Pulmonary Vascular Resistance, Collateral Flow, and Ventricular Function in Patients With a Fontan Circulation at Rest and During Dobutamine Stress

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Background — The role, interplay, and relative importance of the multifactorial hemodynamic and myocardial mechanisms causing dysfunction of the Fontan circulation remain incompletely understood.

Methods and Results — Using an MRI catheterization technique, we performed a differential analysis of pulmonary vascular resistance and aortopulmonary collateral blood flow in conjunction with global ventricular pump function, myocontractility (end-systolic pressure-volume relation), and diastolic compliance (end-diastolic pressure-volume relation) in 10 patients with a Fontan circulation at rest and during dobutamine stress. Pulmonary and ventricular pressures were measured invasively and synchronized with velocity-encoded MRI-derived pulmonary and aortic blood flows and cine MRI-derived ventricular volumes. Pulmonary vascular resistance and end-systolic and end-diastolic pressure-volume relations were then determined. Aortopulmonary collateral flow was calculated as the difference between aortic and pulmonary flow. Compared to rest, dobutamine caused a small increase in mean pulmonary pressures ($P<0.05$). Collateral flow was significantly augmented ($P<0.001$) and contributed importantly to an increase in pulmonary flow ($P<0.01$). Pulmonary vascular resistance decreased significantly ($P<0.01$). Dobutamine did not increase stroke volumes significantly despite slightly enhanced contractility (end-systolic pressure-volume relation). Active early relaxation ($\tau$) was inconspicuous, but the end-diastolic pressure-volume relation shifted upward, indicating reduced compliance.

Conclusions — In patients with a Fontan circulation, aortopulmonary collateral flow contributes substantially to enhanced pulmonary flow during stress. Our data indicate that pulmonary vascular response to augmented cardiac output was adequate, but decreased diastolic compliance was identified as an important component of ventricular dysfunction. (Circ Cardiovasc Imaging. 2010;3:623-631.)

Key Words: heart defects, congenital ■ pulmonary heart disease ■ heart failure ■ magnetic resonance imaging

Ventricular function and pulmonary vascular resistance (PVR) are important variables that determine the outcome of patients with a Fontan circulation. Impaired growth of the pulmonary arteries failing to match somatic growth was described in recent studies. Other authors have reported significant left-to-right shunting through aortopulmonary collaterals. Both factors may have a direct impact on the PVR that cannot be measured in the Fontan circulation by conventional techniques, such as thermodilution or oxymetry.

Clinical Perspective on p 631

In addition to pulmonary vascular factors, heart failure was identified as an important cause of morbidity, and the right-type systemic ventricle seems to carry a higher risk for developing heart failure than the left-type ventricle. However, the onset, course, and predominant form of heart failure vary and remain unpredictable. Systolic dysfunction has been described, but the role and mechanisms of diastolic dysfunction are less known. Diastolic filling is considered to be impaired due to low preload that by itself is at least partly controlled by PVR. In addition, ventricular compliance is likely to be altered because congenital abnormalities as well as prolonged cyanosis and volume load may have an impact on the fibrous matrix of the myocardium.

In this study, we performed a differential analysis of PVR and aortopulmonary collateral blood flow in conjunction with global ventricular pump function, ventricular contractility, and diastolic compliance. Measurements were obtained at rest.
and during dobutamine stress using an MRI catheterization technique. We hypothesized that exposure to dobutamine stress would have a specific impact on PVR and aortopulmonary collateral flow as well as on systolic and diastolic ventricular function and, hence, improve our understanding of cardiovascular pathophysiology in patients with a Fontan circulation.

Methods

Study Design

The study was conducted in 10 pre-selected patients with a Fontan circulation. The patients were experiencing decreasing exercise capacity at routine follow-up and, thus, were referred to our institution for cardiac catheterization and MRI to determine ventricular systolic and diastolic function and cardiovascular anatomy. The exercise capacity assessment was based on New York Heart Association classification and ergometry. Only patients with extracardiac total cavopulmonary connection that had no fenestration of the tunnel were included. Exclusion criteria were the presence of pulmonary artery stenosis, atrioventricular valve insufficiency, arrhythmias, protein-losing syndrome, thromboembolism, effusion, or edema. In addition, patients on β-blocker medication were not included because β-blockers would have affected the impact of dobutamine infusion. All patients or their guardians gave informed consent for the study, which was approved by the responsible institutional review board and ethics committee.

Atrioventricular valvar function and ventricular inflow profiles (E/A-wave ratio) were evaluated by Doppler echocardiography. Exercise capacity was quantified by oxygen uptake during ergometry. During catheterization, ventricular pressures were measured with 4- to 5-F fluid-filled pigtail catheters and pulmonary pressures with 5-F wedge catheters. Catheters were advanced over a femoral artery and femoral or cubital vein approach, respectively. At the end of the study, a 24- to 36-mm sizing balloon was placed at the level of the tunnel-to-pulmonary artery connection. Patients then were transferred to the neighboring MRI laboratory, keeping all catheters in place. Details about the use of the catheters during MRI follow.

MRI Assessment of Blood Flow and PVR

All MRI studies were performed with a 1.5-T scanner, with a maximum gradient performance of 30 mT/m and slew rate of 150 T/m per second. A 5-element cardiac phased-array coil was used for signal acquisition. In all patients, MRI was performed without sedation. Quantitative blood flow was measured using velocity-encoded (VEC) MRI orthogonal to the dominating flow direction in the superior and inferior vena cava, left and right pulmonary artery, and the ascending aorta as reported elsewhere. In the ascending aorta, flow was measured just distal to the coronary arteries and the semilunar valves. In the inferior and superior vena cava, flow was measured in a segment approximately 5 to 10 mm below or above their connection to the pulmonary artery. Pulmonary flow was measured simultaneously with invasive pulmonary pressure. Technical details for pressure recording follow. All measurements were performed during free breathing at rest and during continuous infusion of 10 μg/kg per minute dobutamine. Automated correction was performed for potential phase errors arising from the concomitant magnetic field. Sequence parameters were TR and TE, 3.4 and 1.7 milliseconds; slice thickness, 6 mm; no gap; in-plane resolution, 1.9×1.3 mm²; 45 phases per cardiac cycle; number of averages, 1; and sensitivity encoding reduction factor, 2. Analysis was done using View Forum release 6.1 software. Biventricular endo- and epicardial borders were manually traced for computing ventricular volumes and myocardial mass, where the septum was accounted for as left ventricular mass. Papillary muscles and prominent right ventricular trabeculation were excluded for volume measurements. Stroke volume was calculated as the difference between the diastolic and systolic volumes. Ejection fraction was calculated as the ratio of stroke volume to end-diastolic volumes.

MRI Assessment of Global Ventricular Function

Ventricular chamber volumes and myocardial mass were determined from axial stacks of multislice-multiphase steady-state free precession cine MRI covering the entire heart. Sequence parameters were TR and TE, 3.4 and 1.7 milliseconds; slice thickness, 6 mm; gap; in-plane resolution, 1.9×1.3 mm²; 45 phases per cardiac cycle; number of averages, 1; and sensitivity encoding reduction factor, 2. Analysis was done using View Forum release 6.1 software. Biventricular endo- and epicardial borders were manually traced for computing ventricular volumes and myocardial mass, where the septum was accounted for as left ventricular mass. Papillary muscles and prominent right ventricular trabeculation were excluded for volume measurements. Stroke volume was calculated as the difference between the diastolic and systolic volumes. Ejection fraction was calculated as the ratio of stroke volume to end-diastolic volumes.

MRI Assessment of Myocontractile and Diastolic Function

Parameters of myocontractile and diastolic function were derived from pressure-volume loops that were measured by an MRI catheterization technique. This MRI method was previously validated in animal experiments and has been recently described in detail. Briefly, ventricular volumes of the single ventricle were acquired over several cardiac beats with cine MRI. During MRI, invasive ventricular pressures were measured and averaged. At postprocessing, volumes and pressures were synchronized in time using a trigger signal. From these measures, a pressure-volume loop under steady-state conditions was constructed. The end-systolic pressure-volume relation was estimated from this loop using a single-beat approach as previously described. Effective arterial elastance (Ea), which is the slope of the end-systolic pressure-volume relation, was defined as the sum of contractility and indexed to 100 mg myocardial muscle mass (Emax,i).

Effective arterial elastance (Ea) was calculated as end-systolic pressure divided by stroke volume. Ventricular-arterial coupling was determined as the ratio of Emax to Ea. In a second step, instantaneous blood flows were measured using real-time VEC MRI in the ascending aorta just distal to the orifices of the coronary arteries. The sequence parameters were TR and TE, 23 and 6.5 milliseconds; matrix, 128×256; field of view, 400 mm; slice thickness, 8 mm; encoding velocity, 150 cm/s; sensitivity encoding reduction factor, 3; half-scan factor, 0.6; and echo planar imaging factor, 41. The scan time was 31 milliseconds for the acquisition of 1 phase-contrast image. During flow measurement, the respiratory excitation reduced by transient balloon occlusion of the vena cava. The balloon was inflated with saline solution. For each unloaded beat, we determined ventricular chamber volumes and synchronized them with ventricular pressures to generate a set of pressure-volume loops, as previously described. The absolute end-diastolic volumes were determined by matching the VEC MRI-derived volumes with the intercept of the end-systolic pressure-volume relation. The resulting end-diastolic pressure-volume points were used to determine the end-diastolic pressure-volume relation. The stiffness constant B, a load-independent measure of ventricular compliance, was calculated from the end-diastolic pressure-volume relation with an exponential regression as follows: EDP=Ae⁻BPDV, where EDP indicates end-diastolic pressure; EDV, end-diastolic volume; and A, curve-fitting constant. B was indexed to ventricular volumes to create a dimensionless index (B; δ). From

PVR was the quotient between transpulmonary gradient and effective antegrade pulmonary flow. The transpulmonary gradient was calculated as the difference between mean pulmonary and ventricular end-diastolic pressures. Total effective pulmonary flow was defined as the sum of antegrade flow as measured with VEC MRI in the right and left pulmonary artery plus collateral blood flow.

The Nakata index was calculated as the sum of the cross-sectional areas of the left and right pulmonary artery divided by body surface area. The areas were obtained from the magnitude images of the right and left pulmonary VEC MRI measurements.
pressure measurements, we derived relaxation time constant $\tau$ as a parameter of early diastolic relaxation.

**Pressure Recordings and Catheter Visualization During MRI**

The fluid-filled catheters were connected to pressure transducers, and pressures were amplified, recorded, and analyzed with Ponemah software. An additional pressure transducer was positioned within the bore of the scanner to obtain a trigger signal for synchronizing measured pressures with cine and VEC MRI-derived ventricular and blood flow volumes.21 The position of the catheters was visualized on cine MRI images (Figure 1). Appropriate inflation of the balloon catheter with saline solution was confirmed on interactive real-time MRI (Figure 1).26

**Statistical Analysis**

Measurements at rest and during dobutamine stress were analyzed with paired Student $t$ test and Bonferroni-Holm correction for multiple comparisons of 20 parameters. Data are expressed as mean±SD. The correlation was determined among ventricular volumes, cardiac index, and aortopulmonary collateral flow. In addition, correlation was determined among measurements of collateral flow, PVR, and ergometry-derived parameters of functional capacity. The agreement between pulmonary and caval flow volumes was assessed using the Bland-Altman test.

**Results**

**General Characteristics**

We investigated 10 patients with a Fontan circulation (5 each with a right- and left-type single ventricle). Eight patients were white, and 2 were of Arabic ethnicity. All patients were compliant to the study. The duration of dobutamine exposure ranged from 15 to 25 minutes. There were no side effects to dobutamine. Due to the length of the study protocol, flow measurements in the inferior and superior vena cava were not performed in 2 patients at rest and in 4 patients during dobutamine stress.

All patients were New York Heart Association class I to II. Ergometry showed decreased functional capacity compared to published reference levels (Table 1).27 Angiograms revealed no obstruction within the Fontan circulation and either no or only visibly small venovenous or aortopulmonary collaterals. Oxygen saturation at rest ranged from 91% to 97% and did not decrease significantly during dobutamine stress. There were no statistically significant differences between parameters as measured for the left- versus right-type single ventricle. This finding also comprises the functional parameters as given in the next sections.

**Blood Flow and PVR**

The Nakata index of the pulmonary arteries was 150±45 mm$^2$/m$^2$ and, thus, substantially below published reference values of healthy controls.1,18 Quantitative flow volumes measured in the inferior and superior vena cava were similar to those measured in the left and right pulmonary artery, and they all increased during dobutamine stress ($P<0.05$) (Table 2). In all patients,

<table>
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<tr>
<th>Table 1. Patient Characteristics</th>
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<td>2. Tricuspid atresia</td>
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<td>10. DORV, heterotaxia</td>
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<td>Mean±SD</td>
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</table>

$AV$ indicates atrioventricular; $BSI$, body surface index; $DILV$, double inlet left ventricle; $DORV$, double outlet right ventricle; $LV$, left ventricle; $MM$, muscle mass; $NYHA$, New York Heart Association; $RV$, right ventricle; $TGA$, transposition of the great arteries; $VE/V_{CO_2}$ slope, minute ventilation to carbon dioxide production relationship; $V_o_{max}$, peak oxygen uptake.
there was only trivial retrograde flow in the pulmonary arteries both at rest and during stress (Figure 2). The Bland-Altman analysis showed good agreement between flow measurements obtained in the vena cava and the pulmonary arteries (Figure 3). During augmented pulmonary flow, mean pulmonary artery pressure and transpulmonary pressure gradient only changed slightly, and consequently, vascular resistance was decreased (Table 3). Blood flow volumes were significantly larger when measured in the aorta than when measured in the pulmonary arteries, and compared to rest, this difference increased during stress (Table 2). Thus, the calculated collateral blood flow increased significantly during dobutamine stress ($P<0.01$). There was no significant correlation between collateral blood flow and ventricular end-diastolic volumes (at rest, $r=-0.072$;

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<td>2.0</td>
<td>3.4</td>
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</table>

**Mean±SD** 1.9±0.4 3.0±0.7 2.0±0.5 3.1±1.0 2.2±0.6 3.8±1.3 0.3±0.1 0.8±0.4 13.1±3.5 25.6±8.3

$P$ values were adjusted by Bonferroni-Holm correction for multiple comparisons. Uncorrected $P$ values were derived from paired Student t tests for differences between rest and dobutamine. APC indicates aortopulmonary collateral; Dobu, dobutamine; IVC, inferior vena cava; LPA, left pulmonary artery; Qp, pulmonary blood flow; RPA, right pulmonary artery; SVC, superior vena cava.

*Significant differences after Bonferroni-Holm correction.

Figure 2. Representative flow volumes and pressures of a patient with Fontan measured at rest and during dobutamine stress. The pulmonary flow is shown as the sum of the flow measured in the left and right pulmonary artery. For illustration purposes, data measured at 2 different heart rates (rest and dobutamine stress) were scaled to 35 heart phases.
during dobutamine stress, \( r = -0.062 \) or between collateral blood flow and cardiac index (at rest, \( r = -0.072 \); during dobutamine stress, \( r = -0.062 \)). However, there were statistically significant inverse correlations between collateral blood flow (aortopulmonary collateral) and both PVR (\( r = -0.6 \); \( P = 0.03 \)) and ergometry-derived peak oxygen uptake (\( r = -0.7 \); \( P = 0.01 \)). Blood flow patterns in the pulmonary arteries were similar at rest and during dobutamine stress (Figure 2). In concordance with other reports, the profiles showed some degree of interindividual variability.\(^{28,29}\)

**Global Pump Function**

During dobutamine stress, heart rate and cardiac output increased significantly, but stroke volume did not (Tables 4 and 5). Differences in ejection fraction just fell short of being significant when adjusting for multiple comparisons (\( P = 0.009 \)) (Table 5).

**Myocontractile and Diastolic Function**

During dobutamine stress, there was an increase of \( E_{max,i} \) that was not significant when adjusting for multiple comparisons (\( P = 0.026 \)) (Table 4). Efficiency of ventricular-arterial coupling did not improve during dobutamine stress due to a concomitant increase in \( \tau \).\(^{25}\) By echocardiography, the E/A-wave ratio was above 0.7 in all patients. During MRI catheterization at rest, the relaxation time constant \( \tau \) was at published reference levels for healthy controls and shortened significantly during dobutamine stress (Table 4). At the same time, there was a decrease of end-diastolic volumes (Figure 4 and Table 5). End-diastolic pressure increased slightly but not significantly. There were no significant changes of the stiffness constant \( \beta \), but the pressure-volume loops shifted toward the left in the pressure-volume diagram in all patients (Figure 4 and Table 4).

**Discussion**

A progressive decrease of exercise capacity is commonly observed in patients with Fontan circulation, and at late follow-up, heart failure contributes importantly to morbidity.\(^5\) The pathophysiologic causes for heart failure seem to be multifactorial. In this study, MRI catheterization was used at rest and during dobutamine stress to obtain information about PVR, global ventricular pump function, myocardial contractility, and diastolic function. The major findings are that left-to-right shunt through aortopulmonary collaterals increased during dobutamine stress, but PVR decreased. In addition, during stress, the single ventricle had signs for abnormal diastolic compliance.

**Blood Flow and PVR**

Several authors reported a diminished growth of the pulmonary arteries despite somatic growth and assumed that this might have an impact on PVR.\(^{1,2}\) However, only sparse data are available

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### Table 3. Ventricular Pressures and Pulmonary Pressures and Resistance

<table>
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<tr>
<th>Patient no.</th>
<th>EDP, mm Hg</th>
<th>ESP, mm Hg</th>
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<th>TPG, mm Hg</th>
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\[ \text{Mean} \pm \text{SD} \]

\[ \begin{array}{c}
5.6 \pm 1.7 \\
6.9 \pm 1.4 \\
90.5 \pm 8.0 \\
104.4 \pm 9.7 \\
11.1 \pm 1.3 \\
12.7 \pm 0.6 \\
5.5 \pm 1.3 \\
5.5 \pm 1.4 \\
2.7 \pm 1.0 \\
1.6 \pm 0.5
\end{array} \]

\[ \begin{array}{c}
P \quad 0.084 \\
0.0034^* \\
0.0057^* \\
0.986 \\
0.0022^*
\end{array} \]

\( * \)Significant differences after Bonferroni-Holm correction.

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about the functional status of the pulmonary arteries at rest and
during stress partly because vascular properties like PVR cannot
be evaluated using conventional techniques, such as thermodi-
lution or the Fick method, in patients with a Fontan circulation.
In the present setting, MRI catheterization is a unique tool that
combines invasive pressures and VEC MRI-derived flow data
that also account for collateral aortopulmonary blood flow.3,16,28
For reliable assessment of the PVR in the Fontan circulation,
which is very susceptible to changes in volume load, pulmonary
pressures and blood flow were measured in our study simulta-
neously but not sequentially.

The MRI method used in this study for measuring collateral
blood flow was adopted from the work published by Grosse-
Wortmann et al3 and Whitehead et al.14 In these studies,
collateral flow was estimated by 2 approaches. Simplified,
collateral flow was defined as the differences between flow
volumes measured in the ascending aorta and the 4 pulmonary
veins or, alternatively, as the difference between flow volumes
in the ascending aorta and the systemic venous return. The latter
was determined in the descending aorta3 or the inferior and
superior vena cava.14 In both studies, the different methods had
overall good agreement. In the present study, we modified the
approach of Whitehead and colleagues slightly by directly
measuring pulmonary arterial flow instead of caval flow. Com-
paring pulmonary with caval flow volumes showed good agree-
ment (Figure 3).

Table 4. Pulmonary Function

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Heart Rate, bpm</th>
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<th>Coupling $E_{\text{max}}/E_a$</th>
<th>Diastolic Compliance $\beta$, 1/mL/100 mL EDV</th>
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<td>6.8</td>
<td>0.9</td>
</tr>
<tr>
<td>Mean±SD</td>
<td>84±14</td>
<td>126.1±21.6</td>
<td>3.2±0.9</td>
<td>4.3±1.1</td>
<td>0.6±0.2</td>
</tr>
<tr>
<td>$P$</td>
<td>0.00002*</td>
<td>0.0264</td>
<td>0.2171</td>
<td>0.5212</td>
<td>0.0023*</td>
</tr>
</tbody>
</table>

$P$ values were adjusted by Bonferroni-Holm correction for multiple comparisons. Uncorrected $P$ values were derived from paired Student t tests for differences between rest and dobutamine. $\beta$ indicates stiffness constant indexed to 100 mL of end-diastolic volume; Dobu, dobutamine.

*Significant differences after Bonferroni-Holm correction.

Table 5. Ventricular Volumes

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>EDV, mL/m²</th>
<th>ESV, mL/m²</th>
<th>SV, mL/m²</th>
<th>EF, %</th>
<th>Cardiac Index, L/min/m²</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rest</td>
<td>Dobu</td>
<td>Rest</td>
<td>Dobu</td>
<td>Rest</td>
</tr>
<tr>
<td>1</td>
<td>86.4</td>
<td>77.8</td>
<td>49.5</td>
<td>48.7</td>
<td>36.9</td>
</tr>
<tr>
<td>2</td>
<td>83.9</td>
<td>77.2</td>
<td>48.2</td>
<td>41.5</td>
<td>35.7</td>
</tr>
<tr>
<td>3</td>
<td>72.3</td>
<td>66.1</td>
<td>49.4</td>
<td>43.3</td>
<td>22.9</td>
</tr>
<tr>
<td>4</td>
<td>45.3</td>
<td>36.3</td>
<td>22.3</td>
<td>13.4</td>
<td>23.0</td>
</tr>
<tr>
<td>5</td>
<td>77.9</td>
<td>69.3</td>
<td>53.3</td>
<td>43.7</td>
<td>24.5</td>
</tr>
<tr>
<td>6</td>
<td>46.3</td>
<td>37.6</td>
<td>20.1</td>
<td>12.9</td>
<td>26.3</td>
</tr>
<tr>
<td>7</td>
<td>38.0</td>
<td>38.2</td>
<td>19.5</td>
<td>9.2</td>
<td>18.5</td>
</tr>
<tr>
<td>8</td>
<td>71.5</td>
<td>61.7</td>
<td>43.4</td>
<td>31.2</td>
<td>28.1</td>
</tr>
<tr>
<td>9</td>
<td>89.9</td>
<td>71.5</td>
<td>54.1</td>
<td>40.0</td>
<td>28.0</td>
</tr>
<tr>
<td>10</td>
<td>48.6</td>
<td>43.8</td>
<td>25.7</td>
<td>18.0</td>
<td>22.9</td>
</tr>
<tr>
<td>Mean±SD</td>
<td>66±18.5</td>
<td>57.9±16.2</td>
<td>38.6±14</td>
<td>30.2±14.5</td>
<td>26.7±5.5</td>
</tr>
<tr>
<td>$P$</td>
<td>0.0004*</td>
<td>0.0001*</td>
<td>0.6877</td>
<td>0.0092</td>
<td>0.0002*</td>
</tr>
</tbody>
</table>

$P$ values were adjusted by Bonferroni-Holm correction for multiple comparisons. Uncorrected $P$ values were derived from paired Student t tests for differences between rest and dobutamine. Dobu indicates dobutamine; EDV, end-diastolic volume; EF, ejection fraction; ESV, end-systolic volume; SV, stroke volume.

*Significant differences after Bonferroni-Holm correction.
In concordance with the studies by Whitehead et al and Grosse-Wortmann et al, we noted an important contribution of aortopulmonary collateral flow to total effective pulmonary blood flow. The latter is considered being the amount of blood that passes through the pulmonary arteriole level, thus the sum of antegrade pulmonary and collateral flow. Recirculating blood through collaterals contributed about 13% to the total effective pulmonary flow at rest, and this percentage increased substantially to \( \frac{1}{25} \) during dobutamine stress. Interestingly, there was statistically significant inverse correlation between the amount of collateral flow and peak oxygen uptake during ergometry. Collateral flow also correlated inversely with PVR, but the relatively small sample size in the present study limits the clinical interpretation of this finding. This issue must be addressed systematically in future research.

In the studied patients, PVR at rest was slightly above published control values, which were determined in a previous study using the same MRI catheterization method. During dobutamine stress, mean pulmonary pressures increased, but transpulmonary gradient did not, and thus, PVR decreased in the presence of augmented pulmonary throughput. PVR generally is considered a valid indicator of structural changes at the small resistive pulmonary arteriole level. Hence, we concluded that in the studied patients, there is at least a partially functioning pulmonary vasculature regulation to variation in pulmonary perfusion. However, one must keep in mind when interpreting these data that dobutamine was shown to increase pulmonary blood flow, but it does not affect the pulmonary vascular tone. In addition, Hjortdal and colleagues demonstrated that in patients with a Fontan circulation with total cavopulmonary connection, blood flow through the lung is driven by cardiac, respiratory, and peripheral muscular mechanisms. The relative contributions of these pumping mechanisms are influenced by many factors that include cardiac performance, physical exercise, body position, and respiratory patterns. These different mechanisms cannot be realistically simulated in the MRI environment.

Global Ventricular, Myocontractile, and Diastolic Function

Similar to earlier studies, we noted no substantial stroke volume augmentation under dobutamine stress in the patients with a Fontan circulation. Myocardial contractility increased only slightly and not significantly during inotropic stimulation, and thus, the increase in cardiac output was mainly regulated by heart rate. This finding, again, is in line with earlier studies. In conjunction with slightly improved parameters of contractility, end-systolic volumes decreased adequately, suggesting that systolic dysfunction is not the predominant cause of the abnormal response to stress. At the same time, end-diastolic volumes decreased, again similar to previous observations, and Emax/Ea, a parameter for the efficiency of ventriculoarterial coupling, remained at a low level. These findings suggest an abnormal diastolic function of the single ventricle during dobutamine stress. In Fontan, diastolic filling is thought to be affected by a limited preload reserve because there is no subpulmonary ventricle actively pumping an appropriate amount of blood through the pulmonary system. From elderly patients with atrial-septal defect, it is known that chronic underloading can lead to a small and stiff left ventricle. In these patients, pharmacological priming before defect closure mostly improved diastolic function. On the contrary, recirculating blood through aortopulmonary collaterals contributes increasingly to ventricular filling under stress and, thus, would attenuate a deficient preload reserve. Other authors even discussed that collateral flow can impose a volume load on the single ventricle. In patients with a Fontan circulation with total cavopulmonary connection, blood flow through the lung is driven by cardiac, respiratory, and peripheral muscular mechanisms. The relative contributions of these pumping mechanisms are influenced by many factors that include cardiac performance, physical exercise, body position, and respiratory patterns. These different mechanisms cannot be realistically simulated in the MRI environment.

In the present study, active early diastolic relaxation appeared to be normal, as indicated by a decrease of \( \tau \) during dobutamine stress. However, there was evidence of abnormal diastolic compliance. During dobutamine stress, the stiffness constant \( \beta \) remained at similar levels as measured at rest, but the end-diastolic pressure-volume relation shifted toward the upper-left in
the pressure-volume diagram. Such a shift of the end-diastolic pressure-volume relation was not observed in recent studies that were performed in healthy pig left and right ventricles.\textsuperscript{21,39} In addition, these studies showed that dobutamine has no major impact on the stiffness constant $\beta$. It seems that chamber properties for filling do not improve during dobutamine stress; rather, filling must be accomplished in a system with increased stiffness. In the present study, we exposed the patients to moderate dobutamine stress that caused no substantial increase in end-diastolic pressures. In more severe stress situations, diastolic dysfunction might unmask even further, which could go along with more increased end-diastolic pressures. An abnormal ventricular stiffness could be explained by several reasons. The geometry of the single ventricle has a direct impact on its mechanical pump function and, thus, on its systolic and diastolic properties.\textsuperscript{80} In addition, prolonged cyanosis and volume load during infancy are thought to induce myocardial fibrosis.\textsuperscript{6,40} Finally, histopathologic studies in tricuspid atresia showed abnormal formation and arrangement of the fibrous matrix and the aggregation of myocytic chains.\textsuperscript{11} Thus, the potential causes for the development of heart and pulmonary vascular dysfunction are multifactorial, as are the resulting forms of dysfunction, implying that it is essential to investigate these patients with methods that give a differential insight into the predominant form of failure that, in turn, will allow optimizing treatment concepts.

In summary, the findings of this study indicate that during dobutamine stress, blood flow through aortopulmonary collaterals contributes progressively to pulmonary perfusion. The pulmonary arteries had an abnormal growth index, but vascular regulation appeared to be unsuspicious. PVR decreased during stress and, thus, did not contribute to impaired diastolic filling in the patients studied. In contrast, we noted in the presence of normal early relaxation alteration of ventricular compliance during stress.

**Limitations**

There is no established animal model for studying the Fontan circulation. Additionally, extrapolating findings from healthy human controls to a univentricular physiology must be made with great care. Therefore, this patient study has a descriptive nature, and findings must be related to parameters that were obtained in other research. Care must be taken when comparing changes of ventricular and pulmonary vascular function induced by physical exercise with dobutamine stress.\textsuperscript{30,32,42,43} Therefore, it would be inappropriate to directly translate our findings to exercise conditions. In addition, heart rate effects must be considered when interpreting our data of diastolic compliance. Collateral flow through intrapulmonary shunts and venovenous collaterals was not determined in our study. However, arterial oxygen saturation did not decrease significantly during stress, and thus, one can assume that flow through these types of shunts was relatively constant during the study protocol. Measuring blood flow in all 4 pulmonary veins would have allowed quantifying the amount of venovenous and intrapulmonary flow but at the expense of a substantially lengthened protocol that was judged too demanding. In general, VEC phase-contrast MRI flow sequences must be used with great care when measuring quantitative flow.

Finally, there is a broad range of varieties in Fontan regarding anatomic conditions and the onset and time course of cardiovascular dysfunction. Therefore, one cannot extrapolate our data of preselected patients to other forms of Fontan. However, the method used in this study allows differentiation among pulmonary, systolic, and diastolic dysfunction, which will potentially improve the planning of individual treatment strategies.

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**Disclosures**

None.

**References**


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