Original Research

Flow-Sensitive Four-Dimensional Cine Magnetic Resonance Imaging for Offline Blood Flow Quantification in Multiple Vessels: A Validation Study

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Purpose: To further validate the quantitative use of flow-sensitive four-dimensional velocity encoded cine magnetic resonance imaging (4D VEC MRI) for simultaneously acquired venous and arterial blood flow in healthy volunteers and for abnormal flow in patients with congenital heart disease.

Materials and Methods: Stroke volumes (SV) obtained in arterial and venous thoracic vessels were compared between standard two-dimensional (2D), 4D VEC MRI with and without respiratory navigator gating (gated/nongated) in volunteers (n = 7). In addition, SV and regurgitation fractions (RF) measured in aorta or pulmonary trunk of patients with malformed and/or insufficient valves (n = 10) were compared between 2D and nongated 4D VEC MRI methods.

Results: In volunteers and patients, Bland–Altman tests showed excellent agreement between 2D, gated, and nongated 4D VEC MRI obtained quantitative blood flow measurements. The bias between 2D and gated 4D VEC MRI was <0.5 mL for SV; between 2D and nongated 4D VEC MRI the bias was <0.7 mL for SV and <1% for RF.

Conclusion: Blood flow can be quantified accurately in arterial, venous, and pathological flow conditions using 4D VEC MRI. Nongated 4D VEC MRI has the potential to be suited for clinical use in patients with congenital heart disease who require flow acquisitions in multiple vessels.

Key Words: blood flow quantification; congenital heart disease; cardiac
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TWO-DIMENSIONAL (2D) velocity encoded cine magnetic resonance imaging (VEC MRI) is a well-established technique for blood flow quantification (1). Quantitative flow assessment is an important element of cardiovascular MRI studies in patients with congenital heart disease and, in many cases, information about blood flow is required in multiple arterial and venous vessels (2–4). However, repeat planning and acquisition of 2D VEC MRI can be time-consuming. In addition, data analysis is limited to those vessel sections that were targeted during the scan.

Flow-sensitive four-dimensional (4D) VEC MRI allows for acquisition of three-directional blood flow velocity information within a 3D anatomical volume (5). This technique was initially introduced to visualize blood flow patterns qualitatively in normal and pathological hemodynamic conditions (6–8). More recently, the accuracy of 4D methods was assessed as an alternative to 2D VEC MRI for blood flow quantification (9–11). So far, studies focused mainly on the systematic assessment of measurement accuracy of 4D VEC MRI quantification of arterial flow in volunteers. However, quantitative data of simultaneously acquired venous and arterial blood flow in volunteers, as well as blood flow quantification in patients with congenital heart diseases and abnormal flow conditions are sparse (10).

In this study we aimed to validate the quantitative use of 4D VEC MRI for simultaneously acquired venous and arterial blood flow in healthy volunteers and for abnormal flow conditions across the pulmonary or aortic valve in patients with congenital heart disease.

MATERIALS AND METHODS

Volunteer and Patient Characteristics

The study was conducted in seven volunteers (female/male = 4/3, 34 ± 7 years old, 74 ± 12 kg, 1.7 ± 0.1 m)

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Table 1
Sequence Parameters

	2D	4D gated	4D nongated
Field of view (mm)	300 × 150	185 × 240 × 80	185 × 240 × 80
Matrix size	128 × 256	100 × 128	100 × 128
Number of slices	1	32	32
Acquired voxel size (mm)	2.3 × 2.3 × 7	2.5 × 2.6 × 2.5	2.5 × 2.6 × 2.5
Reconstructed voxel size (mm)	1.2 × 1.2 × 7	1.9 × 1.9 × 2.5	1.9 × 1.9 × 2.5
TR (ms) / TE (msec)	5.1/3	3.2/1.9	3.2/1.9
Flip angle (°)	10	5	5
Cardiac gating	Retrospective	Retrospective	Retrospective
Reconstructed cardiac phases	35	24	24
VEC venous vessels (cm/s)	100	150 (max 400)	150 (max 400)
VEC arterial vessels (cm/s)	200 (max 400)	150 (max 400)	150 (max 400)
NSA	2	1	1

2D = two-dimensional, 4D = four-dimensional, TR = repetition time, TE = echo time, VEC = velocity encoding, NSA = number of signal averages.

and in 10 patients with congenital heart disease (female/male = 2/8, 19 ± 9 years old, 59 ± 20 kg, 1.6 ± 0.2 m). Patients had corrected tetralogy of Fallot with mild or moderate pulmonary valve insufficiency ($n = 4$), malformed tricuspid aortic valve with moderate aortic valve insufficiency ($n = 1$), or bicuspid aortic valve with ($n = 2$) or without ($n = 3$) moderate aortic valve insufficiency.

The Institutional Review Board approved the study and the patients or guardians of patients gave informed consent.

Location and Method of Flow Measurements

Volunteers were studied with 2D VEC MRI, gated and nongated 4D VEC MRI. Arterial flow was measured in 1) the ascending aorta distal to coronary artery orifices; 2) the mid portion of the pulmonary trunk; 3) the main stem of the right; and 4) left pulmonary artery at least 4 mm distal to the bifurcation. Venous flow was measured in i) the superior vena cava directly cranial to the inflow into the right atrium and ii) the right lower pulmonary vein (RLPV) just proximal to its drainage into the left atrium.

Patients

The protocol for the patient part of the study was adapted according to the results of measurements in the volunteers. Therefore, the patients were studied with 2D and nongated 4D VEC MRI, but not with gated 4D VEC MRI. Measurements were made in the ascending aorta distal to coronary artery orifices or in the mid portion of the pulmonary trunk.

VEC MRI methods

The study was conducted on a whole-body 3T MR scanner (Achieva R2.6.3, Philips Medical Systems, Best, Netherlands) using a six-element cardiac phased-array coil (Philips Medical Systems). All flow measurements were done with automatic correction of concomitant phase errors.

2D VEC MRI

Steady-state free-precession MRI acquisitions were used for anatomical planning. Flow measurements were done perpendicular to each targeted vessel and with a free-breathing phase contrast cine MRI technique (12). The sequence parameters are given in Table 1.

4D VEC MRI

Anisotropic 4D segmented *k*-space phase contrast gradient echo sequence with retrospective ECG gating was performed with and without navigator-gating of respiratory motion. In all volunteers and patients, flow velocities were measured in a 3D volume that covered the thorax from apex of the heart to the aortic arch in the feet-to-head (FH) direction, the sternal border and spine in the anterior-to-posterior (AP) direction, and the main stem of the right and left pulmonary artery until further branching in the right-to-left (RL) direction. Sequence parameters are shown in Table 1.

Postprocessing

Postacquisition analysis of 2D flow measurements was performed with the software View Forum (Release 6.1, Philips Medical Systems). 4D flow parameters were analyzed using the software GTFlow (Release 1.3.3, Gyrotools, Zurich, Switzerland). Stroke volume was defined as the effective antegrade flow, regurgitation fraction (expressed as a percentage) was calculated as the proportion of the retrograde flow relative to the total antegrade flow (12). The software GTFlow allows for reformatting 4D flow data in any arbitrary direction. Quantitative 4D measurements were obtained at the same anatomical region and with the same plane angulation as the 2D measurements (Fig. 1). The image planes for blood flow quantification in the 4D volume were related and set manually to the image parameters from the respective 2D measurement. The region of interest of each vessel was manually traced in each cardiac phase to obtain average flux along the RR interval.

Statistical Analysis

Bland–Altman tests were performed to compare the three different techniques (2D vs. gated 4D, 2D vs. nongated 4D, and gated 4D vs. nongated 4D VEC MRI). For Bland–Altman testing in healthy volunteers,

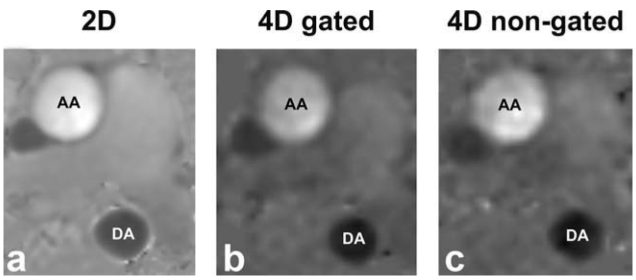

Figure 1. Representative example of comparable anatomical regions for blood flow quantification in a volunteer. 2D **(a)**, 4D gated **(b)**, and 4D nongated **(c)** phase contrast image of aortic blood flow. AA, ascending aorta; DA, descending aorta; 2D, two-dimensional; 4D, four-dimensional.

measurements of ascending aorta, pulmonary trunk, right and left pulmonary artery were combined and labeled "arterial"; measurements of superior vena cava and right lower pulmonary vein were combined and labeled "venous." One-way analysis of variance (ANOVA) testing was used to compare stroke volumes derived by 2D, gated 4D, and nongated 4D VEC MRI. The Mann–Whitney test was used to assess statistical differences of total acquisition times. Data are expressed as mean ± standard deviation where appropriate. Statistical analyses were performed on GraphPad Prism 4 analysis software (GraphPad Prism 4, San Diego, CA).

The authors had full access to the data and take responsibility for its integrity. All authors read and agreed to the article as written.

RESULTS

Measurements in Volunteers

Stroke volumes and flux curves obtained in arterial and venous vessels of healthy volunteers showed good agreement without significant differences between 2D, gated 4D, and nongated 4D VEC MRI methods (Table 2; Fig. 2). Bland–Altman tests confirmed these findings (Fig. 3). When comparing the gold standard 2D VEC MRI with gated and nongated 4D techniques, the mean of differences (bias) represents <1% of the overall mean value for arterial and <3% for venous stroke volume. Comparing these two techniques, all measured parameters were not significantly different. However, mean acquisition time was significantly shorter for nongated vs. gated 4D VEC MRI (8.6 ± 1.2 vs. 13.9 ± 2.5 minutes, respectively, $P < 0.001$).

Measurements in Patients

In each patient, measurements were made either in the aorta or in the pulmonary trunk dependent on the underlying congenital heart disease. Patients with corrected tetralogy of Fallot displayed mild or moderate pulmonary valve insufficiency ($n = 4$). The regurgitation fraction was 29.8 ± 12% as measured by 2D VEC MRI and 27.8 ± 12.7% as measured by nongated 4D VEC MRI. The patient with a malformed tricuspid aortic valve showed moderate aortic valve insufficiency ($n = 1$). The regurgitation fraction was 29.3% as measured by 2D VEC MRI and 28% as measured by nongated 4D VEC MRI. The patients with bicuspid aortic valve demonstrated nonlaminar blood flow in the ascending aorta ($n = 5$). In two of these patients a moderate aortic valve insufficiency was present. The regurgitation fraction was 34.4 ± 2.6 as measured by 2D VEC MRI and 34 ± 0.5% as measured by nongated 4D VEC MRI.

There were no significant differences between 2D and nongated 4D VEC MRI for measuring antegrade and retrograde flow across the valves (Table 3). Bland–Altman tests and flux curves showed good agreement between 2D and nongated 4D VEC MRI derived stroke volumes and regurgitation fractions (Figs. 4, 5).

DISCUSSION

We demonstrated in a single-center study that 4D VEC MRI is suited to measure accurately quantitative arterial and venous blood flow within the same scan. In addition, we showed that this technique can also be applied for blood flow quantification in patients with congenital heart disease and pathological flow across the pulmonary or aortic valve. The nongated 4D VEC MRI method had short total scan time and showed good agreement with conventional 2D and gated 4D VEC MRI methods.

Quantitative flow measurements are an important element of cardiovascular MRI studies that are performed in patients with congenital heart disease (2–4,13,14). Therefore, the validation of novel 4D VEC MRI techniques is crucial for their successful introduction into clinical practice. So far, validation studies comparing the current gold standard 2D VEC MRI with 4D methods focused mainly on arterial flow (9–11). However, one major indication of using 4D flow application in congenital heart disease would be the

Table 2
Stroke Volumes Derived by Different Techniques for Arterial and Venous Blood Flow in Healthy Volunteers

Vessel	2D	4D gated	4D non-gated	*P*-value
Aorta	88.5 ± 10.3	88.0 ± 9.7	88.4 ± 9.9	1.00
Pulmonary trunk	88.3 ± 10.0	88.5 ± 11.8	88.2 ± 11.2	1.00
Right pulmonary artery	43.4 ± 6.7	44.1 ± 6.8	43.5 ± 6.2	0.98
Left pulmonary artery	38.5 ± 4.7	37.7 ± 5.2	38.6 ± 6.3	0.95
Superior vena cava	27.6 ± 3.2	28.5 ± 2.4	26.9 ± 3.6	0.63
Right lower pulmonary vein	21.4 ± 3.4	21.5 ± 3.1	20.8 ± 3.5	0.91

Values represent mean ± standard deviation (mL). There was no statistically significant difference between stroke volumes derived by the three methods according to one-way ANOVA testing. 2D = two-dimensional, 4D = four-dimensional.

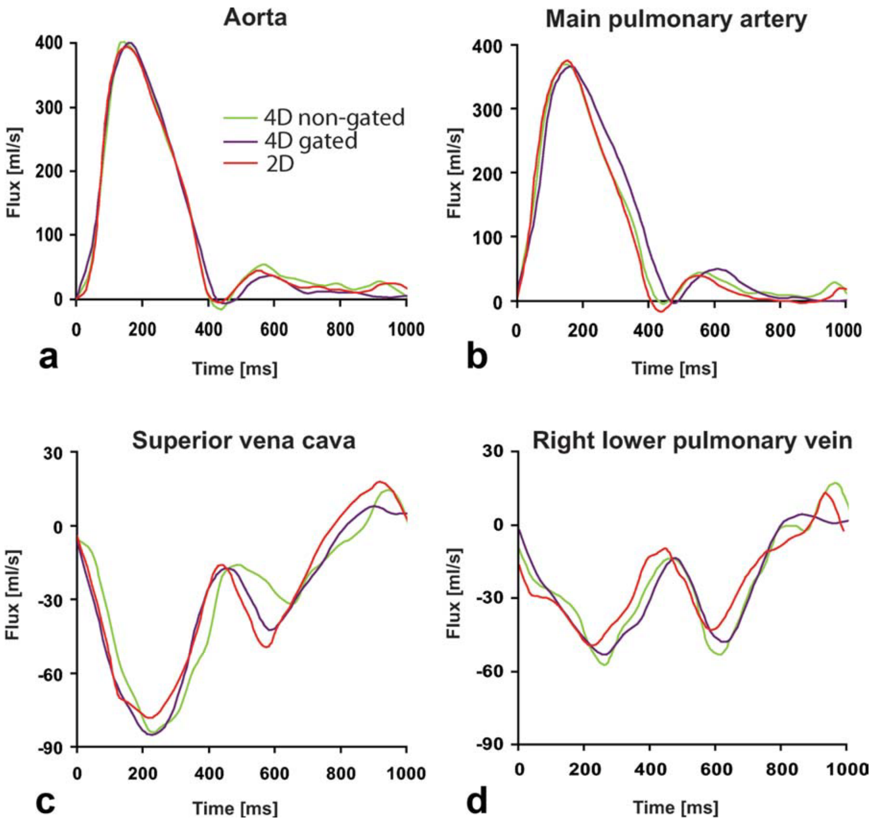

Figure 2. Representative flux curves derived by different techniques for arterial and venous blood flow in healthy volunteers. 2D, two-dimensional; 4D, four-dimensional.

diagnostic work-up of complex cases that require multiple quantitative flow acquisitions in arterial and venous vessels with normal and abnormal flow patterns. The strategy of using 4D VEC MRI would provide several advantages: this method could save scan time by avoiding repeat planning and acquisition of imaging planes that are perpendicular to the targeted vessels. Second, data analysis would not be limited to the acquired single predefined 2D imaging plane and, thus, would help avoid incomplete or falsely registered

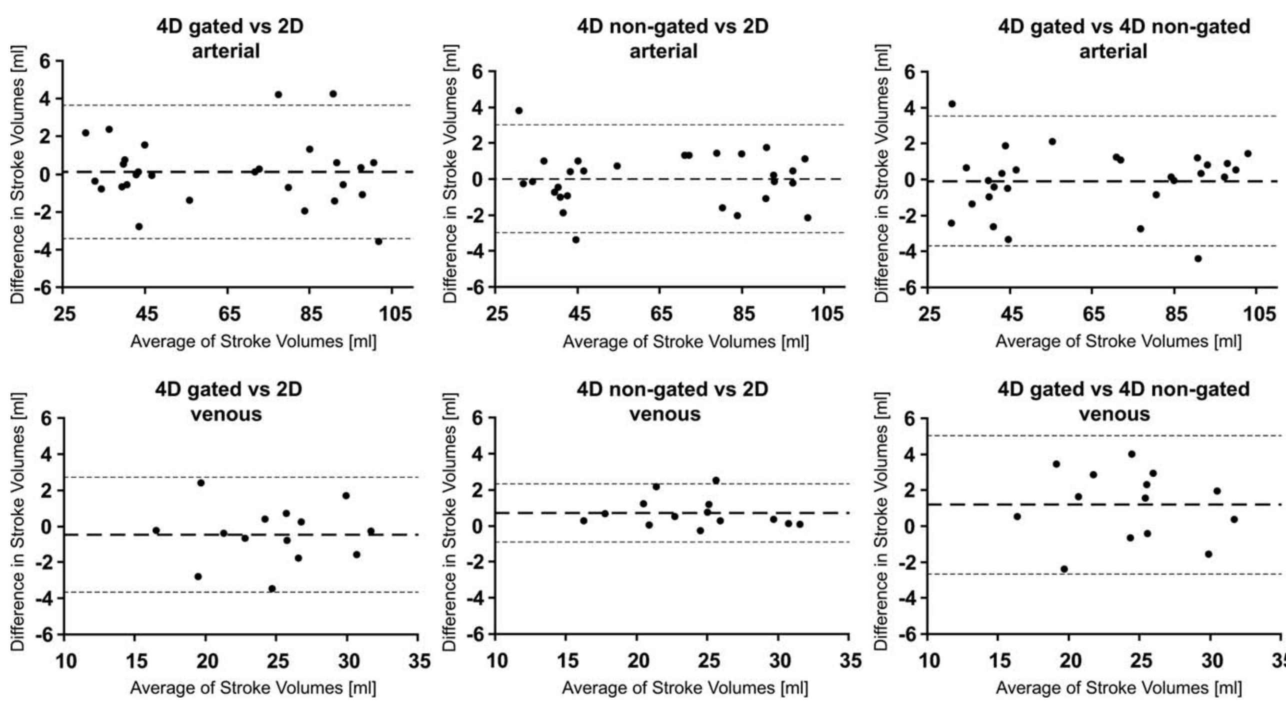

Figure 3. Bland–Altman plots showing agreement between 2D and 4D methods for the quantification of stroke volumes in healthy volunteers. Arterial, ascending aorta, pulmonary trunk, right and left pulmonary artery. Venous, superior vena cava and right lower pulmonary vein. 2D, two-dimensional; 4D, four-dimensional.

Table 3
Stroke Volumes and Regurgitation Fractions Derived by 2D and Nongated 4D VEC MRI in Patients With Congenital Heart Disease

	SV (mL)	SV (mL)	RF (%)	RF (%)
Patient	2D	4D nongated	2D	4D nongated
1	58.7	59.6	32.4	30.2
2	60.3	59.2	30.4	29.2
3	17.5	17.6	42.7	41.3
4	84.9	85.2	13.6	10.5
5	113.8	118.6	29.3	28.0
6	85.3	86.6	36.2	34.6
7	99.9	98.8	32.5	33.9
8	76.2	75.5	3.3	3.5
9	54.9	55.5	1.1	2.8
10	82.0	81.1	5.7	3.5

Stroke volumes and regurgitation fractions of patients with pulmonary valve insufficiency (patients 1-4), with aortic valve insufficiency (patient 5), with bicuspid aortic valve and valve insufficiency (patients 6-7) and with bicuspid aortic valve without valve insufficiency (patient 8-10). SV = stroke volume, RF = regurgitation fraction, 2D = two-dimensional, 4D = four-dimensional.

datasets. In addition to the quantitative flow data, 4D flow application has the further potential advantage of measuring novel hemodynamic parameters such as shear stress, vortex formation, or pressure fields; all of which are areas of current research (15–17).

Former studies report good agreement between 2D and 4D VEC MRI derived arterial blood flow quantification in healthy volunteers (9–11). The results of our study are in line with these findings. In the main pulmonary artery and ascending aorta of healthy volunteers, flow can be expected to have a relatively laminar or parabolic profile (6). However, nonlaminar flow is frequently present in patients with valvar abnormalities (8,18) and is known to represent a potential source of error due to a loss of phase signal (19). To reduce the susceptibility to spin dephasing short echo-times can be applied in phase contrast MRI techniques (20); in our study, the echo-times of the 2D and 4D VEC MRI were comparable. In our study with healthy volunteers we found good agreement between 2D, gated, and nongated 4D VEC MRI obtained quantitative blood flow measurements. Based on these results, the study protocol for the patients only included 2D and nongated 4D VEC MRI methods in order to make the protocol less time extensive and demanding for the patients. Since we found comparable flow measurements between conventional 2D and nongated 4D VEC MRI in patients with malformed semilunar valves, we speculate that even in pathological flow conditions the diagnostic performance of 4D VEC MRI is not inferior to that of the conventional 2D method.

For the simultaneous acquisition of flow data in multiple vessels with different velocities (arterial vs. venous) using 4D VEC MRI, the velocity encoding must be adjusted to the highest expected velocity within the chosen 4D volume to prevent aliasing; this presents a potential level of inaccuracy for blood flow quantification in vessels with low velocities within the acquired volume (21). The conventional 2D method offers the advantage of a sequential acquisition of flow data in different vessels with individually adjusted velocity encodings. However, inaccuracies also exist for 2D acquisitions because flow velocities within a single vessel vary substantially over the cardiac cycle. In addition, the results of our 4D VEC MRI data show that the degree of underestimation of slow flow with high encoded velocities represents less than 3% of the overall mean of measured flow volumes, which might be acceptable from a clinical perspective. Apart from aliasing and the selection of velocity encodings, there are several other operational or technical sources of errors that could affect the measurement accuracy of VEC MRI. Gatehouse et al (22) demonstrated that velocity offset errors can vary largely between different institutions and scanners of different vendors. Such errors depend, among others, on the software used to correct for phase offsets or the distance of the region of interest from the magnetic isocenter.

Uribe et al (10) compared arterial flow volumes derived by standard 2D, nongated 4D, and self-gating 4D and found no significant differences between the measurements. However, the bias and scatter of measured stroke volumes were larger for nongated 4D compared to 2D or self-gating 4D methods. In our study, the bias and range of scatter were at nearly identical levels when comparing nongated 4D VEC MRI with gated 4D or 2D techniques. In quantitative flow acquisition, respiratory gating is usually applied for reducing bias that is introduced by respiratory motion (5,23). Alternatively, two or more signal averages can be obtained during free-breathing 2D flow acquisitions. Both methods require prolonged scan times; in our study, the approximate scan time was 14 minutes for the gated 4D acquisition, which seems borderline from a clinical perspective. Respiratory

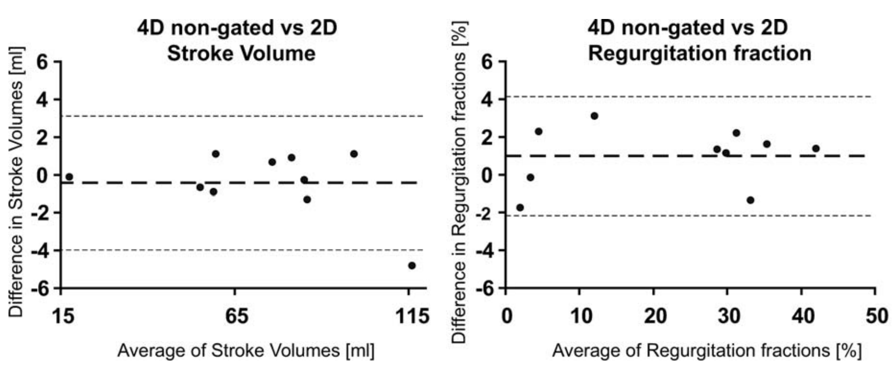

Figure 4. Bland–Altman plots showing agreement between 2D and 4D nongated method for the quantification of stroke volumes and regurgitation fractions in patients with congenital heart disease. 2D, two-dimensional; 4D, four-dimensional.

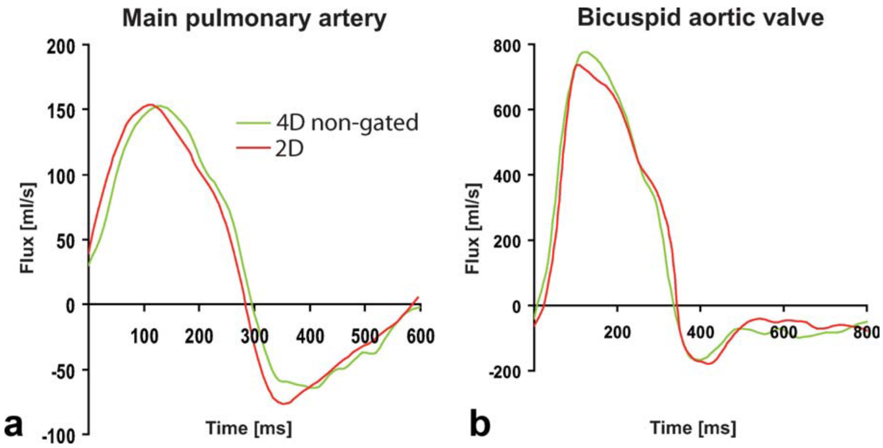

Figure 5. Flux curves derived by 2D and 4D nongated methods in patients with congenital heart disease. Flux curve obtained in the pulmonary trunk of a patient with an insufficient pulmonary valve **(a)**. Flux curve obtained in the ascending aorta of a patient with bicuspid aortic valve and insufficiency **(b)**. 2D, two-dimensional; 4D, four-dimensional. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

motion can also be avoided by breath-hold 2D flow techniques. However, flow patterns, particularly in the venous system, are coupled to respiration and were shown to vary largely between in- and expiration (24). Interestingly, the nongated, single-average 4D acquisition used in our study obtained nearly identical measurements compared to conventional 2D or gated 4D acquisition. However, future research in a larger group of patients is required to identify how susceptible nongated 4D flow techniques are to individual differences in breathing patterns or other artifacts that are induced by motion. In addition, future research is warranted to explore methods that will further accelerate the acquisition speed of 4D VEC MRI.

In conclusion, blood flow can be quantified accurately in arterial, venous, and pathological flow conditions using 4D VEC MRI. With an approximate acquisition time of 9 minutes, the nongated 4D VEC MRI method appears to be suited for clinical use in patients who require flow acquisitions in multiple vessels.

Limitations

This is a single-center study in healthy volunteers and in a preselected group of patients with congenital heart disease. Additional research is needed to further validate technical and operator dependent sources of error for the quantitative assessment of blood flow using 4D flow techniques including measurements in vessels of different sizes and in a larger group of patients. Ideally, this should be performed in a larger group of patients and in a multicenter approach as performed by Gatehouse et al (22). Furthermore, similar to real-time flow measurements with echo-planar imaging, anatomical images derived by 4D VEC MRI are less defined than anatomical images derived by conventional 2D VEC MRI and must be improved (25). A recent study by Beerbaum et al (12) reported that there is only small interinstitutional variance for the postprocessing (analysis) of VEC MRI flow parameters in patients with congenital heart disease and healthy controls. Therefore, we did not repeat the assessment of interobserver variability in this study.

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