Blood flow conditions in the proximal pulmonary arteries and vena cavae: healthy children during upright cycling exercise

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Blood flow conditions in the proximal pulmonary arteries and vena cavae: healthy children during upright cycling exercise. Am J Physiol Heart Circ Physiol 287: H921–H926, 2004. First published March 18, 2004; 10.1152/ajpheart.00022.2004.—Diagnostic testing in patients with congenital heart disease is usually performed supine and at rest, conditions not representative of their typical hemodynamics. Upright exercise measurements of blood flow may prove valuable in the assessment of these patients, but data in normal subjects are first required. With the use of a 0.5-T open magnet, a magnetic resonance-compatible exercise cycle, and cine phase-contrast techniques, time-dependent blood flow velocities were measured in the right (RPA), left (LPA), and main (MPA) pulmonary arteries and superior (SVC) and inferior (IVC) vena cavae of 10 healthy 10- to 14-yr-old subjects. Measurements were made at seated rest and during upright cycling exercise (150% resting heart rate). Mean blood flow (l/min) and reverse flow index were computed from the velocity data. With exercise, RPA and LPA mean flow increased 2.0 ± 0.5 to 3.7 ± 0.7 (P < 0.05) and 1.6 ± 0.4 to 2.9 ± 0.8 (P < 0.05), respectively. Pulmonary reverse flow index (rest vs. exercise) decreased with exercise as follows: MPA: 0.014 ± 0.012 vs. 0.006 ± 0.006 (P = not significant [NS]), RPA: 0.005 ± 0.004 vs. 0.000 ± 0.000 (P < 0.05), and LPA: 0.041 ± 0.019 vs. 0.014 ± 0.016 (P < 0.05). SVC and IVC flow increased from 1.5 ± 0.2 to 1.9 ± 0.6 (P = NS) and 1.6 ± 0.4 to 4.9 ± 1.3 (P < 0.05), respectively. A 56/44% RPA/LPA flow distribution at both rest and during exercise suggests blood flow distribution is dominated by distal pulmonary resistance. Reverse flow in the MPA appears to originate solely from the LPA while the RPA is in relative isolation. During seated rest, the SVC-to-IVC venous return ratio is 50/50%. With light/moderate cycling exercise, IVC flow increases by three-fold, whereas SVC remains essentially constant.

Current methods to obtain such data, however, are insufficient, since nearly all diagnostic testing is performed with patients supine and at rest, neither of which represents the predominant physiological state. As a result, although these exams provide useful data, and, to date, may represent the only methods practically available to clinicians, the data obtained may or may not have clinical validity. Physical exercise can drastically alter blood flow patterns, and hemodynamic inefficiencies are often more pronounced during physical stress. However, no simple correlation exists between rest and exercise states as, in fact, physical exercise exacerbates some conditions and attenuates others. Additionally, it has been shown in both normal individuals and those with congenital heart disease that posture has a significant effect on central hemodynamics, associating supine postures with lower cardiac outputs, higher stroke volumes, and lower heart rates compared with an upright position (3, 15, 16).

To address the shortcomings in current diagnostic testing and the applicability of sporadic testing to long-term outcomes, we developed a magnetic resonance imaging (MRI) protocol to measure blood flow characteristics in seated subjects at rest and with upright cycling exercise, states that provide additional, important data relevant to a patient’s daily circumstances. In the present study, we have applied these techniques in healthy children aged 10–14 yr to quantify blood flow in the main, right, and left pulmonary arteries and superior and inferior vena cavae.

MATERIALS AND METHODS

Ten healthy children (6 males, 4 females) aged 10–14 yr with no known history of cardiopulmonary or systemic disease were recruited and successfully imaged in a 0.5-T interventional magnet (GE Signa SP; GE Medical Systems, Milwaukee, WI). The subjects were positioned such that their chests were in the center of the bore of the magnet and they could comfortably pedal a custom-built, MR-compatible, stationary exercise cycle, as described previously (Fig. 1 and Ref. 5). The exercise cycle and seat positions were adjusted to accommodate for subject size, and Velcro straps were used to limit torso motion.

Cardiac gated cine phase-contrast MRI ( cine PC-MRI) techniques were used to obtain time-resolved anatomic and through-plane velocity maps (20) in the main pulmonary artery (MPA), right pulmonary artery (RPA), left pulmonary artery (LPA), superior vena cava (SVC), and inferior vena cava (IVC). With the use of double-oblique localization scans, the MPA image slice was prescribed proximal to the pulmonary bifurcation, RPA and LPA slice locations were immediately distal to...
the pulmonary bifurcation and proximal to the upper lobe branch origins, and the SVC and IVC slice locations were superior and inferior to their insertions in the right atrium, respectively. Subjects breathed normally during the acquisitions, and respiratory bellows were used to perform respiratory compensation (12) while the cine acquisitions were gated to the cardiac cycle using a plethysmograph placed on the right thumb. The cine data were retrospectively reconstructed to 24 time points to represent a cardiac cycle. Scan parameters included 25 ms repetition time, 10 ms echo time, 30° flip angle, 7-mm slice thickness, 28 by 28-cm square field of view, 256 by 192 k-space image matrix, 1 number of excitations, and a 150-cm/s through-plane velocity encoding gradient.

Pulmonary and caval cine PC-MRI scans were performed at seated rest and during steady-state cycling exercise conditions, defined as 150% of resting heart rate. Exercise intensity had to be defined by heart rate because of the cine MRI acquisition requirements, and a 50% increase in heart rate was chosen, since it was the highest exercise level affording adequate image quality. Resistance to pedaling and pedaling speed were adjusted to maximize comfort and minimize torso motion, and the new steady state was maintained for 3–5 min before data acquisition. Cardiac and respiration rates were displayed in real time on a dedicated monitor, and subjects were instructed to adjust their pedaling speed during the scan to maintain a steady heart rate. Imaging time for each scan required 192 heartbeats and was 2–3 min at rest and 1–2 min during exercise.

Instantaneous blood flow rates were computed from the time-resolved series of magnitude and velocity images for each cine acquisition. Lumen segmentations were obtained either by a level set segmentation method (26, 29) or by manual segmentation from the MR magnitude data. As per theory and experimental studies, pixel velocity values within these boundaries were adjusted with second-order spatially dependent baseline corrections to account for phase errors that result from gradient eddy currents and concomitant magnetic fields (2). Instantaneous flow rates were computed by integrating these corrected velocity values over the lumen cross sections (19). All blood flow rates were scaled to body surface area to account for body size (8). Reversal of blood flow was quantified from the computed time-resolved flow rate data over the cardiac cycle. The magnitude of flow reversal was described by a reverse flow index defined as the amount of retrograde flow compared with total flow (27). Note that a reverse flow index of zero corresponds to a positive (i.e., antegrade) flow rate throughout the cardiac cycle, whereas a reverse flow index of 0.5 corresponds to equal amounts of antegrade and retrograde flow (mean flow rate of 0) over the cardiac cycle.

Statistical analysis of mean flow rate and reverse flow index was conducted comparing rest and exercise states for each vessel and for the SVC vs. IVC, MPA vs. LPA, MPA vs. RPA, and RPA vs. LPA. Post hoc two-tailed t-tests with Bonferroni correction for multiple comparisons were used to test for statistical significance with a corrected P value <0.05 considered significant.

Before study initiation, approval was obtained from the Stanford University Panel on Human Subjects in Medical Research. All participants were provided written and verbal information on the protocol, and informed consent was obtained from the subjects and their parents/legal guardians before enrollment in the study.

RESULTS

Each of the 10 subjects was successfully imaged and able to reach his or her target heart rate of 150% of baseline. The subjects had an average age of 11.9 ± 1.1 yr, weight of 48 ± 10 kg, height of 156 ± 14 cm, body mass index of 19.6 ± 3.6, and body surface area of 1.42 ± 0.17 m². The average heart rate increased from 81 ± 12 beats/min at rest to 121 ± 17 beats/min during exercise (P < 0.05) and corresponds to a workload of 33.9 ± 9.8 watts. This falls within the range of light (35–59% of maximum heart rate) to moderate exercise (60–80% of maximum heart rate) for these subjects (21).

Figure 2 shows the time-resolved flow rate curves for the MPA, RPA, LPA, SVC, and IVC for a representative subject at rest and during cycling exercise. As expected, the pulmonary artery flow curves exhibit pulsatility with stagnant or even slightly retrograde flow at end systole (Fig. 2, A-C), whereas the caval veins demonstrate more steady flow throughout the cardiac cycle (Fig. 2, D and E).

Pulmonary artery blood flow characteristics. Average pulmonary flow data for the 10 subjects at seated rest and during seated cycling exercise are shown in Fig. 3. From rest to exercise, MPA flow increased from 2.9 ± 0.3 to 5.2 ± 0.4 l·min⁻¹·m⁻² (P < 0.05), RPA flow increased from 1.4 ± 0.2 to 2.6 ± 0.5 l·min⁻¹·m⁻² (P < 0.05), and LPA flow increased from 1.1 ± 0.3 to 2.0 ± 0.4 l·min⁻¹·m⁻² (P < 0.05; Fig. 3A). The relative flow distribution to the branch pulmonary arteries

Fig. 1. A 13-yr-old healthy subject pedaling a custom magnetic resonance-compatible exercise cycle in the General Electric 0.5-Tesla interventional magnetic resonance imaging (MRI) apparatus during blood flow imaging of the pulmonary arteries and vena cavae.
remained constant from rest to exercise with an RPA flow percentage of 56 ± 7% at rest to 56 ± 8% during exercise and an LPA flow percentage of 44 ± 7% at rest to 44 ± 8% during exercise (Fig. 3B).

There was an overall decrease in the amount of retrograde flow during exercise when compared with rest. The reverse flow index of the LPA decreased from 0.041 ± 0.019 at rest to 0.014 ± 0.016 l/min with exercise \((P < 0.05)\). Reverse flow in the RPA was abolished, and the reverse flow index decreased from 0.005 ± 0.004 to 0.000 ± 0.000 l/min with exercise \((P < 0.05)\). The reverse flow index of the MPA trended down from 0.014 ± 0.012 to 0.006 ± 0.006 l/min \([P = 0.14, \text{not significant (NS)}]\). Significant differences in reverse flow index were found between the RPA and both the LPA and MPA at rest and during exercise. These findings are summarized in Fig. 4.

Vena cavae blood flow characteristics. Average caval flow data for the 10 subjects at rest and during exercise are summarized in Fig. 5. Total caval flow increased from 2.1 ± 0.4 l/min at rest to 4.6 ± 1.1 l/min with exercise \((P < 0.05)\). SVC flow increased from 1.0 ± 0.2 to 1.3 ± 0.3 l/min \((P = 0.057, \text{NS})\) and IVC flow increased from 1.1 ± 0.3 to 3.4 ± 1.0 l/min \((P < 0.05; \text{Fig. 5A})\). This represents an average 36% increase in the SVC and a 238% increase in IVC blood flow with cycling exercise. The upper/lower body blood flow distribution changed significantly with cycling (lower limb) exercise as the SVC flow declined from 49 ± 8 to 27 ± 8% \((P < 0.05)\) and the IVC flow increased from 51 ± 8 to 73 ± 8% \((P < 0.05)\) of total venous return (Fig. 5B).

There was virtually no retrograde flow seen in the portions of either the SVC or IVC examined either at rest or with

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**Fig. 2.** Blood flow rate curves of a representative subject (rest heart rate 65 beats/min, exercise heart rate 100 beats/min, 54% increase) in the main pulmonary artery (MPA; A), right pulmonary artery (RPA; B), left pulmonary artery (LPA; C), superior vena cava (SVC; D), and inferior vena cava (IVC; E) for a cardiac cycle at rest and during upright cycling exercise. A-C: in the pulmonary arteries, diastole shortens significantly from rest to exercise, accounting for most of the increase in heart rate. D and E: in the cavae, blood flow is much more steady than in the pulmonary arteries, and the IVC experiences a greater increase in flow from rest to exercise compared with the SVC.

**Fig. 3.** Average mean flow rate (scaled to body surface area) to the RPA, LPA, MPA (A) and pulmonary flow split percentage (B) for 10 healthy subjects aged 10–14 yr at seated rest during upright cycling exercise. SD are shown with error bars. *Statistical significance between rest and exercise conditions in the vessels \((P < 0.05)\).
exercise. The reverse flow indexes of the SVC and IVC changed nonsignificantly from 0.001 ± 0.001 to 0.004 ± 0.009 and 0.004 ± 0.011 to 0.000 ± 0.000 from rest to exercise, respectively (Fig. 4).

DISCUSSION

As better techniques become available for quantifying blood flow both at rest and during exercise, the additional insight into the complex characteristics they offer will lead to better understanding of flow dynamics and enable the optimization of surgical reconstructions. This study marks the first time that direct quantitative measurements of time-resolved blood flow have been performed in the pulmonary arteries and vena cavae with seated subjects at rest and during cycling exercise using MRI. Other techniques that have been used to quantify pulmonary blood flow characteristics, such as rebreathing (24), scintigraphy (11), indicator dilution/thermodilution (4, 28), and Doppler ultrasound (22), fall short in their ability to acquire the nature and breadth of data reported here using MRI.

Pulmonary artery flow characteristics. Upright cycling exercise intensity, corresponding to a 50% increase in heart rate from a seated resting state, caused mean blood flow to increase in the RPA, LPA, and MPA by 93 ± 51, 97 ± 28, and 91 ± 14%, respectively (Fig. 3A). As shown in the time-resolved flow curves, most of this increase is accounted for by a decrease in diastolic period rather than increased instantaneous flow rate during the cardiac cycle (Fig. 2, A–C). The MPA rest (4.1 ± 0.6 l/min) and exercise (7.2 ± 0.8 l/min) mean flow rates found in this study can be compared with those of Niezen et al. (17), in which the exercise was supine ergometry, and heart rate was increased from 63 beats/min to two exercise intensities of 89 and 105 beats/min for increases of ~40 and 67%, respectively. Niezen et al. (17) reported mean blood flows of 3.95 l/min at rest, 6.13 l/min at the lower exercise state, and 7.76 l/min at the higher exercise state. The exercise intensity of 50% heart rate increase in this study falls between Niezen et al.’s two exercise intensities, as does the average exercise MPA blood flow.

With nearly identical increases in mean blood flow to the RPA, LPA, and MPA, it is expected that the right/left pulmonary flow distribution would remain constant at 56/44% from rest to exercise (Fig. 3B). These ratios are consistent with the 55/45% ratio commonly cited clinically and with the fact that the right lung is somewhat larger than the left because of the position of the heart on the left lung. These data also support the theory that the distal pulmonary vasculature greatly dominates the pulmonary flow resistance over the geometry of the proximal arteries. If proximal artery geometry was a significant factor for determining right and left lung flow split, then one would expect that, in the transition from rest to exercise and the concomitant increase in flow momentum in the direction of the MPA, there would be an increase in relative flow to the LPA because of its more direct geometric route from the MPA compared with the RPA.

The amount of reverse flow observed in the RPA, LPA, and MPA all decreased from rest to exercise (Fig. 4). These results are consistent with a study conducted by Roest et al. (23) who found decreased MPA regurgitation during breaks between exercise bouts compared with rest in patients with repaired tetralogy of Fallot.

We have shown the reverse flow index of the RPA to be zero or near zero both at rest and with exercise, a finding not true of the MPA and LPA. The higher reverse flow index observed in the LPA compared with the MPA is expected, since the retrograde flow is indexed to total flow, and similar amounts of retrograde flow in the two arteries but lower total flow in the LPA compared with the MPA (LPA = 44% of total pulmonary flow, as discussed previously) yield higher reverse flow indexes in the LPA. This LPA/MPA relationship and the near zero RPA reverse flow index suggest that the reverse flow in the MPA originates solely or in large part from retrograde flow arising from the LPA. This phenomenon is consistent with the geometrically advantageous route of the LPA to the MPA compared with the RPA, which arises from the MPA at a nearly right angle.

Vena cavae flow characteristics. The ~50/50% SVC-to-IVC flow ratio observed at rest is different from the quoted 35/65% ratio in the literature (25). We believe this is because all previous blood flow measurements have been performed in the supine position. When sitting upright, lower-extremity vascular resistance increases because of distal vasoconstriction to prevent blood pooling (1) and because resistance also increases because of arterial kinking from hip and knee flexion. The
change in venous return ratio resulting from exercise, causing approximately three times more flow in the IVC compared with the SVC, is a consequence of lower limb exercise and agrees well with the 225% increase in abdominal IVC flow increase documented by Cheng et al. (6).

These observed differences may prove useful in understanding and optimizing long-term outcomes in congenital heart disease patients of the single ventricle variety. It has been shown that, with total cavopulmonary connection Fontan geometries, the majority of SVC flow and pulsatility is directed toward the RPA, whereas most of the IVC flow and pulsatility is directed toward the LPA (10, 14). It is hypothesized that these preferential pathways are the result of the offset of the SVC and IVC anastomoses on the pulmonary artery. The offset is created, in some part, to reduce energy and pressure losses that would result from colliding flow in nonoffset geometries (7, 9). With this preferential flow pattern, the left lung could receive considerably more flow than the right lung, with the imbalance greatly exacerbated with lower body exercise. For example, Pedersen et al. (18) and Hjortdal et al. (13) found that, in total cavopulmonary connection Fontan patients, IVC flow approximately doubled, whereas SVC flow essentially remained the same with supine exercise of similar heart rate increases as in this study. Given that the adult SVC/IVC flow proportions are not reached until between 6 and 7 yr of age (25), this imbalance may not be clinically significant in the early and intermediate postoperative period but may explain currently inexplicable cases of late Fontan failure and may need to be addressed when considering a Fontan operation in an adolescent or adult patient.

**Limitations.** The flow measured in the MPA was, on average, greater than the sum of the flows in the RPA and LPA. We believe this discrepancy is because of motion blurring and a partial-voluming effect. Because the MPA translates more than the RPA or LPA during systole because of its proximity to the contracting right ventricle, there is greater motion blurring in the MPA. This causes greater partial voluming of pixels near the boundary of the lumen, and, because the interior of the vessel exhibits higher signal and higher velocity than the surrounding tissue, flow may be overestimated in the MPA compared with the RPA and LPA (20). Total venous flow was also noted to be less than total pulmonary flow. In addition to motion blurring errors, this is probably the result of IVC flow underestimation given the very small distance in the IVC between the right atrium and the insertion of the hepatic vein and our inability to consistently acquire our MRI slice superior to the hepatic vein. The smaller difference with exercise compared with rest, however, is consistent with hepatic physiology and decreased portal flow with exercise. Also, although our IVC data may be affected by the IVC slice position, the relative changes in flow resulting from exercise are still captured.

While all of the resting measurements were of sufficient image quality, some of the exercise flow measurements were inadequate because of torso motion. Because a small portion of the exercise data could not be used, unpaired t-tests were used for statistical tests. Further refinements in subject stabilization and imaging methods are currently ongoing to contend with this limitation.

In summary, the new findings of this study are as follows. 1) A 56/44% pulmonary flow split was measured in the RPA and LPA at both rest and during exercise, which is consistent with anecdotal reports on pulmonary perfusion at rest and supports the hypothesis that distal pulmonary vasculature dominates pulmonary flow distribution. 2) Regurgitation in the MPA appears to be drawn solely from retrograde flow from the LPA, whereas the RPA is in relative isolation, indicating that reverse flow may be dependent on proximal pulmonary bifurcation geometry. 3) During seated rest, the SVC-to-IVC venous return ratio is closer to 50/50% than previously measured during supine rest, likely because of lower-extremity vasocostriction and arterial kinking associated with an upright posture. 4) With a 50% increase in heart rate generated by cycling exercise, IVC flow increases by threefold, whereas SVC remains essentially constant. If SVC return preferentially flows to the RPA and IVC return preferentially flows to the LPA in current total cavopulmonary Fontan reconstructions, unbalanced lung development may result from chronic uneven perfusion.

As MRI becomes increasingly utilized as a diagnostic modality in patients with congenital heart disease, the pulmonary and caval flow characteristics described in this paper demonstrate the importance of exercise-stress MRI as an additional diagnostic method in the study of long-term outcomes. Also, these data will serve as baseline quantities for future investigations of pre- and postoperative changes in a variety of right heart lesions and may give insight on how to improve upon therapies such that they can be more compatible with multiple physiological states rather than just supine resting conditions.

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