Noninvasive Quantification of Left-to-Right Shunt in Pediatric Patients
Phase-Contrast Cine Magnetic Resonance Imaging Compared With Invasive Oximetry
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Background—Blood flow can be quantified noninvasively by phase-contrast cine MRI (PC-MRI) in adults. Little is known about the feasibility of the method in children with congenital heart disease.

Methods and Results—In 50 children (mean age 6.2 years, range 1.1 to 17.7 years) with an atrial- or ventricular-level shunt, blood flow rate in the great vessels was determined by PC-MRI, and the ratio of pulmonary to aortic flow ($Q_p/Q_s$) was compared with $Q_p/Q_s$ by oximetry. We found a difference of 2% and a range of $-20\%$ to $+26\%$ (limits of agreement, mean $\pm 2\% SD$). In another 7 children with congenital heart disease but no cardiac shunting (mean age 7.9 years, range 1.3 to 13.5 years), $Q_p/Q_s$ by PC-MRI was 1.02 (SD $\pm 0.06$). No difference between systemic venous and aortic flow volumes was found (range $-17\%$ to $+20\%$, n=37). Blood flow through a secundum atrial septal defect as assessed by PC-MRI (n=24) overestimated the shunt compared with the difference between pulmonary and aortic flows. The mean difference between 3 repeated PC-MRI measurements in each location was $5.3\%$ (SD $\pm 4.0\%$, n=522), demonstrating good precision. The interobserver variability was low. The accuracy of PC-MRI was confirmed by in vitro experiments.

Conclusions—Determination of $Q_p/Q_s$ by PC-MRI in children is quick, safe, and reliable compared with oximetry. Systemic venous flow can be quantified by PC-MRI, whereas through-plane shunt measurement within an atrial septal defect is inaccurate. (Circulation. 2001;103:2476-2482.)

Key Words: heart defects, congenital ■ pediatrics ■ magnetic resonance imaging ■ shunts ■ veins

Shunt quantification is essential in the management of congenital heart disease. Clinical methods available to yield quantitative flow data have major drawbacks. Doppler ultrasound methods are noninvasive but highly observer-dependent. Radionuclide angiocardiology (RNAC) is restricted to simple left-to-right shunt lesions with normal ventricular function, and patients are exposed to ionizing radiation. Indicator dilution techniques are invasive, as is oximetry, a method complicated by variations of oxygen consumption and difficulties in estimating a mixed venous oxygen content in atrial-level shunt patients. In contrast, phase-contrast cine MRI (PC-MRI) is noninvasive and can determine aortic and pulmonary flow volumes in patients with congenital heart disease, thus adding functional information to a morphological cardiac MR investigation. In adults, good agreement with invasive oximetry and RNAC, and ventricular stroke volumes as obtained by cine MRI was demonstrated. Flow-phantom and animal studies suggested a high degree of accuracy and precision with various flow-sensitive pulse sequences. Information is limited, however, about the feasibility of PC-MRI in pediatric patients, whose higher peak velocities and blood pulsation rates may hamper velocity quantification. The objective of this investigation was to evaluate pulmonary, aortic, and systemic venous flows by PC-MRI in a larger number of pediatric patients with congenital heart disease in a prospective and blinded manner. In addition, flow through the defect was evaluated in children with a secundum atrial septal defect (ASD II) by PC-MRI. We chose invasive oximetry for comparison of $Q_p/Q_s$, because the technique still is an accepted clinical standard and is available during cardiac catheterization.

Methods

Study Population
From January 1998 to July 2000, we prospectively enrolled into the study 50 children with an atrial- or ventricular-level left-to-right shunt (mean age 6.2±3.2 years, median 5.1 years, range 1.1 to 17.7
years, 28 girls, 22 boys). Of these 50 patients, 40 had ASD II, 3 partial anomalous pulmonary venous return, 4 sinus venosus defect with partial anomalous pulmonary venous return, and 3 a ventricular septal defect. Only children in sinus rhythm and with evidence of significant shunting were considered eligible.

Moreover, 7 children with congenital heart disease but no cardiac shunts were analyzed for their Qp/Qs ratio by PC-MRI (mean age 7.9 ± 4.4 years, range 1.3 to 13.5 years, 4 boys, 3 girls). Cardiovascular diagnoses were coarctation (n=3), double aortic arch (n=2), and suspected but not confirmed ASD (n=2). The study was approved by the institutional review committee, and informed, written consent was obtained from parents or caretakers.

Study Design
Each patient underwent MRI examination to measure through-plane flow in the ascending aorta and pulmonary artery, and in 37 patients, also in the superior and inferior venae cavae (Figures 1 and 2). Three measurements were acquired in each location to determine repeatability. In 32 patients with an ASD II, flow through the defect was assessed (Figure 3). In 10 randomly selected patients, PC-MRI images were reanalyzed by 2 operators (H.K., P. Barth) blinded to their own former and each other’s results to determine interobserver variability. MRI studies were followed by invasive oximetry during cardiac catheterization performed to assess pulmonary and systemic venous return, exclude pulmonary hypertension and/or associated lesions, quantify left-to-right shunt, and for transcatheter defect closure in suited ASD II patients. The catheterization staff was blinded to the MR investigators’ results and vice versa. Sedation for either procedure was performed with midazolam and thiopental intravenously as needed, and blood pressure, oxygen saturation, heart rate, and respiratory rate were monitored continuously.

Figure 1. PC-MRI flow measurements, pulmonary artery (PA) and aorta (Ao). Plan scans (left) used ECG-triggered segmented k-space turbo field echo (2 shots, TR 9.5 ms, TE 2.4 ms, flip angle 20°, field of view 250 mm², matrix 128×256, 2 signal averages, 6-mm slice thickness) to allow slice positioning for PC-MRI measurements in PA and ascending Ao. In phase images (right), flow information is encoded through-plane in terms of direction and velocity for each pixel. Three flow-vs-time curves (bottom) were obtained in each vessel to assess repeatability of PC-MRI flow measurements.

Figure 2. PC-MRI flow measurements, inferior (IVC) and superior (SVC) venae cavae. Plan scans (left), phase images (right), and flow-vs-time curves (bottom). See also Figure 1.
A pulsatile flow phantom used a glass tube with an inner diameter of 12.4 mm, connected to silicon tubes at both ends and embedded in a glass container, both filled with a copper sulfate solution (3 mmol), designed to minimize susceptibility artifacts. The tube was placed parallel to the bore of the magnet. A 2-roller pump from a heart-lung machine (Fa. Stöckert) delivered flow rates of 0.65 L/min (30 bpm), 0.85 L/min (40 bpm), 1.28 L/min (60 bpm), 1.73 L/min (80 bpm), and 2.63 L/min (120 bpm). Gating was based on a hydrostatically generated signal. Each measurement was repeated twice and controlled by stopwatch and a graded cylinder. The body coil was used, and imaging parameters resembled in vivo measurements (Table), with velocity-encoded values adapted to experimental conditions (40 to 300 cm/s).

**Oximetric Technique**

Blood samples were collected from the caval veins, right heart, pulmonary arteries, and a systemic artery (left heart included when possible) while a stable physiological condition was ensured. Two to 3 samples from the superior and 1 from the inferior vena cava were used to estimate mixed venous saturation in ASD.* \( Q_p/\dot{Q}_s \) was calculated by use of the Fick formula.

**Statistical Analysis**

All data are expressed as mean±SD. In vitro results were analyzed by 2-variable linear regression analysis. Bland and Altman analysis was used to determine PC-MRI interobserver variability and to evaluate the agreement between (1) \( Q_p/\dot{Q}_s \) by PC-MRI and oximetry, (2) systemic venous and aortic flow by PC-MRI, and (3) shunt flow within an ASD and the difference \( Q_p - Q_s \) by PC-MRI. Data were logarithmically transformed when differences and means were linearly related.

**Results**

MRI and catheterization studies were well tolerated, and no adverse effects of sedation were observed. The mean time span between the 2 examinations was 62 days (SD = 49). All PC-MRI measurements were completed within 30 to 40 minutes. Mean heart rate was 99 bpm (SD = 14) at PC-MRI and 99 bpm (SD = 13) at oximetry.

\( Q_p/\dot{Q}_s \) by PC-MRI Compared With Oximetry

The Bland-Altman analysis was applied to the log-transformed data, because differences increased linearly with mean \( Q_p/\dot{Q}_s \) values. Estimation of precision of the limits of agreement (defined as mean±2 SD) was based on calculation of 95% confidence intervals (CI). A mean value of 1.0 after antilog transformation (dimensionless ratio) is expected in the case of no difference between 2 tested methods.

As to the \( Q_p/\dot{Q}_s \) ratio by PC-MRI and oximetry, we found a negligible difference of 2% (mean 0.98) between the 2 methods. Upper and lower limits of agreement were 1.24 (CI 1.17 to 1.31) and 0.78 (CI 0.73 to 0.82), respectively (Figure 4A and 4B). Thus, both methods to assess \( Q_p/\dot{Q}_s \) may differ by 24% above and 22% below in 95% of the cases.

This fairly good agreement did not improve in 29 of the 50 patients, in whom the heart rate differed by <10% between the 2 examinations: mean difference 2%, range 1.23 to −0.78 (mean±2 SD, CI 1.14 to 1.32 and 0.72 to 0.84). The mean \( Q_p/\dot{Q}_s \) ratio by PC-MRI in the 7 children without shunting was 1.02 (SD±0.06, range 0.92 to 1.10).

**Shunt Flow Through an ASD II**

Shunt assessment by PC-MRI measurement within the ASD plane (Figure 3) was performed in 32 children with interpretable results in 24 subjects (mean age 5.5 years, SD = 2.3
years). Results were compared with the difference of the pulmonary and aortic flow volumes (Qp – Qs) by PC-MRI (Figure 5, data log-transformed) and differed significantly (mean difference 0.88, \( P < 0.01 \), 2-sided Student’s \( t \) test). Upper and lower limits of agreement were 1.29 (mean \( \pm 2 \) SD, CI 1.12 to 1.47) and –0.60 (mean \( \pm 2 \) SD, CI 0.53 to 0.69), respectively. Thus, there was significant shunt overestimation and a wide scatter compared with the difference Qp – Qs.

**Systemic Venous Flow**
Venous flow was measured by PC-MRI in the superior and inferior venae cavae in 37 patients with normal venous connections (mean age 5.8 years, SD \( \pm 3.3 \) years). The results were compared with aortic flow (Figure 6A and 6B). We found no difference (mean 1.0), with a range of \( +20\% \) to \( -17\% \) (CI 1.14 to 1.27 and 0.79 to 0.88). Venous flow was biphasic in all children, with a peak in ventricular systole and diastole (Figure 2). The Qp/Qs ratio as derived from pulmonary and systemic venous flows obtained by PC-MRI agrees fairly well with oximetry data: mean difference 0.96, range 1.29 to 0.79 (mean \( \pm 2 \) SD, CI 1.19 to 1.41 and 0.65 to 0.78).

**PC-MRI: Interobserver Variability, Repeatability, and Accuracy In Vitro**
Three measurements each in the ascending aorta, pulmonary artery, and superior and inferior venae cavae in 10 randomly selected patients yielded 120 flow-data sets that were independently reevaluated by 2 observers. The mean difference was \( +0.2 \) mL (SD \( \pm 1.5 \)), range \( +3.2 \) mL to \( -2.8 \) mL (mean \( \pm 2 \) SD, CI \( +2.4 \) to \( +4.2 \) mL and \( -2.0 \) to \( -3.6 \) mL),
demonstrating a low interobserver variability by use of a computer algorithm for semiautomatic vessel border detection.

In each vessel, 3 measurements were performed to assess repeatability for PC-MRI flow measurements (Figures 1 and 2). The overall mean variation of flow results was 5.3% (SD 6 4.0%, 522 flow-data sets), reflecting good precision.

PC-MRI flow phantom measurements were repeated twice over a range of 0.65 to 2.63 L/min and controlled by stopwatch and graded cylinder. A strong correlation was found between PC-MRI and manually performed measurements ($y=0.075+0.915x$, $r=1.000$, $P<0.001$), demonstrating a high level of accuracy in vitro.

**Discussion**

Blood flow quantification by PC-MRI is a potentially valuable diagnostic method in the evaluation of patients with congenital heart disease. Over the past 14 years, the technique has been validated in adult patients and healthy volunteers as well as in phantom studies using various pulse sequences. In children, however, higher rates of blood pulsation, flow acceleration, and respiration are present, along with higher peak velocities and smaller vessels. Well-known possible sources of error that may be even more apparent in children are (1) signal loss from intravoxel phase dispersion resulting from higher-order motion components, (2) in-plane and through-plane vessel motion, (3) phase offsets from residual eddy current effects, (4) a shorter cardiac cycle length limiting temporal resolution, (5) misalignment of flow direction and flow-encoding gradients, (6) partial volume effects from edge voxels containing information from both static and moving spins, and (7) velocity-encoded values too small (aliasing) or too large (loss of signal).

**Pediatric Validation Studies**

Investigations on the use of PC-MRI to quantify Qp/Qs in children are sparse and sample sizes small. Rebergen et al compared Qp/Qs assessed by PC-MRI (pulmonary and aortic flow) with Qp/Qs values as calculated from ventricular stroke volumes acquired by transverse multislice-multiphase MRI. Their total of 12 patients included 6 children, 2 of them 10 years old. Good agreement was demonstrated in all but 1 of the pediatric cases. Sieverding et al reported a good correlation between Qp/Qs by PC-MRI and oximetry in 6 children (mean age 4.9 years, range 0.25 to 13.4 years, 4 with a left-to-right shunt), but MR results compared less well to MRI ventricular volumetric data. Arheden et al compared Qp/Qs values by PC-MRI with RNAC in 24 patients with a cardiac left-to-right shunt, 6 of whom were children and 2 adolescents. The 2 methods differed considerably, by 14% (SD ±13%), and no subgroup analysis for the pediatric patients was presented. In a retrospective study on 20 patients (mean age 12.8 years, range 0.7 to 49 years) with congenital heart disease but no shunts, Powell et al found a mean Qp/Qs ratio of 0.99 ±0.1 and limits of agreement from 0.79 to 1.19.

**Qp/Qs by PC-MRI and Oximetry**

To provide more extensive validation data, we evaluated PC-MRI in 57 pediatric patients with congenital heart disease, 50 children with a left-to-right shunt and 7 without. We used a moderately short TE of 6 ms (Table), recommended to limit intravoxel phase dispersion and sensitivity to higher-order motion components. The relatively large voxel size of 2×2.5×5 mm³ was considered still small enough to avoid significant partial-volume effects while ensuring a good signal-to-noise ratio (SNR) for computer-based semiautomatic vessel border detection. Scan time was kept to a minimum to allow repeated measurements in each location.

![Figure 6. Systemic venous vs aortic flow. Plot of flow rates (A) of both caval veins and aorta, demonstrating good correlation ($y=0.051+1.008x$, $r=0.986$ by linear regression). Agreement should be addressed by Bland-Altman analysis (B), however, plotting difference against mean for systemic venous and aortic flow. Upper and lower limits of agreement: mean ±2 SD.](image-url)
within a reasonable total imaging time. We did not use the full strength of the gradients (TE<3.5 ms), because otherwise a substantial increase of non-flow-related phase shifts was observed both in vivo and in vitro, most likely from residual eddy current effects degrading PC-MRI measurement results. With our protocol (Table), data sampling with a repetition time (TR) of 20 ms yielded 15 to 20 phase images per average cardiac cycle, depending on the heart rate, thought to be sufficient to avoid significant flow volume underestimation.

Therefore, we did not reduce TR to improve the temporal resolution at the expense of a lower SNR, because SNR was already suboptimal as a result of use of the body coil for signal detection. This was unavoidable, because the reconstruction time was unacceptably long with use of a cardiac multielement phased-array coil to optimize SNR. Retrospective ECG gating was preferred to conventional ECG triggering to include end-diastolic flow. Accuracy and precision of this protocol was demonstrated in vitro with a pulsatile flow phantom.

We compared Qp/Qs results by PC-MRI with oximetry, because this method is an accepted clinical standard and is available during cardiac catheterization routinely performed in these patients in our hospital. A negligible bias of 2% and a scatter of +24% to −22% was found, suggesting a fairly good agreement between the 2 methods, well acceptable for clinical purposes. Oximetry may contribute substantially to the scatter because of the predominance of atrial level shunt patients in our study, in which estimation of a mixed-venous saturation is difficult.1,4 We were unable to prove any superiority of PC-MRI over oximetry, however, because repeatability, interobserver variability, and in vitro accuracy were determined in PC-MRI but not in oximetry. In the 7 children with congenital heart disease but no shunts, Qp/Qs values by PC-MRI were close to unity, confirming the results of others11,24,25 demonstrating the ability of PC-MRI to exclude significant shunting in children.

Shunt Flow Through an ASD II

Direct shunt assessment by phase images obtained within the ASD plane (Figure 3) was carried out in 32 patients with an ASD II, with interpretable phase maps in only 24 children, in whom a significant shunt overestimation and a wide scatter were observed compared with the difference of pulmonary and aortic flows (Figure 5). This disagreement is most likely due to inaccuracy of direct shunt assessment: (1) misalignment of shunt flow direction and flow-encoding gradients, because the shunt flow direction is oblique to the orientation of the ASD plane; (2) ROIs difficult to define, because clear defect borders are lacking in late diastole and early systole, when shunt flow is minimal; and (3) movement of the atrial septum out of the imaging plane with respiration and cardiac motion. Given the good agreement between Qp/Qs values by PC-MRI and oximetry, it seems reasonable to conclude that PC-MRI measurements in the great arteries are more accurate.

Systemic Venous Flow

Superior and inferior vena cava flow volumes (Figure 2) obtained in 37 children with normal venous connections served as an internal reference10 for aortic flow rates by PC-MRI. Agreement of venous with aortic flow was acceptable (no difference, range +20% to −17%, Figure 6), as was the agreement of the ratio of pulmonary and systemic venous flow to Qp/Qs by oximetry. Surprisingly, inferior vena cava flow rate was not significantly altered by shunt influx in patients with a large ASD. As observed in healthy adults27 and well known from Doppler studies in children, systemic venous flow was biphasic, with peaks in ventricular systole and diastole.

Limitations

First, in some patients, a considerable time span was allowed between MRI and cardiac catheterization. Although overall agreement between Qp/Qs by PC-MRI and oximetry was good under these conditions, some improvement might be possible with the 2 examinations performed in a row. Second, heart rate was different between the 2 examinations in some patients, but no significant bias seemed to be introduced, because agreement of Qp/Qs did not improve in children with a heart rate difference <10%. Third, no conclusions from our data are applicable to children with arrhythmia or valvular disease.

To quantify blood flow in newborns and infants with higher heart rates and smaller vessels, stronger gradients will be needed to shorten TE and TR to overcome the problem of limited temporal and spatial resolution as well as to reduce the sensitivity to higher-order motion components. Ultafast imaging by use of a segmented echo-planar technique may be an option. Dedicated phase-correction algorithms are likely to be mandatory, however, to avoid substantial errors in flow volume estimates as introduced by effects of residual eddy currents and concomitant fields. Because more powerful reconstruction computers are now available, phased-array cardiac surface coils can be used to further improve SNR for better spatial resolution and/or faster image acquisition.

In children with congenital heart disease, determination of Qp/Qs by use of a conventional PC-MRI pulse sequence is safe, accurate, and reliable compared with oximetry. Systemic venous flow can be quantified by PC-MRI, whereas through-plane shunt measurement within an ASD is inaccurate.

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