Right ventricular absolute myocardial blood flow in complex congenital heart disease

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Right ventricular absolute myocardial blood flow in complex congenital heart disease

Tobias Rutz, Stefano F de Marchi, Markus Schwerzmann, Rolf Vogel, Christian Seiler

ABSTRACT

Objective A consequence in patients with d-transposition of the great arteries (d-TGA) and tetralogy of Fallot (TOF) is right ventricular hypertrophy (RVH) and right ventricular failure. Myocardial contrast echocardiography (MCE) permits the determination of the myocardial microvascular density reflected by the relative myocardial blood volume (rBV; ml/ml). This study was conducted to elucidate the relationship between RVH and myocardial microvascular changes by quantitative MCE in patients with d-TGA and TOF.

Methods Three groups of individuals were included in the study: 22 patients with d-TGA, 18 patients with TOF and 22 healthy individuals (controls). MCE was performed at rest and during adenosine-induced hyperaemia. RVB and myocardial blood flow (MBF; ml/ min per gram) were derived from steady state and refill sequences of ultrasound contrast agent.

Results Hyperaemic septal rBV differed significantly between the groups and was highest in controls: d-TGA 0.141±0.080 ml/ml, TOF 0.134±0.080 ml/ml, controls 0.189±0.074 ml/ml, p=0.005. Myocardial blood flow reserve (MBFR), that is the ratio of hyperaemic to baseline MBF, differed significantly between the groups and was lowest in d-TGA (2.68±1.13) versus TOF (3.37±1.57) and controls (4.22±1.17, p=0.001). Hyperaemic septal rBV, MBF and MBFR showed a significant correlation with right ventricular systolic function as determined by tricuspid annular plane systolic excursion.

Conclusions Right ventricular myocardial microvascular density of the septal wall in d-TGA and TOF patients with RVH due to pressure and/or volume overload is reduced. This appears to be related to a reduced myocardial perfusion reserve and impaired right ventricular systolic function.

Patients with congenital heart disease (CHD) in whom the right ventricle is exposed to pressure or volume overload present with progressive systolic right ventricular dysfunction, the fact of which conveys substantial morbidity and mortality.

Surgical treatment of patients with d-transposition of the great arteries (d-TGA) by the atrial switch procedure implies a systemic right ventricle, which has to sustain systemic arterial resistance leading to pathological hypertrophy and finally to right ventricular failure with elevated mortality. Right ventricular hypertrophy (RVH) increases myocardial oxygen demand leading to ischaemia, as shown by several studies.

In tetralogy of Fallot (TOF), the aim of surgical repair is to relieve right ventricle outflow tract (RVOT) obstruction and to close the ventricular septal defect. Although the postoperative survival rate is excellent, follow-up studies have elucidated the consequences of chronic pulmonary regurgitation due to generous transannular patch-type repair resulting in right ventricular volume overload. This leads to eccentric RVH with impaired systolic right ventricular function. The mechanisms of right ventricular failure in d-TGA and TOF remain unclear. In left ventricular pathological hypertrophy microvascular density is reduced relative to myocardial mass. In contrast, little information is available according vascular density and myocardial blood volume in RVH. Quantitative myocardial contrast echocardiography (MCE), which has been validated and applied to left ventricular pathologies, allows the measurement of absolute myocardial blood flow (MBF; ml/min per gram) and its constituents, relative myocardial blood volume (rBV, ml/ml) and the volume exchange frequency β (per min). MBF is the product of rBV and the volume exchange frequency β divided by myocardial density.

rBV, determined by quantitative MCE, reflects myocardial arteriolar and capillary density. Our study aims at elucidating the differences in microvascular density and myocardial perfusion in patients with d-TGA and TOF compared with a healthy control group.

Therefore, the goal of this study is to test the following hypotheses:

1. MCE-derived right ventricular rBV is smaller in patients with CHD than in the systemic ventricle of an adult healthy control group.
2. MCE obtained myocardial blood flow reserve (MBFR) of the right ventricle (ie, the ratio of hyperaemic to resting perfusion) is smaller in patients with CHD than in the systemic ventricle of controls.

METHODS

Study individuals

Three groups of individuals were included in the study: 22 patients with d-TGA (nine women), 18 patients with TOF (nine women) and 22 healthy controls (nine women). Both patient groups consisted of individuals who presented for yearly follow-up examinations. The healthy control group consisted of individuals with a normal Doppler echocardiographic examination and no history of cardiopulmonary or other relevant disease.

The study protocol was approved by the Ethics Committee of the Kanton of Bern, Switzerland, and all the participants gave written informed consent to participate in the study.

Study protocol

All subjects abstained from methyl-xanthines including caffeine for at least 24 h before the start.
of the protocol. Baseline echocardiography was performed in all participants. Patients with right to left shunt as well as those with an internal cardiodefibrillator were excluded from the study due to contraindications for the administration of Sonovue.

In all individuals, the right ventricular diameter at tricuspid and mid-ventricular level and the mid-ventricular right ventricular wall thickness at end-diastole were obtained. A right ventricular wall thickness of 5 mm or greater served as cut-off for RVH.

Right ventricular systolic function was measured using the tricuspid annular plane systolic excursion (TAPSE, mm).

All patients underwent supine bicycle stress echocardiography with an increase of workload every 2 min by 25 Watt starting with 25 Watt. The percentage of predicted workload was calculated by dividing the achieved workload by the age-predicted workload.

Myocardial contrast echocardiography

Data acquisition

A Sequoia C512 ultrasound scanner (Siemens Medical Solutions, Mountain View, California, USA) equipped with a 4V1c transducer and the contrast echo software CFS (Coherent Pulse Sequences) was used for real-time MCE. The machine settings were as follows: mechanical index for microsphere detection less than 0.20; mechanical index for microsphere destruction 1.3; dynamic range 50dB; linear post-processing; clip length 500 frames with intervals of 75 ms for rest and stress imaging, respectively. Refill sequences were generated using the manual bubble destruction feature of the scanner and were captured digitally for offline quantification. Images for MCE were obtained from apical chamber views (d-TGA, TOF; controls) and parasternal long axis (PLAX) views (d-TGA, TOF).

The ultrasound contrast agent V08DA (SonoVue, Bracco SA, Mendrisio, Switzerland) was infused into the right cubital vein at a constant rate of 0.5–1 ml/min. At rest, saline was infused at a rate of 2.8 ml/kg per hour as a substitute for the adenosine infusion in order to have the same steady state concentration of the contrast agent in the intravascular compartment as during hyperaemia. When stable myocardial enhancement was reached, the contrast infusion rate was kept constant, and baseline image acquisition was performed. Steady state and refill sequences of contrast agent were derived before and after microsphere destruction, respectively. After completion of resting perfusion sequences, contrast and saline infusion were stopped, and hyperaemia was induced by intravenous adenosine 140 μg/kg per minute (adenosine 3 mg/ml diluted in NaCl 0.9%) over a parallel port resulting in an infusion rate of 2.8 ml/kg per hour. After 5 min of adenosine infusion, contrast infusion was started at the same rate as during resting conditions. After 6 min of adenosine infusion, hyperaemia perfusion sequences were obtained. Examinations and analyses were performed by a single observer (TR).

Data analysis

Offline image analysis and quantification were performed with customised Matlab software. Logarithmic signal compression was removed, and linearised signal intensity data were expressed in arbitrary units (AU). MBF was calculated as previously described and validated by our group.12 End-systolic frames were selected for analysis. Regions of interest (ROI) were placed as follows: in d-TGA and TOF in the basal and mid-right ventricular free wall from the apical four-chamber view as well as in the mid-lateral segment from the PLAX view. In all three groups ROI were also placed in the midseptal segment. The ROI were tracked manually within the myocardium and in the adjacent right ventricular cavity for d-TGA and in the left ventricle for TOF and controls, respectively. Myocardial intensity data were corrected for non-contrast signals arising from the tissue by subtracting the signal intensity of the first frame after manual bubble destruction. Myocardial plateau signal intensity A was calculated by averaging the myocardial signal intensity data from end-systolic frames before manual bubble destruction. Averaging adjacent left ventricle signal intensities of all end-systolic frames except those during and the first two after manual bubble destruction yielded the signal intensity in the nearly left ventricle A_{LV}; rBV in ml/ml was calculated according to the following equation:

\[
rBV = A/A_{LV}.
\]

The product of rBV and \( \beta \) divided by tissue density (1.05 g/ml) yielded MBF. MBFR was calculated as the ratio of hyperaemic and resting MBF.

Statistical analysis

Data are expressed as mean value±SD. All statistical tests were two-sided. Between-group comparison of categorical parameters was performed by the \( \chi^2 \) test. Between-group comparison of continuous demographic, echocardiographic, microvascular circulation parameters and ergometry data were performed by analysis of variance followed by Scheffe’s test for post-hoc analysis. Correlations were assessed using linear regression analysis. The statistical level of significance was defined at a value of p<0.05.

RESULTS

Patient characteristics

The characteristics of the patients are depicted on table 1. No differences existed between the groups regarding age, gender, body mass index and body surface area. Diastolic blood pressure was lowest in the controls. By definition, all healthy control individuals had a normal Doppler echocardiogram and no history of cardiac disease or other relevant health problems. The groups of d-TGA and TOF patients presented with a significant decreased exercise capacity compared with controls (table 1).

The d-TGA group consisted of 14 patients with atrial switch operation according to Senning1 and eight with a Mustard2 procedure. In the TOF group, 17 patients had undergone ventricle septal defect patch closure, six RVOT resection or enlargement and/or pulmonary patch enlargement, eight pulmonary valvulotomy, four right ventricular myectomy, three atrial septal defect closure and five implantation of a pulmonary conduit. At study inclusion, three d-TGA patients were equipped with a pacemaker for sinus node disease. Significant pulmonary regurgitation was present in 11 TOF patients (four of moderate, seven of severe degree). Mild left ventricle outflow tract obstruction was present in two d-TGA patients. Pulmonary stenosis or RVOT obstruction was present in eight TOF patients, one of severe degree.
Congenital heart disease

Table 1  Study population characteristics

<table>
<thead>
<tr>
<th></th>
<th>d-TGA</th>
<th>TOF</th>
<th>Controls</th>
<th>p Value (all)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of individuals</td>
<td>22</td>
<td>18</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>27±6</td>
<td>31±11</td>
<td>27±6</td>
<td>0.336</td>
</tr>
<tr>
<td>Men</td>
<td>13</td>
<td>10</td>
<td>13</td>
<td>0.968</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>22±2</td>
<td>24±3</td>
<td>24±10</td>
<td>0.697</td>
</tr>
<tr>
<td>Body surface area (m²)</td>
<td>1.81±0.22</td>
<td>1.78±0.18</td>
<td>1.74±0.18</td>
<td>0.551</td>
</tr>
<tr>
<td>Haemodynamic variables at rest</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>62±12</td>
<td>63±15</td>
<td>73±13</td>
<td>0.051</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>111±11</td>
<td>116±14</td>
<td>106±10</td>
<td>0.055</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>71±8</td>
<td>71±9</td>
<td>62±8*</td>
<td>0.001</td>
</tr>
<tr>
<td>Haemodynamic variables, hyperaemia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>84±22</td>
<td>80±16</td>
<td>82±19</td>
<td>0.846</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>109±9</td>
<td>109±13</td>
<td>107±10</td>
<td>0.786</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>67±10</td>
<td>67±11</td>
<td>63±8</td>
<td>0.455</td>
</tr>
<tr>
<td>Supine bicycle stress test parameters</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximum workload achieved (Watt)</td>
<td>122±34</td>
<td>136±48</td>
<td>185±40†</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Percentage of predicted workload</td>
<td>70±13</td>
<td>83±26</td>
<td>104±19†</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

d-TGA, d-transposition of the great arteries; TOF, tetralogy of Fallot.
*p<0.05 controls to d-TGA.
†p<0.0001 controls to d-TGA and TOF.
‡p<0.005 controls to d-TGA and TOF.

Systemic hypertension was present in one patient in both groups of d-TGA and TOF and a family history of coronary artery disease in one individual of the controls. Seven individuals in d-TGA, three in TOF and two in the control group had a history of smoking. Five individuals with d-TGA and one with TOF took beta-blockers, 10 patients with d-TGA and three with TOF used ACE inhibitors or angiotensin receptor 1 blockers, which was significantly different to the group of control individuals. One TOF patient took a statin, three patients used diuretics (one d-TGA, two TOF) and five patients were taking oral anticoagulation: three d-TGA, two TOF (all not significant).

Doppler echocardiographic parameters

Doppler echocardiographic data are summarised in table 2. Significant differences were found regarding systolic left ventricular function and end-diastolic diameter with the highest left ventricular ejection fraction and lowest left ventricular end-diastolic diameter in d-TGA patients. Systolic right ventricular function and right ventricular diameter also differed significantly with the highest right ventricular ejection fraction in controls and the lowest end-diastolic diameter also in controls.

MCE data

Feasibility of MCE according to myocardial regions

MCE was feasible in 100% in the septal region of all three groups. Right ventricular free wall measurements from the apical view could be obtained in 50% with d-TGA and in one patient with TOF. Measurements of right ventricular free wall from the PLAX view were feasible in 81% with d-TGA and 94% with TOF. No right ventricular free wall measurements from either the apical or PLAX view were possible in controls.

Comparison of perfusion parameters between groups

Resting and hyperaemic perfusion parameters for each group are depicted in table 3. Resting myocardial perfusion parameters did not differ in the septal region between the groups. Hyperaemic rBV differed significantly between the three groups and was highest in controls (figure 1). Hyperaemic MBF was significantly reduced in d-TGA compared with TOF and controls. MBFR in d-TGA and TOF differed significantly to controls and was highest in controls. Right ventricular perfusion parameters were similar between d-TGA and TOF.

Four patients with TOF and normal systolic right ventricular function showed no difference to controls regarding hyperaemic septal rBV, MBF and MBFR (table 4).

Perfusion parameters and systolic right ventricular function

Hyperaemic septal rBV, MBF as well MBFR showed a significant correlation with the right ventricular systolic function parameter TAPSE (figure 2): rBV 0.051+0.04 TAPSE, r=0.574, p=0.008; MBF 4.68+0.107 TAPSE, r=-0.501, p=0.001, MBFR, see figure 2.

Right ventricular free wall hyperaemic MBF but not resting MBF and MBFR correlated significantly with right ventricular systolic function: Resting MBF 0.377+0.027 TAPSE, r=0.248, p=0.150; hyperaemic MBF, see figure 3.

DISCUSSION

Systolic right ventricular failure was identified as a risk factor for mortality and adverse events in patients with d-TGA and systemic right ventricle and in corrected TOF.1 4 15 The common denominator in both entities is RVH. In the present study we document for the first time a reduced myocardial microvascular density in the ventricular septal region of patients with corrected d-TGA and TOF, which is, by means of impaired perfusion, directly related to right ventricular systolic function.

d-Transposition of the great arteries

RVH in our d-TGA patients is caused by pure pressure overload as no patient had aortic regurgitation. rBV and MBF during hyperaemia as well as MBFR were reduced. Under physiological conditions the coronary artery lumen area and the downstream myocardial mass present a curvilinear relationship. This is

Table 2  Echocardiographic parameters

<table>
<thead>
<tr>
<th></th>
<th>d-TGA</th>
<th>TOF</th>
<th>Controls</th>
<th>p Value (all)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left ventricle</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left ventricular ejection fraction (%)</td>
<td>72±9*</td>
<td>62±6</td>
<td>63±4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Left ventricular end-diastolic diameter (mm)</td>
<td>37±9†</td>
<td>44±4</td>
<td>48±5</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Interventricular septum (end-diastolic, mm)</td>
<td>10±2</td>
<td>11±2</td>
<td>9±2</td>
<td>0.057</td>
</tr>
<tr>
<td>Posterior wall (end-diastolic, mm)</td>
<td>6±2</td>
<td>8±2</td>
<td>8±2</td>
<td>0.077</td>
</tr>
<tr>
<td>Left ventricular mass index (g·m⁻³)</td>
<td>49±31†</td>
<td>84±30</td>
<td>86±24</td>
<td>0.003</td>
</tr>
<tr>
<td>Right ventricle</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tricuspid annulus diameter (mm)</td>
<td>35±5</td>
<td>34±6</td>
<td>27±45†</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Right ventricular free wall thickness (mm)</td>
<td>12±0.3</td>
<td>9.1±0.3</td>
<td>4.2±0.1</td>
<td>&lt;0.0015</td>
</tr>
<tr>
<td>Mid-ventricular right ventricular diameter (mm)</td>
<td>43±7</td>
<td>39±8</td>
<td>29±6‡</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TAPSE (mm)</td>
<td>10±4</td>
<td>17±4</td>
<td>24±3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diastolic left ventricular parameters</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early diastolic peak flow velocity (cm/s)</td>
<td>92±23</td>
<td>82±13</td>
<td>0.118</td>
<td></td>
</tr>
<tr>
<td>Late diastolic peak velocity (cm/s)</td>
<td>57±16</td>
<td>46±12</td>
<td>0.026</td>
<td></td>
</tr>
<tr>
<td>E/A (early to late diastolic flow velocity)</td>
<td>1±0.8</td>
<td>1.9±0.6</td>
<td>0.518</td>
<td></td>
</tr>
<tr>
<td>Early diastolic deceleration time (ms)</td>
<td>158±40</td>
<td>173±27</td>
<td>0.195</td>
<td></td>
</tr>
<tr>
<td>Isovolumetric relaxation time (ms)</td>
<td>83±14</td>
<td>75±10</td>
<td>0.05</td>
<td></td>
</tr>
</tbody>
</table>

d-TGA, d-transposition of the great arteries; TAPSE, tricuspid annular plane systolic excursion; TOF, tetralogy of Fallot.
*p<0.001 d-TGA to controls and TOF.
†p<0.05 d-TGA to controls and TOF.
‡p<0.005 controls to d-TGA and TOF.

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expressed by a 2/3 power law relating vascular area to regional mass. Different physiological and pathological stimuli can provoke an increase in myocardial mass. Endurance exercise leads to physiological hypertrophy, which is characterised by a proportional increase in myocardial mass and vascularisation. With pressure overload, however, the vascularisation only incompletely follows the increase in myocardial muscle mass. Histologically, an increased level of fibrosis and apoptosis is observed. The increased ventricular wall stress during pressure overload leads to augmented wall thickness in order to keep it constant and within normal limits. In coronary arteries and also according to La Place’s law, an increased pulse pressure leads to hyperplasia of the media. It is well known that pathological left ventricular hypertrophy is related to an exhausted autoregulation of the microcirculation with reduced vasodilatory capacity. The present study demonstrates similar results for the systemic right ventricle, that is, an impaired microcirculation reflected by a reduced rBV with impaired vasodilatory capacity in patients with RVH.

Such a mismatch of myocardial mass and microvasculature has not been shown in humans but in experimental studies. In dogs with RVH due to pressure overload, the microvascular density and its cross-sectional area are decreased. At the capillary level, this may result in an increase in the diffusion distance for oxygen to the mitochondria. Consequently, the resistance vessels are predilated at rest, which leads to a reduced dilatation capacity. In rats with congenital pulmonary stenosis, microcirculatory density was inadequate in contrast to rats with adult onset of pulmonary stenosis, thus highlighting the relevance of the onset of hypertrophy with regard to the microcirculatory sequelae. The changes in the microvascular level lead to a reduced vasodilatory capability and coronary flow reserve, which is also seen in our patient group.

Myocardial Doppler tissue imaging echocardiography and cardiac MRI studies have demonstrated an impaired right ventricular systolic function and wall motion abnormalities in d-TGA patients, the latter had been linked to impaired perfusion. Patients with TOF present with right ventricular dilatation and systolic dysfunction, a finding also seen in our study, that is, a linear correlation was found between the hyperaemic septal, the right ventricular MBF and the septal MBFR to right ventricular systolic function.

### Tetralogy of Fallot

TOF patients present with right ventricular dilatation and hypertrophy. The principal cause is believed to be right ventricular volume overload in the context of pulmonary regurgitation due to transvalvular patch repair of RVOT obstruction. It can be expected that in pure volume overload, the vascularisation follows more adequately the muscle mass increase. In our patient group with TOF, a reduced microcirculatory density was found in the septal region. This is probably due to the fact that on average TOF is not a picture of pure right ventricular volume but a mixed pressure/volume overload. In a volume overload rat model, no differences to normal controls have been found regarding the volume density of cardiomyocytes.

### Table 3  Myocardial blood flow parameters

<table>
<thead>
<tr>
<th>Septal region</th>
<th>d-TGA</th>
<th>TOF</th>
<th>Controls</th>
<th>p Value (all)</th>
</tr>
</thead>
<tbody>
<tr>
<td>rBV, rest (ml/ml)</td>
<td>0.13±0.043</td>
<td>0.154±0.099</td>
<td>0.119±0.047</td>
<td>0.296</td>
</tr>
<tr>
<td>MBF, rest (ml/min per gram)</td>
<td>6.8±0.36</td>
<td>0.80±0.32</td>
<td>0.82±0.41</td>
<td>0.391</td>
</tr>
<tr>
<td>MBF, hyperaemia (ml/ml)</td>
<td>0.132±0.042</td>
<td>0.124±0.063</td>
<td>0.189±0.074</td>
<td>0.005</td>
</tr>
<tr>
<td>MBF, hyperaemia (ml/min per gram)</td>
<td>1.42±0.68</td>
<td>2.44±1.40</td>
<td>3.27±1.42</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MBFR</td>
<td>2.68±1.13</td>
<td>3.37±1.57</td>
<td>4.22±1.17</td>
<td>0.001</td>
</tr>
<tr>
<td>Right ventricular free wall PLAX</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>rBV, rest (ml/ml)</td>
<td>0.098±0.043</td>
<td>0.12±0.068</td>
<td></td>
<td>0.188</td>
</tr>
<tr>
<td>MBF, rest (ml/min per gram)</td>
<td>6.8±6.3</td>
<td>7.9±7.8</td>
<td></td>
<td>0.065</td>
</tr>
<tr>
<td>MBF, hyperaemia (ml/ml)</td>
<td>0.527±0.33</td>
<td>0.79±0.48</td>
<td></td>
<td>0.072</td>
</tr>
<tr>
<td>MBF, hyperaemia (ml/min per gram)</td>
<td>1.29±0.063</td>
<td>1.63±0.083</td>
<td></td>
<td>0.219</td>
</tr>
<tr>
<td>MBFR</td>
<td>3.44±1.353</td>
<td>3.370±2.041</td>
<td></td>
<td>0.908</td>
</tr>
</tbody>
</table>

* p<0.013 controls to TOF, p<0.029 controls to d-TGA.

† p<0.01 d-TGA to TOF, p<0.032 d-TGA to controls.

‡ p<0.001 TOF to d-TGA.

§ p<0.001 TOF to d-TGA.

¶ p<0.001 controls to d-TGA.

### Figure 1  Hyperaemic septal myocardial blood volume in d-transposition of the great arteries (d-TGA), tetralogy of Fallot (TOF) and healthy controls (C). Hyperaemic septal relative myocardial blood volume (rBV in ml/ml, vertical axis) in the different study groups. Box plots indicate the three groups of d-TGA, TOF and healthy controls.

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*Congenital heart disease*


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and connective tissue, whereas in the pressure overload model the volume density of cardiomyocytes decreased and the connective tissue increased. Capillary density remained constant in the pressure overload group. As outlined before, the TOF group represents a mixed picture of pathologies. In 11 of 17 patients volume overload due to significant pulmonary regurgitation was present. In eight patients pressure overload as a consequence of insufficiently corrected RVOT obstruction in addition to volume overload contributed to the variability of our findings. Also, until surgical correction of the RVOT obstruction, all patients were exposed to pressure overload, which induced concentric RVH. Our study was too small to show differences between the two subgroups of patients with and without significant pulmonary regurgitation. In one third of our TOF patients presented with normal right ventricular systolic function in contrast to d-TGA patients, who all had a reduced right ventricular systolic function. The patients with normal right ventricular systolic function showed no differences in hyperaemic rBV, MBF or MBFR compared with the group of healthy controls (table 4).

**Clinical implications**

Patients with systemic right ventricles are known to have a reduced perfusion reserve in positron emission tomography examinations, which correlates with the exercise capacity. As one mechanism a reduced capillary density is discussed, which we were able to document. In our study all participants underwent a supine bicycle stress test. A direct relationship was found between the impaired septal perfusion reserve and exercise capacity (septal MBFR $1.915\pm0.016$ percentage of predicted workload, $r=0.312$, $p=0.023$). This is consistent with the findings in dogs with experimentally induced RVH. Contrary to the present study and the aforementioned positron emission tomography perfusion study, a single-photon emission CT study has found a surprising discrepancy between perfusion defects and exercise tolerance. However, the patient group examined was much younger than our study group (mean 13 years).

### Table 4

Comparison of septal perfusion parameters between the groups with normal versus impaired right ventricular systolic function determined by right ventricular DTI (cut-off 11 cm/s)

<table>
<thead>
<tr>
<th>Group</th>
<th>Right ventricular DTI $\geq11$ cm/s</th>
<th>Right ventricular DTI $&lt;11$ cm/s</th>
<th>Controls</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>rBV, rest (ml/ml)</td>
<td>0.13±0.043</td>
<td>0.182±0.129</td>
<td>0.147±0.091</td>
<td>0.119±0.0470</td>
</tr>
<tr>
<td>MBF, rest (ml/min per gram)</td>
<td>0.68±0.36</td>
<td>0.99±0.45</td>
<td>0.745±0.266</td>
<td>0.82±0.41</td>
</tr>
<tr>
<td>rBV, hyperaemia (ml/ml)</td>
<td>0.132±0.042</td>
<td>0.148±0.03</td>
<td>0.115±0.071</td>
<td>0.189±0.074*</td>
</tr>
<tr>
<td>MBF, hyperaemia (ml/min per gram)</td>
<td>1.42±0.68</td>
<td>2.97±1.14</td>
<td>2.24±1.47</td>
<td>3.27±1.42†</td>
</tr>
<tr>
<td>MBFR</td>
<td>2.68±1.13</td>
<td>3.49±1.88</td>
<td>2.96±1.35</td>
<td>4.22±1.175§</td>
</tr>
</tbody>
</table>

- d-TGA, d-transposition of the great arteries; DTI, Doppler tissue imaging; MBF, myocardial blood flow; MBFR, myocardial blood flow reserve; TOF, tetralogy of Fallot; rBV, relative myocardial blood volume.
- *$p=0.027$ controls to TOF right ventricular DTI $<11$ cm/s.
- †$p=0.067$ controls to d-TGA.
- ‡$p=0.001$ controls to d-TGA.
- §$p=0.005$ controls to d-TGA and $p=0.076$ controls to right ventricular DTI $<11$ cm/s.

**Figure 2** Relationship of septal myocardial blood flow reserve (MBFR) and right ventricular systolic function. Linear regression analysis of the septal MBFR (vertical axis) and the right ventricular systolic function (horizontal axis), determined by tricuspid annular plane systolic excursion. C, healthy controls; d-TGA, d-transposition of the great arteries; TOF, tetralogy of Fallot.

**Figure 3** Relationship of hyperaemic right ventricular (RV) myocardial blood flow (MBF) and right ventricular systolic function. Linear regression analysis of hyperaemic right ventricular MBF (vertical axis) and right ventricular systolic function (horizontal axis), determined by tricuspid annular plane systolic excursion. d-TGA, d-transposition of the great arteries; TOF, tetralogy of Fallot.
Study limitations
One limitation is the reduced number of participants in the group with TOF. As TOF patients present mainly with a good quality of life, they appear to be less interested in participating in scientific studies. Another limitation is that we were not able to obtain reliable MCE measurements in the right ventricular free wall from the apical view. Even in very hypertrophied right ventricles, MCE measurements remained difficult, most probably due to motion artefacts by the lung. Therefore, the PLAX view was chosen. No measurements in the right ventricular free wall were possible in controls, probably also due to motion artefacts and a too thin myocardium. The exact mechanism of why vascular growth does not follow the development of myocardial mass is unclear. With our data we are not able to distinguish cause from effect of this relationship. We only indirectly show a relationship of impaired septal MBFR and right ventricular systolic function. Further studies are needed to elucidate the relationship of impaired myocardial perfusion and right ventricular systolic function. In contrast to patients with arterial hypertension resting rBV was not decreased in d-TGA and TOF patients compared with controls. Probably the early onset of the stimulus preserves capillarisation. In arterial hypertension in addition structural changes of the capillaries with an increase of media thickness develops. The onset of hypertrophy probably plays an important role, as in rats with congenital pulmonary stenosis a normal vascularisation was observed. Therefore, congenitally corrected transposition of the great arteries would be a better model for studying the onset of hypertrophy. Provenance and peer review

REFERENCES


Images in cardiology

Pacemaker-mediated tachycardia

A patient with a dual-chamber permanent pacemaker for complete heart block presented with chest discomfort and a sensation of his heart fluttering. His electrocardiogram demonstrated a broad complex tachycardia (panel A). The presence of pacing spikes preceding each broad complex beat led to a diagnosis of pacemaker-mediated tachycardia (PMT). The arrhythmia responded to his pacemaker being reprogrammed with a longer postventricular atrial refractory period (PVARP).

Pacemaker-mediated tachycardia is a malfunction of dual-chamber pacing, in this case relying on retrograde atrioventricular conduction. A ventricular impulse such as a ventricular ectopic conducts retrogradely through the atrioventricular node to the atrium: normally, the pacemaker ignores atrial signals for a set period after a ventricular signal (termed PVARP), but if the retrograde impulse arrives after this blanking period, it is interpreted as a legitimate p-wave. The pacemaker then sends a pacing impulse to the ventricle, which can again conduct retrogradely to the atrium, and the process repeats, creating a tachycardia circuit. The acute treatment for this arrhythmia is the external application of a magnet on the pacemaker. This forces the pacemaker to pace at a fixed rate, ignoring the impulses it receives through its leads (VOO mode), so breaking the tachycardia circuit. Prevention of recurrence involves lengthening the PVARP, so the retrograde atrial signal falls within the blanking period and is not misinterpreted as a legitimate p-wave.

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Competing interests None.
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Panel A Electrocardiograms: (A) A broad complex tachycardia with pacing spikes (arrowed) preceding each broad complex beat. (B) After pacemaker reprogramming, showing dual-chamber pacing.