05$), and to relatives without LVE (351 (201) pg/ml *v* 228 (80) pg/ml, $p < 0.05$).

Pearson correlation coefficients between N-ANP and percentage LVE calculated for LVE > 112% gave a value of 0.76 ($p < 0.0001$), while for LVE < 112% no significant correlation was found. Analysis of the ROC curve showed the area under the curve $c = 0.69$. We selected a cut-off point of N-ANP = 214 pg/ml, for which the sensitivity was 72% and specificity 44%.

DISCUSSION

In this study significantly higher concentrations of N-ANP were found in relatives with LVE as compared with both the control group and relatives with normal heart function. Identification of patients with asymptomatic LV dysfunction who would possibly benefit from early pharmacologic interventions is crucial in order to decrease the substantial mortality associated with overt DCM. Echocardiographic evaluation is a practical means to assess minor changes in left ventricular structure and function and may represent early disease changes. However, when established cut-offs for the echocardiographic measurements are used, there may be an overlap of measurements between normal and abnormal values in early disease, suggesting the need for an additional marker. We believe that N-ANP, one of the parameters of early neurohormonal activation, may play an important role in this setting.

Because other studies have not used N-ANP assessment in relatives of DCM patients, comparison of our findings with other studies is difficult. In the general population setting, N-ANP was found to be useful as a screening test for the detection of asymptomatic LV systolic dysfunction.[4] Recently it was shown by McKenna's group that cardiopulmonary exercise variables are abnormal in asymptomatic relatives of patients with DCM who have LVE.[5] Our findings of increased plasma concentrations of N-ANP in relatives with LVE provide further evidence that LVE may represent subclinical disease

Abbreviations: ACE, angiotensin converting enzyme, DCM, dilated cardiomyopathy; LV, left ventricular; LVE, left ventricular enlargement; N-ANP, N-terminal atrial natriuretic peptide; ROC, receiver operator characteristic

and may help identify patients at risk of developing overt heart failure.

In summary, our study found that plasma N-ANP concentrations were significantly increased in DCM relatives with symptomless LV dysfunction as compared with both a control group and relatives with normal heart function. Signs of neurohumoral activation may be used as an additional marker, confirming the need for early treatment with ACE inhibitors to prevent progress to overt DCM.

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Authors' affiliations
J Grzybowski, Z T Bilinska, W Ruzyllo, Department of General Cardiology, Institute of Cardiology, Warsaw, Poland
J Janas, Department of Clinical Biochemistry, Institute of Cardiology, Warsaw
E Michalak, Department of Noninvasive Diagnostics, Institute of Cardiology, Warsaw

Correspondence to: Dr J Grzybowski, Department of General Cardiology, Institute of Cardiology, Alpejska 42, 04628, Warsaw, Poland

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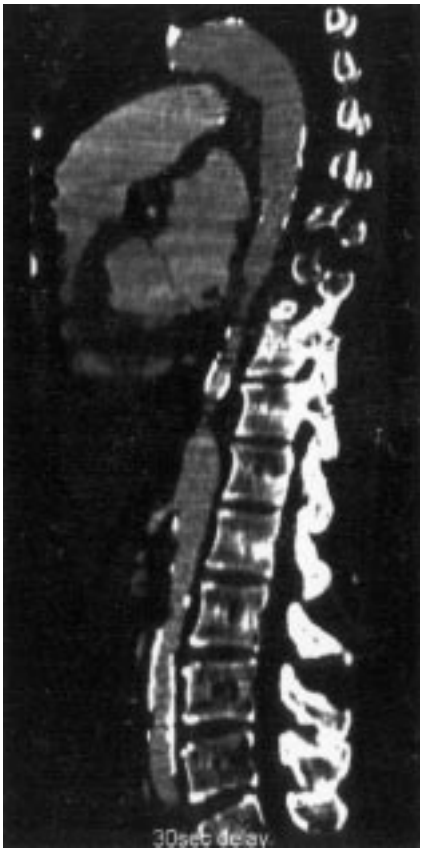
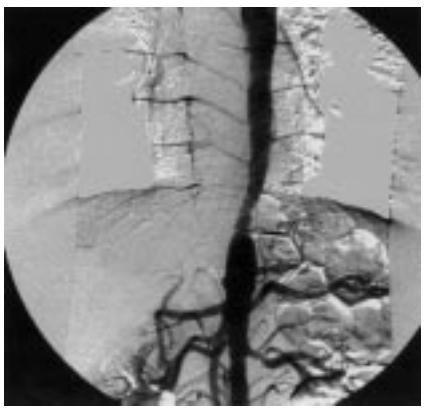
IMAGES IN CARDIOLOGY

Narrowing of the thoraco-abdominal aorta



A 57 year old woman, who had suffered from hypertension for 37 years, consulted our hospital because of palpitations, headache, dyspnoea, and paraesthesia in both legs. Physical examination revealed that her blood pressure was 186/86 mm Hg in both arms and 128/94 mm Hg in both legs. Auscultation revealed an aortic systolic murmur with radiation to the epigastrium. Serological examination revealed no abnormality.

Computed tomographic scanning revealed diffuse narrowing with severe calcification at the diaphragmatic level of the descending aorta (left). Digital subtraction angiography confirmed the narrowing of the thoraco-abdominal aorta (below). A gradient of 87 mm Hg was measured across the narrowed segment of the abdominal aorta. There was no stenosis in coronary, carotid, renal, axillary, iliac, and pulmonary arteries. Because the stenotic lesion was diffuse with severe calcification, surgery was recommended instead of balloon dilatation. A left axillary–left iliac artery bypass was performed. After the operation, there was no difference in blood pressure between the upper and lower limbs. The patient recovered uneventfully and has no residual hypertension.



M Shimoyama
T Doi
K Uchida
masaki-tky@umin.u-tokyo.ac.jp