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REGIONAL AND GLOBAL RIGHT VENTRICULAR DYSFUNCTION IN ASYMPTOMATIC OR MINIMALLY SYMPTOMATIC PATIENTS WITH CONGENITALLY CORRECTED TRANSPOSITION OF THE GREAT ARTERIES

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**Objective:** Patients with congenitally corrected transposition of the great arteries (ccTGA) are at risk of right ventricular (RV) dysfunction and failure, but the factors contributing to this problem are poorly understood.

**Patients and Methods:** Thirteen patients with ccTGA (7 unoperated and 6 physiologically repaired) and 6 age and sex-matched healthy controls underwent cardiac magnetic resonance imaging at rest and during dobutamine stress in order to determine regional and global RV response to stress conditions.

**Results:** At rest, patients had a significantly decreased overall wall motion compared to controls (7.2±0.5 vs 9.8±0.4mm, p<0.006). During dobutamine infusion, overall wall motion increased to 12.8±0.4mm in controls vs 8.8±1.0mm in patients (p<0.006). At the regional level, significant differences in wall motion between patients and controls were found in the anterior (9.5±1.1 vs 13.2±0.6mm, p=0.02), posterior (10.2±1.6 vs 13.2±0.8mm, p=0.01), and septal segments (5.0±0.8 vs 11.2±0.6mm, p<0.001).

At rest, overall wall thickening in patients was similar to that of controls, but significantly less in patients during stress. During dobutamine stress, patients showed significantly less regional wall thickening than controls, particularly in the septal (2.7±0.6 vs 6.0±0.4mm, respectively, p<0.002) and in the anterior segments (4.2±0.6 vs 7.8±0.6mm, respectively, p<0.002). RV ejection fraction (EF) strongly correlated both with wall motion at rest and during stress (r=0.83, p<0.001, r=0.89, p<0.003, respectively), and with wall thickening at rest and during stress (r=0.81, p<0.0008, r=0.90, p<0.002, respectively).

**Conclusion:** Abnormal regional function in the systemic ventricle may occur in patients with ccTGA. The regional abnormalities strongly correlated with RVEF. This study supports the hypothesis that ischemia of the RV myocardium contributes to the development of RV dysfunction in patients with ccTGA.
INTRODUCTION

Congenitally corrected transposition of the great arteries (ccTGA) combines atrio-ventricular and ventriculo-arterial discordance, and has an incidence of 0.5% of all forms of congenital heart disease\(^1\). In patients with ccTGA, the right ventricle (RV) and the tricuspid valve are supporting the systemic circulation\(^1\). In the course of time, systemic ventricular dysfunction and failure may occur\(^1,2\). The factors contributing to this problem are poorly understood, but it has been hypothesized that myocardial ischemia may contribute to RV dysfunction in patients with ccTGA\(^3,4\). Chronic systemic pressure overload increases wall stress in the morphological RV, resulting in hypertrophy and myocardial ischemia causing abnormalities in regional myocardial function\(^5,6\). Abnormalities of ventricular wall dynamics, such as wall motion and wall thickening at rest and during stress determined by magnetic resonance imaging (MRI), are sensitive markers of myocardial ischemia\(^5,7\).

The aims of this study were: 1) to quantify regional wall motion and wall thickening, both at rest and during stress, as possible parameters for early detection of RV dysfunction in patients with ccTGA, and 2) to examine the correlation between regional myocardial function (wall motion and wall thickening) and global RV function (ejection fraction (EF)).

METHODS

**Patient group:** Thirteen asymptomatic or minimally symptomatic adults with ccTGA (mean age 28.7 +/- 3.3 years), and 6 aged-matched healthy volunteers were included in our study. Six patients with ccTGA had undergone multiple operations along the physiologic repair pathway, between 1978 and 1995. Preoperatively, 2 patients had presented with cyanosis, and 4 patients had been in intractable heart failure. All patients were in New York Heart Classification (NYHA) class III-IV preoperatively. Palliative procedures were performed in 3 patients at a mean age of 1.1 years (range 0.4-2 years), including pulmonary artery banding (n=2), and a modified left Blalock-Taussig shunt (n=1). Intracardiac physiologic repair was performed at a mean age of 15.8 years (range 3-61 years), and included closure of a ventricular septal defect (n=3) or an atrial septal defect (n=3), tricuspid valve replacement (n=2) or repair (n=1; reoperation), pulmonary valve comissurotomy (n=1), and insertion of a left ventricular-to-pulmonary artery valved homograft conduit (n=1). There was no operative mortality, and no incidence of postoperative complete heart block. At the time of the MRI-dobutamine study, mean age was 29.5 +/- 18 years (range 17-65 years).

Equally studied were 7 asymptomatic adult patients with unoperated ccTGA, with a mean age of 26.7 years (range 22-35 years). One patient had a spontaneous complete atrioventricular heart block without a pacemaker, and the other 6 patients had regular sinus rhythm. Five of these patients had associated intracardiac anomalies which were an atrial septal defect in 2 patients, a ventricular septal defect in 3 patients, pulmonary valve stenosis in 2 patients and Ebstein's anomaly in 2 patients. Six aged-matched healthy adults (mean age 26.1 +/- 1.5 years) underwent the same study protocol. The RV function of patients with ccTGA, unoperated or after physiologic repair, was compared to the systemic left ventricle of the control subjects.
### 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 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. Then an ECG-triggered, ultrafast, breath-hold gradient-echo cine sequence with the following parameters: repetition time = R-R interval, time of echo = 4.8ms, slice thickness 10mm, imaging matrix = 256x256, field of view = 350mm, flip angle = 20°, was used. With this images in the short axis plane in contiguous 10mm slices encompassing the heart from the valve plane to the apex were acquired. End-systolic and end-diastolic volumes were calculated from this multislice, multiphase image set.

### Dobutamine Infusion

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 the dobutamine study started 3 minutes after the maximum dose.

During each MRI examination, the electrocardiogram and heart rate were monitored. Systolic and diastolic blood pressures were measured using a brachial artery sphygmomanometer cuff every 3 minutes.

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**Figure 1.** MR image showing the morphological right midventricular slice of a patient with ccTGA. Indicated are the endocardial and epicardial contours and 100 centerline chords of systemic ventricle.
The MRI study was discontinued in case of ventricular tachycardias, an increase > 50% or a decrease >20% in systolic blood pressure from the resting state, an increase in heart rate >50% from the resting state, or significant patient discomfort.

**IMAGE ANALYSIS**

A Unix workstation (Sun Microsystems, Palo Alto, California, U.S.A.) 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. For quantitative assessment, endocardial and epicardial contours of the systemic ventricle were outlined manually in all images (Figure 1). Papillary muscles, trabeculae and the moderator band were not included in the calculation of ventricular volumes.

A marker was placed at the posterior junction of the right ventricle and the interventricular septum. Wall motion and wall thickening were computed for 100 centerline chords (starting from the marker point proceeding clockwise), based on the centerline method8 (Figure 1). Each slice was divided into 4 equally sized regions, representing the septal, anterior, lateral and posterior segments. Wall motion was defined as the motion of each chord relative to the center of the systemic ventricle in each respective slice. Wall thickening was defined as the change of end-diastolic and end-systolic wall thickness in each respective slice.

Wall motion and wall thickening were analyzed using 4 segments (anterior, lateral, inferior and septal).

**STATISTICAL ANALYSIS**

Differences between groups were compared with the unpaired t test. The effects of dobutamine within groups were compared with the paired t test. A p value < 0.05 was considered statistically significant. For descriptive purposes, quantitative variables with a normal distribution were presented as mean ± standard error of the mean.

**RESULTS**

All patients tolerated and completed the protocol. Details of results are given in Table 1. At rest and at dobutamine stress, heart rate was similar for patients with physiological repair, unoperated patients with ccTGA, and control subjects. Mean arterial blood pressure was similar amongst all 3 groups at rest, but remained lower in unoperated ccTGA patients at stress compared to the control subjects.
WALL MOTION
At rest, overall wall motion was significantly decreased in ccTGA patients compared to controls (7.2±0.5 vs 9.8±0.4, p<0.006). During dobutamine infusion, overall wall motion increased to 12.8±0.4mm in controls vs 8.8±1.0mm in patients (p<0.006). At the regional level, dobutamine stress showed significant differences between patients and controls in the anterior wall (9.5±1.1 vs 13.2±0.6mm, p=0.02), posterior wall (10.2±1.6 vs 13.2±0.8mm, p=0.01), and the septum (5.0±0.8 vs 11.2±0.6mm, p<0.001) (Table 1).

WALL THICKENING
At rest, no differences in overall wall thickening were found between patients and controls (4.1±0.4 vs 5.2±0.4mm, p=ns). During dobutamine stress, overall wall thickening failed to increase in patients compared to controls (4.7±0.6 vs 7.5±0.4mm, p<0.005). Regional wall thickening was significantly less in the septum (2.7±0.6 vs 6.0±0.4mm, p<0.002) and in the anterior segments (4.2±0.6 vs 7.8±0.6mm, p<0.002) (Table 1, Figures 2a + 2b). There were no significant differences in wall motion and wall thickening between operated and unoperated patients with ccTGA.
REGIONAL FUNCTION ANALYSIS IN RELATION TO GLOBAL FUNCTION

RVEF correlated strongly with wall motion in patients with ccTGA both at rest and during dobutamine stress ($r=0.83$, $p<0.001$), and $r=0.89$, $p=0.003$, respectively (Figure 4a). Also, a strong correlation between RVEF and wall thickening was found in patients at rest and during dobutamine stress ($r=0.81$, $p=0.0008$, and $r=0.90$, $p=0.002$, respectively, Figure 4b).

DISCUSSION

In this study, we found RV wall motion and thickening abnormalities at rest and during dobutamine stress in asymptomatic or minimally symptomatic patients with ccTGA. The regional abnormalities strongly correlated with global RV dysfunction as determined by RVEF. Our findings support the hypothesis that ischemia of the RV may contribute to the development of RV dysfunction in patients with ccTGA.

RV subjected to systemic pressure shows extensive and global hypertrophy compared to the thin wall of the RV when functioning under normal pressure (Figure 3). Hypertrophy places additional demand on the right coronary arterial supply and progressive ischemia may develop leading towards ventricular dysfunction. RV hypertrophy also gives rise to a decrease in diastolic function compromising RV global function.

Isolated case reports already suggested that myocardial perfusion defects may be present in the RV of patients with ccTGA. In two studies of ccTGA patients using sestamibi perfusion gated SPECT imaging, Hornung et al. found substantial RV myocardial perfusion defects. The perfusion defects were associated with wall motion and wall thickening abnormalities in the anterior, posterior and septal segments, and with a reduced RVEF. The authors proposed a causal relation between myocardial ischemia and ventricular dysfunction due to an inadequate right coronary supply of the hypertrophied ventricle.

In our patients, wall thickening disorders were less pronounced or even absent at rest, but they were present during dobutamine stress predominantly in the anterior and septal segments. Interestingly, the oldest patient in our study, who was 65 years of age at the time of the study,
had wall motion and wall thickening disorders in all segments accompanied by poor global function, both during rest and dobutamine stress, supporting the hypothesis of the gradual onset of RV dysfunction.

Comparable to healthy controls, ccTGA patients responded appropriately to dobutamine stress\textsuperscript{13}. However, the increase in RVEF and stroke volume was less compared to the healthy controls, suggesting global RV dysfunction. It might be argued that the RV normally operates at a lower EF than the left ventricle. However, in our study, diminished global RV function, as assessed by RVEF, strongly correlated with reduced regional function suggesting a causal relation between regional and global RV function.

In earlier studies, we already showed that the increase of stroke volume in these patients was impeded by the limited or even absent increase of end-diastolic volume during dobutamine stress\textsuperscript{13,14}. One may speculate that the oversized, hypertrophied RV has compromised compliance and therefore abnormal diastolic function superimposed by suboptimal coronary supply.

**STUDY LIMITATIONS**

As a group, patients with ccTGA present with a wide variety of morphology and resulting physiology, potentially precluding generalizations and recommendations across such a heterogeneous group. To that purpose, larger sample sizes should be studied.

**CONCLUSIONS**

We found evidence of abnormal global and regional cardiac function in the systemic ventricle of asymptomatic or slightly symptomatic patients with ccTGA. The regional abnormalities strongly correlated with global dysfunction. This study supports the hypothesis that silent ischemia of the RV myocardium has an important contribution to the development of RV dysfunction in the course of time.
REFERENCES


