Effects of Exercise and Respiration on Blood Flow in Total Cavopulmonary Connection
A Real-Time Magnetic Resonance Flow Study

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Background—Little is known about blood flow and its relationship to respiration during exercise in patients with total cavopulmonary connection (TCPC).

Methods and Results—We studied 11 patients 12.4±4.6 years (mean±SD) of age 5.9±2.8 years (mean±SD) after TCPC operation. Real-time MRI was used to measure blood flow in the superior vena cava (SVC), inferior vena cava (IVC), and ascending aorta under inspiration and expiration during supine lower-limb exercise (rest, 0.5 and 1.0 W/kg) on an ergometer bicycle. IVC and aortic flow increased from 1.60±0.52 and 2.99±0.83 L/min per m² at rest to 2.58±0.71 and 3.97±1.20 L/min per m² at 0.5 W/kg and to 3.25±1.23 and 4.62±1.49 L/min per m² at 1.0 W/kg (P<0.05). SVC flow remained unchanged. Resting flow in the IVC was greater during inspiration (2.99±1.25 L/min per m²) than during expiration (0.83±0.44 L/min per m²) (inspiratory/mean flow ratio, 1.9±0.5), and retrograde flow was present during expiration (11±12% of mean flow). The predominance of inspiratory flow in IVC diminished with exercise to an inspiratory/mean flow ratio of 1.5±0.2 (P<0.05) and 1.4±0.3 at 0.5 and 1.0 W/kg, respectively.

Conclusions—In the TCPC, circulation IVC and aortic but not SVC flows increase with supine leg exercise. Inspiration facilitates IVC flow at rest but less so during exercise, when the peripheral pump seems to be more important.

Key Words: exercise • Fontan procedure • magnetic resonance imaging • heart defects, congenital

Total cavopulmonary connection (TCPC) is a palliative operation used in patients with complex cardiac malformations that preclude a biventricular repair. The fundamental physiology of the TCPC circulation is a dissociation of the venous return from a ventricular power source.

We previously used MRI to study flow during breath hold in the TCPC circulation. At rest, the pulmonary and caval circulation was characterized by biphasic flow and pressure waveforms with maxima in atrial systole and late ventricular systole.1 With supine bicycle exercise, blood flow increased, primarily attributable to an increase in heart rate and only slightly attributable to an increased stroke volume.2

Breathing has a pronounced effect on flow rates in the Fontan circulation at rest,3–7 leading to a concept of a respiratory pump that sucks blood into the lungs during inspiration.8 However, it is largely unknown how breathing affects flow during exercise.

The aim of the present investigation was to study the influence of breathing on real-time antegrade and retrograde flow in the caval veins and in the aorta during exercise in patients with TCPC.
their feet strapped in the pedals of an ergometer bicycle mounted on the scanner table (MRI cardiac ergometer, Lode BV). Heart rate was monitored by a standard ECG-monitoring system and by pulse oximetry (Nonin 8600 FO). Inspiration and expiration were monitored with an air-filled belt mounted on the abdomen and connected by a 2-m-long air tube to a pressure transducer.

Magnetic Resonance Imaging
MRI was performed using a Philips NT 1.5 Tesla whole-body scanner equipped with 21- and 105-mT/m per ms gradients and CPR6 research software and using an 18-cm receiver coil. Standard scout images of the heart and great vessels were acquired in 3 orthogonal planes. From the scout images, double angulated flow measurement planes were planned orthogonally to the SVC, IVC, and ascending aorta. In the SVC, flow was measured immediately above the pulmonary anastomosis. Flow in the IVC was measured at the level of the lateral tunnel, above the coronary sinus. Aortic flow was measured in the ascending aorta.

Real-time flow measurements were performed in random order in the IVC, SVC, and aorta at rest and during exercise. Each measurement consisted of 120 consecutive, real-time (no ECG triggering) phase-contrast flow acquisitions, each lasting 48 to 56 ms, giving a frame rate of approximately 20 frames per second.

A segmented gradient-echo phase contrast (echo planar imaging technique) with a field of view of 90×136 mm and 26×64 matrix (pixel size, 3.4×2.1 mm², reconstructed to 1.1×1.1 mm²), 5- to 7-mm slice thickness, 13 readouts, 0.8 half-scan factor, echo time 4 to 5 ms, and repetition time 12 to 13 ms was used. Velocity encoding varied from 50 to 120 cm/s depending on vessel and exercise level.

ECG and respiratory waveforms were synchronized with each flow measurement and saved for later analysis. Manual segmentation of vessels was performed using dedicated software and volume flow for each of the 120 measurements calculated (Figure).

For each flow measurement, 2 to 4 respiratory cycles with 6.5 to 10 cardiac cycles were obtained. The air-filled system for respiratory measurement gave a delay of approximately 500 ms between the respiratory movement of the patient and the appearance of the respiratory signal. All respiratory curves were corrected 500 ms backwards accordingly.

The beginning of the inspiratory phase was set to the start of the upward deflection and the beginning of expiration to the start of the downward deflection of the respiratory signal.

Exercise Protocol
Resting flow measurements were performed with the feet in the pedals, positioned between 4 and 22 cm above the scanner table. Hereafter, the patients performed continuous leg exercise at workloads of 0.5 and 1.0 W/kg. At each workload, exercise was continued until the heart rate was stable for 2 minutes. Flow measurements were then performed while the patient was still exercising. If

<table>
<thead>
<tr>
<th>TABLE 1. Patient Characteristics</th>
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</thead>
<tbody>
<tr>
<td>Age, y</td>
</tr>
<tr>
<td>Sex, male/female</td>
</tr>
<tr>
<td>Age at surgery, y</td>
</tr>
<tr>
<td>Time since surgery, y</td>
</tr>
<tr>
<td>Weight, kg</td>
</tr>
<tr>
<td>Height, cm</td>
</tr>
<tr>
<td>Diagnosis, n</td>
</tr>
<tr>
<td>Tricuspid atresia</td>
</tr>
<tr>
<td>Double-inlet left ventricle</td>
</tr>
<tr>
<td>Mitral atresia</td>
</tr>
</tbody>
</table>

Values are mean (SD).

Volume flow data from 1 patient synchronized to ECG and respiratory signal for both aorta, IVC and SVC at rest (left), and at 1 W/kg exercise (right). Values for all 120 real-time measurements are shown as a function of time for each series. With exercise, the ECG signal became increasingly distorted.
exercise led to misplacement of the measurement plane, a real-time scout lasting 15 seconds was obtained, and the slice was repositioned and the flow measurement repeated.

Calculations
Heart and respiratory rates at each work level were calculated as the mean values over the time during which flow measurements were performed in the 3 different measurement positions. Blood flow and stroke volume were measured for 2 respiratory cycles. The start and the end of the 2 inspiratory and expiratory phases were determined from the respiratory waveforms. The length of the inspiratory phase relative to the whole respiratory cycle (inspiratory fraction) was calculated. The mean flow rate from 2 inspiratory and from 2 expiratory phases, respectively, was computed, as well as overall mean flow. Inspiratory flow rates relative to mean flow rates during expiration, and the retrograde flow percentage was compared between exercise levels using 2-tailed paired t test. P≤0.05 was considered significant.

Results
All patients completed the protocol. The heart rate and respiratory rate increased with increasing levels of exercise (P<0.05) (Table 2). The inspiratory fraction increased from the resting state to the exercise level of 0.5 W/kg (P<0.05), with no additional increase at 1.0 W/kg.

Flows and Respiratory Influence
Table 3 shows flow rates for the study group and the impact of respiration. Mean aortic and IVC flow rates increased significantly with increasing exercise, whereas SVC flow rates were unchanged. Aortic flow rates were slightly lower (P<0.05) during inspiration at rest, and this was unchanged with exercise. At rest, the flow rate in IVC during inspiration was significantly higher than during expiration. With exercise, this inspiratory predominance was still present but the magnitude decreased significantly. SVC flow rates did not change with respiration.

Inspiratory stroke volumes were 46.3±12.8 mL/m² at rest and 47.4±13.2 and 48.2±15.6 mL/m² at the 2 exercise levels, respectively. The corresponding expiratory stroke volumes were 49.0±13.2, 50±14.7, and 50.7±16.1 mL/m², respec-

### Statistical Analysis
All variables are expressed as mean±SD. Variables measured at exercise levels were compared with resting values by the use of 2-tailed, paired Student’s t test.

The aortic and caval flow values were compared in inspiration and expiration, and the retrograde flow percentage was compared between exercise levels using 2-tailed paired t test. P≤0.05 was considered significant.

<table>
<thead>
<tr>
<th>Rest</th>
<th>0.5 W/kg</th>
<th>1.0 W/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flow in respiratory cycle</td>
<td>2.99±0.83</td>
<td>3.97±1.20*</td>
</tr>
<tr>
<td>Flow in inspiration</td>
<td>2.85±0.73</td>
<td>3.84±1.24</td>
</tr>
<tr>
<td>Flow in expiration</td>
<td>3.24±0.91†</td>
<td>4.33±1.48</td>
</tr>
<tr>
<td>Inspiratory flow fraction</td>
<td>1.0±0.1</td>
<td>1.0±0.1 (NS)</td>
</tr>
</tbody>
</table>

Data are mean±SD of measurements in the 11 patients. Inspiratory flow rates relative to mean flow rates in a full respiratory cycle (inspiratory flow fraction) are given for each vessel at each exercise level. NS indicates no significant difference compared with flow rate at previous exercise level.

*Significant (P<0.05) difference compared with flow rate at previous exercise level.
†Significant (P<0.05) difference between inspiratory and expiratory flow rates.

### Table 2. Heart Rate, Respiratory Rate, and Duration of Inspiratory Phase Relative to the Entire Respiratory Cycle (Inspiratory Fraction) During Flow Measurements at Rest and During Exercise

<table>
<thead>
<tr>
<th></th>
<th>Heart Rate, min⁻¹</th>
<th>Respiratory Rate, min⁻¹</th>
<th>Inspiratory Fraction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rest</td>
<td>74±14</td>
<td>21±4</td>
<td>0.35±0.05</td>
</tr>
<tr>
<td>0.5 W/kg</td>
<td>90±11*</td>
<td>30±7*</td>
<td>0.41±0.04*</td>
</tr>
<tr>
<td>1.0 W/kg</td>
<td>104±8*</td>
<td>35±8*</td>
<td>0.41±0.04</td>
</tr>
</tbody>
</table>

Data are mean±SD. *P<0.05 compared with previous exercise level.

### Table 3. Mean Blood Flow Rates (L/min per m²) in 2 Respiratory Cycles and the Corresponding Mean Flow Rates During Inspiration and Expiration in the Aorta, IVC, and SVC at Rest and at 2 Different Exercise Levels

<table>
<thead>
<tr>
<th></th>
<th>Aorta</th>
<th>IVC</th>
<th>SVC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rest</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flow in respiratory cycle</td>
<td>2.99±0.83</td>
<td>1.66±0.52</td>
<td>1.26±0.34</td>
</tr>
<tr>
<td>Flow in inspiration</td>
<td>2.85±0.73</td>
<td>2.99±1.25</td>
<td>1.26±0.32</td>
</tr>
<tr>
<td>Flow in expiration</td>
<td>3.24±0.91†</td>
<td>0.83±0.44†</td>
<td>1.29±0.42</td>
</tr>
<tr>
<td>Inspiratory flow fraction</td>
<td>1.0±0.1</td>
<td>1.9±0.5</td>
<td>1.0±0.2</td>
</tr>
<tr>
<td>0.5 W/kg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flow in respiratory cycle</td>
<td>3.97±1.20*</td>
<td>2.58±0.71*</td>
<td>1.27±0.42 (NS)</td>
</tr>
<tr>
<td>Flow in inspiration</td>
<td>3.84±1.24</td>
<td>3.86±1.29</td>
<td>1.37±0.56</td>
</tr>
<tr>
<td>Flow in expiration</td>
<td>4.33±1.48</td>
<td>1.79±0.65†</td>
<td>1.21±0.39</td>
</tr>
<tr>
<td>Inspiratory flow fraction</td>
<td>1.0±0.1 (NS)</td>
<td>1.5±0.2*</td>
<td>1.1±0.3 (NS)</td>
</tr>
<tr>
<td>1.0 W/kg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flow in respiratory cycle</td>
<td>4.62±1.49*</td>
<td>3.25±1.23*</td>
<td>1.27±0.46 (NS)</td>
</tr>
<tr>
<td>Flow in inspiration</td>
<td>4.31±1.57</td>
<td>4.63±2.04</td>
<td>1.23±0.47</td>
</tr>
<tr>
<td>Flow in expiration</td>
<td>4.88±1.50</td>
<td>2.39±1.15†</td>
<td>1.36±0.57</td>
</tr>
<tr>
<td>Inspiratory flow fraction</td>
<td>0.9±0.1 (NS)</td>
<td>1.4±0.3 (NS)</td>
<td>1.0±0.3 (NS)</td>
</tr>
</tbody>
</table>

Data are mean±SD of measurements in the 11 patients. Inspiratory flow rates relative to mean flow rates in a full respiratory cycle (inspiratory flow fraction) are given for each vessel at each exercise level. NS indicates no significant difference compared with flow rate at previous exercise level.

*Significant (P<0.05) difference compared with flow rate at previous exercise level.
†Significant (P<0.05) difference between inspiratory and expiratory flow rates.
tively. This slight increase in stroke volume with exercise was not statistically significant.

Figure 2 shows blood flow from 1 patient in relation to the respiratory and cardiac cycle at rest and during exercise at 1.0 W/kg. Aortic flow rate at rest varied mainly in the cardiac cycle with a small retrograde flow during diastole and showed almost no variation with respiration. During exercise, flow rate increased slightly during expiration. Resting IVC flow showed marked respiratory variation, with the highest flow rate occurring during inspiration. During exercise, the flow rate increased and the respiratory fluctuation was still present. SVC flow at rest and during exercise increased slightly with inspiration but varied less with respiration than IVC flow.

Correlation Between Aortic Flow Rates and Systemic Venous Flow Rates
The mean aortic flow rate differed less than 6% from the combined SVC and IVC flow rates. However, when looking separately at the inspiratory and expiratory phases, large variations in blood flow were found. At rest, the combined venous flow rate was 51% higher than the aortic flow during inspiration (P<0.05) and 34% lower during expiration (P<0.05).

At 1.0 W/kg, the combined venous flow rate was 42% higher than aortic flow rates during inspiration (P<0.05) and 23% lower during expiration (P<0.05).

Retrograde Flow
Retrograde flow accounted for 2% to 3% of mean blood flow in the ascending aorta and 0% to 1% in the SVC, with no changes with exercise. Retrograde blood in IVC decreased from 10.5±12.4% of mean blood flow at rest to 2.9±4.0% during exercise (P<0.05).

Flow During Exercise
This is the first quantitative study of MR-measured real-time volume flow in TCPC-operated patients during exercise. Aortic and IVC flows increased with higher levels of supine bicycling whereas SVC flows remained unchanged, reflecting that the work loads were carried predominantly by the muscles of the lower body half. The absolute flow values and the increase in flow are comparable to what has been described using respiratory mass spectrometry.9

To explain the complex hemodynamic changes during exercise, the concepts of a cardiac pump, a respiratory pump, and a peripheral pump have been introduced.12

In the TCPC circulation, we have previously found that during exercise, the cardiac pump increases cardiac output, predominantly by increasing the heart rate and only to a lesser extent by increasing stroke volume.2 This is in accordance with exercise studies in healthy children.13

The respiratory pump had a pronounced effect on IVC flow at rest, with an inspiratory flow fraction of 1.9. Wexler et al14 found that the velocity of IVC flow in healthy adult men increased in inspiration and that this respiratory pump effect was more pronounced with supine lower-leg exercise. Rosenthal et al8 observed that TCPC-operated patients had a higher minute ventilation at rest and a more significant increase in respiratory rate early in exercise than controls, indicating that the work of breathing may also be important for pulmonary flow during exercise.

In our study, breathing became faster, the inspiratory phase longer, and the inspiratory IVC flow rates higher during exercise. However, a similar increase in absolute expiratory flow rates resulted in lesser respiratory variations during exercise. Thus, the effect of the respiratory pump on venous return through the IVC became relatively less important with exercise.

The peripheral pump concept was developed in the 1940s and has been repeatedly demonstrated.12 The increase in flow and the reduction in retrograde flow in the IVC during exercise may be explained by the higher blood flow from working muscles and reduced venous capacitance in the lower body half, attributable to tension and activity of the abdominal and leg muscles.

In healthy subjects, upright bicycle exercise is associated with increasing peripheral muscle contraction that produces an immediate increase in the gradient for venous return of greater than 4 mm Hg and an immediate central volume shift of up to 1 L from the lower limbs.16 In supine bicycle exercise, the peripheral pump has even better working conditions, because gravity is not an issue. After a TCPC, the peripheral pump is probably the most important factor for the doubling of the IVC flow during exercise.

MR Method
This study gave separate quantification of inspiratory and expiratory flow. The real-time technique, although limited in spatial resolution, proved very robust and allowed for measurements...
during physical exercise. No motion artifacts were present, because each image (flow-sensitive and flow-insensitive) was acquired within 25 ms. The image quality was identical for rest and exercise flow measurements (Figure 1). The time resolution of approximately 20 frames per second was acceptable for looking at pulsatile flow phenomena. The comparison between the combined venous and aortic flow rates demonstrated a mean difference between the independently obtained flow measurements of less than 6%.

The absolute exercise flow values were comparable to previous studies using MR flow measurements at held expiration\(^2\) and mass spectrometry,\(^8\) indicating the accuracy of the technique.

Unlike volumetric flow rates acquired from Doppler recordings and single measurement of cross-sectional area,\(^7\) no assumption had to be made with respect to constant cross-sectional area in the veins. This is important, because it has been demonstrated that the inferior vena cava lateral tunnel collapses partially during a drop in intrathoracic pressure.\(^17\)

For the first time, we measured the actual flow in IVC and SVC separately during both inspiration and expiration, and because major fluctuations were present, this turned out to be important.

Unlike previous MR studies,\(^5,18\) our patients were not sedated.

Limitations
Supine lower-limb activity is not the most common type of exercise. However, previous studies have shown that both supine and upright bicycle exercise of comparable workloads results in similar increments in heart rate in TCPC-operated patients and controls.\(^5,19\) Our choice of supine exercise was dictated by the design and capacity of the MR scanner. MR scanners in which patients can sit up do not yet have enough resolution to perform this type of real-time flow measurements.

Spatial resolution was limited because of the real-time flow technique used and might have given rise to partial volume-related flow overestimation in the smallest vessels. However, no systematic errors related to this phenomenon were present.

Because of the small field of view, no stationary tissue was present to be used as reference for phase correction. However, preliminary testing as well as the present results indicated that this was not a major problem. The use of a high-echo planar imaging factor did not induce flow void or other detectable phase errors, and echo time was kept between 4 and 5 ms.

Conclusion and Perspectives
In summary, the TCPC circulation works with only 1 pumping chamber and the 2 circulations in series. However, the lack of a subpulmonary ventricle does not mean that flow to and through the lungs is a passive phenomenon. The present study indicates that the venous return in the TCPC circulation is influenced by the cardiac output, respiration, and probably also a peripheral pump that acts through the muscles surrounding venous capacitance vessels in the body and that the relative contribution of those 3 mechanisms changes from rest to exercise states.

Our findings are important not only because they confirm that detailed and selective flow responses to exercise can be investigated in children after complex cardiac surgery but also because they provide “normal values” for subjects with a good medium-term outcome after cavopulmonary surgery.

The possibility of obtaining detailed physiological flow data during exercise in this group of patients with complex circulations provides clinicians with new opportunities. It will be possible to prospectively evaluate how these flows change over time with alterations in ventricular function, arrhythmias, pregnancy, and the effects of exercise training and drugs in the steadily increasing group of patients who have undergone TCPC.

Acknowledgment
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References
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