The right ventricle under acute and chronic overload: early detection of right ventricular dysfunction
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DOBUTAMINE-INDUCED INCREASE OF RIGHT VENTRICULAR CONTRACTILITY
WITHOUT INCREASED STROKE VOLUME IN ADOLESCENT PATIENTS WITH
TRANSPOSITION OF THE GREAT ARTERIES: EVALUATION WITH MAGNETIC
RESONANCE IMAGING

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Departments of Cardiology, Leiden University Medical Center³ and Academic Hospital
Groningen⁴

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Objective: Prognosis in patients with surgically corrected (Senning or Mustard) transposition of the great arteries (TGA) depends mainly on right ventricular (RV) function and RV functional reserve. We examined the role of dobutamine stress in the early detection of RV dysfunction in asymptomatic or slightly symptomatic patients with TGA using magnetic resonance imaging (MRI).

Patients and Methods: Twelve asymptomatic or slightly symptomatic patients with chronic RV pressure overload, surgically corrected (Mustard or Senning) TGA (age 22.8(3.4) years; NYHA class I/II) and nine age matched healthy volunteers (age 27.3(4.4) years) were included. MRI was applied both at baseline and during dobutamine stress (start dose 5μg/kg/min to maximum dose 15μg/kg/min) to determine RV and left ventricular (LV) stroke volumes (SV) and ejection fraction (EF).

Results: At baseline only RVEF was significantly higher in controls than in patients (71(9) v 57(10)%, p<0.001), other RV parameters were not significantly different between the two examined groups: RVSV (86(21) v 72(27)ml, p=ns), RV end-diastolic volume (EDV) (123(37) v 123(33)ml, p=ns), and heart rate (61(10) v 69(14)bpm, p=ns), respectively. During dobutamine stress RVEF increased significantly both in controls and patients (20(16) v 17(18)%, p<0.01 and p<0.02 v rest, respectively), but stress RVEF was significantly higher in controls than in patients (85(3) v 66(7)%, p<0.0001). RVSV increased significantly in controls (22(19)%, p<0.02), and there was no significant increase in RVSV in patients (-10(28)%, p=ns). The controls showed no change in RVEDV (2(17)%, p=ns), but in patients a significant decrease in RVEDV (-24(15)%, p<0.001) was observed. Maximal heart rate was significantly higher in patients than in controls (122(20) v 101(14)bpm, p<0.02).

Conclusion: In asymptomatic or slightly symptomatic patients with surgically corrected TGA dobutamine had a positive inotropic effect on RV, but the increased contractility was not accompanied by an appropriate increase in SV. Our data suggest inadequate RV filling in this category of patients, possibly due to rigid atrial baffles and compromised atrial function or decreased compliance due to RV hypertrophy.
INTRODUCTION

Improvement in management of congenital malformations of the heart has resulted in increased life expectancy in this group of patients. In a substantial part of these patients, the morphologic right ventricle (RV) is subjected to chronic pressure overload. Controversy exists regarding the ability of the RV to function under these conditions over prolonged periods of time. A population with excessive high RV pressures, now reaching well into adulthood, is represented by the patients who were operated with intra-atrial repair (Mustard or Senning procedure) for complete transposition of the great arteries (TGA) since the mid-sixties. Within the exception of patients with significant arrhythmias, adult TGA patients generally lead normal lives and are usually asymptomatic or slightly symptomatic. However, progressive deterioration of RV function has been reported. The percentage of patients developing RV failure during 10-20 years of follow up is yet unknown but has been estimated to approach 10-20%. Mismatch between resting functional parameters and symptomatology have emphasized the need for exercise studies to monitor RV function in this patient category. Several studies, with a wide range of approaches to exercise testing and conflicting results regarding mechanism of cardiac reserve, have been performed relatively shortly after intra-atrial correction (up to 10 years). Patients with TGA generally show reduced exercise tolerance, which has been attributed to abnormally low heart rate response, filling abnormalities of the RV and systolic dysfunction.

Magnetic resonance imaging (MRI) is an accurate and reproducible method in the quantitative assessment of RV function and allows in-vivo assessment of various RV function parameters. Additionally, stress testing assists in the assessment of cardiac reserve. Dobutamine, a relatively selective beta-1-adrenoreceptor agonist, can be used as a pharmacological stress agent during MRI investigation. Although the positive inotropic action of dobutamine on RV function seems clinically evident, few data are available regarding normal contractile reserve of the RV following beta-adrenergic stimulation. The aim of this study was to assess RV contractile reserve by dobutamine infusion in healthy volunteers and adult patients with intra-atrial repair for TGA.

PATIENTS AND METHODS

Twelve consecutive asymptomatic or slightly symptomatic patients (mean age 22.8(3.4) years, range 18-28 years) with intra-atrial repair (Mustard and Senning) for TGA and nine age matched normal control subjects (mean age 27.3 (4.4) years, range 21-35 years) were studied. Population characteristics are summarized in table 1. All patients were in functional class I (n=6) or II (n=6) according to the New York Heart Association (NYHA). Exclusion criteria were: valvular regurgitation determined by echocardiography and confirmed by means of MR flow measurements (>10 ml per cardiac cycle), contraindications for MRI (serious claustrophobia, pacemakers, vascular clips, atrial fibrillation) and contraindications for dobutamine (history of ventricular fibrillation and ventricular tachycardia, low potassium values, unstable angina pectoris, hypertrophic cardiomyopathy and untreated hypertension). The local ethical committee approved this study. Informed consent was obtained from each participant before entering the study.


### Table 1. Clinical Characteristics of the Study Population

<table>
<thead>
<tr>
<th></th>
<th>Patients</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men/women</td>
<td>75/6</td>
<td>45/6</td>
</tr>
<tr>
<td>Age, years</td>
<td>22.8 (3.4)</td>
<td>27.3 (4.4)</td>
</tr>
<tr>
<td>NYHA class</td>
<td>6/6</td>
<td>9/0</td>
</tr>
<tr>
<td>Mustard/Sennett</td>
<td>1/1</td>
<td>0/0</td>
</tr>
</tbody>
</table>

Values are mean (SD); NYHA, New York Heart Association.

## Magnetic Resonance Imaging

Study subjects were placed supine in a 1.5 Tesla MRI scanner with high power gradients (Vision, Siemens, Erlangen Germany). MRI acquisition involved a standardized protocol. Imaging sessions were initiated with scout images to determine the position of the heart in the thoracic cavity. Based on these images an electrocardiogram (ECG) triggered T1-weighted turbo spin echo series of axial images was acquired. A gradient-echo cine sequence was then performed in a plane bisecting the mitral valve orifice and passing through the apex visualizing the long-axis view in order to localize the atrioventricular valve plane. An ECG-triggered, ultrafast, breath-hold gradient-echo cine sequence with the following parameters: repetition time (TR) = R-R interval, time of echo (TE) = 4.8ms, slice thickness 10mm, imaging matrix = 256x256, field of view (FOV) = 350mm, flip angle = 20°, was then used to acquire images in the short axis plane in contiguous 10mm slices encompassing the heart from the valve plane to the apex. End-systolic and end-diastolic volumes were calculated from this multislice, multiphase image set. Volumetric flow from the RV was assessed by MR velocity mapping. Velocity maps were acquired with a flip angle of 30°, TE = 24 ms, slice thickness = 6mm, FOV = 320 mm and imaging matrix = 256x256, velocity encoding = 250cm/s. The MRI protocol was repeated during dobutamine infusion.

## Dobutamine Infusion

An intravenous line was inserted into the antecubital vein prior to the MRI procedure. Dobutamine was administered by a digital infusion pump, which was placed outside the scanner. 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.

## 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 (maximal ventricular volume) (EDV) and end systolic (minimal ventricular volume) (ESV) 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 LV were outlined manually. Papillary muscles and the moderator
band were not included in the ventricular volume. The enclosed RV and LV cross-sectional areas were measured by computer, multiplied by section thickness, and summed up according to Simpson’s rule to provide LV and RV volumes. Total MRI examination time was approximately 90 minutes.

**VALIDATION OF VOLUME MEASUREMENTS**
The accuracy of multislice, multiphase ultrafast gradient echo RV volume measurements was assessed by comparison of RV stroke volume (SV) with LVSV in all study subjects (n=21) both at rest and during dobutamine infusion.

**CALCULATIONS**
SV was defined as EDV minus ESV, and RVEF was calculated as SV divided by EDV. The dobutamine stress values were calculated as percentage increase from values at rest. The mean blood pressure was calculated as 2 times diastolic blood pressure + systolic blood pressure divided by 3.

**STATISTICAL ANALYSIS**
The effects of dobutamine within groups were compared with the paired t test. Differences between groups were compared with the unpaired t test. The agreement between RVSV and LVSV measurements was assessed by linear regression analysis. A p value < 0.05 was considered statistically significant.

**RESULTS**
Acquisition of MR images could be performed in all 21 subjects. Images of good quality were obtained both at rest and during dobutamine infusion. No significant differences in mean blood pressure or heart rate were found between the groups at rest. During dobutamine infusion maximal heart rate became significantly higher in patients than in controls (122(20) v 101(14)bpm, p<0.02)(table 2). Heart rate response in the patient group increased from 69(14) bpm at rest to 122(20) bpm during stress (p<0.0001), and in the controls from 61(10) bpm at rest to 101(14)bpm during stress (p<0.0001). The results of all measurements are shown in table 2.

**COMPARISON OF VOLUME MEASUREMENTS**
There was a good agreement between LVSV and RVSV measured both at rest and during dobutamine stress in all 21 subjects: r=0.97, p<0.0001 (Figure 1).

**RIGHT VENTRICULAR EJECTION FRACTION**
Table 2 and Figure 2 show RV volumes and RVEF measurements of the controls and patients at rest and during dobutamine infusion. Resting RVEF was significantly different between controls and patients 71(9) v 57(10)%, p<0.01. During dobutamine infusion RVEF increased significantly both in controls and patients (20(16) v 17(18)%, p<0.01 and p<0.02 v rest, respectively) (Figure 3), but stress RVEF was significantly higher in controls than in patients (85(3) and 66(7)%, p<0.0001).
Table 2. Effects of Dobutamine Stress

<table>
<thead>
<tr>
<th></th>
<th>Patients (n=12)</th>
<th>Control Subjects (n=9)</th>
<th>Differences Between Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>rest</td>
<td>stress</td>
<td>p value</td>
</tr>
<tr>
<td>heart rate (bpm)</td>
<td>69 (14)</td>
<td>122 (23)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>mean RR (mmHg)</td>
<td>80 (8)</td>
<td>100 (14)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>RV EDV (ml)</td>
<td>123 (33)</td>
<td>90 (18)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>RV ESV (ml)</td>
<td>51 (18)</td>
<td>30 (8)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>RV SV (ml)</td>
<td>72 (27)</td>
<td>66 (14)</td>
<td>ns</td>
</tr>
<tr>
<td>RV EF (%)</td>
<td>57 (10)</td>
<td>66 (7)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LV EDV (ml)</td>
<td>108 (38)</td>
<td>79 (24)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>LV ESV (ml)</td>
<td>36 (14)</td>
<td>22 (10)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LV SV (ml)</td>
<td>72 (29)</td>
<td>57 (17)</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>LV EF (%)</td>
<td>67 (11)</td>
<td>73 (7)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CO (l)</td>
<td>4.9 (1.9)</td>
<td>7.1 (1.3)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CI (l/min/m²)</td>
<td>2.7 (0.9)</td>
<td>4.0 (0.8)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Values are mean (SD); CI, cardiac index; CO, cardiac output; EDV, end-diastolic volume; ESV, end-systolic volume; EF, ejection fraction; LV, Left Ventricle; RR, Blood Pressure; RV, Right Ventricle; SV, stroke volume.

STROKE VOLUME

At rest RVSV was slightly, but not significantly, higher in the controls group compared to the patients (86(21) vs 72(27) ml, respectively, p=ns). During dobutamine stress RVSV increased significantly in the controls to 105(33) ml, (22(19)%), p<0.02), while there was no significant increase of RVSV in the patient group 60(14)ml, (-10(28)%), p=ns (Figure 2 and 3).

Figure 1. Linear regression analysis of left ventricular stroke volume (LVSV) and right ventricular stroke volume (RVSV) assessed with multi-slice, multi-phase gradient echo magnetic resonance imaging of patients (n=12) and controls (n=9) at rest and during dobutamine infusion.
**Chapter 2**

Figure 2. Right ventricular ejection fraction (RVEF) (A), right ventricular stroke volume (RVSV) (B), right ventricular end-diastolic volume (RVEDV) (C) and right ventricular end-systolic volume (RVESV) (D), in patients and controls at rest (white bars) and during dobutamine infusion (black bars).

**RIGHT VENTRICULAR VOLUMES**

At rest no significant differences between controls and patients were found in RVEDV (123(37) v 123(33)ml, respectively, p=ns), and RVESV (37(19) v 51(16)ml, respectively, p=ns). In the patient group the increase of RVEF was accompanied by a significant decrease of RVEDV (-24(15)% , p<0.001) without an increase in RVSV. RVESV decreased significantly and similarly in both controls and patients (-39(27)% , p<0.02 v -39(17)% , p<0.001, p=ns).

**LEFT VENTRICLE**

Table 2 shows LVEF measurements of the controls and patients at rest and during dobutamine infusion. Resting LVEF was not significantly different between controls and patients (74 (8)% v 67 (11)% , p=ns). During dobutamine infusion LVEF increased significantly both in controls and patients to maximal EF (86(2)% and 73 (7)% , p<0.001, p<0.01, respectively), but stress LVEF was significantly higher in the controls than in the patients (p<0.0001).
DISCUSSION

With this study we showed the usefulness of beta-adrenergic stimulation of RV, which is of clinical importance for treatment of RV failure. Conflicting reports using various techniques and inhomogeneous groups of patients have precluded definite conclusions on the role of various RV function parameters in adult patients with chronic RV pressure overload. In our study we used validated MRI techniques in an asymptomatic or slightly symptomatic patient group with chronic RV pressure overload without additional cardiac lesions or LV dysfunction.

MAIN FINDINGS

There were no significant differences in resting heart rate, mean blood pressure and RVSV between asymptomatic or slightly symptomatic patients with surgically corrected TGA and healthy volunteers. At rest, RVEF was significantly higher in controls than in patients. During dobutamine stress, RVEF increased significantly in both groups, but stress RVEF was significantly lower in patients than in controls. The increase of RVEF was accompanied by a significant increase of RVSV in controls. By contrast, in patients the increase of RVEF was accompanied by a significant reduction of RVEDV and no change in RVSV.

MRI-determined RV volumes showed a good correlation with both MRI-determined LV volumes and stroke volumes. This internal validation demonstrates accurate RV volume measurements in healthy individuals as well as in patients with chronic RV pressure overload.

RIGHT VENTRICULAR FUNCTION

The cause for RV dysfunction in patients with intra-atrial repair for TGA is undoubtedly multifactorial; contributory factors include preoperative myocardial damage caused by cyanosis before surgery, perioperative damage due to inadequate myocardial protection during repair, and the inability of RV to function appropriately under chronic pressure overload.

In clinical practice, characterization of systolic RV function mostly relies on assessment of RVEF. In our study, RVEF at rest was significantly higher in healthy volunteers than in asymptomatic patients and increased significantly during dobutamine stress in both groups. Benson et al19, using radionuclide angiography, found normal resting RVEF and an increase of RVEF during physical stress test in asymptomatic patients with congenitally corrected TGA and impaired pulmonary ventricular function. Redington20, using invasive techniques, also observed increased RVEF in response to dobutamine stress test in patients with surgically corrected TGA. Data from other studies, using radionuclide angiography, indicated depressed resting RVEF in patients with TGA and no increase or even a decrease in RVEF during stress15. The controversial findings of these studies can be explained by the used technique. Radionuclide studies have several limitations in assessing RV volumes and function as a result of the geometrically complex RV shape and overlap with LV21. These studies addressed patients in different age groups and with additional cardiac lesions, such as tricuspid regurgitation, which may interfere with resting RV values and response to exercise. In our study, patients with additional lesions were excluded. Similar to our results, two studies using MRI did show a lower RVEF at rest in patients with TGA17,22 compared to control subjects.

Despite a significant increase of RVEF during dobutamine stress, RVSV did not increase appropriately in patients, which can be explained by the significant reduction of RVEDV. A significant decrease of RVEDV and inappropriate SV response have previously been reported using various techniques in asymptomatic patients with TGA in response to physical exercise23,24. A possible explanation for a decline in RVEDV and SV during dobutamine stimulation could be
impaired filling due to impaired compliance due to RV hypertrophy as a result of chronic pressure overload. Another possible cause for a falling SV at higher heart rates could be the small baffle size and compromised atrial function of the postoperative Mustard and Senning atria with subsequent inadequate filling of the ventricles. As a third possible explanation for abnormal SV response during stress the role of chronotropic impairment has been debated. However, all our patients showed normal chronotropic response to dobutamine stress test, taking into account that patients with pacemakers were excluded.

In our study it seems likely that impaired RV filling due to rigid atrial baffles or to decreased compliance of hypertrophic RV might be responsible for the inappropriate response of RVSV during stress. However, additional MRI information about diastolic filling characteristics will be helpful to investigate the possible diastolic dysfunction in these patients.

**CLINICAL IMPLICATIONS**

During inotropic stimulation a significant increase of heart rate and abnormally low change of RVSV was observed in the patients with intra-atrial repair for TGA. This may have important implications, as for example in the response to arrhythmias.

Timely recognition of RV dysfunction is essential for the management of patients with chronic RV pressure overload. This requires adequate monitoring of quantitative parameters for RV function with techniques that may be applied serially during follow-up, which should preferably be noninvasive such as MRI.

**CONCLUSIONS**

Dobutamine has a positive inotropic effect on RV contractility, which can appropriately be assessed with MRI. In asymptomatic or slightly symptomatic patients with surgically corrected TGA increased contractility was not accompanied by an appropriate increase in stroke volume. Our data suggest inadequate RV filling in this category of patients, possibly due to rigid atrial baffles and compromised atrial function or decreased compliance due to RV hypertrophy.
REFERENCES


