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Original contribution

Validation of non-contrast multiple overlapping thin-slab 4D-flow cardiac magnetic resonance imaging

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ABSTRACT

Background: Cardiac magnetic resonance (CMR) flow quantification is typically performed using 2D phase-contrast (PC) imaging of a plane perpendicular to flow. 3D-PC imaging (4D-flow) allows offline quantification anywhere in a thick slab, but is often limited by suboptimal signal, potentially alleviated by contrast enhancement. We developed a non-contrast 4D-flow sequence, which acquires multiple overlapping thin slabs (MOTS) to minimize signal loss, and hypothesized that it could improve image quality, diagnostic accuracy, and aortic flow measurements compared to non-contrast single-slab approach.
Methods: We prospectively studied 20 patients referred for transesophageal echocardiography (TEE), who underwent CMR (GE, 3 T). 2D-PC images of the aortic valve and three 4D-flow datasets covering the heart were acquired, including single-slab, pre- and post-contrast, and non-contrast MOTS. Each 4D-flow dataset was interpreted blindly for ≥moderate valve disease and compared to TEE. Flow visualization through each valve was scored (0 to 4), and aortic-valve flow measured on each 4D-flow dataset and compared to 2D-PC reference.
Results: Diagnostic quality visualization was achieved with the pre- and post-contrast 4D-flow acquisitions in 25% and 100% valves, respectively (scores 0.9 ± 1.1 and 3.8 ± 0.5), and in 58% with the non-contrast MOTS (1.6 ± 1.1). Accuracy of detection of valve disease was 75%, 92% and 82%, respectively. Aortic flow measurements were possible in 53%, 95% and in 89% patients, respectively. The correlation between pre-contrast single-slab measurements and 2D-PC reference was weak (r = 0.21), but improved with both contrast enhancement (r = 0.71) and with MOTS (r = 0.67).
Conclusions: Although non-contrast MOTS 4D-flow improves valve function visualization and diagnostic accuracy, a significant proportion of valves cannot be accurately assessed. However, aortic flow measurements using non-contrast MOTS is feasible and reaches similar accuracy to that of contrast-enhanced 4D-flow.

1. Introduction

Cardiac magnetic resonance (CMR) is the non-invasive reference standard for the quantification of blood flow, which is typically performed using two-dimensional phase contrast (2D-PC) imaging [1–3]. However, for this technique to be accurate, it requires acquisition of a carefully selected imaging plane perpendicular to the flow direction, as well as a breath-hold to avoid respiratory motion. Recently, it has become possible to acquire a three-dimensional (3D) volume of phase contrast images resolved over time, commonly referred to as the "4D-flow" technique [4,5]. Because all of the anatomy within the acquired dataset is 3D velocity-encoded, it is possible to quantify blood flow in any structure as a post-processing task, without having to specifically acquire pre-planned imaging planes. This free-breathing volumetric imaging technique of flow velocity data is increasingly used to simplify CMR image acquisition and has been of particular clinical value in

Abbreviations: (CMR), cardiovascular magnetic resonance; (CoV), coefficient of variation; (CNR), contrast-to-noise ratio; (ICC), intraclass correlation; (LOA), limits of agreement; (MOTS), multiple overlapping thin slabs; (PC), phase contrast; (SSFP), steady-state free-precession; (SV), stroke volume; (TEE), transesophageal echocardiography

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patients with congenital and valvular heart diseases [6–10].

The most common implementation of 4D-flow is acquisition of a single large slab of data that fully covers the anatomical structures of interest. While this approach has been used successfully in several recent studies [11–17], it can be associated with poor image quality in some patients, because blood spins remain in the scan volume for much longer period of time compared to 2D-PC, generating saturated low blood signal. This issue is currently resolved in such cases with the use of either gadolinium- or iron-based contrast agents. Unfortunately, gadolinium-based contrast agents are problematic in patients with advanced renal disease, and the Food and Drug Administration has issued a black-box warning regarding iron-based contrast agents.

Multiple thin-slab acquisition has been successfully applied to improve MR angiography images [18]. Similar to this previous work, we developed a novel non-contrast 4D-flow imaging approach designed to circumvent the low blood signal problem, in which multiple overlapping thin slabs (MOTS) of data covering the desired anatomy are acquired instead of the conventional single thick slab. Because the slabs are thin, the signal generated by the blood entering the scan volume is refreshed as it crosses into each thin slab, thereby minimizing the above problem of signal saturation. We hypothesized that this non-contrast MOTS 4D-flow approach would result in: (i) improved image quality and diagnostic accuracy compared to non-contrast single-slab 4D-flow imaging, and (ii) aortic flow measurements superior to the non-contrast approach.

2. Methods

2.1. Study design

The pilot study included two separate protocols, designed to test the above hypothesis in two phases. Protocol 1 was designed to compare the image quality of valve function visualization using the new non-contrast MOTS acquisition to those of the pre- and post-contrast single-slab acquisitions, as well as their accuracy for the diagnosis of significant valve pathology using transesophageal echocardiography (TEE) as a reference standard. Protocol 2 was designed to compare the ability of these three 4D-flow approaches to accurately measure aortic flow using 2D-PC measurements as a reference.

2.2. Patients

We prospectively recruited 20 patients referred for TEE for the evaluation of suspected valvular heart disease (Table 1), who agreed to undergo additional CMR imaging for the purpose of this study.

Table 1
Baseline characteristics of the study patients ($N = 20$).

Age (years)	53 ± 21
Gender	8 M, 12F
Height (cm)	168 ± 10
Weight (kg)	75 ± 19
BSA (m^2)	1.83 ± 0.20
Heart rate (bpm)	75 ± 14
Systolic blood pressure (mmHg)	125 ± 20
Diastolic blood pressure (mmHg)	72 ± 13
Cardiac history	
Valvular heart disease	15
Coronary artery disease	4
Heart failure	3
Atrial fibrillation	1
Endocarditis	1
Congenital heart disease	2
Left ventricular size and function	
End-systolic volume (ml)	173 ± 70
End-diastolic volume (ml)	85 ± 52
Ejection fraction (%)	52 ± 11

Exclusion criteria included: age < 18 years, severe claustrophobia, inability to fit into CMR scanner, presence of pacemaker or ICD, glomerular filtration rate < 30 mL/min, as well as contra-indications to CMR such as allergy to gadolinium-based contrast agents, significant arrhythmias and pregnancy. The Institutional Review Board approved this study and each patient provided written informed consent.

2.3. CMR imaging

CMR image acquisition was performed on a 3 T scanner (MR750W, software version DV26, GE Healthcare, Waukesha, Wisconsin) using the 32-channel GEM body coil. The basic CMR protocol included scout images, steady-state free-precession (SSFP) cine images acquired in the 2-, 3-, 4-chamber, left ventricular short-axis, left ventricular outflow tract, and aortic valve planes. The cine-images were used to plan a 2D-PC imaging plane through the aortic valve. Subsequently, prior to the administration of any contrast, a single thick slab 4D-flow acquisition in the axial plane covering the entire heart and a MOTS 4D-flow acquisition in the short-axis plane were performed during free breathing. An additional single thick-slab 4D-flow scan was acquired during the slow infusion of gadolinium-based contrast agent (Dotarem or Multihance). A total of 0.2 mmol/kg of the contrast agent was infused. The first 10 ml were injected at a rate of 2 ml/ s, followed by the remainder of the contrast dose slowly infused at a rate of 0.1 ml/s.

Typical scan parameters were as follows: (1) For 2D-PC: reconstructed resolution 1.41 × 1.41 mm, flip angle 25°, TR 5.9 ms, TE 3.6 ms, views/segment 6, VENC 200 cm/s; (2) for non-contrast single thick slab 4D-flow: acquisition time ~ 5 min, reconstructed matrix 1.48 × 1.48 × 1.2 mm, flip angle 6°, TR 4.2 ms, TE 2.3 ms, views/segment 3, VENC 200 cm/s; (3) for the contrast-enhanced single thick slab 4D-flow: same parameters as 2), except higher flip angle of 15–25° due to shortened blood T1; (4) for the non-contrast MOTS 4D-flow: acquisition time ~ 8 min, 5 slabs, 24 slices/slab with overlaps of 9 slices, flip angle 6°, TR 4.7 ms, TE 2.5 ms, VENC 200 cm/s. Arrhythmia rejection technique was employed during all 2D-PC and 4D-flow acquisitions to discard irregular beats. The k-t based acceleration scheme (~8×) was applied to all 4D-flow acquisitions [19–22].

2.4. CMR image analysis

2D-PC and the above 3 types of 4D-flow images were analyzed to measure forward aortic valve flow, which was quantified as flow per beat, i.e. stroke volume (SV) in units of mL. All images were analyzed using cloud-based processing software (Arterys Inc., San Francisco, CA). All analyses were performed by an independent observer blinded to all prior measurements.

In protocol 1, each 4D-flow dataset was interpreted by an expert blinded to the results of all prior evaluations. For each 4D-flow sequence, the quality of flow visualization through each valve was scored on a 0 to 4 scale, wherein 0 = non-diagnostic (not possible to visualize valve structure), 1 = poor (limited possibility to visualize valve structures with minimal confidence), 2 = fair (possibility to visualize valve structures with reasonable confidence, but with limited detail), 3 = adequate (possibility to visualize valve structures with confidence, including most detail), and 4 = excellent (as in 3 but including complete detail) (Fig. 1).

These grades were then averaged for all patients, separately for each of the three 4D-flow acquisitions. The expert evaluation of the images included detection of at least moderate disease for each valve, which was compared to the TEE reference diagnosis. To achieve this goal, images were viewed as follows. For the single thick slab 4D-flow pre- and post-contrast acquisitions, datasets were initially presented in 4 different planes: thin axial, sagittal and coronal reformats as well as thicker axial slices. For the MOTS 4D-flow acquisition, the dataset was also presented in 4 different planes: short-axis, vertical long axis and horizontal long axis as well as thicker short axis slice. The different

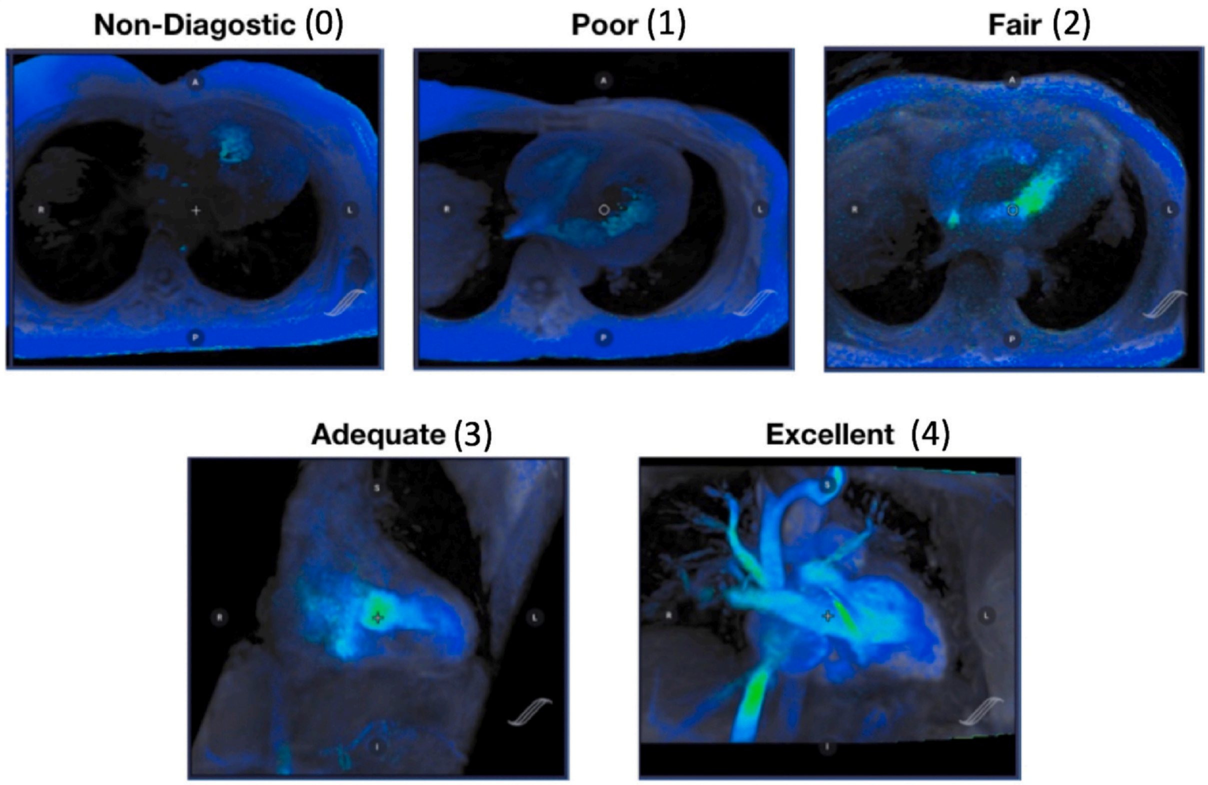

Fig. 1. Examples of multiple thin-slab 4D-flow images of varying quality of valve visualization, graded as shown in parentheses.

images were then rotated until standard cardiac imaging views were displayed, while cine images were used to better identify dephasing acceleration flow jets. Each valve was then interrogated in two orthogonal planes for the presence of at least moderate regurgitation or stenosis.

In protocol 2, the blood flow through the aortic valve was determined for each of the datasets after applying a semi-automatic eddy-current correction algorithm to remove background phase off-set errors prior to image analysis. To analyze the 2D-PC images, a region of interest was manually traced around the aortic valve (Fig. 2**, A**). For each of the 4D-flow datasets, multiplanar reconstructions were used to create an imaging plane representing the cross section of the aortic valve. A region of interest was then manually traced around the aortic valve (Fig. 2**, B–D**). The corrected flow through the aortic valve was then measured.

Additionally, the signal-to-noise ratio (SNR) and contrast-to-noise ratio (CNR) were measured for all three 4D-flow imaging techniques to assess the effects of the different acquisition approaches on the quality of the resultant images. For each approach, SNR was calculated as a ratio between the mean tissue pixel value (representing the signal intensity) and its standard deviation (reflecting the noise level), and CNR was measured as the difference in the mean signal of the aorta and neighboring myocardium divided by the standard deviation.

2.5. Transesophageal echocardiography

The clinically indicated TEE studies were performed as a standard of care using the Philips iE33 imaging system with an X7-2t transducer. TEE images were reviewed by an expert echocardiographer who assessed all cardiac valves and provided reference for presence and nature of at least moderate disease in each valve, according to the published guidelines of the American Society of Echocardiography [23]. These determinations were used as the reference standard in Protocol 1.

2.6. Reproducibility analysis

To test the reproducibility of the 4D-flow analysis, we used all patients in whom aortic flow measurements were possible using all three 4D-flow approaches. In these patients, all measurements were repeated by a second observer, as well as by the first reader at least one week later, both blinded to the results of all prior measurements. Inter- and intra-observer variability was quantified by calculating intraclass correlation (ICC) and coefficients of variation (CoV), calculated as the absolute difference between pairs of repeated measurements in percent of their mean value.

2.7. Statistical analysis

Data were expressed as mean ± SD and p-values ≤ 0.05 were considered significant in two-tailed student's t-tests. Linear regression and Bland-Altman analyses were used to compare 4D-flow measurements to each other and to those made with the reference standard 2D-PC technique. All statistical analyses were performed using Microsoft Excel.

3. Results

Of the 20 patients, one patient was unable to complete the study prior to receiving gadolinium contrast agent due to symptoms of shortness of breath and nausea. The remaining 19 patients had undergone imaging using 2D-PC and all 4D-flow sequences, including the pre- and post-contrast thick single-slab, as well as non-contrast MOTS.

In protocol 1, one additional patient was excluded due to refusal to complete the clinically indicated TEE study. In the remaining 18 patients, diagnostic quality visualization was achieved with the pre- and post-contrast 4D-flow acquisitions in 18/72 (25%) and 72/72 (100%) valves, respectively (scores 0.9 ± 1.1 and 3.8 ± 0.5; $p < 0.001$), and in a higher number of valves with the non-contrast MOTS acquisition,

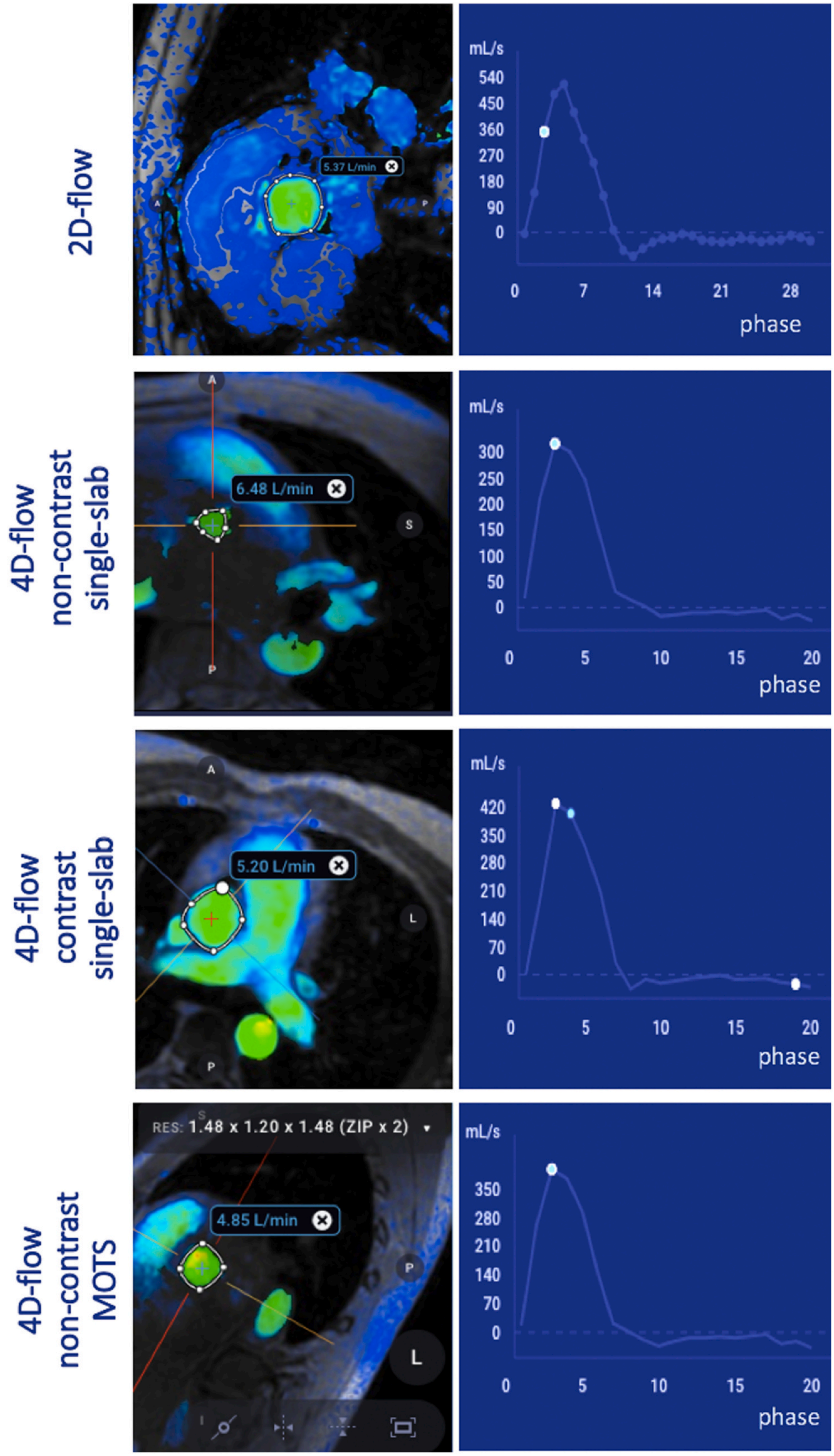

Fig. 2. Example of aortic flow measurements made in one patient using the 2D-PC imaging (top) and the three different 4D-flow techniques (below). See text for details.

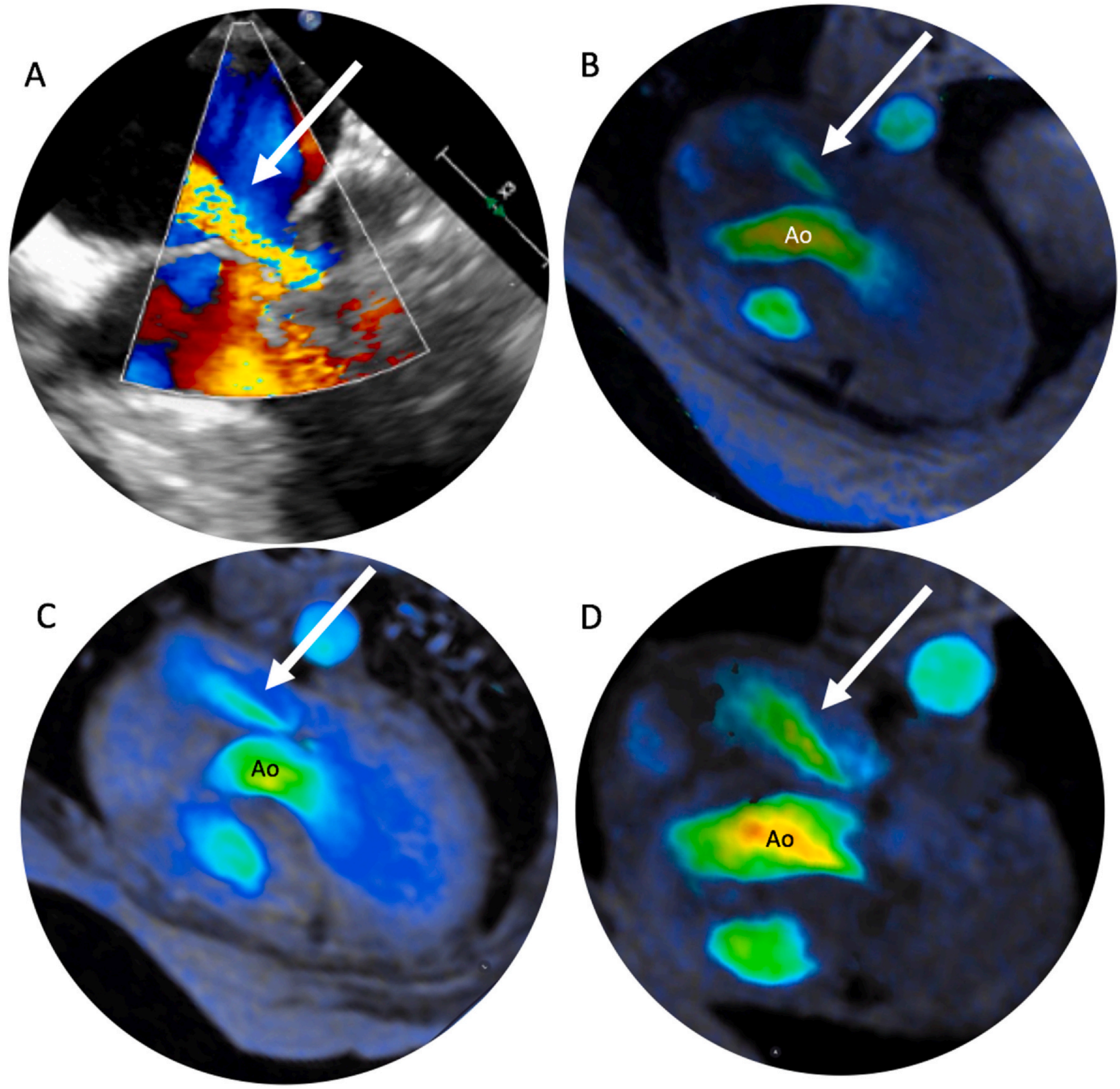

Fig. 3. Example of visualization of mitral regurgitation (MR, white arrow) as shown in TEE (A), single slab non-contrast 4D-flow (B), single slab post-contrast 4D-flow (C), and non-contrast MOTS 4D-flow (D). The signal intensity of the MR jet and aortic flow is worst in the single slab non-contrast, best in the single slab post-contrast, and intermediate in the non-contrast MOTS.

compared to the pre-contrast 4D-flow: 42/72 (58%) (score 1.6 ± 1.1; $p = 0.027$ and $p < 0.001$, respectively), confirming our hypothesis. The accuracy of the detection of valve disease in images of diagnostic quality was 75% and 92% with the pre- and post-contrast techniques respectively, and 82% (both NS) for the non-contrast MOTS, which again was higher than the pre-contrast 4D-flow. Figs. 3 and 4 show examples of two patients with mitral and tricuspid regurgitation as visualized on TEE and the three different 4D-flow acquisitions.

In protocol 2, aortic valve flow measurements were possible in all 19 patients using the 2D-PC technique, in 18/19 patients using the post-contrast single-slab datasets, in 17/19 patients using the non-contrast MOTS datasets, and only 10/19 patients using the pre-contrast single-slab datasets, because of a poor signal intensity over the aortic root in the remaining 9 patients.

Fig. 2 shows an example of aortic flow measurements made in one patient using the 2D-PC image and the three different 4D-flow techniques. Compared to the 2D-PC reference values of the aortic valve flow, the 4D-flow measurements showed: (1) moderate correlation for the post-contrast single-slab acquisition ($r = 0.71$; $p < 0.002$); (2) slightly lower correlation for the non-contrast MOTS acquisition ($r = 0.67$; $p < 0.01$); (3) poor correlation for the pre-contrast single-slab images even though they involved only a subset of patients with sufficient image quality to allow measurements ($r = 0.21$; p = NS), while the remaining patients' datasets could not even be reliably analyzed (Fig. 5). Bland-Altman analysis for the three techniques compared to the 2D-PC reference showed negative biases across the board (Fig. 5 and Table 2), with the smallest bias and narrowest limits of agreement (LOA) for the post-contrast single-slab technique. While the bias with the non-contrast MOTS approach was larger, the LOA were comparable.

There was a significant improvement in the CNR with the use of the post-contrast single-slab and non-contrast MOTS acquisitions, compared to pre-contrast single-slab images, while no significant differences were noted for SNR ($p < 0.005$, Table 3).

Table 4 summarizes the results of the reproducibility analysis of the three 4D-flow approaches in the subgroup of 9 patients in whom aortic flow measurements were possible using all three approaches. Both ICC and CoV values for both intra- and inter-observer variability indicated that the post-contrast single-slab approach was the most reproducible. While ICC values of the MOTS approach were as high, those of the pre-contrast single-slab were lower, indicating wider variability of the latter. On the other hand, the CoV values of these two techniques were similar.

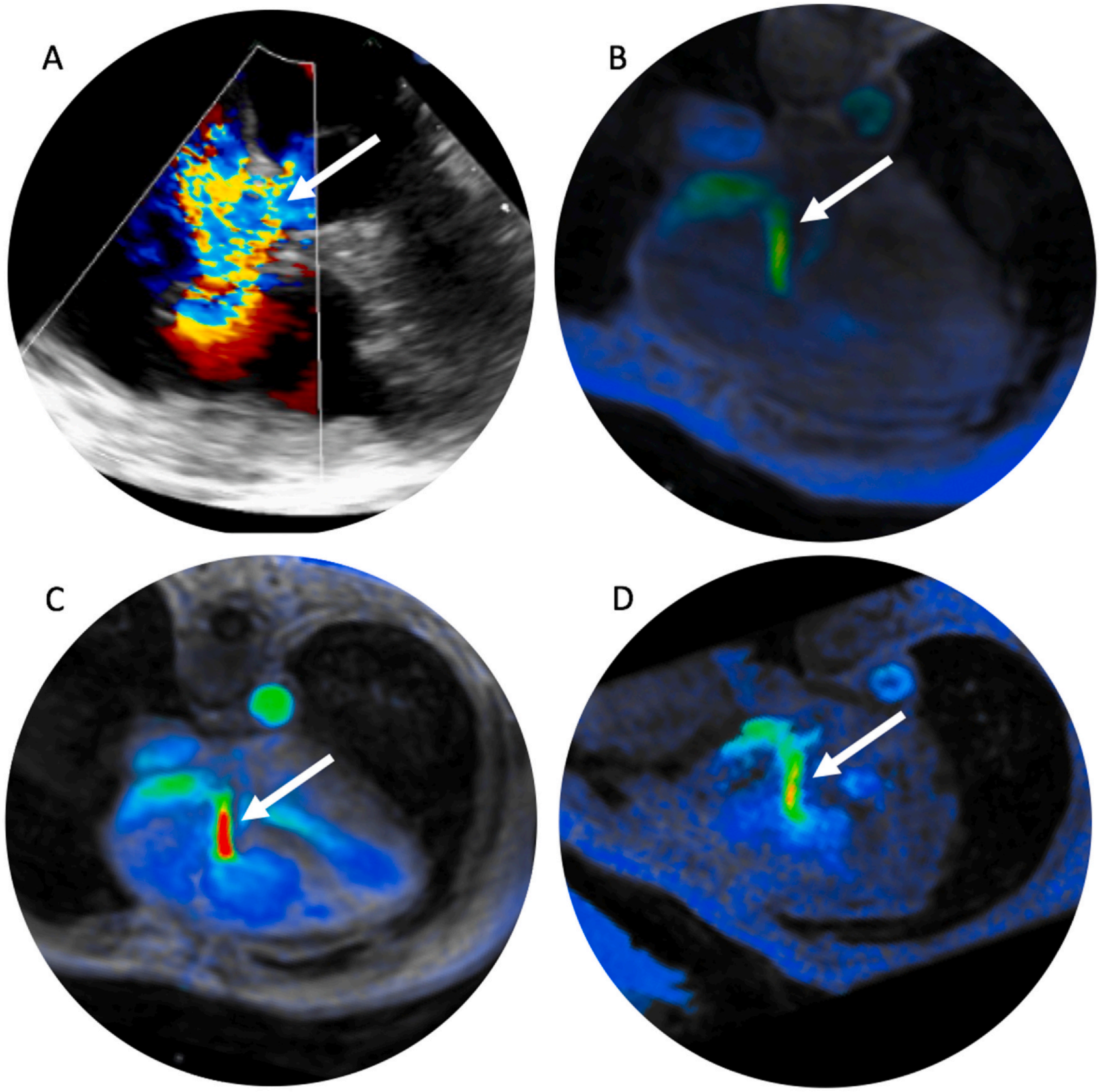

Fig. 4. Example of visualization of tricuspid regurgitation (TR, white arrow) as shown in TEE (A), single slab non-contrast 4D-flow (B), single slab post-contrast 4D-flow (C), and non-contrast MOTS 4D-flow (D). The signal intensity of the TR jet is worst in the single slab non-contrast, best in the single slab post-contrast, and intermediate in the non-contrast MOTS.

4. Discussion

In this prospective study, we sought to determine whether a novel MOTS 4D-flow acquisition technique could improve the image quality of the non-contrast 4D-flow. The main findings of this prospective study were: (i) the use of a non-contrast MOTS 4D-flow acquisition resulted in superior image quality and diagnostic accuracy for qualitatively identifying significant valvular heart disease, when compared to the contemporary non-contrast single-slab acquisition, but not when compared to the contrast-enhanced approach; (ii) the non-contrast MOTS approach was superior to the non-contrast single-slab approach and similar to the contrast-enhanced single-slab approach for quantifying the flow through the aortic valve; and (iii) all three 4D-flow approaches had excellent inter- and intra-observer reproducibility.

2D-PC imaging is an essential CMR tool for the assessment of blood flow. It is commonly used to measure stroke volume, quantify stenotic and regurgitant valvular lesions, and to determine the extent of cardiac shunting [24–28]. However, the technique requires for each desired measurement a separate image to be acquired in a plane perpendicular to the direction of blood flow. Using 2D-PC, it is not possible to perform any quantitative measurement that was not planned for at the time of imaging. Recently, with the development the 4D-flow technique, it has become possible to acquire a single large volume of 3D-PC information resolved over time. The advantage of such an acquisition is that it enables the visualization of blood flow patterns throughout a large volume of interest and allows blood flow quantification through any structure retrospectively, as a post-processing task without the need for separate dedicated images to be acquired while the patient is being scanned [4,5,7,29–36]. In additional, recent pulsatile phantom results demonstrated that the 4D-flow could provide high accuracy and reproducibility with respect to a ground-truth mass flow measurements [37]. Because a volume of 4D-flow data covering much of the chest can be acquired in just 5 min, one can envision image interpretation where the 4D-flow dataset is qualitatively interrogated for potentially significant clinical findings that are then quantified for severity as a post processing task.

An important limitation of 4D-flow is that the current approach requires contrast enhancement to overcome poor image quality created by a loss of signal of the blood flowing into the volume as it reaches the inner volume. In this study, we proposed a novel MOTS 4D-flow acquisition approach to potentially overcome this limitation. The acquisition is free-breathing with an approximate acquisition time of 8 min.

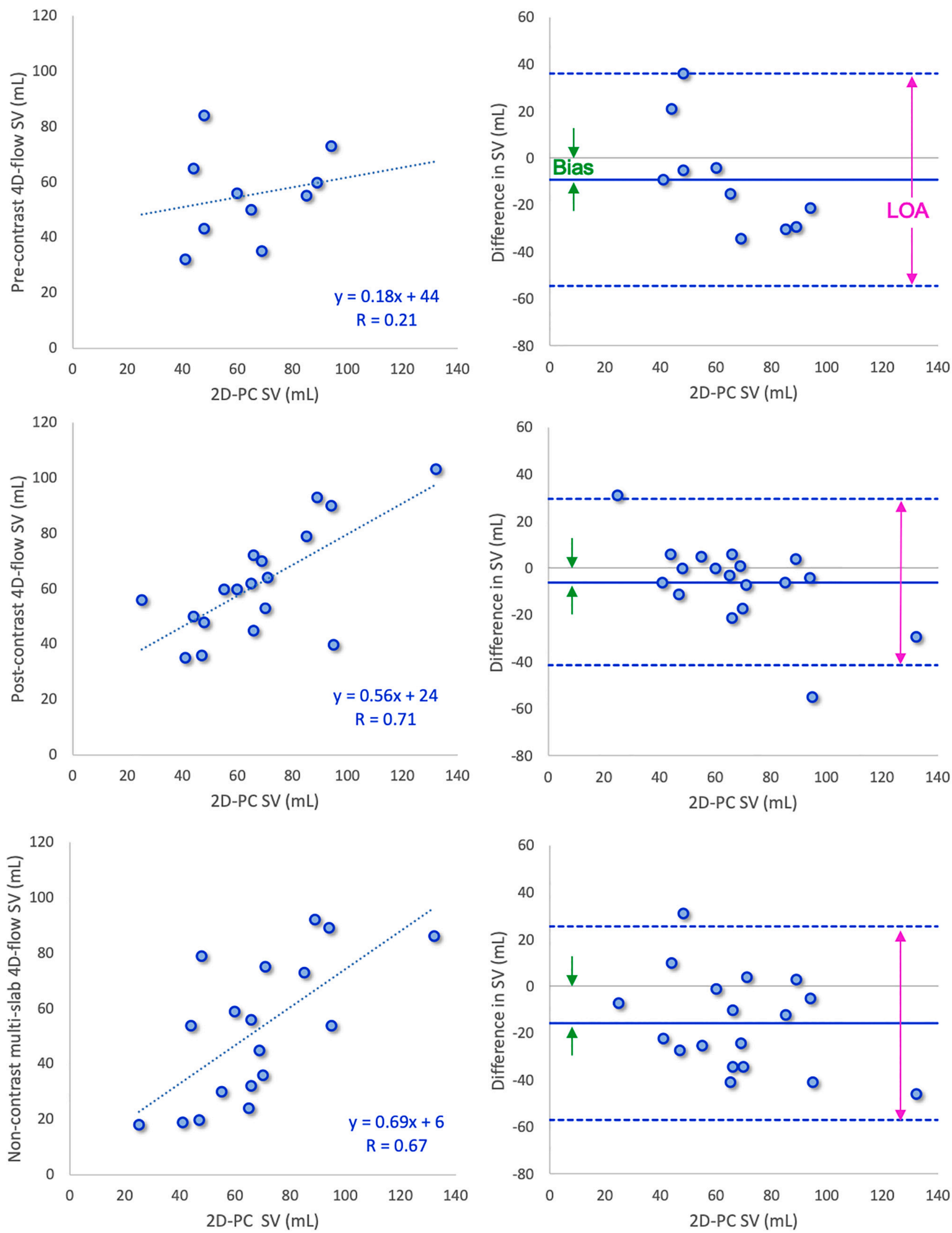

Fig. 5. Comparison between the 4D-flow measurements of the aortic valve flow and the 2D phase-contrast reference values: linear regression (left) and Bland-Altman analyses for pre-contrast single-slab (top), post-contrast single-slab (middle) and non-contrast multi-slice (bottom) techniques. LOA – limits of agreement.

Table 2
Agreement between aortic flow measurements obtained using three different 4D-flow sequences vs. 2D phase-contrast reference values in all patients in whom measurements were possible by each technique.

	N	R-value	Bias	Mean-2SD	Mean + 2SD
Single-slice pre-contrast	10	0.21	-9	−54	36
Single-slice post-contrast	19	0.71	−6	−41	30
Non-contrast MOTS	18	0.67	−16	−57	26

Table 3
Signal-to-noise ratio (SNR) and contrast-to-noise ratio (CNR), measured on images obtained using the three different 4D-flow sequences.

	SNR	CNR
Single-slice pre-contrast	0.16 ± 0.06	0.16 ± 0.07
Single-slice post-contrast	0.17 ± 0.47	0.47 ± 0.28*
Non-contrast MOTS	0.17 ± 0.06	0.27 ± 0.13*^

* $p < 0.05$ compared to pre-contrast single-slice.
^ $p < 0.05$ compared to post-contrast single-slice.

Table 4
Results of the reproducibility analysis of the three 4D-flow approaches.

	Intra-observer		Inter-observer	
	ICC	CoV	ICC	CoV
Single-slice pre-contrast	0.98	5.2 ± 1.7	0.94	7.0 ± 4.4
Single-slice post-contrast	0.99	4.5 ± 1.9	0.99	4.3 ± 1.5
Non-contrast MOTS	0.99	6.5 ± 2.4	0.99	6.1 ± 2.2

Abbreviations: ICC – intraclass correlation; CoV - coefficient of variation (see text for details).

Because multiple thin slabs are acquired, the signal loss from the blood is considerably reduced as it transitions through the respective thin slab. Indeed, we found that the MOTS approach significantly improved both image quality and the diagnostic ability to detect significant valvular heart disease, when compared to the non-contrast single-slab acquisition approach. In fact, all but two patients had interpretable MOTS 4D-flow images, whereas over half of the patients had insufficient image quality for reliable analysis using the contemporary single-slab 4D-flow technique without contrast. Of note however, our implementation of the MOTS approach remained inferior to the standard of care contrast-enhanced approach for the visual assessment of 4D-flow images to detect valvular heart disease. On the other hand, it was equivalent to the contrast-enhanced 4D-flow approach for quantifying the flow through the aortic valve. A limitation of both of the 4D-flow techniques is that they require adequate ECG gating, without which image quality would be substantially impacted.

Our study shows that the sub-optimal image quality of the MOTS approach is related to a relatively poor contrast-to-noise ratio, compared to the contrast-enhanced single-slice approach. In order to optimize image contrast, we had placed the MOTS acquisition in the cardiac short-axis plane to maximize the inflow signal through the mitral valve and designed the pulse sequence with what we believed to be the optimal flip angle. Although it is possible that the use of thinner slabs would improve image contrast, this maneuver would likely result in considerably longer acquisition times that would be impractical for clinical use. It remains to be seen if the application of deep learning could potentially make non-contrast 4D-flow robust enough to use in routine clinical practice. For now, the MOTS approach is a reasonable alternative to be used when there is a contra-indication to contrast agents. However, in the foreseeable future, it is likely that the use of deep learning algorithms to reduce noise in both k-space and in image space will not only improve the image quality of non-contrast 4D-flow acquisitions but also reduce acquisition times.

Another interesting observation from our study was that the quantification of aortic flow using the standard of care contrast-enhanced 4D-flow approach resulted in only a modest correlation with and underestimation compared to 2D-PC measurements. The non-contrast MOTS technique demonstrated the same pattern. Although some previous publications [38] have reported an outstanding correlation between the two approaches, others have shown some degree of discordance between 2D-PC and 4D-flow measurements [39]. Some potential factors that may have contributed to the inter-technique discordance in our study likely include the following: (1) use of a lower relaxivity gadolinium-based contrast agent; (2) difference in temporal and/or spatial resolution, (3) flow difference between 2D-PC imaging during breath-hold and free-breathing 4D-flow scans, and (4) change in heart rate and the occurrence of arrhythmia. Although we used a commercially available and robust eddy-current correction algorithm for our analysis, the impact of residual eddy current on our flow measurements is difficult to assess. The underestimation of the 4D-flow measurements compared to 2D-PC may be due to inability to define regions of interest that encompass the entire cross-section of the aorta because of the differences in image quality.

4.1. Limitations

There are several limitations to our study. First, this is a single-center study with a small sample size. However, including more patients is unlikely to change the overall findings of the study demonstrating that the MOTS acquisition significantly improves image quality and diagnostic performance of 4D-flow imaging compared to a non-contrast approach, but should not be routinely be used in lieu of contrast-enhancement. Secondly, we excluded patients with severe arrhythmias, since the 4D-flow acquisition depends on periodic heartbeats and arrhythmia rejection scheme was employed for the acquisition. The acquisition time for patients with severe arrhythmias could result in prolonged scan times, which are not clinically feasible. Recent research work of 2D real-time PC may provide a potential solution for blood flow visualization and quantification in patients with severe arrhythmias [40,41]. Additionally, we did not acquire any images enhanced with an iron-based contrast agent, which may have yielded a better correlation with 2D-PC imaging. This was not part of our study because these agents currently have an FDA black box label due to safety concerns. Another limitation of the study is that there is no ground truth available to know with certainty which technique might be most correctly measuring the flow. Finally, we only compared quantification of flow through the aortic valve and did not directly quantify flow through the other valves because it would have required additional three 4D-flow acquisitions using a lower aliasing velocity and additional 2D-PC images making the overall imaging protocol unreasonably long. Future studies are needed to determine its ability to quantify flow in other structures.

4.2. Conclusion

Our study shows that the use of non-contrast MOTS 4D-flow significantly improves the diagnostic accuracy of detecting significant valvular disease when compared to the contemporary non-contrast single slab technique, but the technique remains inferior to the contrast-enhanced 4D-flow approach. Importantly, non-contrast MOTS can accurately measure aortic flow. In situations when there is a contra-indication or preference against the use of a contrast agent, non-contrast MOTS 4D-flow may be a reasonable alternative for quantifying aortic flow.

Authors' contributions

Nina Rashedi: acquired data, analyzed images, drafted the manuscript.

Luis Landeras: acquired data, critically reviewed the manuscript.

Victor Mor-Avi: concept development, statistical analysis and drafting the manuscript.

Davide Genovese: analyzed images, critically reviewed the manuscript.

Peng Lai: software development and support, critically reviewed the manuscript.

Kalie Kebed: analyzed images, critically reviewed the manuscript

Isla McClelland: analyzed images, critically reviewed the manuscript.

Anja Brau: software development and support, critically reviewed the manuscript.

Martin Janich: software development and support, critically reviewed the manuscript.

Karima Addetia: analyzed images, critically reviewed the manuscript.

Roberto M. Lang: concept development and critical review of the manuscript.

Amit R. Patel: all aspects of study.

Declaration of Competing Interest

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