**Myocardial Blood Flow in Patients With Transposition of the Great Arteries**

– Risk Factor for Dysfunction of the Morphologic Systemic Right Ventricle Late After Atrial Repair –

Michael Hauser, MD, PhD; Christian Meierhofer, MD; Markus Schwaiger, MD, PhD; Manfred Vogt, MD, PhD; Harald Kaemmerer, MD, PhD; Andreas Kuehn, MD

**Background:** Dysfunction of the morphologic systemic right ventricle (RV) is a sequel in long-term survivors with transposition of the great arteries (TGA) after atrial switch operation (AtSO). Impairment of myocardial blood flow (MBF) and coronary flow reserve (CFR) are hypothesized as predisposing factors.

**Methods and Results:** The study group comprised 20 patients after AtSO (22.7±5.03 years) and 15 individuals with congenitally corrected transposition (ccTGA) (30.6±19.4 years). MBF was quantified by positron emission tomography; controls for coronary flow were 11 healthy volunteers (26.2±5.1 years). Exercise capacity, ventricular mass, function and end-diastolic volume assessed by coronary magnetic resonance (CMR), hemodynamic parameters assessed by cardiac catheterization and echocardiography, and B-type natriuretic peptide levels correlated with MBF. At rest, MBF did not differ between patients and healthy volunteers (MBFrest ml · 100 g⁻¹ · min⁻¹; ccTGA: 75±14 vs. AtSO: 73±16 vs. controls: 77±15; NS). After vasodilatation, MBF increased significantly, but was significantly lower in ccTGA and AtSO groups compared with controls (MBFstress ml · 100 g⁻¹ · min⁻¹; ccTGA: 198±38 vs. AtSO: 167±46 vs. controls 310±74; P<0.001). In ccTGA, CFR correlated significantly with clinical, CMR, echocardiographic and hemodynamic parameters, but for AtSO patients no significant correlation could be calculated.

**Conclusions:** In patients with ccTGA, maximal coronary blood flow is attenuated and significantly correlated with ventricular function, whereas dysfunction of the morphologic systemic RV after AtSO is a multifactorial problem. (Circ J 2015; 79: 425–431)

**Key Words:** Atrial switch operation; Positron emission tomography; Right ventricular dysfunction; Transposition of the great arteries

For patients with transposition of the great arteries (TGA), the Senning¹ and Mustard² procedures with their low peri- and postoperative mortality rates have been the therapies of choice for a long time. However, the long-term prognosis is markedly related to the development of dysfunction of the morphologic systemic right ventricle (RV); after 10 years, more than 10% of the patients develop clinically significant ventricular dysfunction and severe rhythm disturbances.⁴

Abnormalities of the myocardial perfusion of the morphologic systemic RV as assessed by single-photon emission computed tomography (SPECT) and positron emission tomography (PET) are extremely common.⁵–⁷ It remains unclear whether the attenuation of myocardial perfusion results in clinically significant myocardial ischemia; nevertheless, the reduced coronary blood flow might represent a limiting factor for the compensatory mechanism induced by chronic pressure overload, resulting in myocardial dysfunction and electrical instability.⁸

The objective of this study was to test the hypothesis that reduced myocardial perfusion might be an etiologic factor for dysfunction of the morphologic systemic RV in patients after the atrial switch operation (AtSO). Quantitative and qualitative perfusion parameters were correlated with clinical, hemodynamic and morphometric parameters.

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Methods

Patients
We investigated 20 patients with TGA (5 female, 15 male) after they underwent AtSO (10 Senning, 10 Mustard repairs). The operation was performed at a mean age of 15.2±16.4 months and mean age at the time of the investigation was 22.7±5.03 years.

In total, 12 patients had undergone simple d-TGA, and 8 additionally had subpulmonary stenosis, 2 with ventricular septal defect (VSD). None of the patients had severe postoperative complications; there were no signs of myocardial ischemia; 5 patients were treated with angiotensin-converting enzyme inhibitors (ACEIs), 2 with β-blockade because of recurrent supraventricular tachycardia.

Controls were 15 patients (6 female, 9 male) with a history of congenitally corrected transposition (ccTGA; mean age, 30.6±19.4 years), representing a congenital heart defect with a morphologic systemic RV, unaffected by the negative influence of open-heart surgery. Of these patients, 7 had an isolated form of ccTGA and the remaining 8 additionally had moderate subpulmonary stenosis; 4 had a VSD. A total of 4 were treated with ACEIs; 3 patients had sequential atrioventricular pacing because of complete atrophicventricular block.

The study protocol was approved and accepted by the Institutional Review Board of the Technical University of Munich. All subjects were given extensive information about the aim of the study and agreed to participate. All data gathered and technical investigations performed were part of regular clinical follow-up. All patients or legal guardians gave written informed consent.

Clinical Investigations
All patients were investigated clinically and their functional class was assigned according the classification of Perloff and Child;9 12-lead resting, stress and 24-h ECG recordings were obtained for all patients.

Cardiopulmonary Exercise Testing
The patients were exercised on a treadmill, using the Bruce protocol. To examine their cardiopulmonary exercise capacity, testing using non-invasive determination of gas exchange parameters was used. Oxygen uptake (V˙O₂) and CO₂ output (V˙CO₂) were measured by an automated O₂ and CO₂ analyzer system; minute ventilation and respiratory rate were measured by a pneumotachometer. The V-slope method according to Beaver et al10 was used to determine the anaerobic threshold and maximal V˙O₂ during treadmill exercise. Controls were 20 healthy volunteers matched for age and body surface area.

Echocardiography
Echocardiography was performed by 2 experienced operators, who were unaware of all other results, by the transthoracic approach using a Vingmed Vivid 7 Pro (General Electrics, Horten, Norway). Because of the cardiac anatomy and upright position of the interventricular septum, we used a qualitative, subjective assessment of systemic ventricular function using multiview 2D echocardiography, grading it as normal or mildly, moderately, or severely impaired. Atrioventricular valve regurgitation was graded semiquantitatively by Doppler color flow mapping and graded as trivial, mild, moderate, and severely insufficient.11

Coronary Magnetic Resonance (CMR)
Patients (with the exception of 3 ccTGA patients with pacemakers) were examined in the supine position with a standard cardiac 1.5-Tesla MRI-scanner (Gyroscan ACS NT, Intera; Philips Electronics, The Netherlands) using a dedicated cardiac phased-array surface coil. Ventricular function was calculated from volume data for the morphologic systemic RV measured by multiphase balanced fast-field echo sequences as previously described.12 For ventricular volume measurements, short-axis slices were acquired for the whole heart (slice thickness 6 mm; flip angle 30°, receiver bandwidth 31.25 kHz, field of view 350–400 mm; matrix 256×256). Each slice was imaged in 25 phases of the cardiac cycle with breath-holding in expiration and retrospective ECG gating. Ventricular function was measured at rest and with dobutamine stress scanning; dobutamine infusion with an initial dosage of 5 µg · kg⁻¹ · min⁻¹ was given for 10 min, followed by 10 µg · kg⁻¹ · min⁻¹ for another 10 min to reach a steady-state at each step for the CMR cine scans. The mass of the morphologic systemic RV was measured in the dataset at rest. The morphologic systemic RV volume was calculated from the short-axis data sets using standard analysis software as previously described (MASS; Medis Inc., Leiden, The Netherlands).13,14 Thereby the phases of the end-diastole and end-systole were defined. The endocardial contours of the morphologic systemic RV were traced manually in every slice.

PET
MBF was quantified noninvasively at rest and during adenosine-induced vasodilatation15-18 by dynamic PET with 13N ammonia. Images were acquired using an ECAT EXACT or an ECAT 951 scanner (Siemens/CTI, Knoxville, TN, USA). After positioning the patient, a transmission scan was acquired for correction of photon attenuation. Subsequently, 13N ammonia (~0.3 mCi/kg) was injected intravenously at rest and a dynamic sequence of 21 frames was acquired over 20 min. After 50 min to allow for decay of 13N ammonia, adenosine (0.14 mg · kg⁻¹ · min⁻¹) was infused continuously over 5 min and 2 min after the onset of adenosine infusion, a second dose of 13N ammonia was administered and a dynamic imaging sequence similar to the rest study was started. Heart rate, blood pressure, and 12-lead ECG were monitored continuously throughout the procedure. MBF at rest and during hyperemia were quantified using a volumetric sampling approach and a validated 3-compartment model, which is also applicable for patients with ccTGA and morphologic systemic RV.19,20

Because of the relationship between MBF at rest and the rate-pressure product (RPP) as an index of cardiac work,21 resting flow was normalized to the corresponding RPP. In addition to quantification of global MBF, regional myocardial perfusion was analyzed visually. Summed images of tracer distribution in the last 3 frames of the dynamic sequence were interpreted for the presence of reversible or persistent defects.

To obtain an index of coronary vascular resistance, mean aortic blood pressure as a measure of coronary perfusion pressure was divided by blood flow values at rest and during adenosine infusion.
Dysfunction of the RV in TGA

Table 1. Clinical Results for Patients With ccTGA or AtSO and Control Group

<table>
<thead>
<tr>
<th></th>
<th>ccTGA</th>
<th>AtSO</th>
<th>Normals</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>15</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Functional class</td>
<td>I (n=11), II (n=3), III (n=1)</td>
<td>I (n=17), II (n=3)</td>
<td></td>
</tr>
<tr>
<td>BNP mg/dl</td>
<td>Median 38.5 (7.3–366)</td>
<td>Median 29.4 (3.2–193)</td>
<td></td>
</tr>
<tr>
<td>VF (echo)</td>
<td>Normal (n=11)</td>
<td>Normal (n=7)</td>
<td></td>
</tr>
<tr>
<td>Reduced (n=4)</td>
<td>Reduced (n=13)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TR (echo)</td>
<td>I (n=9), II (n=5), IV (n=1)</td>
<td>O (n=7), I (n=6), II (n=5), III (n=2)</td>
<td></td>
</tr>
<tr>
<td>VO2maxml · kg⁻¹ · min⁻¹</td>
<td>30.1±13.9</td>
<td>31.2±9.6</td>
<td>51.9±14.7</td>
</tr>
<tr>
<td>HRrest/min</td>
<td>35±15</td>
<td>52±20 (P&lt;0.01)</td>
<td></td>
</tr>
</tbody>
</table>

AtSO, after atrial switch operation; BNP, brain natriuretic peptide; ccTGA, congenitally corrected transposition; echo, echocardiography; HR, heart rate; TR, tricuspid regurgitation; VF, ventricular function; VO2max, maximal oxygen uptake.

The control group comprised 11 healthy young adults (mean age 26.2±5.1 years, range 21–35 years) with no evidence of cardiovascular disease on the basis of the absence of symptoms and risk factors, normal resting-ECG, and normal exercise test. This group was used as the control group in a previously published study.15

B-Type Natriuretic Peptide (BNP)

A venous blood sample (EDTA) was taken for measuring BNP by fluorescence-immunoassay (Triage BNP-test, Biosite, San Diego, CA, USA). The normal reference range was <50 ng/ml; specific concentrations for NYHA I are 83 ng/ml, NYHA II 233 ng/ml, NYHA III 459 ng/ml, NYHA IV 1,124 ng/ml. For practicability, values <100 ng/ml were estimated as normal.22

Statistical Analysis

Mean and standard deviation were calculated for all continuous variables. Differences between groups were tested for significance by 1-way analysis of variance and the post hoc test (least-squares difference). Changes from baseline to adenosine stress were compared by paired Student’s t test. Univariate analysis of the effects of each continuous variable was performed with linear regression. All tests of significance were 2-tailed and P<0.05 was considered to be significant.

Results

Clinical Parameters

All patients were normally active and clinically asymptomatic. Only 1 patient with ccTGA was graded as functional class III, with moderate impairment in managing normal daily activities.9

BNP levels were normal in all patients (ccTGA median 38.5 mg/dl; AtSO median 29.4 mg/dl); only the patient with ccTGA in functional class III had an elevated BNP level of 366 mg/dl (Table 1).

Resting-ECG, exercise-ECG and Holter-monitoring did not show any ectopy or rhythm disturbances.

According to the criteria of Kugler,23 9 of the 20 patients with TGA after AtSO had sinus node dysfunction, whereas no patient with ccTGA had signs of sick sinus syndrome.

Cardiopulmonary Exercise Testing

In the patients after AtSO, basal heart rate was significantly lower, compared with patients with ccTGA (AtSO: HRrest 63±11 beats/min vs. ccTGA: HRrest 75±16 beats/min; P<0.01), with a significantly higher increase after exercise (AtSO: ΔHR 52±20 beats/min vs. ccTGA: ΔHR 35±15 beats/min; P<0.01).

Maximal oxygen uptake (VO2max) as a measure of cardiopulmonary exercise capacity was calculated with 31.2±4.9 ml · min⁻¹ · kg⁻¹ for the patients after AtSO and 30.1±13.9 ml · min⁻¹ · kg⁻¹ for patients with ccTGA. VO2max did not differ between groups, but the values were significantly reduced in comparison with normal healthy volunteers (51.9±14.7 ml · min⁻¹ · kg⁻¹) (P<0.001) (Table 1).

Echocardiography (TTE)

Patients with TGA after AtSO had no signs of systemic or pulmonary venous baffle obstruction. The estimated ventricular function of the morphologic systemic RV was normal in 7 and moderately impaired in 13 patients; 7 patients had no tricuspid regurgitation (TR), in 6 the tricuspid valve insufficiency was mild, moderate in 5, and moderate-severe in 2.

All patients with isolated ccTGA had normal function of the morphologic systemic RV; 4 patients had mild and 3 had moderate insufficiency of the systemic atrioventricular valve (tricuspid valve).

In patients with complex ccTGA, ventricular function was normal in 6, and moderately reduced in 2 patients, who additionally had a VSD. The Doppler gradient across the subpul-

Table 2. Cardiac Catheterization AtSO

<table>
<thead>
<tr>
<th></th>
<th>ccTGA</th>
<th>AtSO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rv (Em²)</td>
<td>1.28±0.8</td>
<td></td>
</tr>
<tr>
<td>Rs (Em²)</td>
<td>27.6±11.4</td>
<td></td>
</tr>
<tr>
<td>Cardiac index (L · min⁻¹ · m⁻²)</td>
<td>2.8±0.9</td>
<td></td>
</tr>
<tr>
<td>EDP (mmHg)</td>
<td>7.2±3.2</td>
<td></td>
</tr>
</tbody>
</table>

EDP, end-diastolic pressure; Rv, pulmonary vascular resistance; Rs, systemic vascular resistance. Other abbreviations as in Table 1.

Table 3. Coronary Magnetic Resonance Data for Patients With ccTGA or AtSO

<table>
<thead>
<tr>
<th></th>
<th>ccTGA</th>
<th>AtSO</th>
</tr>
</thead>
<tbody>
<tr>
<td>RV mass (g/m²)</td>
<td>99.9±7.9</td>
<td>106.1±26.8</td>
</tr>
<tr>
<td>EFrest (%)</td>
<td>51.4±4.5</td>
<td>48.8±3.2</td>
</tr>
<tr>
<td>EFDobutamin (%)</td>
<td>61.3±6.8*</td>
<td>52.9±5.5</td>
</tr>
<tr>
<td>EFdelta (%)</td>
<td>9.9±3.4</td>
<td>5.3±5.7*</td>
</tr>
<tr>
<td>RVEDV ml/m² BSA</td>
<td>102±7.5</td>
<td>109±8.2</td>
</tr>
</tbody>
</table>

*R<0.001. BSA, body surface area; EFDobutamin, increase of systolic ventricular function after dobutamine; EFdelta, systolic ventricular function at rest and after dobutamine; RVEDV, right ventricular end-diastolic volume. Other abbreviations as in Table 1.
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Table 4. Hemodynamic Parameters Before and After Adenosine Administration in Patients With ccTGA or AtSO and Control Group

<table>
<thead>
<tr>
<th>Parameter</th>
<th>ccTGA</th>
<th>AtSO</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>HRrest (beats/min)</td>
<td>65±7</td>
<td>59±10</td>
<td>68±10</td>
</tr>
<tr>
<td>HRadenosine (beats/min)</td>
<td>97±20*</td>
<td>85±19*</td>
<td>107±13*</td>
</tr>
<tr>
<td>RRest (mmHg)</td>
<td>118±8</td>
<td>124±14</td>
<td>121±16</td>
</tr>
<tr>
<td>RRadenosine (mmHg)</td>
<td>119±9</td>
<td>125±16</td>
<td>121±17</td>
</tr>
<tr>
<td>RRrest (mmHg)</td>
<td>72±11</td>
<td>75±21</td>
<td>67±6</td>
</tr>
<tr>
<td>RRadenosine (mmHg)</td>
<td>69±12</td>
<td>73±22</td>
<td>64±6</td>
</tr>
<tr>
<td>RPPrest</td>
<td>7,705±1,120</td>
<td>7,432±1,483</td>
<td>8,192±672</td>
</tr>
<tr>
<td>RPPadenosine</td>
<td>11,574±2,925*</td>
<td>10,918±2,086*</td>
<td>12,832±2,230</td>
</tr>
</tbody>
</table>

*P<0.01 vs. rest. RPP, rate-pressure product; RR, blood pressure. Other abbreviations as in Table 1.

Table 5. Quantitative- and Qualitative PET Results for Patients With ccTGA or AtSO and Control Group

<table>
<thead>
<tr>
<th>Parameter</th>
<th>ccTGA</th>
<th>AtSO</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>MBFrest (ml·100 g⁻¹·min⁻¹)</td>
<td>75±14</td>
<td>73±16</td>
<td>75±15</td>
</tr>
<tr>
<td>MBFstress (ml·100 g⁻¹·min⁻¹)</td>
<td>198±38*</td>
<td>167±46*</td>
<td>310±74</td>
</tr>
<tr>
<td>CFR</td>
<td>2.6±0.4*</td>
<td>2.3±0.6*</td>
<td>4.1±0.7</td>
</tr>
<tr>
<td>Perfusion defects</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*P<0.001. CFR, coronary flow reserve; MBF, myocardial blood flow; PET, positron emission tomography. Other abbreviations as in Table 1.

Pulmonary stenoses was calculated as 63.8±9.9 mmHg (mean); TR was mild in 5, moderate in 2 and severe in one of the patients (Table 1).

Cardiac Catheterization

None of the patients after AtSO had systemic or pulmonary venous baffle obstruction; there were no interatrial or interventricular shunts. The epicardial coronary arteries were normal on selective coronary angiography without stenosis or obstruction.

Cardiac output was reduced (2.8±0.9 L·min⁻¹·m⁻²), and peripheral vascular resistance was elevated (27.6±11.4 Em²); pulmonary vascular resistance was within the normal range (Table 2).

CMR

In patients with ccTGA, mean systolic ventricular function (VFrest) measured at rest was 51.4±4.5%; during pharmacologic dobutamine stress, there was a significant increase in VFstress up to 61.3±6.8% (ΔVF mean 9.9±3.4%) (P<0.001).

In the AtSO patients, VFrest was 48.8±3.2; with dobutamine there was a nonsignificant increase up to 52.9±5.5 (ΔVF mean 5.3±5.7).

There was a significant increase in VF after dobutamine stress in patients with ccTGA in comparison with those with AtSO (9.9±3.4 vs. 5.3±5.7; P<0.001).

The mean mass of the morphologic systemic RV was calculated in patients with ccTGA as 99.9±27.9 g/m²; in patients with AtSO it was 106.1±26.8 g/m²; there was no significant difference between these groups of patients (Table 3).

PET

Hemodynamic Parameters

The hemodynamic findings of both groups of patients (ccTGA, AtSO) and the healthy young adults at rest and during adenosin are listed in Table 4. In all 3 groups there was a significant increase in heart rate and the corresponding RPP as an index of cardiac work (P<0.01).

Under rest and hyperemic conditions, hemodynamic parameters such as systolic, diastolic and mean aortic pressure were not significant different among the groups.

Quantitative Assessment of MBF

At rest, MBF before and after normalization to the corresponding RPP did not differ between the groups of patients (ccTGA, AtSO) and the healthy young adults (MBFrest ml·100 g⁻¹·min⁻¹; ccTGA: 75±14 vs. AtSO: 73±16 vs. controls: 77±15; NS).

After adenosine-induced vasodilation, MBF increased significantly in all 3 groups. Hyperemic blood flow, however, was significantly lower in patients with ccTGA and AtSO compared with the control group (MBFstress ml·100 g⁻¹·min⁻¹; ccTGA: 198±38 vs. AtSO: 167±46 vs. controls 310±74; P<0.001).

As a result of lower MBF during adenosine infusion, CFR was markedly attenuated in both groups of patients (ccTGA and AtSO) compared with the healthy young adults (ccTGA: 2.6±0.4 vs. AtSO: 2.3±0.6 vs. controls 4.1±0.73; P<0.001) (Table 5).

The MBF parameters did not differ between patients with ccTGA and AtSO; the administration of ACEI, the degree of TR, the presence of sinus node dysfunction, or the duration of cyanosis before operation did not influence MBF parameters.

The BNP values negatively correlated with CFR in both groups of patients; in ccTGA patients the correlation was statistically significant (r=−0.69; P<0.01).

The spiro-ergometrically estimated VO₂max, as an index of cardiopulmonary exercise capacity, correlated significantly with CFR in the ccTGA patients (r=−0.63; P<0.014), but in the group of patients with AtSO no significant correlation could be calculated.

CFR was significantly attenuated in ccTGA patients with reduced function of the morphologic systemic RV as estimated on echocardiography; a significant correlation could be calculated between MBF parameters (MBFAdenosine, CFR) and the degree of TR.

In patients with AtSO, MBFAdenosine and CFR were reduced in patients with attenuation of ventricular function, but no...
statistically significant correlation could be calculated; TR did not correlate with MBF parameters either.

The CMR calculated mass of the morphologic systemic RV negatively correlated with CFR in both groups of patients. Only for patients with ccTGA was the correlation statistically significant (ccTGA: r=−0.66, P<0.001; AtSO: r=−0.55; NS).

RV end-diastolic volume (RVEDV; ccTGA: 102±7.5 ml/m\(^2\) vs. AtSO 109±8.2 ml/m\(^2\), NS) did not differ significantly between the groups of patients. MBF parameters at rest and after maximal vasodilatation with adenosine did not correlate significantly with RVEDV in the AtSO group of patients. In patients with ccTGA, RVEDV correlated significantly with MBF\(_{\text{ad}}\) (r=−0.69, P<0.001) and CFR (r=−0.71, P<0.001).

No significant correlation could be calculated between MBF\(_{\text{rest}}\) and VF\(_{\text{rest}}\) function calculated by CMR or after dobutamine administration (VF\(_{\text{dobutamine}}\) ) in either group of patients.

In patients with ccTGA, MBF after maximal vasodilatation (MBF\(_{\text{ad}}\) ) and CFR correlated significantly with VF\(_{\text{rest}}\) (MBF\(_{\text{ad}}\): r=0.69, P<0.001; CFR: r=0.70; P<0.001) and VF\(_{\text{dobutamine}}\) (MBF\(_{\text{ad}}\): r=0.71, P<0.001; CFR r=0.73, P<0.001); patients with ventricular dysfunction showed significantly reduced MBF after maximal vasodilatation with adenosine and significantly reduced CFR.

For patients with AtSO, no significant correlation could be calculated.

In patients with ccTGA, CFR correlated significantly with the increased ventricular function during dobutamine administration (r=0.71; P<0.01); for patients after AtSO no significant correlation could be calculated.

**Qualitative Assessment of Myocardial Perfusion**

Visual analysis revealed an adenosine-induced reversible perfusion defect in the apical region of the systemic ventricle in one of the patients with ccTGA, who belonged to the subgroup of patients with subpulmonary stenosis and VSD. A stenosis of the epicardial coronary arteries could be excluded by selective coronary angiography.

In the group of patients after AtSO no perfusion defects could be visualized at rest or after maximal vasodilatation with adenosine.

**Discussion**

The atrial redirection of the systemic and pulmonary venous return (AtSO) was first described by Senning in 1958 and later by Mustard and was the therapy of choice for patients with TGA before the era of the arterial switch operation.

The long-term outcome of these patients is negatively influenced by a potential failure of the morphologic systemic RV. The pathomechanism of this dysfunction is unclear. Besides inadequate ventricular filling in the case of baffle obstruction with reduced preload, the structural morphology of the myocardium of the morphologic systemic RV and its atypical spherical shape, with elevated end-systolic and end-diastolic volumes, are possible explanations. The chronic pressure overload is compensated by an increase in myocardial muscle mass, with consequent elevated myocardial oxygen demand.

ccTGA represents a natural model of a morphologic systemic RV. First described by Rokitsansky in 1875, it is a rare congenital anomaly with atrophicventricular and ventricular-arterial discordance.

The objective of the present study was to assess the MBF and CFR of the morphologic systemic RV in long-term survivors after AtSO and in individuals with ccTGA as a control group not having the negative influence of open-heart surgery such as cardiopulmonary bypass, hypothermia, cardiac arrest and reperfusion injury. The coronary flow parameters correlated with clinical and hemodynamic findings.

The MBF of the morphologic systemic RV was compared with the flow parameters of a normal left ventricle (LV). In vivo quantification of the MBF of the normal RV is not reliable in healthy control subjects because of a partial-volume effect, as the RV mass is approximately one-sixth that of the LV, and the free wall of the RV is one-third to one-quarter that of the LV thickness. However, the vascular density is similar in the normal RV and LV, as well as the coronary hyperemic response, as has been demonstrated in a series of animal models. Several studies have compared pressure-loaded RVs with the RVs of normal subjects and demonstrated that the myocardial flow reserve values of the pressure-loaded RVs were similar CFR values of the LV.

So it is feasible to compare myocardial flow parameters of the normal LV with that of pressure-loaded RVs.

The present study demonstrated that maximal MBF and CFR were attenuated in patients with morphologic systemic RVs after AtSO and in individuals with ccTGA, whereas MBF at rest did not differ between patients and normal subjects.

Abnormalities of the epicardial coronary arteries can be excluded by selective coronary angiography, so altered global vasoreactivity and impaired microcirculation are possible explanations.

Attenuation of myocardial perfusion is thought to be an important etiologic factor for ventricular dysfunction and a number of studies have demonstrated perfusion abnormalities in the compensatory hypertrophied myocardium of the morphologic systemic RV.

In both groups of patients in the present study (ccTGA, AtSO), chronic pressure overload was compensated by hypertrophy of the morphologic systemic RV. Although this mechanism is initially an adaptive response that temporarily augments or maintains cardiac output, reduced capillary density in relation to the hypertrophied myocardium with consequent reduced MBF may be a leading cause of the development of systolic and diastolic heart failure, electrical instability and sudden death.

We could substantiate this hypothesis, because maximal MBF and CFR were significantly reduced in patients after AtSO and in individuals with ccTGA; in patients with ccTGA a significant correlation could be calculated between MBF parameters (MBF\(_{\text{ad}}\), CFR) and ventricular function.

In patients after AtSO, ventricular dysfunction seems to be a multifactorial problem, because a significant correlation between coronary flow and clinical parameters could not be calculated.

Impaired atrial compliance induced by redirection of blood flow at the atrial level by baffle implantation results in a relative reduction of preload, so an adequate increase of cardiac output can be only maintained by increasing heart rate, as was demonstrated in patients after AtSO. According to the Frank-Starling mechanism, preload reduction is a limiting factor and explains the inadequate increase of ventricular function under physical stress observed on CMR after dobutamine administration.

In contrast to patients with ccTGA, hemodynamic parameters such as \(\text{VO}_{2\text{max}}\), VF at rest and after pharmacologic stress, the ventricular mass and end-diastolic volume of the morphologic systemic RV did not correlate significantly with flow parameters in patients after AtSO. A combination of attenuated MBF and morphological and hemodynamic parameters of the heart after AtSO may contribute to myocardial dysfunction.
In comparison to healthy young adults, end-systolic and end-diastolic volumes are augmented in patients with a morphologic systemic RV and are not reduced in the presence of increased afterload.

In patients with ccTGA, a significant correlation could be calculated between the RV end-diastolic volume and myocardial flow parameters such as MBF and CFR. According to Laplace’s law, wall tension correlates with the diameter of the corresponding ventricle, so wall stress is elevated in patients with increased end-diastolic volumes. Wall stress is an important determinant of myocardial oxygen consumption, the myocardial contractile state, and diastolic function. The rise in systolic wall stress, a measure of afterload most closely related to systolic function, results in decreased ventricular performance. High wall stress has been associated with a less favorable prognosis, because of electrical instability and myocardial hypoperfusion.

Thus, not only is the oxygen supply reduced (decreased CFR) but at the same time oxygen demand is enhanced (increased wall stress). One can hypothesize that this mismatch between supply and demand may lead to the occurrence of potential ventricular dysfunction.

As end-diastolic volume did not correlate with myocardial flow parameters after ASO, this might underline the multifactorial genesis of ventricular dysfunction in patients after Senning or Mustard repair. The exposure of the RV to a high-resistance systemic circulation results in remodeling and compensatory myocardial hypertrophy. The mismatch between RV blood supply and demand may lead to myocardial scarring and thus, systemic RV failure, as hypothesized in previous SPECT studies; those studies concluded that myocardial scars are common in patients after ASO and in patients with ccTGA. However, using the reference standard method PET, we did not find myocardial scars in patients after ATSO and only in 1 patient with complex ccTGA. Direct imaging of myocardial scars is also possible by delayed-enhancement magnetic resonance imaging (MRI) after the intravenous administration of a gadolinium chelate. A previously published study on patients after ATSO and ccTGA using PET and CMR showed that the hypothesis of myocardial scarring being common in patients with a morphologic systemic RV is not correct. Myocardial scars are not related to reduced RV ejection fraction or wall motion abnormalities. Myocardial scars are therefore not a reason for failure of the morphologic systemic RV.

The discrepancy between studies supporting or denying scarring in the morphologic systemic RV may be explained, because previous SPECT studies finding myocardial scars had a methodological problem. Those studies did not consider regional wall thickness for the assessment of segmental tracer uptake, which usually varies substantially, as many hypertrophied trabeculae, resulting in various segmental wall thicknesses, are found in systemic morphologic RVs. For nuclear imaging techniques such as SPECT, regional wall thickness is a determinant of measured regional tracer uptake, because of the lower recovery of radioactivity from structures below or in the range of the spatial resolution of the system. A myocardial segment with a thinner wall than other segments may therefore artificially appear as a segment with impaired tracer uptake, which may be misleadingly interpreted as a scar. These observations show that the influence of myocardial scars has been overestimated.

Hayes et al hypothesized that the negative influence of open-heart surgery itself, with the attendant cardiac arrest and cardiopulmonary bypass, may induce myocardial damage, with consequent ventricular dysfunction; the authors thus speculated that microcirculation caused by embolism during surgery may be a potential explanation for these findings. Alternatively, abnormalities in MBF may be caused by myocardial fibrosis secondary to prolonged hypoxemia during infancy while awaiting surgical correction.

In patients with ccTGA, CFR is significantly related to TR, a finding we could not assess in patients after ATSO. In ccTGA, ventricular dysfunction often is the result of TR, caused by a dysplastic valve with apical displacement of the septal and/or inferior leaflet, in ATSO patients, ventricular dysfunction is not inevitably generated by regurgitation of a morphologically normal tricuspid valve; TR is usually the consequence of dilatation of the valvular ring caused by ventricular dysfunction.

According to the literature, impaired MBF is associated with ventricular arrhythmia inducibility. Coronary perfusion abnormalities generate electrical instability of the myocardium and as a predisposing factor for rhythm disturbances this may be an important prognostic factor concerning postoperative morbidity and mortality. These results are hypothesis-generating for a potential role of quantitative PET perfusion imaging in the risk stratification for arrhythmias in patients with morphologic systemic RV.

Conclusions

Coronary perfusion abnormalities are common findings in patients with a morphologic systemic RV. In patients with ccTGA, there is a significant correlation between MBF parameters and clinical findings such as cardiopulmonary exercise capacity, VO2max, ventricular function at rest and after pharmacological stress, myocardial mass, end-diastolic volume, TR and BNP levels. In patients after ATSO, MBF parameters are also attenuated, but the etiology of ventricular dysfunction is a multifactorial problem. Nevertheless, besides the morphological and hemodynamic parameters, coronary perfusion abnormalities may contribute to dysfunction and electrical instability of the myocardium and quantitative PET perfusion imaging may uncover one of several important predisposing factors in the risk stratification for postoperative morbidity and mortality.

Disclosures

None.

References

Dysfunction of the RV in TGA


