Relation between left ventricular contractile reserve during low dose dobutamine echocardiography and plasma concentrations of natriuretic peptides

A F L Schinkel, E C Vourvouri, J J Bax, F Boomsma, M Bountioukos, V Rizzello, E Biagini, E Agricola, A Elhendy, J R T C Roelandt, D Poldermans

Background: In ischaemic cardiomyopathy, raised plasma concentrations of natriuretic peptides are associated with a poor long term prognosis, while the presence of contractile reserve is a favourable sign.

Objective: To assess the relation between plasma natriuretic peptides and contractile reserve.

Design: Prospective observational study.

Setting: Tertiary referral centre.

Patients: 66 consecutive patients undergoing low dose dobutamine stress echocardiography to evaluate contractile reserve in regions with contractile dysfunction at rest, divided into two groups: group 1, 31 patients with ischaemic cardiomyopathy (left ventricular ejection fraction < 40%) and heart failure symptoms; group 2, 35 patients with normal left ventricular function.

Main outcomes measures: Plasma atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP), measured using immunoradiometric assays. Contractile reserve was defined as an improvement in segmental wall motion score during infusion of low dose dobutamine.

Results: Plasma ANP and BNP concentrations were higher in group 1 than in group 2 (mean (SD): ANP, 17.8 (32.8) v 7.2 (9.7), p < 0.005; BNP, 24.4 (69.0) v 5.0 (14.3) pmol/l, respectively; p < 0.001). In group 1, the presence of contractile reserve was inversely related to ANP and BNP levels; however, patients with contractile reserve had lower ANP and BNP concentrations than patients without contractile reserve (ANP, 14.2 (9.1) v 24.2 (44.2), p < 0.05; BNP, 20.2 (25.5) v 37.5 (93.8) pmol/l, respectively; p < 0.05).

Conclusions: Plasma natriuretic peptide concentrations are raised in patients with left ventricular dysfunction, but in the presence of preserved myocardial contractile reserve, relatively low levels of ANP and BNP are present.

Cardiac peptide measurements
Before stress echocardiography, blood samples were drawn from a peripheral vein, after the patient had rested for at least 30 minutes in a supine position. The blood samples were measured using resting cross sectional echocardiography.
collected in prechilled tubes containing edetic acid (EDTA, 1.9 mg/ml) and the protease inhibitor aprotinin (Trasylol, 100 kIU/ml) to prevent breakdown of the cardiac peptides. Samples were stored on ice and promptly centrifuged at 3000 rpm (4°C) for 10 minutes. The plasma was separated and stored at −80°C. Plasma concentrations of ANP and BNP were determined using standard commercially available immunoassay kits (Shionoria ANP and BNP kits, Shionogi, Osaka, Japan).

**Echocardiography**

We employed a commercially available imaging system (Hewlett Packard Sonos 5500, Andover, Massachusetts, USA) and a 1.8 MHz transducer using second harmonic imaging to optimise endocardial border visualisation. Cross sectional imaging was done with the patient in the left lateral position, and standard views (in cine-loop format) were recorded on optical disk. Resting images were obtained first, followed by low dose dobutamine stress echocardiography. Dobutamine was given intravenously at a dose of 5 μg/kg body weight per minute for five minutes, followed by a 10 μg/kg/min dose for five minutes.

**Assessment of the left ventricular ejection fraction**

The left ventricular ejection fraction (LVEF) was determined off-line by the cross sectional biplane method using the modified Simpson’s rule. The endocardial borders of the two and four chamber apical views were digitally traced at end diastole and end systole. Subsequently, left ventricular end diastolic and end systolic volumes were derived and the LVEF was calculated. An LVEF of ≤40% was considered indicative of severe left ventricular dysfunction.

**Assessment of contractile reserve**

Two experienced observers, unaware of the clinical data, scored the digitised echocardiograms off-line. In case of disagreement, a majority decision was achieved by a third observer.

The left ventricle was divided into 16 segments according to the American Society of Echocardiography. Regional wall motion and systolic wall thickening were scored using a five point grading scale: 1, normal; 2, mildly hypokinetic; 3, severely hypokinetic; 4, akinetic; 5, dyskinetic. Segments with severe hypokinesia, akinesia, or dyskinesia were considered abnormal. The presence of contractile reserve was defined as an improvement in segmental wall motion score by ≥1 grade following infusion of low dose dobutamine (5 μg/kg/min or 10 μg/kg/min) in two or more severely dysynergic segments.

**Statistical analysis**

Continuous data are expressed as mean (SD). Natriuretic peptide concentrations are presented as medians (SD). Percentages are rounded. Continuous variables are compared using the Student’s t test for unpaired samples. Comparisons between the natriuretic peptide concentrations were done on log transformed concentrations. A probability value of p < 0.05 was considered significant.

**RESULTS**

**Patient characteristics**

The clinical characteristics of the total study population of 66 patients are presented in table 1. In all, 31 patients had ischaemic cardiomyopathy, with an LVEF of ≤40% and heart failure symptoms. These comprised group 1. Their New York Heart Association (NYHA) functional class was on average 2.7 (0.6). Group 2 comprised 35 patients with normal left ventricular function and no heart failure symptoms.

<table>
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<tr>
<th>Table 1 Baseline characteristics</th>
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<tr>
<td>Count</td>
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<td>Coronary angioplasty</td>
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**Table 2 Haemodynamic data during dobutamine infusion**

<table>
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<tr>
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<th>Baseline</th>
<th>Dobutamine infusion</th>
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<tbody>
<tr>
<td></td>
<td>5 μg/kg/min</td>
<td>10 μg/kg/min</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>74 (15)</td>
<td>81 (22)*</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>131 (22)</td>
<td>132 (25)</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>76 (12)</td>
<td>75 (13)</td>
</tr>
<tr>
<td>Rate-pressure product</td>
<td>9595 (2446)</td>
<td>10 554 (3039)</td>
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**DISCUSSION**

Previous studies have shown that plasma natriuretic peptide concentrations are raised in patients with congestive heart failure; moreover, raised levels of these peptides are
Natriuretic peptides and contractile reserve

associated with a poor prognosis. In the current study, we found that patients with severe left ventricular dysfunction had markedly raised plasma concentrations of natriuretic peptides, although individual data varied substantially. In group 1 (LVEF < 40%), comparison of patients with and without contractile reserve showed that those with no reserve had significantly higher plasma levels of natriuretic peptides and may be at higher risk of future cardiac events. The natriuretic peptides play a role protecting the heart from volume overload. The cardiac hormones ANP and BNP are produced in the atria and ventricles, respectively, in response to an increase in wall stretch or pressure. Raised plasma ANP and BNP concentrations have a natriuretic and diuretic effect. In addition, a high plasma BNP causes a fluid shift from the capillary bed to the interstitium, thereby decreasing preload and blood pressure. Hence, ANP and BNP are functional counterparts of the renin-angiotensin-aldosterone system. Accordingly, the plasma levels of these peptides have been used to diagnose patients with heart failure. In the present study, the plasma ANP and BNP concentrations were significantly raised in the subset of patients with a severely depressed LVEF.

In patients with ischaemic cardiomyopathy, the presence of contractile reserve is related to the extent of viable tissue. Histopathological analysis of biopsies taken (during surgical revascularisation) from segments with and without contractile reserve showed that a higher percentage of fibrosis was present in the segments without contractile reserve. In studies assessing prognosis, the presence of contractile reserve has been shown to have a positive influence on long term outcome.

It is of interest that in the current study, patients with contractile reserve had significantly lower plasma concentrations of natriuretic peptides than patients without contractile reserve. Accordingly, both prognostic indices appear to point in the same direction. From the current study, the precise interrelations between these two variables cannot be derived, and further studies are needed to provide insight in the pathophysiology underlying our observations. However, the combined assessment of (high plasma levels of) natriuretic peptides and (absence of) contractile reserve may help to identify patients at relatively high risk for future events.

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REFERENCES
IMAGES IN CARDIOLOGY

Dynamic respiratory changes in hypertrophic cardiomyopathy

A 50 year old woman presented with severe exertional dyspnoea. On physical examination, she had a 3/6 systolic ejection murmur that virtually disappeared with inspiration. Transthoracic echocardiography demonstrated findings typical of hypertrophic cardiomyopathy with a pronounced increase in ventricular septal thickness and an outflow gradient of 100 mm Hg. The patient underwent cardiac catheterisation (panel below: Ao, aortic pressure, LA, left atrial pressure, LV, left ventricular pressure, PA, pulmonary artery pressure). In the resting state, there was a significant outflow tract gradient between the left ventricular and aortic pressure. However, with each inspiration, there was a large decrease in the left ventricular outflow tract gradient. The “spike and dome” morphology of the aortic pressure curve virtually disappeared during peak inspiration, indicating a notable resolution of the outflow obstruction.

The pronounced decrease in the intensity of the systolic murmur with inspiration is unique to hypertrophic cardiomyopathy, secondary to the dynamic nature of the obstruction. The left ventricular outflow tract obstruction in patients with hypertrophic cardiomyopathy is highly dependent upon preload, afterload, and contractility. With inspiration, the intrathoracic and intrapericardial pressures decrease to a greater extent than the intracardiac pressures. As a result, the left ventricular transmural pressure increases, increasing the afterload on the left ventricle, thus decreasing the obstruction and the left ventricular outflow tract gradient.

The dynamic changes of the murmur intensity with respiration may help in the differential diagnosis of a systolic murmur. In patients with hypertrophic cardiomyopathy, there may be a notable decrease in the intensity of the murmur during peak inspiration. Since the outflow tract obstruction is also decreased, there may even be an increase in arterial pressure, which has been called “reverse pulsus paradoxus”. In contrast, patients with right sided murmurs will have an increase in the intensity of the murmur with inspiration. In patients with murmurs of fixed outflow tract obstruction or mitral regurgitation, there may be a slight decrease in the intensity of the murmur with inspiration from a slight decrease in preload but the aortic pressure will also decrease.

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**Notes**