Reduced contractile reserve of the systemic right ventricle under Dobutamine stress is associated with increased brain natriuretic peptide levels in patients with complete transposition after atrial repair

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Aims To compare B-type natriuretic peptide (BNP) levels with response of systemic right ventricular function to Dobutamine stress.

Methods and results Sixteen patients aged 25.6 ± 3.7 years (eight each after Senning or Mustard repair of complete transposition) were studied. Transoesophageal imaging was performed in the catheterization laboratory under general anaesthesia before and at the end of a 10 min infusion of 5 μg/kg/min of Dobutamine. The BNP levels were measured at rest. Myocardial Doppler data were acquired before and at peak stress in a four-chamber view. The BNP (pg/mL) values of 67.3 ± 47.5 (14–189) were elevated. There was no correlation between BNP and IVA, strain, or systolic and diastolic velocities at rest. Dobutamine stress led to a significant increase in IVA, s-velocity, and strain but no significant change in e-velocity. A correlation was found between increase in IVA under Dobutamine and BNP levels (r = 0.57, P < 0.02).

Conclusion Elevated BNP levels correlate with response of systolic right ventricular function assessed by IVA to Dobutamine stress.

Introduction

Impairment of systemic (right) ventricular function is an important problem in the long term for patients with complete transposition of the great arteries following Mustard or Senning type of atrial repair.1–3 Overall more than 20% of patients who have had a Senning or Mustard operation develop congestive heart failure with a high mortality rate in symptomatic patients. However, it remains difficult to predict, which individual patient will develop congestive heart failure over time. Evaluation of ventricular function under Dobutamine stress to assess contractile reserve may be helpful to prospectively identify patients with risk of systemic ventricular failure.4

Recently, brain natriuretic peptide (BNP) has been found to be a valuable diagnostic tool in predicting both left and right (systemic) ventricular dysfunction in adults with congenitally malformed hearts.5,6

The question whether there is any relation between an abnormally high BNP and contractile reserve has not yet been addressed.

The purpose of this study was to compare systemic ventricular function at rest and during Dobutamine infusion with BNP levels in patients with a systemic right ventricle who previously had undergone atrial repair of complete transposition by either the Mustard or the Senning technique.

Methods

Patient selection

We studied 16 patients with complete transposition of the great arteries and intact ventricular septum (n = 13) or ventricular septal defect (n = 3), who had undergone atrial redirection by either Mustard (n = 8) or Senning (n = 8) technique (Table 1). The study protocol had been approved by the local institutional review board. These patients come from a cohort of 419 patients, who had undergone an atrial redirection procedure at our centre. The patients were selected on the basis that they consented to the study protocol with Dobutamine stress during cardiac catheterization, which was performed for clinical reasons [suspicion of systemic pathway obstruction (n = 8),...
reduced exercise tolerance \( (n = 6) \), or assessment of anatomic and functional results before undergoing a pregnancy \( (n = 2) \).

### Tissue Doppler echocardiography

Transoesophageal imaging of the heart was performed using the GE Vingmed System V (GE Vingmed, Horten, Norway) with a frame rate between 128 and 231 Hz. The right ventricle was separately imaged from an oesophageal position in a four-chamber like view and colour coded myocardial velocities were recorded at the base immediately below the insertion of the atrioventricular valve leaflets. Recordings were made simultaneous with ECG. A cineloop of at least three consecutive heart beats was stored digitally for offline analysis. Echopac software (GE Vingmed) was used to analyse the stored myocardial Doppler data. The peak myocardial velocities during isovolumic contraction, systole (s-wave), early diastole (e-wave), and late diastole (a-wave) as well as myocardial acceleration during isovolumic contraction (IVA) were measured. Measurements of myocardial acceleration and velocities were performed on three consecutive heart beats, and the average of the three measurements was calculated. The myocardial Doppler measurements were compared with those of 55 age matched normals, which had been used as a control group in a previous study on patients with complete transposition.4

Myocardial Doppler data were acquired at baseline and at the end of a 10 min infusion of 5 \( \mu g/kg/min \) of Dobutamine. The persons analysing the myocardial Doppler data (J.W. and M.V.) were blinded to the BNP data.

### Study preparation and protocol for invasive study

Cardiac catheterization was performed under general anaesthesia. After constitution of acceptable haemodynamics or following a successful interventional procedure, we evaluated contractile reserve during Dobutamine infusion. Dobutamine was given intravenously at a rate of 5 mcg/min for 10 min; the infusion was stopped earlier than 10 min, if the heart rate exceeded 120 b.p.m.

### Brain natriuretic peptide measurements

Venous blood was taken in hospital on the day before cardiac catheterization and immediately sent for centrifugation. The plasma BNP was measured using fluorescence immunoassay (Triage BNP test, Biosite Inc., CA, USA). In our laboratory, a value of \( > 100 \text{ pg/mL} \) is considered to be abnormally high.

### Statistical analysis

Data are listed a mean \( \pm \) standard deviation. Changes in haemodynamic parameters between rest and Dobutamine stress in the 16 patients were compared using a paired Student’s \( t \)-test. A \( P \)-value of 0.05 was considered to represent a significant difference between groups.

Linear regression analysis was used to assess the relationship between BNP, NYHA functional class, degree of tricuspid regurgitation, and changes in myocardial Doppler measurements of right (systemic) ventricular function. A \( r \)-value of \( > 0.5 \) and a \( P \)-value of \( < 0.05 \) were considered to represent a significant correlation. Statview software was used for the computations.

### Results

At rest, all patients had a reduced IVA, s-velocities, e-velocities, and IVA when compared with normal subjects with a systemic ventricle of left ventricular morphology. During Dobutamine stress, systolic ventricular function improved in the patient group (Table 2), whereas early diastolic velocities did not change. There was no correlation between right (systemic) ventricular function at rest as assessed by IVA, systolic velocity or strain, and BNP levels. There was a negative correlation \( (r = 0.57, P < 0.02) \) between BNP levels and the increase in IVA with Dobutamine stress (Figure 1), i.e. patients with the largest improvement in IVA under Dobutamine had the lowest BNP levels. There was no correlation between changes in systolic velocities or peak systolic strain with Dobutamine stress and BNP levels.

BNP levels correlated with the severity of tricuspid regurgitation \( (r = 0.55, P < 0.03) \). There was no correlation between IVA at rest or during stress and the severity of tricuspid regurgitation.

There was no correlation between BNP levels and NYHA functional class. IVA at rest or during Dobutamine stress did not correlate with NYHA class and there was no correlation between the change in IVA with stress and NYHA class.

### Table 1: Demographic and clinical data in patients with complete transposition after Mustard/Senning operation

<table>
<thead>
<tr>
<th>Age (years) at examination</th>
<th>Type of surgery</th>
<th>NYHA class</th>
<th>Grade TR</th>
<th>IVA m/s² rest</th>
<th>IVA m/s² Dobutamine</th>
<th>BNP (pg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>18.7</td>
<td>Senning</td>
<td>1</td>
<td>3</td>
<td>0.6</td>
<td>1.0</td>
<td>107</td>
</tr>
<tr>
<td>19.6</td>
<td>Senning</td>
<td>1</td>
<td>1</td>
<td>0.8</td>
<td>2.3</td>
<td>30</td>
</tr>
<tr>
<td>20.8</td>
<td>Senning</td>
<td>1</td>
<td>2</td>
<td>0.6</td>
<td>2.0</td>
<td>77</td>
</tr>
<tr>
<td>22.0</td>
<td>Senning</td>
<td>2</td>
<td>3</td>
<td>0.8</td>
<td>1.3</td>
<td>104</td>
</tr>
<tr>
<td>22.2</td>
<td>Mustard</td>
<td>2</td>
<td>1</td>
<td>0.6</td>
<td>1.2</td>
<td>99</td>
</tr>
<tr>
<td>23.1</td>
<td>Senning</td>
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<td>1</td>
<td>1.2</td>
<td>1.9</td>
<td>14</td>
</tr>
<tr>
<td>23.8</td>
<td>Senning</td>
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<td>1</td>
<td>0.7</td>
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<td>25</td>
</tr>
<tr>
<td>24.0</td>
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<td>53</td>
</tr>
<tr>
<td>24.3</td>
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<td>2</td>
<td>0.7</td>
<td>1.4</td>
<td>18</td>
</tr>
<tr>
<td>28.0</td>
<td>Senning</td>
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<td>2</td>
<td>0.9</td>
<td>1.2</td>
<td>31</td>
</tr>
<tr>
<td>28.4</td>
<td>Mustard</td>
<td>3</td>
<td>3</td>
<td>0.3</td>
<td>0.4</td>
<td>121</td>
</tr>
<tr>
<td>29.2</td>
<td>Mustard</td>
<td>1</td>
<td>3</td>
<td>0.4</td>
<td>1.1</td>
<td>32</td>
</tr>
<tr>
<td>29.7</td>
<td>Mustard</td>
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<td>0.8</td>
<td>1.0</td>
<td>60</td>
</tr>
<tr>
<td>30.7</td>
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<td>1</td>
<td>0.7</td>
<td>1.5</td>
<td>39</td>
</tr>
<tr>
<td>31.6</td>
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<td>0.6</td>
<td>0.6</td>
<td>79</td>
</tr>
<tr>
<td>35.1</td>
<td>Mustard</td>
<td>3</td>
<td>3</td>
<td>1.1</td>
<td>0.8</td>
<td>189</td>
</tr>
</tbody>
</table>

NYHA, New York Heart Association; TR, tricuspid regurgitation; IVA, Myocardial acceleration during isovolumic contraction; BNP, brain natriuretic peptide.
Reduced contractile reserve of the systemic right ventricle under Dobutamine stress

Table 2  Effect of Dobutamine stress on myocardial Doppler derived parameters of right ventricular function in patients with TGA after atrial redirection

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Rest</th>
<th>Dobutamine stress</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IVA (m/s²)</td>
<td>0.7 ± 0.25 (0.4–1.1)</td>
<td>1.5 ± 0.9 (0.6–1.2)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>s-Velocity (cm/s)</td>
<td>1.8 ± 0.9</td>
<td>3.3 ± 1.6</td>
<td>&lt; 0.002</td>
</tr>
<tr>
<td>e-Velocity (cm/s)</td>
<td>4.3 ± 2.2</td>
<td>3.3 ± 1.6</td>
<td>NS</td>
</tr>
<tr>
<td>Strain</td>
<td>21.5 ± 4.3</td>
<td>27.5 ± 6.7</td>
<td>&lt; 0.008</td>
</tr>
</tbody>
</table>

Figure 1  Correlation between change in IVA (x-axis) in percent and serum concentration of BNP (brain natriuretic peptide) in pg/mL (y-axis) in 16 patients with complete transposition following atrial repair (r = −0.57, P > 0.02).

Discussion

There was no correlation between elevated BNP levels and reduced myocardial Doppler parameters of right ventricular function at rest in our patients with complete transposition who had undergone atrial redirection procedures by Mustard or Senning operation. However, there was a significant correlation between response to Dobutamine stress and BNP levels when function was measured by IVA.

The only other functional parameter that correlated with BNP levels was the severity of tricuspid regurgitation. This increase of BNP levels is probably merely a reflection of the increased volume load in the atria.

We had previously validated IVA in patients with a Mustard or Senning operation by comparison to the invasive ‘golden’ standard the measurement of end-systolic elastance (Ees) using conductance catheterization and found a good correlation between increase in IVA and Ees in the systemic right ventricle.

IVA is a myocardial Doppler based tool to evaluate right or left ventricular function. In experimental and clinical studies, it has been shown to be relatively independent to changes in loading conditions. It is thus well suited for the evaluation of right ventrices with abnormal loading conditions such as found in patients after a Mustard or Senning atrial repair of complete transposition of the great arteries. These frequently have associated lesions such as tricuspid incompetence or obstruction of venous pathways which alter loading conditions.

Brain natriuretic peptide has been measured in many adults with congenitally malformed hearts and a systemic right ventricle. Although in most studies in adults with congenitally malformed hearts and systemic right ventricles, BNP values were found to be abnormally high, there have been no consistent data showing a clear correlation between BNP and resting ventricular function or exercise capacity. Likewise, in our study, we found no correlation between NYHA functional class and BNP. Thus the diagnostic and prognostic values of BNP in adults with a systemic morphologically right ventricle have been limited.

However, a significant number of patients with a systemic right ventricle and Mustard or Senning operation experience a late deterioration of ventricular function with a cardiac mortality of 13% during the second and third decade of life. As many of these patients remain asymptomatic early in life and may continue to do well, it is important to prospectively identify those who may be at risk for developing right ventricular failure. Exercise testing or pharmacological stress may reveal an abnormal contractile reserve and help to early identify patients at risks for congestive heart failure. In our study, those with an abnormal response to pharmacological exercise had elevated BNP levels. Further studies need to be performed to establish whether abnormally high BNP levels are related to an impaired response to exercise.

From our data, we conclude that although abnormal BNP levels may not be related to abnormal systemic right ventricular function at rest, they may be a marker of reduced contractile reserve.

Conflict of interest: none declared.

References


8. Vogel M, Cheung MM, Li J, Kristiansen SB, Schmidt MR, White PA et al. Noninvasive assessment of left ventricular force–frequency relationships...


