The right ventricle under acute and chronic overload: early detection of right ventricular dysfunction
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COMPARABLE SYSTEMIC VENTRICULAR FUNCTION IN HEALTHY ADULTS AND PATIENTS WITH UNOPERATED CONGENITALLY CORRECTED TRANSPOSITION USING MRI DOBUTAMINE STRESS

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ABSTRACT

Background: Failure of the systemic right ventricle (RV) often complicates adult survival in unoperated (UN) or physiologically repaired (PHYS) congenitally corrected transposition (ccTGA). Healthy controls schematically represent an optimal outcome anatomic repair, which is increasingly performed to treat ccTGA. Magnetic Resonance Imaging (MRI) dobutamine stress testing measures cardiac reserve, and sets to compare the left ventricle of controls with the systemic RV of UN and PHYS patients with ccTGA.

Methods: Baseline and stress MRI (maximum dobutamine dose 15 μg/kg/min) assessed systemic RV function in 13 minimally or asymptomatic adult patients with ccTGA (unoperated; n=7, and physiologically repaired; n=6). The left ventricles (LV) of eleven healthy age-matched adults served as controls.

Results: Baseline and stress end-diastolic volumes were similar between the systemic RV of unoperated patients and the left ventricle of controls, as well as baseline end-systolic volumes. Stress ejection fraction was lower in UN and PHYS patients (70+/-6% and 60+/-5% respectively, versus healthy= 84+/-8%). However, comparable to healthy controls, both subsets of ccTGA patients responded appropriately to dobutamine stress, as illustrated by similar RV stroke volume, heart rate, mean blood pressure, and cardiac index.

Conclusions: Compared to the LV of healthy controls, both patient groups had larger systemic RV ventricular volumes, diminished ejection fraction, but an appropriate response to dobutamine stress. Values of unoperated patients are closer to normal than PHYS patients. MRI dobutamine may help to define the subgroups of ccTGA patients with favorable anatomy, whereby asymptomatic adult survival could be anticipated without need for surgery.
INTRODUCTION

Right ventricular (RV) failure, tricuspid valve insufficiency, and complete heart block are established causes of morbidity and mortality in patients with congenitally corrected transposition of the great vessels (ccTGA)\textsuperscript{1-7}. This may occur either in unoperated patients, or after variants of the so-called “classical” or physiological repair, in which the morphological right ventricle and atrioventricular valve remain in the systemic circulation. The disappointing natural history and surgical results of physiologic repair\textsuperscript{8-10} led to the concept of anatomic repair, either the double switch procedure, or an atrial switch plus Rastelli repair, which is increasingly proposed to treat symptomatic young patients with ccTGA. Although the mid-term follow-up of the anatomic repair has shown encouraging results when performed early on\textsuperscript{5,11}, the indication to do so remains uncertain in adults. Issues pertaining to left ventricular retraining prior to anatomic repair are paramount, and the extent to which this may be achieved is a major determinant of operative success\textsuperscript{11}. Furthermore, anatomic repair has met with its own set of complications, namely atrial arrhythmias, baffle obstructions, neoaoartic valve insufficiency after pulmonary artery banding, and the need for repeat conduit changes if a Rastelli repair is involved\textsuperscript{6,11,12}. In asymptomatic and/or older patients with ccTGA, a large undertaking such as the anatomic repair would seem questionable.

Magnetic resonance imaging (MRI) coupled with dobutamine stress testing can accurately assess cardiac reserve, and represents an ideal non-invasive follow-up modality in all patient groups with right ventricular overload\textsuperscript{13-15}. It allows for early detection of ventricular dilation and impending failure, and may guide medical or surgical management before symptoms appear\textsuperscript{13}. Our study uses dobutamine stress MRI in an attempt to define and predict the eventual subsets of patients who will never need surgery, rather than an anatomic repair.

PATIENTS AND METHODS

Thirteen asymptomatic or minimally symptomatic adults with ccTGA (mean age 28.1 +/- 11.5 years), and 11 age-matched healthy volunteers were enrolled in our study. Six patients with congenitally corrected transposition had undergone multiple operations along the physiologic repair pathway, between 1978 and 1995. Preoperatively, two patients had presented with cyanosis, and four had been in intractable heart failure. All were in New York Heart Classification (NYHA) classes III-IV preoperatively, and all were in sinus rhythm. 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 (VSD) (n=3) or an atrial septal defect (ASD) (n=3), tricuspid valve replacement (n=2) or repair (n=1; reoperation), pulmonary valve commissurotomy (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). Three patients had residual 2-3+ tricuspid valve regurgitation, as assessed by echocardiography.

Equally studied were 7 asymptomatic adult patients with unoperated ccTGA (UN), with a mean age of 26.7 years (range 22-35 years). One patient was in spontaneous complete heart block without a pacemaker, and the other 6 were in sinus rhythm. Five of these patients have associated intracardiac anomalies, namely an ASD in 2 patients, a VSD in 3 patients, pulmonary
valve stenosis in 2, and Ebstein’s anomaly of the tricuspid valve in 2. Tricuspid valve regurgitation (2-3+), as assessed by echocardiography, was present in four patients.

Eleven aged-matched healthy adults underwent the same study protocol, and served as controls (mean age 31 +/- 11 years).

<table>
<thead>
<tr>
<th>Effects of dobutamine stress</th>
<th>Controls (C)</th>
<th>PHYS-CCTGA</th>
<th>UN-CCTGA</th>
<th>C vs. PHYS</th>
<th>C vs. UN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (bpm)</td>
<td>65 (12)</td>
<td>66 (15)</td>
<td>65 (14)</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Mean BP (mmHg)</td>
<td>82 (8)</td>
<td>70 (9)</td>
<td>70 (6)</td>
<td>87 (10)</td>
<td>p&lt;0.02</td>
</tr>
<tr>
<td>SV EDV/BSA (mL/m²)</td>
<td>62 (17)</td>
<td>92 (12)</td>
<td>79 (7)</td>
<td>76 (5)</td>
<td>ns</td>
</tr>
<tr>
<td>SV ESV/BSA (mL/m²)</td>
<td>19 (9)</td>
<td>45 (6)</td>
<td>26 (12)</td>
<td>22 (10)</td>
<td>p&lt;0.005</td>
</tr>
<tr>
<td>SV sVBSA (mL/m²)</td>
<td>43 (10)</td>
<td>48 (11)</td>
<td>52 (15)</td>
<td>53 (25)</td>
<td>ns</td>
</tr>
<tr>
<td>SV EF (%)</td>
<td>71 (8)</td>
<td>52 (8)</td>
<td>84 (4)</td>
<td>70 (6)</td>
<td>p&lt;0.002</td>
</tr>
<tr>
<td>CI (l/min/m²)</td>
<td>2.7 (0.6)</td>
<td>3.2 (0.1)</td>
<td>3.4 (1.3)</td>
<td>4.8 (1.8)</td>
<td>ns</td>
</tr>
</tbody>
</table>

Table 1. BSA, body surface area; CCTGA, congenitally corrected transposition of the great arteries; PHYS, physiologically repaired; UN, unoperated; CI, cardiac index; SV, systemic ventricle; EDV, end-diastolic volume; ESV, end-systolic volume; EF, ejection fraction; BP, blood pressure; bpm, beats per minute; sv, stroke volume; ns, not significant. Values in parentheses represent standard deviation.

MAGNETIC RESONANCE IMAGING

Study subjects were placed supine in a 1.5 Tesla MRI scanner with high power gradients (Vision, Siemens, Erlangen Germany). Electrocardiogram (ECG) triggered T1-weighted turbo spin echo axial images were acquired, followed by four-chamber views of the heart. An ECG-triggered, ultrafast, breath-hold gradient-echo cine sequence with the following parameters: repetition time (TR) = R-R interval, time of echo (TE) = 4.8 ms, slice thickness 10 mm, imaging matrix = 256x256, field of view (FOV) = 350mm, flip angle = 20°, was then used to acquire images in the short axis plane in contiguous 10 mm slices. End-systolic (ESV) and end-diastolic volumes (EDV) were calculated from this multislice, multiphase image set. Velocity maps were acquired with a flip angle of 30°, TE = 5.0 ms, slice thickness = 6 mm, FOV = 320 mm and imaging matrix = 256x256, velocity encoding = 250 cm/s. The MRI protocol was repeated during dobutamine infusion, with an initial dose of 5 µg/kg/min. The 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, heart rate, systolic and diastolic blood pressures were monitored.

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. EDV and ESV frames were determined by manual outlining of a mid-ventricular slice. 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.

**Calculations**
Stroke volume (SV) was defined as EDV minus ESV, and RV ejection fraction (EF) was calculated as SV divided by EDV. The dobutamine stress values were calculated as a percentage increase from values at rest. All volumetric measurements were corrected for body surface area.

**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.

**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 comparable between patients with physiological repair, unoperated patients with ccTGA, and controls. Mean arterial blood pressure was similar amongst all 3 groups at rest, but remained lower in unoperated ccTGA patients at stress, as compared to controls. While assessing systemic ventricles, the right ventricle of patients with ccTGA, unoperated or after physiologic repair, was compared to the systemic left ventricle of controls. Baseline mean systemic ventricular end-diastolic volumes (SV EDV) were larger in the PHYS group per body surface area, as compared to controls. After dobutamine infusion, there was no significant difference in end-diastolic volumes between the three groups (Figure 1). At rest, the indexed mean systemic ventricle end-systolic volume (SV ESV) was similar amongst UN and controls, but larger with dobutamine stress in UN patients, as compared to controls. Mean SV ESV was significantly larger in the PHYS group, both at rest and with dobutamine stress, as compared to controls. Mean systemic ventricular ejection fraction was lower at baseline (p<0.002) and at stress (p<0.001) in PHYS patients, as compared to controls. Baseline mean systemic ventricular ejection fraction was similar in UN patients, as compared to controls, but was lower after dobutamine stress (p<0.005). Mean indexed systemic ventricular stroke volume, and cardiac index were similar at baseline values amongst the three groups, and increased appropriately during dobutamine infusion (Figures 2 and 3).

![SVDV](image1)

**Figure 1.** Variation of systemic ventricular end-diastolic volume (SVDV) between baseline values and after dobutamine stress. PHYS, physiologically repaired; UN, unoperated; ns, not significant.

![Percentage Change](image2)

**Figure 2.** Variations in percentage between baseline values (0) and after dobutamine stress testing. PHYS, physiologically repaired; UN, unoperated; CI, cardiac index; SV, systemic ventricle; EDV, end-diastolic volume; ESV, end-systolic volume; EF, ejection fraction; BP, blood pressure; HR, heart rate; sv, stroke volume.
DISCUSSION

This is the first study to evaluate cardiac reserve in patients with congenitally corrected transposition, either without previous operations, or after physiologic repair, using stress dobutamine MRI. MRI dobutamine provides for an accurate and reproducible quantitative assessment of RV volumes and function, and its routine use in the follow-up of patients with RV overload has been validated\textsuperscript{13-15}, to detect right ventricular dilation, and/or impending failure.

Disadvantages include the cost, and the general contraindications to MRI, namely the presence of metal implants, claustrophobia, and arrhythmia\textsuperscript{13-15}.

Assuming that the perfect result after anatomic repair entails normalization of systemic left ventricular function and reserve, the left ventricle (LV) of healthy controls was used to compare with the systemic RV of ccTGA patients. In our study, the systemic right ventricle of asymptomatic adults with unoperated ccTGA showed similar ejection fraction at rest, and lesser values at stress, as compared to the systemic left ventricle of age-matched healthy controls. Suboptimal results were noted in patients after physiologic repair. In these patients, both at baseline and at stress testing, we found larger systemic ventricular end-systolic volumes. Also, baseline systemic ventricular end-diastolic volumes were larger after physiologic repair, as compared to controls. As a snapshot value, the significance of this is unknown, and difficult to interpret. Is this the result of surgical insult to the right ventricle, the result of long-standing volume overload of the RV, or the normal response of a morphologic right ventricle, when chronically faced with systemic pressures? Furthermore, what are the true implications of these morphometric deviations, in light of an apparent proper response to effort? Indeed, with stress testing, we found cardiac index to increase appropriately in both subsets of patients with ccTGA, without undue increase in heart rate or mean blood pressure, as compared to controls.

![Cardiac index](image)

Figure 3. Variation of cardiac index between baseline values and after dobutamine stress. PHYS, physiologically repaired; UN, unoperated.
Symptomatic patients with ccTGA were originally treated with a combination of surgical procedures, either palliative or corrective, known as the "classical" or physiological repair of ccTGA, leaving the right ventricle and tricuspid valve in the systemic circulation. In general, the results of physiological repair have been disappointing, despite an acceptable operative mortality rate of 2-15%1,8,10,16,17. In a 40-year review from the Toronto Hospital for Sick Children including 118 patients having undergone a physiological repair for ccTGA, Yeh et al. reported a 6% operative mortality.1 However, 10 years after repair, survival was only 74%, and at 20 years, an unsatisfactory 48%. Termignon, et al. reported an even more concerning 55% survival rate at 10 years, when obstruction to the pulmonary ventricle was associated.16 Major concerns with physiological repair include the non-negligible incidence of complete heart block (14-38%)8,10,16,18, the frequent need for reoperation on the tricuspid valve (Figure 4), but more importantly, long term failure of the right ventricle which must chronically sustain systemic pressures.

These imperfections led to the development of the anatomic repair concept, combining an atrial and arterial switch, also known as the double switch, or an atrial switch with a Rastelli procedure in patients with left ventricular outflow tract obstruction19. The current operative mortality after anatomic repair varies between 0-15%6,11,12,19,22. However, anatomic repair is not exempt of its own set of complications, and increasing concern is present as to the long term development of atrial dysrhythmias and venoatrial obstructions, which are well-documented after the atrial switch procedures.5,12,19,21,22. Furthermore, certain timing issues remain unanswered. The proponents of the anatomic repair insist on the better outcome of the procedure when it is performed in a younger age group, namely before 15-16 years of age.6,11. This presumably relates to the degree to which the left ventricle may be retrained as the neo-systemic ventricle, by pulmonary artery banding13. Indeed, older patients have higher early and late mortality when submitted to the anatomic repair protocol, and the results of LV retraining have been more uncertain when performed after the age of 15 years11.

The driving impetus towards the development of the anatomic repair of ccTGA stems from the preformed concept that a left ventricle, with or without retraining, will ultimately better perform in the systemic circulation than the right ventricle. However, there is no long-term data to
support this. In a series of 27 patients undergoing anatomic repair without early or late mortality, Imamura, et al. reported normal postoperative ejection fractions of both left and right ventricles, as assessed by echocardiography, at the time of hospital discharge, without further follow-up. Imai, et al. reported an operative mortality of 7.9% in a series of 76 patients with ccTGA, who underwent anatomic repair under 16 years of age. At a mean postoperative follow-up of 4.9 years, they actually observed a slight decrease in left ventricular ejection fraction, no increase in RV ejection fraction, and unchanged left ventricular end-diastolic volumes. Yagihara, et al. found subnormal postoperative left ventricular ejection fractions as assessed by cardiac catheterization, at a mean follow-up of 11 months after anatomic repair, in their series of 10 patients.

Frequent failure of the right ventricle to chronically function as a systemic ventricle is another driving force to promote anatomic repair. However, findings across the literature differ, and multiple reports of normal adult survival without limitation to effort or arrhythmia exist, in unoperated ccTGA without associated intracardiac anomalies (Figure 5). Peterson, et al. compared 17 children after atrial baffle procedures for complete transposition of the great arteries, with 8 unoperated patients with uncomplicated ccTGA, and 10 normal controls. Using radionuclide angiography, stress testing revealed a normal increase in pulmonary ventricular ejection fraction in patients with ccTGA, as compared to controls. However, the systemic ventricle of patients with ccTGA did not significantly increase their ejection fractions with exercise, and both end-diastolic and end-systolic volumes were larger than controls. Cardiac index augmented appropriately in all groups, mainly due to an increase in heart rate in the ccTGA group. In accordance with these findings, Parrish, et al. found subnormal increases in right and left ventricular ejection fractions in response to effort in 5 children with ccTGA, although their exercise capacity, heart rate and blood pressure responded appropriately.

Supporting our findings, Benson, et al. found normal systemic right ventricular ejection fractions at exercise, in 8 patients with uncomplicated and unoperated ccTGA, while the function of the pulmonary ventricle was subnormal. In their study using radionuclide angiography, end-diastolic and systolic volumes of the systemic right ventricle decreased appropriately, from rest to exercise.

Surgery is inevitable and clearly warranted in one form or another for symptomatic patients presenting in failure or cyanosis. In patients with associated intracardiac anomalies, such as pulmonary valve stenosis, Ebstein’s malformation with severe insufficiency of the tricuspid valve, or important degrees of intracardiac shunting, early right ventricular dilation and failure occurs, indicating early surgical intervention. For these patients, we acknowledge the anatomic repair as the surgical procedure of choice. However, we question the recommendation for anatomic repair in asymptomatic patients by some, based on echocardiographic evidence of an enlarged right ventricle and tricuspid valve insufficiency. Our findings and other evidence of satisfactory long-term RV function in unoperated adults with ccTGA would suggest a more conservative attitude in the management of asymptomatic patients, which includes patients with and without associated lesions. Although it is intuitive and generally agreed that asymptomatic patients with ccTGA and intact ventricular septum require no surgery, they represent a minority. Given the potential complications of both surgical pathways and the relative unfavorable long-term outcome of physiological repair, we make a case for surgical abstinence even in ccTGA patients with associated lesions. Indeed, 5 out of 7 of our studied patients with unoperated ccTGA have intracardiac anomalies, but are otherwise asymptomatic, without medication, have near normal ventricular volumes, and respond appropriately to stress testing.
In conclusion, defining the eventual subsets of patients with ccTGA who may never require an operation is of paramount clinical importance. With current diagnostic modalities, no such definition exists, and the therapeutic dilemma persists. Even respectable centers with a larger experience of the anatomic repair provide no long-term follow-up data to demonstrate improved systemic left ventricular function postoperatively. Accordingly, the open-ended question remains as to the true benefit and age cut-off to perform an anatomic repair in asymptomatic patients with ccTGA. Robust evidence is needed before more ccTGA patients with normally functioning right ventricles are enrolled in anatomic repair protocols. In those asymptomatic or minimally symptomatic patients, the use of a non-invasive follow-up modality such as MRI dobutamine stress could help to define morphologic and hemodynamic criteria justifying non-operative management. As a corollary, deviations from these criteria, especially in asymptomatic patients, could serve as an early indicator of impending cardiac failure, and indicate timely surgical intervention, preferably in the form of anatomic repair.

STUDY LIMITATIONS
Our ongoing MRI dobutamine stress protocol strives to define non-invasive criteria, whereby asymptomatic patients with ccTGA may be judged as not requiring surgery, or on the contrary, in impending failure and candidates for a timely anatomic repair. The small number of patients diminishes statistical power, which limits the significance of our results, and does not yet allow for a clear-cut management protocol according to the sought-after criteria. To date, perhaps by unfortunate serendipity, we have had no patients enrolled who either presented initially with normal values, which then degraded over time, or presented in failure with highly abnormal MRI dobutamine stress values. These findings would strengthen the definitions of “normality” and deviations therefrom.

Using the LV of controls as a measuring stick to compare with the RV of patients with ccTGA is a potential weakness of the study. Although the two respective ventricles perform the same function in each group, their intrinsic morphology and geometry clearly differ.

As a group, patients with ccTGA present with a wide variety of morphology and resulting physiology, making generalizations and recommendations across such a heterogeneous group hazardous. Owing to unfavorable anatomy and physiology in many instances, we fully recognize that anatomic repair is often inevitable and indicated. Our data only illustrates and quantifies the potential for a morphologic right ventricle to sustain the systemic circulation, even in the presence of associated intracardiac lesions. This view is supported by other reports, which show normal exercise tolerance and quality of life, in asymptomatic and unoperated adults with ccTGA.

23,24
REFERENCES


