Magnetic resonance imaging techniques for risk stratification in cardiovascular disease

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Chapter 6

Flow assessment through four heart valves simultaneously using 3-dimensional 3-directional velocity-encoded magnetic resonance imaging with retrospective valve tracking in healthy volunteers and patients with valvular regurgitation

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Abstract

Objectives

To validate three-dimensional (3D) three-directional velocity encoded (VE) magnetic resonance imaging (MRI) for flow assessment through all four heart valves simultaneously with retrospective valve tracking during off-line analysis in healthy volunteers and in patients with valvular regurgitation.

Material and methods

Three-dimensional three-directional VE MRI was performed in 22 healthy volunteers and in 29 patients with ischemic cardiomyopathy who were suspected of valvular regurgitation and net flow volumes through the four heart valves were compared. Furthermore, the analysis was repeated for each valve in 10 healthy volunteers and in 10 regurgitant valves to assess intra- and interobserver agreement for assessment of respectively net flow volumes and regurgitation fraction.

Results

In healthy volunteers, the average net flow volume through the mitral valve, tricuspid valve, aortic valve, and pulmonary valve was 85 ± 20 ml, 85 ± 21 ml, 83 ± 19 ml, 82 ± 21 ml, respectively. Strong correlations between net flow volumes through the four heart valves were observed (intraclass correlation coefficients [ICC] 0.93 to 0.95) and the coefficient of variance (CV) was small (6-9%). The repeated analysis by the same observer and by a second observer yielded good agreement for measurement of net flow volumes (ICC 0.93 to 0.99 and CV 3-7%). Strong correlations between the net flow volumes through the four heart valves were also observed in the patients with valvular regurgitation (ICC 0.85 to 0.95 and CV 7-18%). The average net flow volume through the mitral valve, tricuspid valve, aortic valve, and pulmonary valve was 63 ± 20 ml, 63 ± 20 ml, 63 ± 20 ml, 63 ± 20 ml, respectively. Furthermore, the intra- and interobserver agreement for assessment of regurgitation fraction was good (ICC 0.86 and 0.85, CV 12% and 13%).

Conclusion

Flow assessment using 3D three-directional VE MR with retrospective valve tracking during off-line analysis enables accurate quantification of net flow volumes through four heart valves within a single acquisition in healthy volunteers and in patients with valvular regurgitation.

Introduction

Valvular regurgitation is frequently encountered in clinical practice and can be due to primary abnormalities of the valvular apparatus or secondary to other cardiac disorders such as ischemic or non-ischemic dilated cardiomyopathy (1-5). Volume overload due to valvular regurgitation may cause (or aggravate) ventricular remodeling which can ultimately result in heart failure and death (1,6). Surgical repair or replacement of the regurgitant valve may reduce heart failure symptoms and improve survival (6,7). Accordingly, quantitative assessment of valvular regurgitation is important for evaluation of disease progression, optimization of treatment, and timing of surgical intervention (1,7).

Doppler Echocardiography (8) is most commonly used for detection of valvular regurgitation and enables semiquantitative assessment of its severity (1,2,4,9). This technique is however prone to inaccuracies due to technical limitations, modeling assumptions, and its dependency on operator experience (9).

Two-dimensional (2D) one-directional velocity-encoded (VE) magnetic resonance imaging (MRI) (10) enables quantification of valvular regurgitation and is frequently used in different clinical settings (11-13). However, conventional 2D one-directional VE MRI may lead to imprecise quantification of regurgitant volume, as the location and angulation of the acquisition plane can not be corrected for movement of valve planes during cardiac contraction and relaxation (14). In fact, previous studies showed no conservation of mass and moderate correlations between stroke volume through the mitral valve (MV) and tricuspid valve (TV) and stroke volume measured in the ascending aorta (15,16). Kozerke et al. (17) introduced the Slice Track-method where prior to VE MRI, the basal level of the left ventricle was labeled in the septum and the lateral wall and the excursion of the basal level determined the positioning and angulation of the acquisition. This technique makes use of navigator with prospective triggering for cardiac synchronization. Acquisition of part of the diastole can be missed, leading to an underestimation of the mitral or tricuspid valvular inflow, or an underestimation of the regurgitation at the aortic or pulmonary valve (PV). Furthermore, when information on more than one heart valve is required, VE MRI has to be performed at each heart valve separately, which significantly increases examination time. Three-dimensional (3D) three-directional VE MRI (18-21) with retrospective valve tracking has recently been validated in vitro, in healthy volunteers, and in patients with valvular regurgitation for simultaneous flow assessment through the MV and TV (16).

Thus far, no studies have reported yet on the application of one VE MRI data acquisition for flow assessment through all four heart valves simultaneously.

Accordingly, the purpose of the present study was to validate 3D three-directional VE MRI for flow assessment through all four heart valves simultaneously with retrospective valve tracking during off-line analysis in healthy volunteers and in patients with valvular regurgitation.

Materials and methods

Subjects

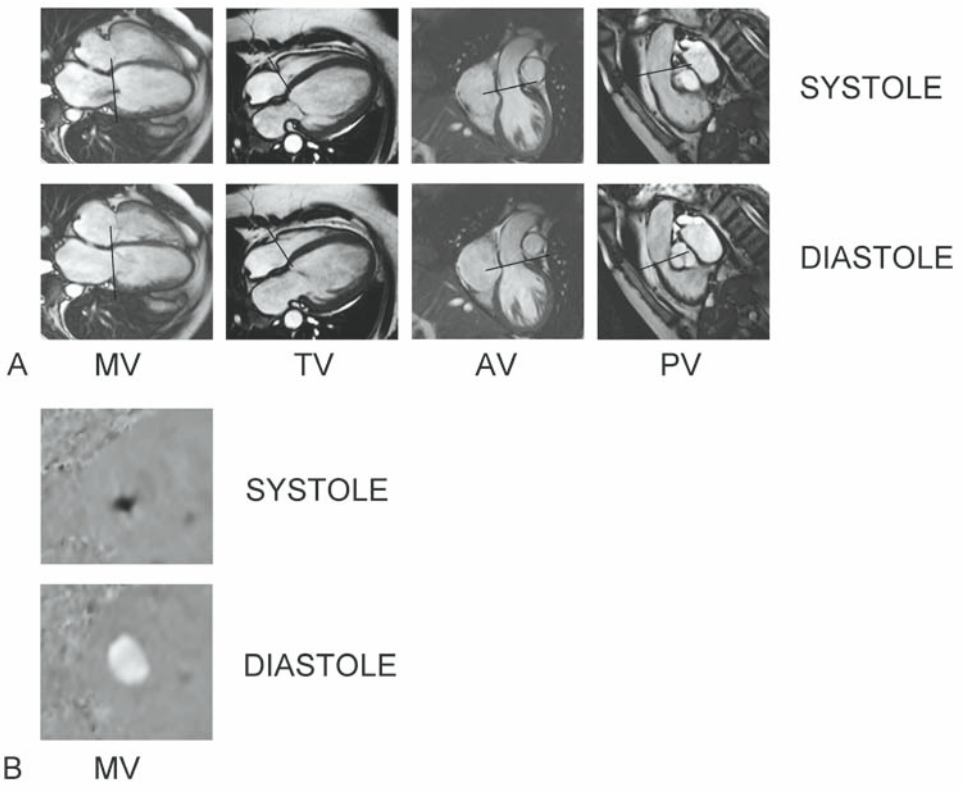
Twenty-two healthy volunteers (16 men, 6 women; mean age 22 ± 8 years) without a history of cardiac disease were included in the study. Furthermore, 29 patients (21 men, 8 women; mean age, 61 ± 13 years) with ischemic cardiomyopathy who were suspected of having aortic valve (AV), PV, TV, or MV regurgitation, or regurgitation of more than one heart valve were evaluated. All patients and volunteers gave informed consent and the local medical ethics committee approved the study.

MR imaging methods

MR imaging was performed on a 1.5T pulsar gradient system (Intera, release 11; Philips Medical Systems, Best, the Netherlands) with 33 mT/m amplitude, 100 mT/m/ms slew rate, and 0.33-ms rise time. A 5-element cardiac coil placed on the chest was used for signal reception. First, a series of thoracic scout images were acquired for planning purposes. Subsequently, cine MR imaging was performed in left ventricular (LV) and right ventricular (RV) two-chamber view and in four-chamber view. Furthermore, cine MR imaging was performed in two orthogonal views (double oblique coronal and double oblique sagittal view) of the LV and RV outflow tract separately. All cine scans were acquired using a steady state free precession sequence (repetition time 3.0 ms, echo time 1,5 ms, 350-mm field of view, 8-mm slice thickness, 50° flip angle, 1.8 × 2.0 × 8.0-mm acquisition voxel reconstructed into a 1.4 × 1.4 × 8.0-mm voxel, one signal acquired, 30 phases reconstructed during one average cardiac cycle) that lasted 10–15 seconds and covered one breath-hold at end-expiration.

For quantification of blood flow through the four heart valves, 3D three-directional VE MR imaging was performed, which was recently validated in-vitro, in healthy volunteers, and in patients with valve regurgitation for assessment of TV and MV flow (16). Data were acquired using velocity encoding in three orthogonal directions (repetition time 7.5 ms, echo time 4.3 ms, 370-mm field of view, 3D volume imaging with 48-mm slab thickness reconstructed into 12 4-mm slices, 10° flip angle, 2.9 × 3.8 × 4.0-mm acquisition voxel reconstructed into a 1.4 × 1.4 × 4.0-mm voxel, one signal acquired, retrospective gating with 10% acceptance window, with 30 phases reconstructed during one average cardiac cycle, resulting in an average temporal resolution of 30 ± 7ms, 150 cm/sec maximal velocity encoding in all three directions). The 3D volume slab was placed at the base of the heart and the cine scans of the LV and RV two-chamber, four-chamber view and LV and RV outflow tract views were used to ensure that all four heart valves were included in the 3D volume throughout the whole cardiac cycle (Figure 1). To reduce acquisition time, echo planar imaging (22) was used with a factor of five, resulting in an acquired temporal resolution (23) of 37.5 ms. The average acquisition duration of the 3D three-directional VE MR imaging is ~ 4.2 ± 0.8 minutes (16).

Figure 1.



3D three-directional VE MRI for flow assessment through four heart valves. A. illustration of how the reformatting planes were chosen an adapted during the cardiac cycle. B. Phase maps of the flow through the mitral valve (of the same patients as shown in A, MV) showing backward flow (regurgitation) during systole and forward flow during diastole.
AV: aortic valve, MV: mitral valve, TV: tricuspid valve, PV: pulmonary valve.

Image processing

The 3D three-directional VE MR images were analyzed using MASS research software developed at our institution. A schematic illustration of this reformatting procedure is shown in Figure 1. First, from the 3D three-directional VE MR data, blood flow velocity through all four heart valves was reconstructed by reformatting each valvular plane from the 3D dataset consecutively. The location and angulation of the valvular plane of interest was indicated manually by using the intersection lines of this valvular plane with the two orthogonal views acquired for each valve. The intersection line of the valvular plane was placed on the annulus in each of the 30 phases, in the four-chamber view for reformatting the MV and TV, in the double oblique coronal LV outflow tract for the AV, and in the double oblique sagittal RV outflow tract for the PV. If necessary, the angulation of the intersection line of the valvular plane was manually adjusted in the second orthogonal

view (i.e., LV and RV two-chamber, double oblique sagittal LV outflow tract, double oblique coronal RV outflow tract). For an open valve, the intersection line was placed on the annulus of the valve and for a closed valve on the leaflets. In case of valve regurgitation, the line was placed perpendicular to the regurgitant jet.

For each valvular plane and each phase, all three velocity vector components were reformatted from the original three-directional velocity data set. In each reformatted plane, the same inplane spatial resolution of the original data set was preserved (1.4 × 1.4 mm) and tri-linear interpolation was used for resampling. The velocity maps of five parallel planes (the indicated valvular plane and two planes on either side, parallel to the valvular plane) with an interplane distance of 5 mm were reformatted. For each of these five planes, the through-plane velocity values perpendicular to the planes were determined from the dot product of the normal vector of these planes and the velocity vectors which were constructed from the vector components. The resulting through-plane velocity values were presented for each voxel, each phase, and each of the five reformatted planes.

Next, contours were manually drawn around the heart valve of interest in each phase in the central plane of the five planes (i.e., the valvular plane) reconstructed for that particular heart valve. Background correction was performed to correct for through-plane motion correction (24) and local phase offset (14). For flow assessment through the MV and TV, a region-of-interest (ROI) for background corrections was placed at the central plane in the lateral wall of the LV and in the RV free wall, respectively. For assessment of the AV and PV flow, the background ROI was placed at the most caudal plane, e.g., at 10 mm distance from the central plane, since not in all phases of the cardiac cycle, myocardium was present in the central plane for positioning of the ROI. In this most caudal plane, the background ROI for assessment of the AV flow was placed in the LV anterior wall and the ROI was positioned in the septum for assessment of the PV flow. To obtain the flow in each phase, the average velocity measured over the annulus was first subtracted from the average velocity measured in this background ROI, and then multiplied with the area of the annulus.

When a high-velocity regurgitant jet occurs, phase dispersion can result in signal loss at the location of the valve (25) with possible underestimation of regurgitation. In such cases, phases with regurgitant flow were analyzed in the first or second plane next to the center plane inside the atrium (for MV and TV) or in the ventricle (AV or PV).

The net flow volume through the valves was defined as the forward flow volume minus the regurgitant backward flow volume. The severity of regurgitation was expressed as regurgitation fraction calculated as the regurgitant flow volume divided by the forward flow volume through the valve. Regurgitation was considered significant when the regurgitation fraction was ≥ 5%.

The reformatting procedure took 5 minutes for each valve, and subsequent image analysis took 5 minutes.

The reformatting procedure and segmentation was repeated for each valve in 10 volunteers and in 10 regurgitant valves by the same observer (observer 1) four weeks later

and by a second observer (observer 2) to evaluate intra- and interobserver agreement for measurement of net flow volume and regurgitation fraction, respectively.

Statistical analysis

Continuous data were normally distributed (as evaluated by Q-Q plots of residuals) and expressed as mean ± standard deviation (SD). The net flow through the four heart valves were compared using the paired *t*-test. The correlation between the net flow through the four heart valves was assessed using Pearson's correlation coefficient (r). Furthermore, intraclass correlation coefficients (ICC) for absolute agreement were calculated for the net flow through the four heart valves and the coefficient of variance (CV) was determined. The CV was defined as the SD of the differences between the two series of measurements divided by the mean of both measurements. Furthermore, Bland-Altman plots were computed.

In addition, the net flow volumes and the regurgitation fraction obtained from the repeated analysis from observer 1 and from observer 2 were compared with the initial results of observer 1 (reference standard) using the paired *t*-test. Furthermore, the Pearson's coefficient (r) and the ICC for absolute agreement to assess intra- and interobserver agreement were calculated. A p-value < 0.05 was considered statistically significant.

Results

Validation in volunteers

In the healthy volunteers, no distortion or susceptibility artifacts caused by echo-planar imaging were observed.

Table 1. Statistics for comparison of net flow volumes through the four heart valves in healthy volunteers.

	MV vs. TV	MV vs. AV	MV vs. PV	TV vs. AV	TV vs. PV	AV vs. PV
Correlation r (p-value)	0.93 (< 0.001)	0.97 (< 0.001)	0.95 (< 0.001)	0.93 (< 0.001)	0.93 (< 0.001)	0.93 (< 0.001)
ICC (p-value)	0.94 (< 0.001)	0.96 (< 0.001)	0.95 (< 0.001)	0.92 (< 0.001)	0.93 (< 0.001)	0.93 (< 0.001)
CV (%)	9	6	8	9	9	9
P-value*	0.7	0.1	0.1	0.1	0.1	0.7

* P-values were calculated with the paired-*t* test.
AV: aortic valve, CV: coefficient of variance, ICC: intraclass correlation coefficient, MV: mitral valve, PV: pulmonary valve, r: Pearson's correlation coefficient, TV: tricuspid valve.

The average net flow volume through the four valves and the Pearson correlation coefficient, ICC and CV between the net flow volumes through the four heart valves

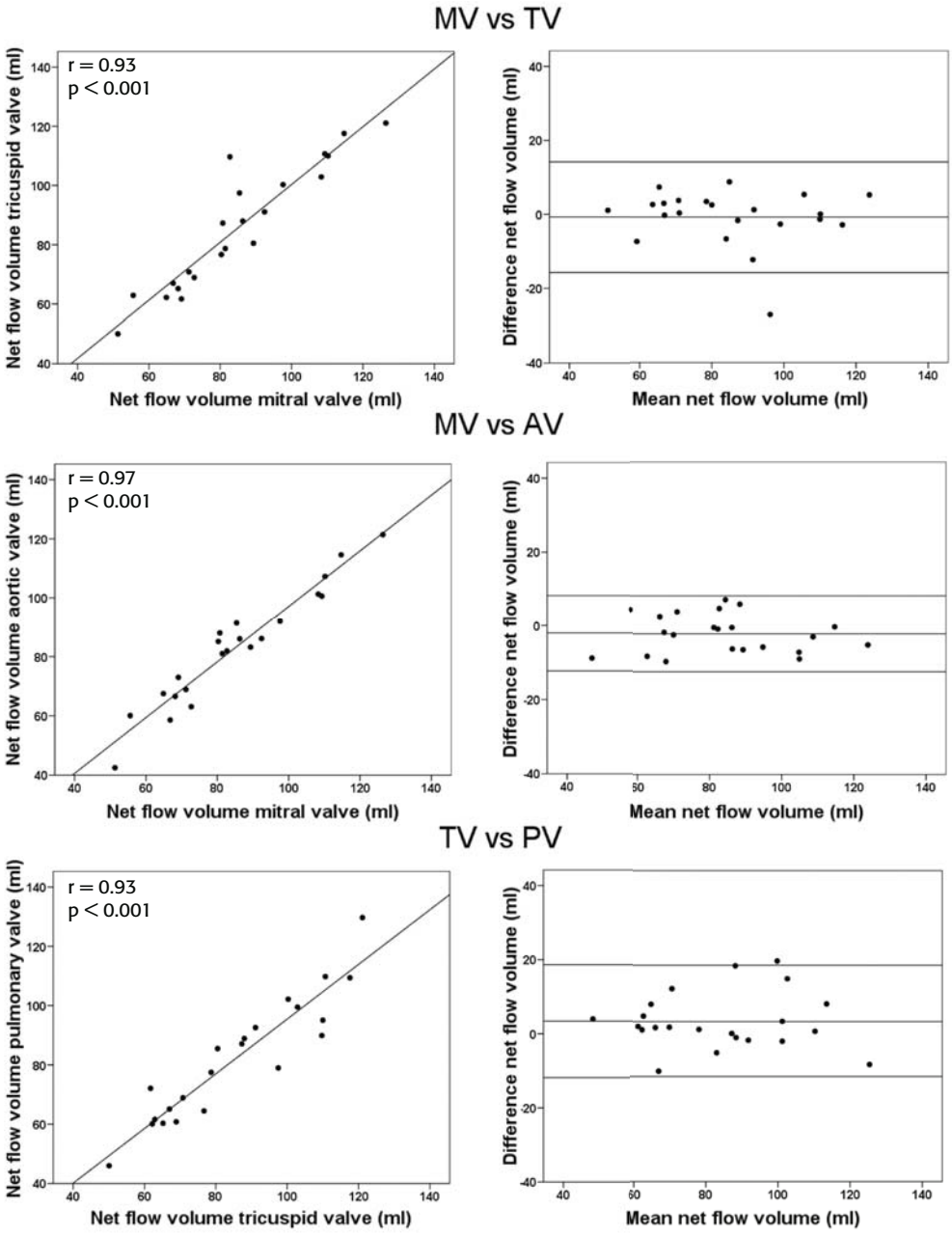
are presented in Table 1. The average net flow volume through the MV, TV, AV, and PV was 85 ± 20 ml, 85 ± 21 ml, 83 ± 19 ml, 82 ± 21 ml, respectively, and no significant differences between the net flow volumes were detected, indicating conservation of mass through the four heart valves. A strong correlation between the net flow volume through the four valves was observed (MV-TV $r = 0.93$, $p < 0.001$, MV-AV $r = 0.97$, $p < 0.001$, MV-PV $r = 0.95$, $p < 0.001$, TV-AV $r = 0.93$, $p < 0.001$, TV-PV $r = 0.93$, $p < 0.001$, AV-PV $r = 0.93$, $p < 0.001$). The ICCs of the net flow volume through the valves were also excellent. Scatter plots of the net flow volumes through the different valves and Bland-Altman plots are shown in Figure 2 and no systematic trends are present in de differences between the net flow volumes through the valves.

Table 2. Statistics for comparison of net flow volumes through the four heart valves in healthy volunteers for assessment of intra- and interobserver agreement.

		MV	TV	AV	PV
Correlation r (p-value)	Repeated analysis observer 1	0.98 (< 0.001)	0.94 (< 0.001)	0.99 (< 0.001)	1.00 (< 0.001)
	Observer 2	0.91 (< 0.001)	0.96 (< 0.001)	0.98 (< 0.001)	0.95 (< 0.001)
ICC (p-value)	Repeated analysis observer 1	0.97 (< 0.001)	0.93 (< 0.001)	0.93 (< 0.001)	0.99 (< 0.001)
	Observer 2	0.91 (< 0.001)	0.94 (< 0.001)	0.98 (< 0.001)	0.95 (< 0.001)
CV (%)	Repeated analysis observer 1	4	7	4	3
	Observer 2	8	6	4	7
P-value*	Repeated analysis observer 1	0.5	0.1	0.7	0.5
	Observer 2	0.4	0.1	0.8	0.3

* P-values were calculated with the paired-*t* test.
AV: aortic valve, CV: coefficient of variance, ICC: intraclass correlation coefficient, MV: mitral valve, PV: pulmonary valve, r: Pearson's correlation coefficient, TV: tricuspid valve.

Figure 2.



Scatter plots of net flow volumes and Bland-Altman plots showing the difference in net flow volume between measurements through the four heart valves in healthy volunteers
AV: aortic valve, MV: mitral valve, TV: tricuspid valve, PV: pulmonary valve.

The results of the repeated analysis of observer 1 and the analysis of observer 2 are presented in Table 2. No significant differences between the net flow volumes through the valves were observed. Furthermore, the Pearson's correlation and ICCs were strong and the CV was small, indicating good intra- and interobserver agreement.

Table 3. Statistics for comparison of net flow volumes through the four heart valves in patients with valvular regurgitation.

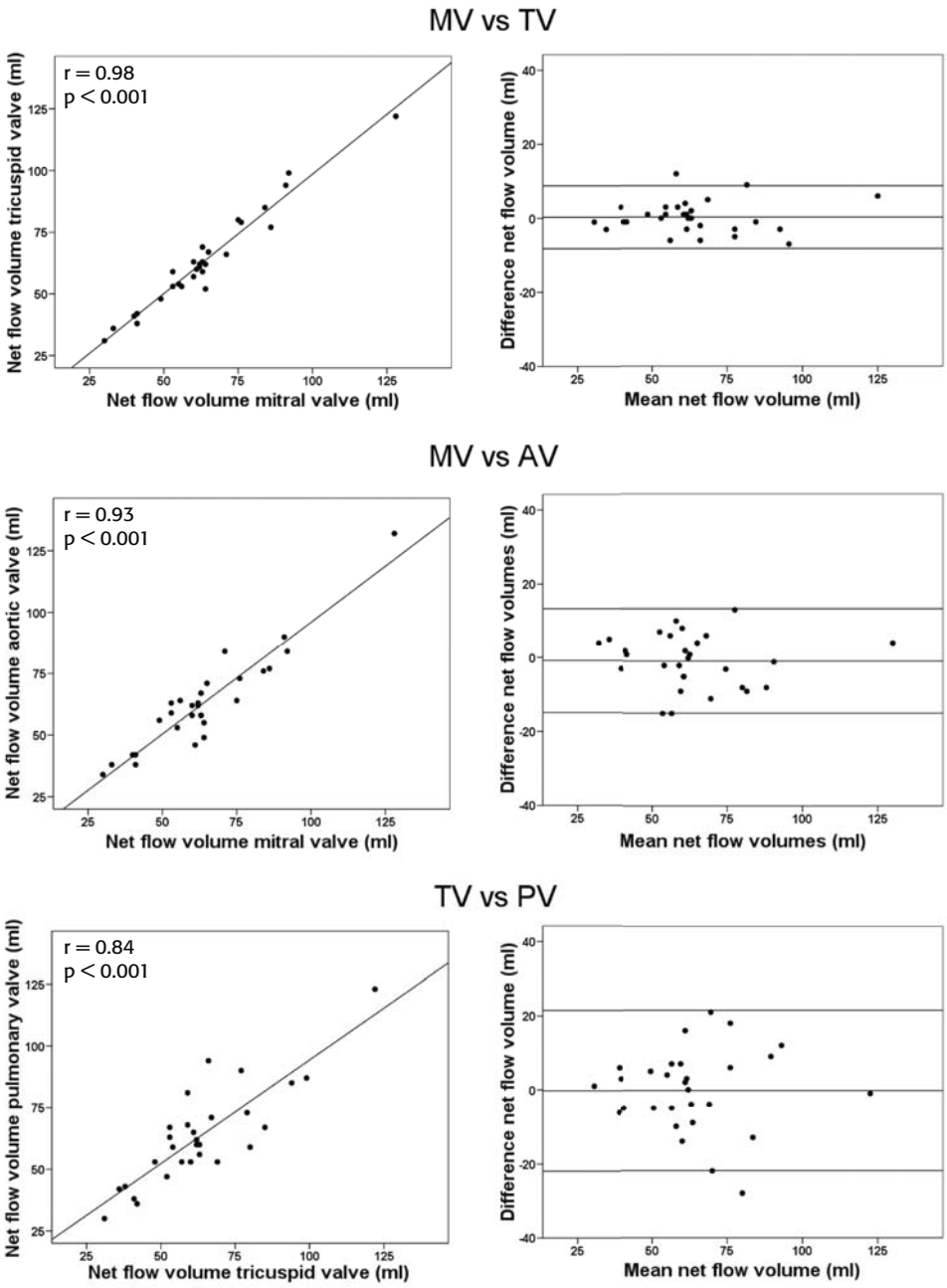
	MV vs. TV	MV vs. AV	MV vs. PV	TV vs. AV	TV vs. PV	AV vs. PV
Correlation r (p-value)	0.98 (< 0.001)	0.93 (< 0.001)	0.88 (< 0.001)	0.92 (< 0.001)	0.84 (< 0.001)	0.95 (< 0.001)
ICC (p-value)	0.98 (< 0.001)	0.94 (< 0.001)	0.88 (< 0.001)	0.92 (< 0.001)	0.85 (< 0.001)	0.95 (< 0.001)
CV (%)	7	11	16	13	18	10
P-value*	0.7	0.6	1.0	0.8	0.9	0.6

* P-values were calculated with the paired-*t* test.
AV: aortic valve, CV: coefficient of variance, ICC: intraclass correlation coefficient, MV: mitral valve, PV: pulmonary valve, r: Pearson's correlation coefficient, TV: tricuspid valve.

Application in patients

No artifacts caused by echo planar imaging were observed. Five patients presented with a single regurgitant valve, 19 patients with two regurgitant valves, and 5 patients with three regurgitant valves (range regurgitation fraction: 5 – 29%). The average net flow volume through the MV, TV, AV, and PV was 63 ± 20 ml, 63 ± 20 ml, 63 ± 20 ml, 63 ± 20 ml, respectively, and no significant differences between the net flow volumes were observed (Table 3). The correlation and the ICCs between the net flow through the valves were strong and the CV was small (Table 3), indicating good agreement of the net flow volumes through the four valves in the presence of valvular regurgitation. Scatter plots of the net flow volumes through each valve and Bland-Altman plots are shown in Figure 3. One single outlier can influence the correlation; exclusion of the patients with the highest net flow volume (~125 ml, see Figure 3) yielded only slightly lower Pearson's correlation coefficients ranging from 0.77 to 0.97.

Figure 3.



Scatter plots of net flow volumes and Bland-Altman plots showing the difference in net flow volume between measurements through the four heart valves in patients with valvular regurgitation.
AV: aortic valve, MV: mitral valve, TV: tricuspid valve, PV: pulmonary valve.

The repeated measurement of the regurgitation fraction of observer 1 and observer 2 yielded no significant differences in regurgitation fraction compared with the reference standard (regurgitation fraction of 18 ± 7%, 16 ± 8%, 17 ± 7% for the reference standard, repeated analysis observer 1, and observer 2, respectively). The Pearson's correlation and ICCs were strong and the CV was small, indicating good intra- and interobserver agreement (Table 4).

Table 4. Statistics for comparison of regurgitation fraction for assessment of intra- and interobserver agreement.

Correlation r (p-value)	Repeated analysis observer 1	0.90 (< 0.001)
	Observer 2	0.91 (< 0.001)
ICC (p-value)	Repeated analysis observer 1	0.86 (< 0.001)
	Observer 2	0.85 (< 0.001)
CV (%)	Repeated analysis observer 1	12
	Observer 2	13
P-value*	Repeated analysis observer 1	0.07
	Observer 2	0.3

* P-values were calculated with the paired-*t* test.
CV: coefficient of variance, ICC: intraclass correlation coefficient, r: Pearson's correlation coefficient.

Discussion

The main finding of the present study is that 3D three-directional VE MR imaging of four heart valves simultaneously enables accurate quantification of flow volumes in healthy volunteers as well as in patients with valvular regurgitation. The regurgitation fraction, indicating the severity of valvular regurgitation, can be quantified accurately. Conservation of mass is valid for the net flow volume through the four heart valves, even in the presence of singular or multiple valvular regurgitation. Furthermore, repeated analysis including the reformatting procedure and segmentation demonstrated excellent intra- and interobserver agreement for the flow volume measurements as well as the regurgitation fraction.

The correlation between net flow volumes through the four heart valves was lower in patients compared to healthy volunteers, however the ICC varied between 0.85 and 0.98, indicating good to excellent agreement.

Quantification of valvular regurgitation is clinically important since the severity of regurgitation is associated with clinical outcome and serial evaluation of progression of regurgitation is essential for optimization of treatment of patients, including timing of surgical intervention (1,7,26). Currently, Doppler echocardiography is the most commonly used technique for detection and quantification of valvular regurgitation in clinical practice (27). Echocardiography is however limited because of technical limitations, modeling assumptions, and its dependency on operator experience, which may lead to inaccurate quantification of valvular regurgitation (9).

VE MRI (or phase-contrast MRI) also enables flow quantification based on phase differences of hydrogen protons (spins) in moving blood and stationary tissue: precession frequency of the moving spins changes and they accumulate phase while moving along a magnetic gradient (28,29). Conventional 2D one-directional through-plane VE MRI is currently frequently applied in clinical practice for quantification of valvular regurgitation (28,30). However, previous studies evaluating 2D one-directional VE MRI in the presence of valvular regurgitation showed only moderate correlations between stroke volume through the MV and TV and stroke volume measured in the ascending aorta (15,16). These imprecise measurements are a result of the fact that with 2D one-directional VE MRI, the location and angulation of the acquisition plane can not be corrected for movement of the valvular annulus during cardiac contraction and relaxation (14). In addition, in case of an eccentric regurgitant jet, the acquisition plane is not perpendicular to the flow direction, leading to underestimation of the severity of regurgitation.

Kozerke et al. (17) introduced a moving slice velocity mapping method which enables data acquisition at the level of the valvular plane thereby adapting the acquisition plane continuously to the valvular motion during cardiac contraction and relaxation. A disadvantage of this technique however, is the use of prospective triggering which implies that flow information during the final part of RR-interval is not acquired, resulting in an underestimation of end-diastolic forward (i.e., for MV and TV) or regurgitant (i.e., for AV and PV) flow volume. Furthermore, in case multiple valves are studied, the acquisition needs to be performed sequentially, which increases scan time.

3D three-directional VE MRI was recently introduced and validated in a phantom model, in healthy volunteers, and patients with valvular regurgitation for simultaneous flow assessment of TV and MV (16). This study demonstrated excellent agreement between net flow volumes measured through the two valves of interest and the stroke volume in the ascending aorta, in contrast to the conventional 2D

one-directional VE MRI which resulted in an large overestimation (15-25%) of the net flow volumes through the MV and TV (16).

In the previous study, only the ability for flow assessment through the MV and TV was tested. Aortic and pulmonary regurgitation and combined valvular regurgitation involving 2 or more heart valves however commonly occur in clinical practice (1,6,31). The current study demonstrates that 3D three-directional VE MRI enables quantification of forward and regurgitant flow volumes through the four heart valves simultaneously with conservation of mass by positioning the 3D volume on all four heart valves.

Limitations of the current study include the use of echo planar imaging to reduce scan time (22). However, no distortion or susceptibility artifacts were seen and extensive validation in a phantom model demonstrated excellent agreement with the actual flow without systematic differences when using low echo planar imaging factor (i.e., factor 5 was used) (16). Furthermore, data were acquired during free breathing which may possibly result in overestimation of the valvular area and possible spatial misregistration between the cine scans used as reformatting guides and the 3D three-directional velocity encoded MRI, of either valvular plane. Next, signal loss due to phase dispersion in patients with a high-velocity regurgitant jet, may lead to underestimation of the regurgitant volume (14). The true spatial resolution (i.e., 2.9 × 3.8 mm) of the 3D three-directional VE MRI technique may hamper a clear delineation of the valve borders due to partial volume effects. However, the spatial resolution is comparable to the resolution of the widely accepted 2D one-directional velocity-encoded MRI acquisition (i.e., 2.7 × 3.4 mm) (16). Furthermore, post-processing including the reformatting procedure and subsequent segmentation is operator dependent, the high intra- and interobserver agreement observed in this study however, indicates excellent reproducibility.

In conclusion, flow assessment using 3D three-directional VE MR with retrospective valve tracking during off-line analysis enables accurate quantification of net flow volumes through four heart valves with conservation of mass within a single acquisition in healthy volunteers and in patients with valvular regurgitation.

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