A Real-time 3-dimensional Digital Doppler Method for Measurement of Flow Rate and Volume Through Mitral Valve in Children: A Validation Study Compared with Magnetic Resonance Imaging

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We developed and assessed a real-time 3-dimensional (3D) digital Doppler method for measurement of flow volumes through the mitral valve in children. A total of 13 children (aged 10.46 ± 2.5 years; 8 boys/5 girls) were enrolled. An ultrasound system (Sonos 7500, Philips, Andover, Mass) was used to acquire raw 3D velocity data for flow measurement based on Gaussian control surface theorem [flow (mL/s) = mean velocity × flow area]. Stroke volume (SV) measured by real-time 3D digital Doppler with the control surface at the mitral valve annulus or orifice was compared with the SV by phase velocity cine magnetic resonance imaging (MRI) at the ascending aorta and by left ventricular volumetric MRI measurement. The best correlation and agreement were seen at the mitral valve orifice by real-time 3D digital Doppler compared with SV by phase velocity cine MRI at the ascending aorta (r = 0.92, mean difference = −5.2 ± 12.0 mL) and SV by left ventricular volumetric MRI measurement (r = 0.94, mean difference = −0.2 ± 10.3 mL). (J Am Soc Echocardiogr 2005;18:1–7.)

Noninvasive measurement of flow rates and volumes has important applications in clinical cardiovascular medicine and research. Stroke volume (SV), cardiac output, and cardiac index can be determined by measuring flow volumes through cardiac valve orifices for assessment of systolic function. Flow abnormalities such as left-to-right and right-to-left shunt lesions, and valve insufficiencies in congenital and acquired heart diseases, can also be evaluated quantitatively by measuring different flow volumes through two valve orifices.

Both 1- and 2-dimensional (2D) Doppler methods for measurement of flow volumes have limited accuracy and clinical use.[1-10] It has been shown that the flow velocity profiles at the cardiac valve orifices, such as the mitral valve orifice (MVO) or aortic valve orifice, are not flat but quite skewed.[6-8] Measurement of flow volumes by the conventional pulse wave Doppler methods may result in significant measurement errors.[6-8] Two-dimensional Doppler methods have also been developed and validated.[9,10] These methods seem to be useful for more circular orifices but may not be robust enough for more complex flow profiles. Three-dimensional (3D) velocity profiles can be acquired and reconstructed with respiratory and electrocardiographic (ECG) gating for calculation of flow volumes as demonstrated in a number of in vitro and animal studies[11-19] with promising results. However, this approach is time consuming and technically cumbersome. There are few data comparing this approach with more established methods for flow measurement, such as phase velocity cine (PVC) magnetic resonance imaging (MRI) in human beings.

A real-time (RT) 3D digital Doppler (RT3DDD) method that uses the 3D velocity profile is the next logical step to improve the accuracy and reproducibility for flow measurements by Doppler echocardiography. Recently, a RT 3D ultrasound system has become available. It is feasible to acquire a composite 3D raw velocity data set rapidly using this system.

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This project was funded in part by a Collaborative Interdisciplinary Project Grant Award from University of Iowa.

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0894-7317/$30.00

doi:10.1016/j.echo.2004.08.021

We have developed algorithms and methods to measure flow rates and volumes using the 3D velocity data acquired using this RT3DDD approach. The objectives of this study were to: (1) evaluate the feasibility of this RT3DDD method for measurement of flow rate and volume through the MVOs in healthy children; and (2) assess the accuracy and reproducibility of this approach by comparing flow volumes measured by this approach with those by MRI methods.

METHODS

Study Population

This prospective study was performed after approval by the institutional review board at the University of Iowa in Iowa City. A total of 13 children were enrolled after written informed consent and assent were obtained. The mean age was 10.5 ± 2.5 years, ranging from 6 to 18 years. There were 8 boys and 5 girls. All participants were healthy except one who was unexpectedly found to have a moderate-sized secundum atrial septal defect.

RT3DDD Data Acquisition and Analysis

Before RT3DDD study, heart rate and blood pressures were obtained for each study participant. The participants were placed in a left recumbent position with ECG attached. After a complete conventional echocardiographic assessment of each participant, RT3DDD was performed using a 2- to 4-MHz X4 matrix array transducer connected to an ultrasound system (Sonos 7500, Philips, Andover, Mass). This transducer houses 2880 elements so that a conical volumetric 3D gray scale tissue and Doppler velocity data set can be acquired. The mitral inflow Doppler velocity data were obtained from an apical window (Figure 1). ECG triggering was required for a composite full volume data set from 7 subvolumes (38 degrees × 35 degrees with High Density off), a process that took 10 to 12 seconds. To optimize RT3DDD data acquisition, the position of the transducer was adjusted to minimize the Doppler/flow angle using gray scale and 2D color Doppler flow guidance from two orthogonal views using the biplane mode. The depth was reduced to achieve highest aliasing velocity and highest frame rates, ie, temporal resolution, but enough to encompass the entire mitral inflow region. Doppler gain and velocity filter was carefully adjusted so that there is no Doppler color "bleeding into the tissue." After each study, all data were saved onto the hard drive and subsequently downloaded to rewritable compact disks for offline analysis.

The RT3DDD data sets were processed offline and the flow rates and volumes measured as shown in Figure 2 using the algorithms and methods developed at the University of Iowa in Iowa City. Briefly, a control surface based on the Gaussian theorem was placed at: (1) mitral valve annulus (MVA); and (2) the tip of the MVO. In both cases, manual adjustment was made to track the MVA or MVO for each frame to account for the mitral valve motion during diastole. The velocities on the control surface were projected onto 2D cross sections and velocity aliases were unwrapped if present. The flow areas were manually traced and the flow rate and volume were calculated (Figure 2).

MRI Data Acquisition and Analysis

Before MRI studies, heart rate and blood pressures were measured for each study participant. MRI was performed using a GE CV/i 1.5T scanner with a torso coil (GE Medical Systems, Milwaukee, Wis). PVC MRI images were acquired in a plane perpendicular to the long axis of the ascending aorta (velocity encoding [VENC] = 150 cm/s, 256 × 160 matrix, 20-degree flip angle, 32-kHz bandwidth, 6 views/segment, 20 cardiac phases) (Figure 3, *A*). SV was measured from PVC MRI phase images (Figure 3, *B*) by manually tracing the boundary of the ascending aorta on magnitude images (Figure 3, *C*).

Left ventricular (LV) SV (LVSV) was also measured volumetrically from LV short-axis 2D Fast Imaging Employing Steady State Acquisition (FIESTA) images by summating the areas enclosed by the LV endocardial borders on contiguous slices in end systole and end diastole (Figure 4). Parameters for 2D FIESTA were 8-mm slice thickness, 224 × 160 matrix, 40-degree flip angle, 125-kHz bandwidth, 12 to 16 views/segment, and 20 cardiac phases. MRI data were transferred to an offline workstation (GE Advantage Windows, GE Medical Systems, Milwaukee, Wis) and analyzed using vendor-provided software.

Statistical Analysis

All numeric values are expressed as mean ± SD. As mentioned above, the SV by PVC MRI at the ascending aorta (AOSV) and LVSV by LV volumetric measurements were first analyzed to validate the accuracy of the MRI methods used in this study. To examine the correlation and agreement between SV measured by RT3DDD at the MVA and MVO levels and AOSV and LVSV measured by MRI methods, Pearson regression and Bland-Altman analyses were used. Statistical significance was defined as $P \leq .05$. All statistical analyses were done using software (Excel, Microsoft, Redmond, Wash) with statistical analysis add-on.

Intraobserver and Interobserver Variability for Measurements by RT3DDD

To determine the intraobserver variability, one observer analyzed and measured the RT3DDD data twice at a 4-week interval, blinded to the results of the first measurements. A second observer also analyzed and measured the RT3DDD data independently, blinded to the results of the first observer, to determine the interobserver variability. Both observers were blinded to results of MRI measurements. The intraobserver and interobserver variabilities were expressed as percentile differences (difference between the measurements/mean of the measurements × 100%).

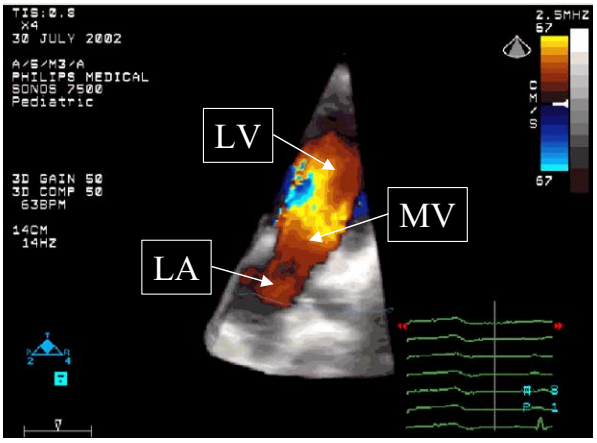

Figure 1 Real-time 3-dimensional digital Doppler image shows color-encoded velocities of flow from left atrium (*LA*) to left ventricle (*LV*) across mitral valve (*MV*) orifice during diastole in a control participant.

RESULTS

There were no statistically significant difference in heart rates (77.0 ± 7.7/min vs 78.4 ± 9.2/min, P = .13) and diastolic blood pressures (60.6 ± 8.4 mm Hg vs 63.2 ± 5.4 mm Hg, P = .14) before RT3DDD and MRI studies but there was a small yet statistically significant difference in systolic blood pressures (101.2 ± 8.7 mmHg vs 105.0 ± 8.3 mmHg, $P < .05$) before RT3DDD and MRI studies. To validate the accuracy of flow measurement by PVC MRI and to serve as an internal control of the MRI methods, AOSV by PVC MRI were compared with LVSV by volumetric measurement using Pearson and Bland-Altman analyses (Figure 5). The SV measured by the two methods correlated well (r = 0.96, y = 0.96 × +7.66, standard error of the estimate = 9.17 mL, $P < .05$) and agreed well (mean difference = 5.08 ± 8.50 mL, P = .06). There was a small but statistically insignificant difference between the SV measurements by the two methods.

After the initial learning curve, the length of time for postprocessing the RT3DDD data to derive a flow volume or SV across the MVO ranged from about 5 to 10 minutes. The SV measurements by the two RT3DDD methods were compared with AOSV by PVC MRI and LVSV by MRI volumetric measurements (Table). When the control surface was placed at MVA, there was statistically significant underestimation (RT3DDD vs AOSV: mean difference = −9.3 ± 22.4 mL, $P < .05$ and RT3DDD vs LVSV: mean difference = −4.2 ± 18.5 mL, $P < .05$). However, when the control surface was place at the MVO, there was good correlation (RT3DDD vs AOSV: r = 0.92, y = 0.92 × +0.91, standard error of the estimate = 12.27 mL, $P < .05$ [Figure 6] and RT3DDD vs LVSV: r = 0.94, y = 0.94 × +3.93,

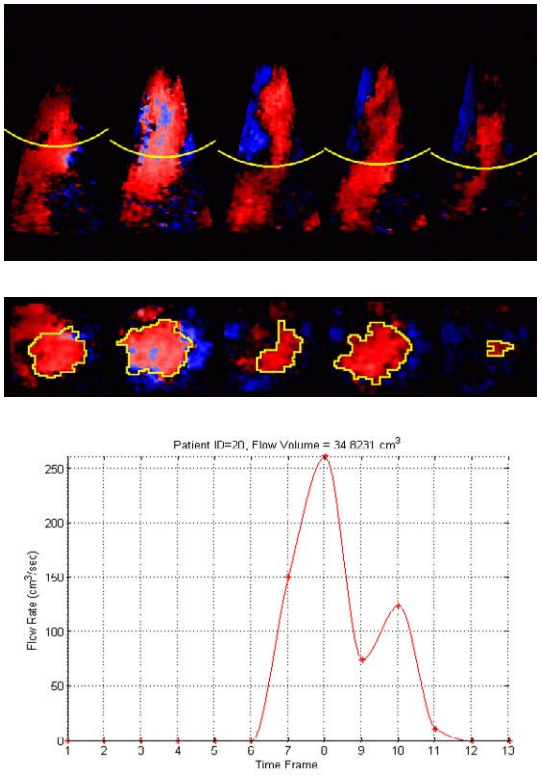

Figure 2 Real-time 3-dimensional digital Doppler (RT3DDD) method. *Upper panel*, Series of 2-dimensional color Doppler flow maps of flow from left atrium to left ventricle through mitral valve during diastole derived from RT3DDD images. Gaussian control surface is placed at level of mitral valve as shown by *yellow arch*. *Middle panel*, Color-encoded velocities from spheric control surface (*upper panel*) are projected onto planar surface and measurement of flow rate is performed by manually tracing area of color-encoded velocities. *Lower panel*, Flow rate curve derived from measurements as shown in *middle panel* and flow volume is derived from area under flow rate curve.

standard error of the estimate = 10.62 mL, $P < .05$ [Figure 7]) and agreement (RT3DDD vs AOSV: mean difference = −5.23 ± 11.55 mL, $P > .05$ [Figure 6] and RT3DDD vs LVSV: mean difference = −0.15 ± 9.92 mL, $P > .05$) [Figure 7] between the RT3DDD method and the AOSV and LVSV by MRI.

Intraobserver and Interobserver Variability

The intraobserver variability was 1.30 ± 6.28% ($P > .05$) and the interobserver variability was 0.72 ± 7.86% ($P > .05$). Both were statistically insignificant.

DISCUSSION

This study demonstrated that measurement of flow volume through the MVO by the RT3DDD method is feasible and that RT3DDD measurements correlated and agreed well with both AOSV by PVC MRI and

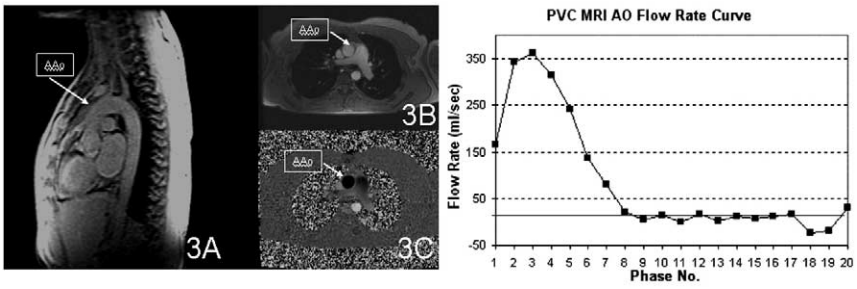

Figure 3 Measurement of flow rate and volume at level of ascending aorta by phase velocity cine (PVC) magnetic resonance image (MRI). **A**, Gradient echo cine MRI of oblique view showing ascending aorta that is used as reference image to obtain cross sections of ascending aorta (AAo). Magnitude (**B**) and phase (**C**) MRI images of ascending aorta in cross sections. Cross section of ascending aorta is manually traced to derive stroke volume by PVC MRI at the ascending aorta (AOSV).

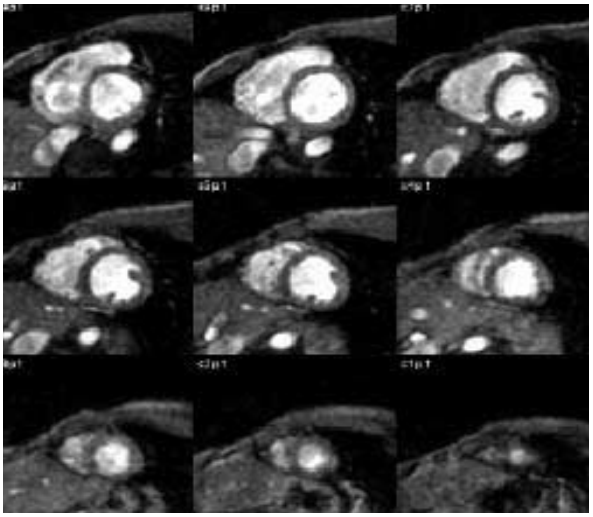

Figure 4 Measurement of stroke volume by left ventricular (LV) volumetric magnetic resonance imaging (MRI) (LVSV). Series of LV short-axis slices from mitral valve annulus (*left upper panel*) to apex (*right lower panel*) are obtained using gradient echo cine MRI technique (FIESTA) during end systole and end diastole. Endocardial borders are traced manually to derive LVSV.

LVSV by MRI volumetric measurements when the control surface was placed at the tip of the MVO.

It is somewhat intriguing that there is significant underestimation by the RT3DDD method when the control surface is placed at the mitral annulus. Because MVO is a funnel-shaped structure, there is less flow acceleration and convergence and the velocities are lower at the annulus than the tip of the mitral valve leaflet.[9] It is likely that the RT3DDD is sensitive to the direction of the flow velocity and/or less reliable for the lower velocity signals at the mitral annulus. Further investigation is needed to resolve this matter.

Current Doppler Echocardiography Method for Measurement Flow Volumes

Conventional pulsed wave Doppler method has limited accuracy and clinical use for quantitative measurements of flow volumes at the cardiac valve orifices because there are several potential sources for measurement error. First, the anatomic valve orifice area is used as an estimate of the flow area. The semilunar valve area is calculated by measuring the diameter of the valve annulus to derive the valve orifice area. Small measurement error in the annular diameter measurement can lead to significant measurement error in area calculation [valve area = π (diameter/2)^2]. The geometry of the atrioventricular valve orifices is particularly complex and quite dynamic during diastole. There are a few available algorithms to derive an estimate of the mean mitral valve area[3,5] but none of them have gained popularity. Second, it is assumed that the velocity profile at the valve orifices is uniformly flat so that a sample volume can be used to represent the velocity profile for flow volume calculation. Studies[6-8] have shown that this is an oversimplification. As a matter of fact, the 3D velocity profiles at the aortic valve orifices and MVOs are quite skewed. If the pulse wave Doppler method is applied for calculation of SV, the estimation error can be as high as 20% to 50% at aortic valve and 10% to 60% at MVO.[6-8]

To account for the variability of the velocity profile at the cardiac valve orifices, 2D color Doppler flow mapping techniques have been developed to measure flow through the mitral valve.[9] An automated cardiac output measurement technique was also developed by Toshiba Medical Systems.[10] These techniques work well for cardiac valve orifices with a circular cross-sectional flow area but have not been validated for noncircular or irregular valve orifices.

Three-dimensional Doppler echocardiography is apparently the next logical step for accurate measurement of flow volumes. Initial studies of in vitro

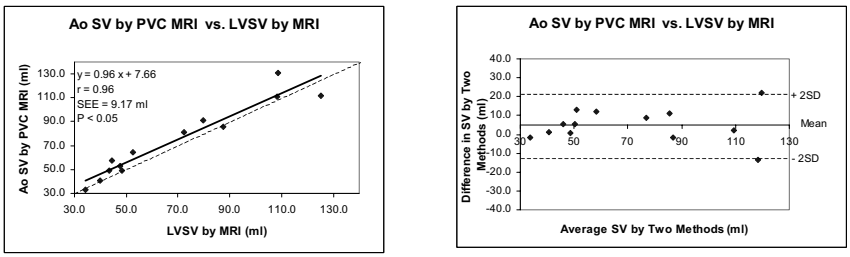

Figure 5 Pearson and Bland-Altman analysis of stroke volume at the ascending aorta measured by phase velocity cine magnetic resonance image (MRI) compared with stroke volume by left ventricular volumetric magnetic resonance imaging.

Table Stroke volume measured by real-time 3-dimensional digital Doppler compared with ascending aorta and left ventricular stroke volume by magnetic resonance imaging

	SV by RT3DDD versus AOSV by MRI				SV by RT3DDD versus LVSV by MRI			
	r	Regression equation	SEE (mL)	Mean Diff ± SD (mL)	*r*	Regression equation	SEE (mL)	Mean Diff ± SD (mL)
MVA	0.85	y = 0.74x + 9.8	16.6	−9.3 ± 22.4*	0.90	y = 0.83x + 7.7	13.9	−4.2 ± 18.5*
MVO	0.92	y = 0.92x + 0.9	12.3	−5.2 ± 12.0†	0.94	y = 0.94x + 3.9	10.6	−0.2 ± 10.3†

AOSV, Stroke volume of the ascending aorta; *Diff,* difference; *LVSV,* left ventricular stroke volume; *MRI,* magnetic resonance imaging; *MVA,* mitral valve annulus; *MVO,* mitral valve ovifice. *RT3DDD,* real-time 3-dimensional digital Doppler; *SEE,* standard error of the estimate; *SV,* stroke volume.
*$P < .05$; †$P > .05$.

and animal preparations using a 3D Doppler reconstruction approach have shown encouraging results.[11-19] Irvine et al[14] used a transesophageal transducer placed epicardially to electronically rotate the scanning plane at 6-degree increments from 0 to 180 degrees triggered by ECG to acquire a 3D digital Doppler data set for reconstruction and flow measurements.[14-19] Tsujino et al[20] analyzed their data to derive aortic flow volumes using a prototype RT 3D Doppler system in an chronic animal model they created for mitral insufficiency. Their study showed that this RT Doppler system was capable of determining the cross-sectional velocity distributions and peak flow rates. The temporal resolution of this prototype RT 3D system is 1 to 3 volumes per systole, which is not high enough to measure flow volumes accurately.

Advantages of the RT3DDD Method

Compared with the previous technologies and methods, the new RT3DDD method used in this study has several important features. First, flow rate is directly measured using the RT3DDD method. Flow rate is the product of mean spatial velocity and flow area. Both mean spatial velocity and flow areas can be measured directly using the RT3DDD method without the need to assume a flat velocity profile. Second, RT3DDD method is technically superior to the previous 3D reconstruction approach because the data acquisition is rapid (acquisition time is about 10-12 seconds for each RT3DDD data set) and the temporal resolution is relatively high with up to 11 to 15 data sets during diastole for the mitral valve flow analysis. Third, studies have shown that the application of the gaussian control surface model is advantageous because it takes into account the angle effect between flow and Doppler ultrasound,[14] an inherent source of measurement error using other Doppler ultrasound techniques. Therefore, the RT3DDD is relatively independent of the angle of incidence.

RT3DDD Versus MRI for Flow Measurements

Both RT3DDD and PVC MRI can provide direct measurement of flow rate and volume. RT3DDD is limited by the acoustic windows but modern MRI systems provide large fields of view and excellent image quality and velocity data.[21-26]

However, RT3DDD has several unique features for flow measurement. First, RT3DDD data acquisition is more rapid than MRI. A full RT3DDD data set for measurement of SV through the MVO takes only 10 to 12 seconds to acquire. Second, RT3DDD instrumentation is less expensive and more portable to the bedside than MRI. Third, RT3DDD may be useful for assessing patients who are critically ill, claustrophobic, unable or unwilling to perform prolonged breath holding, or have other contraindications to MRI such as a cardiac pacemaker.

Limitations

There were a few limitations in this study and the current RT3DDD technology. First, only children from 6 to 18 years were enrolled in this study.

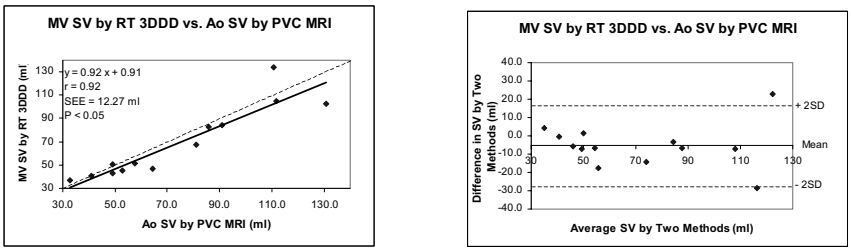

Figure 6 Pearson and Bland-Altman analysis of stroke volume measurements by real-time 3-dimensional digital Doppler at mitral valve orifice compared with measurements by phase velocity cine magnetic resonance imaging at the ascending aorta.

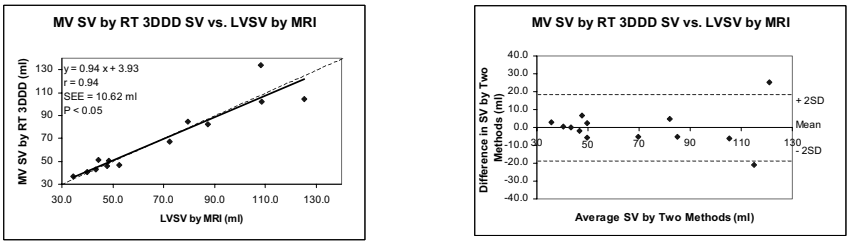

Figure 7 Pearson and Bland-Altman analysis of stroke volume measurements by real-time 3-dimensional digital Doppler at mitral valve orifice compared with measurements by left ventricular volumetric magnetic resonance imaging.

Younger children and infants who cannot perform prolonged breath hold and cooperate may need sedation and possibly endotracheal intubation for MRI studies, which poses a significant ethical challenge for enrollment. Second, there is also a need for ECG triggering for a composite full volume data set from 7 subvolumes (38 degrees × 35 degrees with High Density off), a process that may take 10 to 12 seconds. This is a limitation of the current RT3DDD technology and is also the cause of possible discontinuity and artifacts between subvolumes in some data set. Third, the RT3DDD and MRI data were not obtained simultaneously. Although there were no significant differences in heart rates and diastolic blood pressures at the beginning of RT3DDD and MRI studies, the systolic blood pressures were slightly higher before the MRI studies likely as a result of sympathetic stimulation or claustrophobia, which may affect the comparison between the RT3DDD and MRI measurements. However, such differences appeared small. The interval between RT3DDD and MRI studies was about 30 to 60 minutes. To optimize the comparability of data between the two modalities, no sedation was required for either RT3DDD or MRI studies. There was no food or fluid intake during the interval. However, variables that may alter the heart rate, preload, contractility, and afterload, such as hydration status, respiration, Valsalva maneuver, temperature, vasodilation, constriction, stress, anesthesia, and the use of cardiovascular active agents may affect SV in clinical practice and caution needs to be exercised in these situations to interpret the data. Fourth, the complexity of phasic diastolic filling pattern of the mitral flow requires a high frame rate to optimize flow rate measurement. Finally, measurement of flow by the current RT3DDD is still somewhat painstaking. Future research and application of highly automated algorithms for measurement of flow rate and volume may further facilitate the clinical use of this new technology for quantitative assessment of cardiac function and flow abnormalities in infants and children.

Conclusions

In conclusion, this prospective study demonstrated that the RT3DDD method is a feasible, accurate, and reproducible approach for measuring flow volumes through the mitral valve in healthy children compared with SVs measured by two MRI methods. This RT3DDD method may become a useful clinical tool for assessing cardiac function and flow abnormalities in children with congenital or acquired heart diseases.

The authors wish to acknowledge Philips Inc and TomTec Inc for contributing their updated equipment and software for this study.

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