The right ventricle under acute and chronic overload: early detection of right ventricular dysfunction
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PULMONARY VALVE REGURGITATION AGGRAVATES IMPAIRED RIGHT VENTRICULAR FUNCTION IN PATIENTS WITH CHRONIC RIGHT VENTRICULAR PRESSURE OVERLOAD

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{Submitted for publication}
**Objective:** To assess differences in right ventricular (RV) function between patients with isolated chronic pressure overload and patients with a combination of pressure overload and volume overload. Magnetic resonance imaging (MRI) and brain natriuretic peptide (BNP) were used as quantitative parameters.

**Methods:** Twenty-two patients with chronic RV overload (RV systolic pressure >35 mmHg, mean age 27±6 years, NYHA class I and II), and 10 age and sex-matched healthy volunteers were studied. The patients were divided into two groups: patients with isolated pressure overload (group 1, n=13) and patients with a combination of pressure combined with volume overload (group 2, n=9). Mild pulmonary valvular regurgitation (10-30ml/beat) was the criterion for volume overload. MRI was applied both at rest and during dobutamine stress to determine RV volumes and ejection fraction (RVEF). BNP were determined in all subjects.

**Results:** At baseline, RVEF was significantly lower in group 2 compared to group 1 (53±9% vs 72±9%, p<0.01), and RV end-diastolic volume was significantly larger in group 2 compared to group 1 (109±17 vs 109±31 ml/m², p <0.05). During dobutamine infusion, RV stroke volume significantly increased in controls from 43±9 to 52±12 ml/m², p<0.01). In both patient groups RV stroke volume decreased during dobutamine (group 1: from 44±8 to 38±10 ml/m², p<0.001; group 2: from 57±16 to 47±16 ml/m², p<0.05), accompanied by a decrease in RV end-diastolic volume (group 1: from 63±17 to 54±18 ml/m², p<0.001; group 2 from 109±31 to 93±23 ml/m², p<0.05). Group 2 had significantly higher BNP than group1: 7.8±4.8 versus 2.2±1.5 pmol/l, p<0.01. A significant inverse correlation was found between BNP and the change in RV stroke volume during dobutamine infusion (r=−0.51;p<0.01).

**Conclusions:** In asymptomatic or minimally symptomatic patients with chronic RV pressure and/or mild volume overload, dobutamine stress decreased RV stroke volume, failed to augment RVEF, and revealed impaired RV filling. Although these patients were in apparent good clinical condition, mild pulmonary valve regurgitation has already considerable negative effects on RV global performance. Diminished cardiac reserve correlated with increased plasma neurohormones.
INTRODUCTION

The right ventricle (RV) is often subjected to both pressure and volume overload in patients with congenital heart disease. The ultimate fate of the RV in patients with chronic pressure and volume overload is of increasing concern, both with regard to clinical management and follow-up modalities. Accurate, reproducible and non-invasive diagnostic methods of follow-up are required to allow for early detection of RV dysfunction before the development of failure or irreversible myocardial damage. In particular, these techniques may guide the timing for earlier intervention.

Cardiac magnetic resonance imaging (MRI) is the noninvasive technique of choice for the quantitative evaluation of RV function by its potential to obtain both anatomic and functional information. Mismatch between resting functional parameters and symptomatology has emphasized the need for exercise studies to monitor RV function in patients with RV overload. Dobutamine, a relatively selective beta-1-adrenoreceptor agonist, can be used as a pharmacological stress agent during MRI investigation. Other quantitative parameters such as plasma neurohormones are gaining an important role in the early diagnosis of heart failure and quite a few studies have shown a significant inverse correlation between RV function and brain natriuretic peptide (BNP) levels.

Accordingly, the objective of this study was to assess the differences of RV function, between patients with isolated chronic pressure overload and patients with a combination of pressure and volume overload, using dobutamine stress MRI and BNP plasma neurohormone levels.

METHODS

Twenty-two asymptomatic or minimally symptomatic patients (NYHA class I and II) with chronic RV pressure overload (10 patients with pulmonary artery stenosis, 9 patients with corrected Tetralogy of Fallot, and 3 patients with secondary pulmonary hypertension due to a prior ventricular septum defect) and 10 age and sex-matched healthy volunteers were included (Table 1). Chronic RV pressure overload was diagnosed by Doppler echocardiography (RV systolic pressure >35 mm Hg). The patients were divided into two subgroups depending on the presence of pulmonary regurgitation as determined by MRI and echocardiography. Group 1 consisted of patients with only pressure overload (n=13) and group 2 consisted of patients (n=9) with a combination of pressure and volume overload. Volume overload was defined as a pulmonary regurgitation of 10-30 ml/beat (mild regurgitation). Seven patients included in group 2 had minimal tricuspid regurgitation. Patients with pacemakers, shunts at atrial or ventricular levels, pulmonary atresia, hypoplastic ventricles, and patent ductus arteriosus were excluded. Patients with atrial arrhythmias were excluded from this study for two reasons: 1) arrhythmias affect MRI image quality due to triggering problems, and 2) atrial arrhythmias are known to influence natriuretic peptide levels. Patients with chronic renal impairment (serum creatinine >133 µmol/l) or significant left ventricular abnormalities were also excluded. All patients were free from medication, and informed consent was obtained from all patients and volunteers. Study approval was obtained from the Hospital Research Ethics Committee. Clinical characteristics of the study population are listed in Table 1.

MAGNETIC RESONANCE IMAGING

Study subjects were placed supine in a 1.5 Tesla MRI scanner with high power gradients (Magnetom Vision, Siemens, Erlangen Germany). MRI acquisition involved a standardized protocol. In brief, an electrocardiogram-triggered, ultrafast, breath-hold gradient-echo cine
sequence was used to acquire images in the short axis plane in contiguous 10 mm slices encompassing the heart from the valve plane to the apex. Ultrafast gradient echo with a flow-encoding gradient was used for velocity mapping. The MRI protocol was repeated during dobutamine infusion. Total MRI examination time was approximately 90 minutes.

**DOBUTAMINE INFUSION**

After the MRI acquisition at rest, dobutamine was infused with an initial dose of 5 μg/kg/min. After 3 minutes, the dobutamine infusion rate was increased by 5 μg/kg/min every 3 minutes to a maximum of 15 μg/kg/min. The MRI protocol during dobutamine study started 3 minutes after the maximum dose. During each MRI measurement the electrocardiogram and heart rate were monitored. Systolic and diastolic blood pressures were measured using a brachial artery sphygmomanometer cuff every 3 minutes (Hewlett Packard 548® Palo Alto, California, USA). Serious arrhythmias, such as ventricular tachycardia, an increase >50%, or a decrease >20% in systolic blood pressure, an increase in heart rate >50%, or significant patient discomfort were all considered as reasons to stop the test.

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>Patients with RV pressure overload</th>
<th>Patients with RV pressure &amp; volume overload</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>10</td>
<td>13</td>
<td>9</td>
</tr>
<tr>
<td>Men/women</td>
<td>5/5</td>
<td>5/8</td>
<td>5/4</td>
</tr>
<tr>
<td>Age, years</td>
<td>31 (11)</td>
<td>27 (7)</td>
<td>28 (4)</td>
</tr>
<tr>
<td>NYHA class I/II</td>
<td>10/0</td>
<td>10/3</td>
<td>6/3</td>
</tr>
<tr>
<td>RVSP, mmHg</td>
<td>-</td>
<td>35-100</td>
<td>35-80</td>
</tr>
<tr>
<td>BNP</td>
<td>2.2 (1.7)</td>
<td>2.2 (1.5)</td>
<td>7.8 (4.8)</td>
</tr>
<tr>
<td>Pulmonary regurgitation*</td>
<td>-</td>
<td>-</td>
<td>9</td>
</tr>
<tr>
<td>Tricuspid regurgitation†</td>
<td>-</td>
<td>-</td>
<td>7</td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary artery stenosis</td>
<td>-</td>
<td>9</td>
<td>1</td>
</tr>
<tr>
<td>Pulmonary hypertension</td>
<td>-</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Corrected TOF</td>
<td>-</td>
<td>2</td>
<td>7</td>
</tr>
</tbody>
</table>

**Table 1. Clinical Characteristics of the Study Population.** Values are mean (SD), RVSP is presented as range. BNP, brain natriuretic peptide; NYHA, New York Heart Association; RVSP, right ventricular systolic pressure; TOF, tetralogy of Fallot; *regurgitation 10-30 ml/beat; †regurgitation 10 ml/beat.
**IMAGE ANALYSIS:**
A Unix workstation was used for analysis of the MR images. MASS® (Medis, Leiden, The Netherlands) image analysis software was used to display multislice/multiphase images individually, and in a movie loop mode. End-diastolic volume and end-systolic volume frames were determined by manual outlining of a mid-ventricular slice in all phases. On end-diastolic and end-systolic time frames, endocardial borders of the RV and the left ventricle were outlined manually. Papillary muscles and the moderator band were not included in the ventricular volume. The enclosed RV cross-sectional areas were measured by computer, multiplied by section thickness, and summed up according to Simpson's rule to provide ventricular volumes. Flow® (Medis, Leiden, The Netherlands) image analysis software was used to analyze the velocity maps.

**PLASMA NEUROHORMONES:**
Prior to the MRI examination blood samples were obtained from the antecubital vein of all subjects after they had rested for at least 15 minutes. Blood was collected into chilled tubes containing EDTA and aprotinin (1.9 mg and 100 kIU/ml blood, respectively). The blood samples were promptly centrifuged (3000 rotations/minute for 10 minutes) and stored at minus 70°C until final analysis. BNP concentrations were determined with immuno-radiometric assay kits (Shionoria, Osaka, Japan).

**STATISTICAL ANALYSIS:**
The effects of dobutamine between the groups were compared with a paired t test. Differences between groups were compared with an unpaired t test. A p value < 0.05 was considered statistically significant. Linear regression analysis was performed to correlate BNP and RV parameters. Quantitative variables with a normal distribution are presented as a mean ± standard deviation.

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>Patients with RV pressure overload (group 1)</th>
<th>Patients with RV pressure &amp; volume overload (group 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>At rest Stress p value</td>
<td>At rest Stress p value</td>
<td>At rest Stress p value</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>65 (6)  96 (17) &lt; 0.001</td>
<td>72 (10)  114 (14) &lt; 0.001</td>
<td>66 (6)  109 (23) &lt; 0.01</td>
</tr>
<tr>
<td>Mean blood pressure (mm Hg)</td>
<td>80 (8)  96 (12) &lt; 0.001</td>
<td>82 (7)  94 (11) &lt; 0.01</td>
<td>86 (14)  96 (10) &lt; 0.01</td>
</tr>
<tr>
<td>RV end-diastolic volume (mL/m²)</td>
<td>82 (14) 63 (16) ns</td>
<td>63 (17)  54 (18) &lt; 0.001</td>
<td>106 (31)  93 (23) &lt; 0.05</td>
</tr>
<tr>
<td>RV end-systolic volume (mL/m²)</td>
<td>19 (8)  11 (5) &lt; 0.01</td>
<td>19 (11)  17 (11) ns</td>
<td>52 (21)  45 (13) ns</td>
</tr>
<tr>
<td>RV stroke volume (mL/m²)</td>
<td>43 (9)  52 (12) &lt; 0.01</td>
<td>44 (9)  38 (10) &lt; 0.001</td>
<td>57 (16)  47 (16) &lt; 0.06</td>
</tr>
<tr>
<td>RV ejection fraction (%)</td>
<td>86 (10) 84 (14) &lt; 0.001</td>
<td>72 (6)  72 (12) ns</td>
<td>53 (6)  50 (11) ns</td>
</tr>
<tr>
<td>Cardiac index (L/min/m²)</td>
<td>2.8 (0.6) 5.1 (1.7) &lt; 0.001</td>
<td>3.1 (0.4)  4.2 (1.1) &lt; 0.01</td>
<td>3.9 (0.8)  5.0 (1.9) &lt; 0.05</td>
</tr>
</tbody>
</table>

*Table 2. Effects of dobutamine stress.*

**RESULTS**

**BASELINE**
RV ejection fraction (EF) was significantly higher in group 1 compared to group 2 and end-diastolic volume was larger in group 2 compared to group 1 (72 ± 9 versus 53 ± 9%, p<0.01 and 63 ± 17 versus 109 ± 31 ml/m², p<0.05 respectively). There were no significant differences in
RV parameters between patients with chronic RV pressure overload (group 1) and controls (Table 2). However, significant differences were found between patients with a RV subjected to combined pressure and volume overload (group 2) and controls: RV stroke volume (43 ± 9 versus 57 ± 16 ml/m², p<0.05), RV end-diastolic volume (109 ± 31 versus 62 ± 14 ml/m², p<0.01) and RV EF (53 ± 9 versus 69 ± 10 %, p<0.01).

**DOBUTAMINE STRESS**

After dobutamine infusion, no increase of RV EF was noticed in both patient groups, whereas RV EF increased significantly in the control group (from 69 ± 10 to 84 ± 4 %, p<0.001) (Table 2). There was a significant decrease of RV stroke volume in both patient groups (group 1: from 44 ± 8 to 38 ± 10 ml/m², p<0.001 and group 2: from 57 ± 16 to 47 ± 16 ml/m², p<0.05), whereas the controls showed a significant increase (from 43 ± 9 to 52 ± 12 ml/m², p<0.01)(Figure 1). The decrease of RV stroke volume in both patient groups was accompanied by a significant decrease in RV end-diastolic volume (group1: from 63 ± 17 to 54 ± 18 ml/m² p<0.001 and group 2: from 109 ± 31 to 93 ± 23 ml/m², p<0.05). RV end-diastolic volume remained larger in group 2 (p<0.05).

In the control group there was no significant change in RV end-diastolic volume during dobutamine administration (Figure 1). Heart rate and mean blood pressure increased significantly in controls and both patient groups, resulting in a significant increase of the cardiac index in all three examined groups regardless of the significant decrease of RV stroke volume in the patient groups (Figure 1).

Plasma BNP levels were significantly higher in patient group 2 than in group 1 (7.8 ± 4.8 versus 2.2 ± 1.5 pmol/l, p<0.01). A significant inverse correlation was found between the plasma BNP concentrations and the changes in RV stroke volume during dobutamine stress test (r=0.51; p<0.01)(Figure 2), and between BNP and RV EF (r=0.47; p=0.01). BNP and RV end-diastolic volume showed a significant correlation (r=0.65; p<0.001), and no correlation was found between BNP and RV systolic pressure.
DISCUSSION

Asymptomatic or minimally symptomatic patients with a combination of RV pressure and volume overload had more severe RV dysfunction compared to patients with isolated RV pressure overload. However, in both patients groups, an impaired functional response and diminished cardiac reserve was demonstrated by dobutamine stress MRI. The diminished cardiac reserve correlated inversely with the increased BNP levels.

PRESSURE OVERLOADED RV:
Pressure overload is a stimulus to RV hypertrophy to decrease wall stress. In our population with chronically pressure-overloaded right ventricles, the results suggested compromised systolic and diastolic RV function. Failure to increase RV EF can be considered an indication of systolic dysfunction, and the decrease in RV end-diastolic volume during dobutamine administration a sign of diastolic dysfunction. The increase in heart rate was similar in both patient groups and controls. However, in controls, the RV end-diastolic volume remained unchanged, indicating that the decrease of end-diastolic volume in the patient groups was not only due to shortened filling time, but most probably due to intrinsic diastolic dysfunction. The decrease in RV stroke volume, during dobutamine stress, points to a global adverse reaction to stress. A number of studies have suggested that a mild degree of pressure overload is a benign disorder but in moderate pressure overload the issue is not clear. In our population, RV systolic pressure range was moderate to severe (35-100 mmHg), and patients were asymptomatic or only minimally symptomatic. The present study clearly shows that even in asymptomatic patients with chronic RV overload, a significant difference (compared to healthy volunteers) in RV function can be detected with dobutamine stress MRI and BNP plasma neurohormones. The strong inverse correlation between these two parameters implies that increased BNP plasma levels accompany diminished cardiac reserve.

PRESSURE AND VOLUME OVERLOADED RV
In our study, patients with combined pressure and volume overload failed to increase RV EF during dobutamine infusion, which was associated with a significant decrease in RV stroke volume and RV end-diastolic volume. Our findings suggest more severe RV dysfunction in these patients as compared to those with isolated pressure overload. Similar to our results, Helbing et al. have established impaired RV relaxation and restriction to RV filling, in a group of patients after repair of tetralogy of Fallot with important pulmonary regurgitation. Pulmonary regurgitation and moderate RV dilatation are usually well tolerated in the presence of a competent tricuspid valve and low afterload. However, RV dilatation may result in tricuspid valve annular enlargement and valvular incompetence, thus worsening global RV performance, which was the case in the 7 patients with tricuspid valve regurgitation included in our study.

Using MRI dobutamine stress and BNP plasma neurohormones, we demonstrated significant differences between two groups of asymptomatic or minimally symptomatic patients with chronic RV overload. Even in these patients, although in good clinical condition, mild and moderate pulmonary valve regurgitation has already considerable negative effects on the global RV performance. In patients with severe pulmonary regurgitation, pulmonary valve replacement is considered to preserve and/or restore RV function and to improve prognosis. The optimal time window for this surgical procedure is controversial. According to current guidelines, the decision for pulmonary valve replacement is based on progressive RV dilatation and/or clinical symptoms because of severe pulmonary regurgitation. In a recent study, Therrien et al. reported that in patients with tetralogy of Fallot, no change in mean RV volumes, RV EF or exercise capacity was present after surgery, indicating that pulmonary valve replacement might
have been planned too late with irreversible RV damage. This risk has to be weighed against the possible need for further cardiac surgery after pulmonary valve replacement, as pulmonary homografts need to be replaced (approximately 10 to 15 years) after initial surgery. In contrast to the findings of Therrien et al., Vliegen et al. using MRI in patients with tetralogy of Fallot showed that pulmonary valve replacement resulted in remarkable hemodynamic improvement of RV systolic function accompanied by improvement of validity. However, there is no evidence that cardiac surgery in these patients could not have been delayed without consequences for the RV function.

These two studies illustrate an important clinical problem: the lack of accurate clinically applicable parameters of RV function impedes appropriate stratification, and hence the decision making as to the optimal timing for surgery in patients with valvular regurgitation.

**CLINICAL IMPLICATIONS**

This study combines MRI and BNP plasma neurohormones and shows their potential clinical application for a quantitative and reproducible follow-up in patients with chronic RV overload. Early detection of RV dysfunction may identify patients at risk for RV failure, which allows them to benefit from timely intervention. The results of this study encourage further research for the utilization of quantitative parameters relating to RV function, in order to improve stratification of patients with chronic RV overload, with or without valvular regurgitation.

**CONCLUSIONS**

In asymptomatic or minimally symptomatic patients with chronic RV overload, an impaired functional response can be demonstrated with dobutamine stress MRI. A decrease in RV stroke volume is accompanied by both failure to augment RV EF (systolic dysfunction) and impaired RV filling (diastolic dysfunction) during dobutamine stress. Although these patients are in apparent good clinical condition, in these patients, mild pulmonary valve regurgitation already has considerable negative effects on global RV performance. Diminished cardiac reserve correlated inversely with increased plasma neurohormone levels.
REFERENCES

