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Assessment of shunt volumes in children with ventricular septal defects:

comparative quantification of MR flow measurements and invasive oximetry

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Summary The aim of this study was to compare the results of magnetic resonance based shunt volume measurements with the results of the invasive method by the principle of Fick. In 14 children (median age: 16.5 months) with ventricular septal defects the shunt volume was quantified by magnetic resonance flow measurements under spontaneous breathing conditions as well as with invasive angiography during one sedation. A good correlation between both methods was observed ($r^2 = 0.8$, $p < 0.0001$, $CI_{95\%} = 0.62–1.22$). A tendency towards higher values in the non-invasive technique was found in the Bland-Altman plot (bias = 3.79). Magnetic resonance based shunt measurements are a reliable alternative to the invasive shunt measurement by cardiac catheterization.

Key words Ventricular septal defects – left-to-right shunt – shunt measurement – magnetic resonance flow measurement – heart catheterization – children

Introduction

Ventricular septal defects are among the most common congenital heart abnormalities. Doppler echocardiography is the first imaging method used for assessment. It is a safe and quick method to visualize septal defects, but the reliability of shunt quantification is low. As in first-pass radionuclide scintigraphy, several limitations decrease the clinical validity [5]. Cardiac catheterization is an essential tool in the diagnostic work up of congenital heart disease in children. Moreover, it is the standard of reference for the quantification of shunt volumes in atrial and ventricular septal defects. Using Fick's principle, which was established by Adolf Fick in 1870, intracardiac shunt volumes could be estimated based on measurements of blood oxygenation. The quantity of the intracardiac shunt volume represents one of several important criteria for the indication of surgical or interventional closure of the defect. In elderly children with normal pressure conditions, the indication for closure of a defect [8] with left-to-right shunting is, apart from sinus valsalva aneurysms [7] and development of aortic regurgitation [23], a shunt volume with a pulmonary to systemic flow ratio of above 1.5 to 2.0 [9].

The major drawback of invasive shunt quantification can be attributed to several risks involving the invasiveness of the catheter procedure [25] and the radiation exposure [17]. In addition, some patients may experience a transient increase in pulmonary artery pressure resulting from administration of iodinated contrast agents [19]. An alternative to noninvasive quantification of shunt volumes might be magnetic resonance based flow measurements. This method was established in the early 1980s for flow measurements in large intrathoracic vessels [18] and has been used for other indications as well [11]. The acquisition of magnetic resonance based flow measurements of the pulmonary artery and the ascending aorta allows the comparative quantification of the cardiac output into the systemic and the pulmonary circulation [13, 15]. Thus, shunt volumes can be calculated in shunting congenital heart disease. This has already been shown in older children with atrial septal defects [21]. However, the clinical experience for the diagnostic workup of this method in pediatric patients with ventricular septal defects is limited. Magnetic resonance based flow measurement studies with small numbers of older children suffering from different types of shunt defects showed good correlations to invasively acquired shunt volumes of diagnostic cardiac catheterization if the magnetic resonance images were acquired during breath hold examinations [14].

The aim of this study was to compare invasive oximetry with magnetic resonance based shunt volume quantification in pediatric patients of any age suffering from ventricular septal defects. The application of magnetic resonance based flow measurement might reduce the number of diagnostic heart catheterizations.

Materials and methods

From April 2003 to April 2004, we measured shunt volumes in 14 children with ventricular septal defects and an age range of two weeks to 15 years (mean age: 48 months, median age: 16.5 months) by magnetic resonance based flow measurements. The primary indications for magnetic resonance imaging (MRI) were the following: intraabdominal masses, hydronephrosis, Asplenia, seizures, exclusion of intracerebral malformations, and exclusion of a vascular lung disease. Magnetic resonance based flow measurements of the great arteries were performed in addition to the routine MRI examination. This was done immediately prior to the standard cardiac catheterization procedure including oximetry for shunt quantification. The indication for cardiac catheterization was always the quantification of shunt volume. In all patients, both methods were performed during a single sedation in immediate succession to optimize the comparability between magnetic resonance based flow measurements and cardiac catheterization. Patients with coexisting cardiac anomalies, especially with any kind of pulmonary or aortic valve disease as well as additional extracardiac shunt defects, were excluded from this study, to avoid any inaccuracies in the comparative measurements. All patients were examined with fully informed parental consent.

Sedation

During cardiac catheterization as well as in MRI, patients were sedated with 0.1 mg/kg Midazolam and 0.2 mg/kg Etomidate, followed by a continuous administration of Midazolam of 0.2 mg/kg/h. General anesthesia was not needed. During the entire examination, a pediatrician with experience in pediatric intensive care was present in the scanner room. The continuous recording of vital parameters was performed with a dedicated monitoring device (Omni Trak 3150 Magnet Resonance Imaging Patient monitor, In vivo Research Incorporation, Orlando, Florida, USA).

MRI and Magnetic Resonance based flow measurement

The examinations were performed in a 1.5 Tesla system (Magnetom Sonata, Siemens Medical Solutions, Erlangen, Germany). To optimize the signal-to-noise ratio, the thoracic imaging in infants was performed with a knee coil, small children were examined in a head coil, and the examination of older children was performed with a thoracic circular polarized phased array coil. Magnetic Resonance based flow measurements utilize the phase contrast principle. Therefore, possible phase errors induced by eddy currents should be minimized. Eddy currents may emerge from the gradient coils of the scanner and may cause distortions of the phase contrast signal. These distortions are minimal at the center of the magnetic field of the scanner. Consequently, the children were positioned on the examination table with the main pulmonary artery and the ascending aorta in the center of the magnetic field.

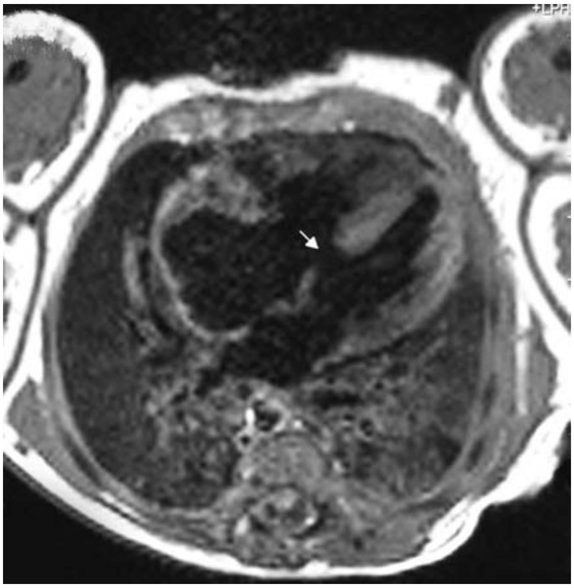

Fig. 1 T1 spin echo sequences of a ventricular septal defect (arrow)

Fig. 2 T1 spin echo sequences of a Gerbode defect (arrow)

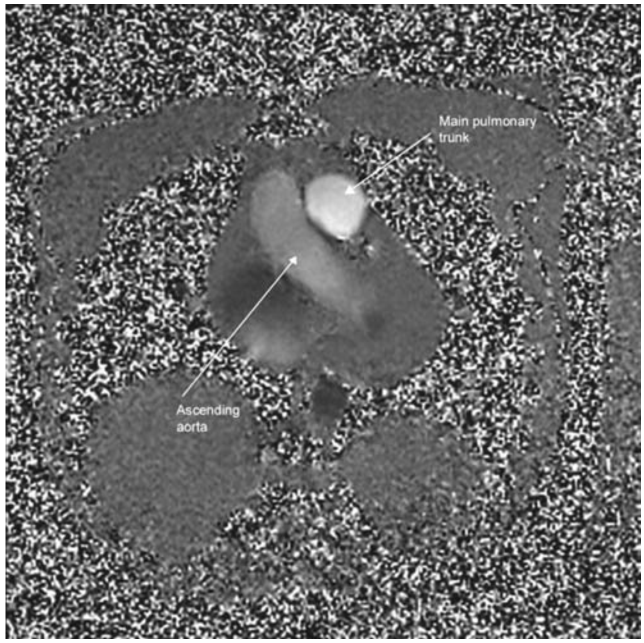

Fig. 3 Phase contrast image acquired orthogonally to main pulmonary artery in systole. Mean grey values represent zero flow. Flow away from the viewer is encoded white, flow towards the viewer is encoded black

The MRI started with standardized electrocardiographically triggered T1-weighted sequences across the entire heart in three orthogonal planes to visualize the ventricular septal defect (Figs. 1 und 2). Using the knee and head coil, spin echo sequences were acquired, whereas in children examined with the thoracic phased array coil, turbo spin echo sequences were performed. Subsequently, true fast imaging with steady-state precession cine-sequences were performed to display the main pulmonary artery and the ascending aorta in three planes. Using these scout images, the flow measurements were acquired 1.0–2.5 centimeter above the valves and orthogonally to the main pulmonary artery (Fig. 3) and the ascending aorta as described before [1]. Especially in younger children, both vessels continuously changed their positions during the cardiac cycle. Therefore, the measurement position of magnetic resonance based flow measurement for each vessel was chosen separately as the bisecting line of the angle between the systolic and the diastolic position. The aim was to maintain a circular presentation of the vessels during the entire cardiac cycle. The angle error, which resulted from the movement of the vessels, was estimated by the cine sequences before magnetic resonance based flow measurement in every patient. Since this angle deviation was always below 15°, the influence of the angle to the result of the measurement was negligible [16].

For the acquisition of the flow data, a 2-dimensional phase contrast fast low angle shot-sequence with Maxwell term correction [4] was used. The temporal resolution was adapted to the age of the patient and varied between 10 and 30 ms, with higher temporal resolution for younger children. Accordingly, the in plane resolution and the slice thickness were adapted to the size of the vessels and varied between 0.9 mm×1.4 mm and 1.9 mm×2.5 mm, as well as 3 mm and 5 mm, respectively. The spatial resolution was constant for the measurements of the main pulmonary artery and the ascending aorta.

To optimize the accuracy of magnetic resonance based flow measurement, the velocity encoding should be as low as possible, while avoiding aliasing artifacts. Therefore, the velocity encoding was set to 100 cm/s for the measurements in the main pulmonary artery and 150 cm/s for the aortic measurements. It is possible to correct the flow results for the velocity encoding (suitable for corrections up to 30 cm/s) with the standard software for the flow evaluation (ARGUS Flow, Siemens Medical Solutions, Erlangen, Germany). This was not required in our patients with the settings given above.

Retrospective cardiac gating was done with a MRI compatible cardiologic control unit (Omni Trak 3150 Magnet Resonance Imaging Patient monitor, In vivo Research Incorporation, Orlando, Florida, USA), which has no relevant trigger delay. The acquisition time of any flow measurement is dependent on the selected temporal and spatial resolution, as well as on the heart frequency of the patient. To achieve the requested temporal and spatial resolution with an adequate signal to noise ratio, two data acquisitions were averaged. Therefore, in this study, the acquisition time varied between 2.5 and 6 min for each magnetic resonance based flow measurement. To prevent inaccuracies, data sets from extrasystoles were not included into the analysis. This was achieved by setting the length of the acquisition window to the average RR-interval ± 15%. Thus, shortened and extended cardiac cycles caused by extrasystoles were rejected and not included in the flow quantification. The acquisition window was set as wide as possible to include the effects of physiologic respiratory arrhythmia in children.

All examinations were performed under free breathing conditions to achieve results that were as physiologic as possible. Sakuma et al [22] showed the importance of non-breath holding during functional cardiac examinations.

After the acquisition of the images, data analyses were performed off line (ARGUS Flow software package, release VA 21, Syngo MR 2004 A). By manual segmentation, the areas of the main pulmonary artery and of the ascending aorta were defined. By analysis of these regions of interest, ARGUS flow calculates the standardized result tables that were used for analysis and shunt volume quantification.

The magnetic resonance based left to right shunt volume was calculated with the cardiac output measured in the main pulmonary artery and in the ascending aorta according to the following equation:

$$\text{Left to right shunt} \equiv \frac{\text{Cardiac output}_{(\text{Main pulmonary artery})} - \text{Cardiac output}_{(\text{Ascending aorta})}}{\text{Cardiac output}_{(\text{Main pulmonary artery})}}$$

Cardiac catheterization

Catheter placement was done after local anesthesia of the right inguinal region and puncture of the femoral vein. Pressure measurements were done with a 5 French balloon catheter (Berman Angiographic Catheter, Arrow International Incorporation) in the right atrium, the right ventricle as well as in the main, right, and left pulmonary artery. In addition to the pressure measurements, blood samples in the upper and lower vena cava and in the main pulmonary artery were taken to determine the oxygen saturation. The shunt volume was calculated by the difference of mixed venous and pulmonary oxygen saturation. The invasive estimation of the blood flow for the systemic and pulmonary circulation was calculated with Fick's principle:

$$\text{Systemic blood flow} \equiv \frac{\text{Oxygen uptake}}{\text{Systemic arterio-venous difference in oxygen content}} \times 10$$

$$\text{Pulmonary blood flow} \equiv \frac{\text{Oxygen uptake}}{\text{Pulmonary arterio-venous difference in oxygen content}} \times 10$$

The values for oxygen uptake were taken from the nomogram of Fleischer [24] and the arterio-venous difference in oxygen content was measured during the cardiac catheterization. The shunt volumes for left to right shunts were calculated from the values in the systemic and the pulmonary circulation by the following formula:

$$\text{Left to right shunt} \equiv \frac{\text{Pulmonary blood flow} - \text{Effective pulmonary blood flow}}{\text{Pulmonary blood flow}}$$

which is well comparable with the formula used for the magnetic resonance based flow measurement.

Statistical analysis

Statistical analyses were done with Graphard Prism version 4.03 (Graphard Software, San Diego, California, USA). Besides descriptive analysis, linear regression between magnetic resonance based flow measurement and cardiac catheterization was performed.

In addition, a Bland-Altman plot was generated. Statistical significance was tested with the Wilcoxon rank test.

Results

MRI and catheterization studies were well tolerated, and no adverse effects of sedation were observed. The basic physiologic data of 14 consecutive patients are given in Table 1. All children had comparable blood pressures, blood gas analysis, oxygen saturation and heart rates during both examinations. Furthermore, no cardiac arrhythmias or irregular breathing patterns were observed during the examinations.

Table 2 shows the cardiac output in the systemic and pulmonary circulation as measured with magnetic resonance based flow measurements as well as pulmonary blood flow and systemic blood flow as assessed by cardiac catheterization. In addition, the classic calculation of pulmonary to systemic flow ratio for both methods is given.

In Table 3, the calculated shunt volumes are shown. The shunt volumes assessed by magnetic resonance based flow measurement and cardiac catheterization ranged between 5 and 81.5% and 3.4 and 76.1%, respectively.

The mean values of the shunt volumes as assessed with magnetic resonance based flow measurement and cardiac catheterization were 48.3% and 44.5%, respectively. The difference of the mean values of the shunt volumes as tested with the Wilcoxon rank test was not significant (p = 0.3). In Fig. 4 the box plots for magnetic resonance based flow measurement and cardiac catheterization are given. The box plots represent the minimum and maximum shunt volumes as well as the median and both quartiles.

The regression analysis (Fig. 5) resulted in a linear regression curve of the shunt volumes in both methods. The correlation coefficient was $r^2 = 0.8$ ($p < 0.0001$), the 95% confidence interval was between 0.62 and 1.22. The distribution of measurement values was more scattered for smaller shunt volumes.

As expected, the Bland-Altman plot (Fig. 6) reveals good agreement of both methods with a ten-

Table 1 Descriptive data of 14 consecutive patients with ventricular septal defects

Patient	Age [years/months]	Average heart frequency [beats/min]	Height [cm]	Weight [kg]	Comment
1	8/1	94	124	23	VSD, ASD II
2	0/10	119	73	6	VSD
3	1/6	119	79	9	VSD
4	0/1	112	54	4	VSD
5	0/0.5	118	48	3.1	VSD
6	1/6	74	86	12	VSD
7	1/10	100	84	10	Gerbode defect
8	12/7	76	167	51	VSD
9	0/7	147	60	5.1	VSD
10	1/3	100	79	10	VSD, ASD II
11	0/1	150	50	3.6	VSD
12	12/1	106	138	35	VSD
13	15/6	82	176	51	muscular VSD
14	0/5	133	66	6.7	VSD

Table 2 Systemic and pulmonary blood flow as assessed with cardiac catheterization and magnetic resonance based flow measurements

Patient	CO_{PA} (MR) [liter/min]	CO_{AAO} (MR) [liter/min]	Qp (CC)	Qs (CC)	Qp : Qs (CC)	Qp : Qs (MR)
1	6.75	2.85	9.79	3.73	2.62	2.37
2	2.84	0.78	3.32	1.39	2.38	3.64
3	1.8	1.71	1.72	1.66	1.03	1.05
4	2.69	0.69	2.1	0.5	4.1	3.9
5	1.25	0.41	0.9	0.36	2.5	3.05
6	1.96	1.38	1.7	1.1	1.47	1.42
7	2.54	1.73	2.45	1.96	1.25	1.47
8	6.82	5.09	5.3	3.1	1.67	1.34
9	2.42	1.26	1.81	1.54	1.18	1.92
10	2.13	1.27	1.9	1.0	1.8	1.68
11	1.96	0.84	1.24	0.54	2.29	2.33
12	5.45	4.97	4.8	4.0	1.2	1.1
13	20.11	3.72	19.4	5.1	3.8	5.41
14	4.12	0.99	3.7	1.15	3.2	4.16

CO_{AAO} Cardiac output in ascending aorta, CO_{PA} Cardiac output in main pulmonary artery, Q_P Pulmonary blood flow, Q_S Systemic blood flow, $Q_P{:}Q_S$ Pulmonary to systemic flow ratio, *CC* Cardiac catheterization, *MR* magnetic resonance based flow measurement

Table 3 Comparison of left-to-right shunt volumes as assessed by cardiac catheterization and by magnetic resonance based flow measurement

Patient	Magnetic resonance based flow measurement-Shunt [%]	Cardiac catheterization-Shunt [%]
1	57.8	61.8
2	72.5	58.1
3	5	3.4
4	74.3	76.1
5	67.2	62
6	29.6	25
7	32	20
8	25.4	41.5
9	47.9	14.9
10	40.4	44
11	57.1	56.4
12	8.8	16.6
13	81.5	73.7
14	76	68.9

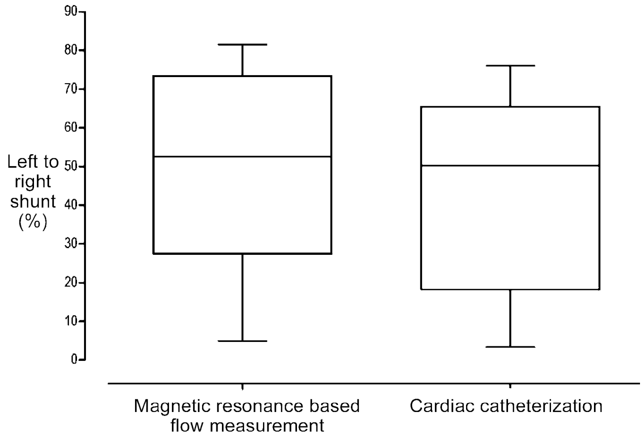

Fig. 4 Box plots for magnetic resonance based flow measurement and cardiac catheterization. The minimum and maximum shunt volumes as well as the median and both quartiles for both measurement techniques are given

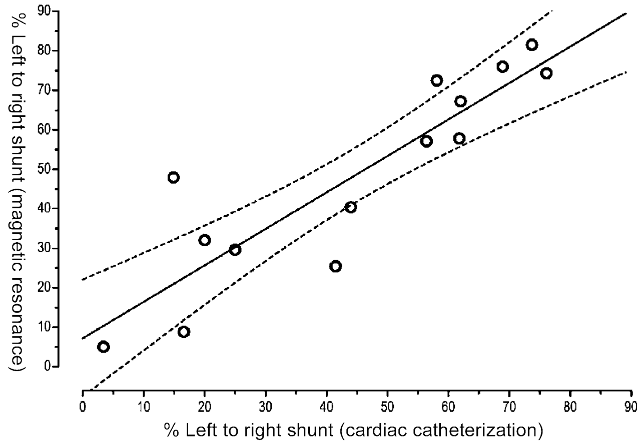

Fig. 5 Linear regression analysis for the comparison of the left-to-right shunt volumes [%] as assessed by magnetic resonance based flow measurement and cardiac catheterization. The correlation coefficient is $r^2 = 0.8$ ($p < 0.0001$, $CI_{95\%} = 0.62–1.22$)

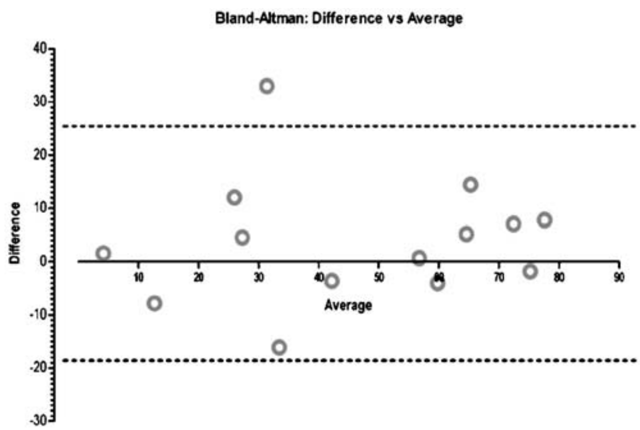

Fig. 6 Bland-Altman plot representing the assessed shunt volumes from magnetic resonance based flow measurement and cardiac catheterization with a tendency towards higher values in the non-invasive method (bias = 3.79)

dency to higher values in the non-invasive method (bias = 3.79).

Discussion

This study integrates several important specific features for the comparison of invasive oximetry during cardiac catheterization with magnetic resonance based flow measurements: 1 exclusively ventricular septal defects were investigated, 2 children with a wide age range (the youngest child was two weeks old) were included, 3 all children were examined under spontaneous breathing conditions, and 4 magnetic resonance based flow measurements and cardiac catheterization were done during one sedation in immediate succession and under the same general conditions.

The major target of this study was to reduce the number of invasive oximetry in the preoperative management of children with ventricular septal defects. Therefore, all children with ventricular septal defects seen in our department who had a clinical indication for an additional MRI received both examinations during a single sedation. Consequently, the number of patients (14 of 460 children seen in the same period) in this study is comparatively low. All patients with coexisting cardiac anomalies were excluded from this study, to avoid any inaccuracies in the comparative measurements.

Including younger children into magnetic resonance based flow studies is technically challenging, since higher rates of blood pulsation and flow acceleration are present in smaller vessels. Especially in infants, several sources of errors in the magnetic resonance based flow measurement measurements may occur (for example intravoxel phase dispersion and partial volume effects from edge voxels). Therefore, optimization of the signal-to-noise ratio and adaptation of the temporal and spatial resolution is mandatory. To increase the signal-to-noise ratio, the coil-filling factor was preserved by the selection of the smallest appropriate receiver coil. Since the highest temporal resolution is required in pediatric cardiologic examinations, the required bandwidth was very high. For this reason, parallel imaging techniques as suggested elsewhere [3] were not applied to avoid an additional loss of signal. Using standard equipment, parallel imaging techniques should be employed in children above an age of 8 to 12 years. Performing the examinations under spontaneous breathing conditions results in more physiologic data acquisition and breath hold related influences on the cardiac output do not occur [22]. According to the cited paper, the cardiac output during measurements in inspiration decreases to about two-thirds of the cardiac output under free breathing conditions. With an accurate planning of the acquisition plane as described above, the influence of the three dimensional movement of the great vessels during the cardiac cycle and under respiration on the flow measurement results are negligible. This was shown before [1]. Meeting these requirements, the comparative evaluation showed a good agreement between the shunt volumes measured with invasive oximetry and non-invasive magnetic resonance based flow measurement. These findings are consistent with prior reports in children and adults with different shunting lesions [2, 6, 9].

In detail, the linear regression curve especially correlates well between both modalities in hemodynamic relevant defects with higher shunt volumes. In smaller shunt volumes, the scattering around the linear regression line seems to be larger. The most likely reason for this is the coronary flow, which in relation to the shunt volume is higher in smaller defects. For magnetic resonance based shunt volume calculation, the coronary flow induces a decrease of the blood flow in the systemic circulation, as flow measurements are acquired distal to the origin of the coronary arteries. Additionally, the blood coming from the coronary sinus increases the flow in the pulmonary circulation. This effect is left out of consideration in invasive shunt volume measurement. In fact, the decrease of mixed venous oxygen saturation by the low saturated blood flow from the coronary sinus causes a mathematical right-to-left shunt. Even in the presence of a ventricular septal defect, this phenomenon creates an underrating of the true shunt volume.

Related to cardiac catheterization, it must be considered that the oxygenation of the venous and the arterial blood is influenced by several factors such as agitation, sedation, ventilation disorder, hypercapnia, acidosis and many more. Consequently, even after accurate measurements, mistakes in the estimation of cardiac output and shunt volume are possible. Apart from hypercapnia, which induces an increased pulmonary resistance detected by both methods, the other factors have no influence on the magnetic resonance based method. The results of magnetic resonance flow measurements might be hampered by severe arrhythmias, which did not occur in any of the patients of this study. The influence of short arrhythmias and extrasystoles was excluded by adequate adjustments of the cardiac gating of the scanner.

As shown before [21], this study also found that magnetic resonance measurements of pulmonary to systemic flow ratio were more reproducible and tended to correlate better with defect areas as compared to the oximetry calculations.

Surgical closure of ventricular septal defects was performed in children above an age of 1 year, if a pulmonary to systemic flow ratio larger than 1.5 was detected with the invasive or with the magnetic resonance based shunt estimation. Patient number 7 with a Gerbode defect has undergone a surgical closure although the pulmonary to systemic flow ratio was less than 1.5. The ventricular septal defects in patient number 8 and 9 were not closed, since they exhibited unaffected clinical conditions.

In conclusion, the accentuated scattering observed in small shunt volumes has no clinical relevance, so that we have to admit that the less invasive magnetic resonance based method is the better method. In our hospital, we therefore favor the magnetic resonance based method instead of the invasive oximetry for the evaluation of shunt volumes. Additionally, magnetic resonance imaging and flow measurements might have an important impact on the follow-up of patients who have undergone invasive interventional procedures [12, 20] and in patients suffering from pulmonary hypertension [10].

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