HHS Public Access
Author manuscript
J Magn Reson Imaging. Author manuscript; available in PMC 2017 December 01.

Published in final edited form as:
J Magn Reson Imaging. 2016 December ; 44(6): 1673–1682. doi:10.1002/jmri.25305.

Efficient Method for Volumetric Assessment of Peak Blood Flow Velocity Using 4D Flow MRI

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Abstract

Purpose—To test the feasibility and effectiveness of using maximum intensity plots (MIPs) based on 4D flow MRI velocity data to assess systolic peak velocities in a cohort of bicuspid aortic valve (BAV) patients.

Materials and Methods—4D flow MRI at 1.5 T was performed on 51 BAV patients. MIPs were generated from the 4D flow MRI velocity data and used by 2 users to determine peak velocities in 3 regions of interest (ROI): ascending aorta (AAo), aortic arch and descending aorta. 4D flow MRI peak velocities in the AAo were compared to peak velocities recorded by 2D phase contrast MRI (2D PCMRI) in a subcohort of 36 patients and by Doppler echocardiography in a subcohort of 34 patients. 4D flow MRI peak velocities recorded by each observer were compared for all ROIs to test for inter-observer variability.

Results—4D flow MRI recorded significantly higher velocities compared to 2D PCMRI (2.04 ± 0.71 m/s vs 1.69 ± 0.79 m/s, 17.2% difference, $p < 0.001$) and similar velocities compared to Doppler echocardiography. There was excellent agreement between the observers with a mean difference of 0.005 m/s and an intraclass correlation coefficient of 0.98.

Conclusion—4D flow MRI velocity MIPs allow for efficient measurement of peak velocities in BAV patients with higher accuracy than 2D PCMRI and similar accuracy to Doppler echocardiography.

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Keywords

4D flow; Bicuspid aortic valve; Phase contrast; Pediatric; MRI

INTRODUCTION

Bicuspid aortic valve (BAV) is the most common congenital cardiac defect and is estimated to affect 0.5-2% of the population.[1] In pediatric BAV patients, aortic stenosis (AS) can be present due to fusion of two aortic valve cusps forming a smaller valve orifice than that of a tricuspid aortic valve. Further, as these patients enter into adulthood they are at greater risk for calcific aortic valve disease, which plays a major role in the progression of AS.[2, 3] Due to the relationship between severe AS and adverse cardiac events,[4, 5] it is important to monitor aortic valve function in BAV patients throughout life. The transvalvular pressure gradient is widely used in identifying AS and its severity can be estimated from the systolic peak blood flow velocity across the aortic valve via the simplified Bernoulli equation.

Currently, the standard noninvasive methods for measuring peak blood flow velocity are Doppler echocardiography, and 2D phase contrast MRI (2D PCMRI). Doppler echocardiography is often preferred due to its low cost, ease of use and short acquisition time,[6] but despite it being considered the clinical reference standard it is limited by being operator dependent and using single-directional velocity encoding. As a result, systolic peak blood flow velocity can be underestimated due to the misalignment of the Doppler beamline with the direction of blood flow.[7] This is especially problematic when assessing patients with aortic valve disease, who can exhibit eccentric flow jets at angles nearly perpendicular to the aortic wall.[8]

Compared to Doppler echocardiography, 2D PCMRI is not limited by acoustic window and beamline incidence issues.[9, 10] In 2D PCMRI, data is typically acquired using 2D planes normal to the aortic lumen and through-plane velocity encoding.[9] Through-plane velocity encoding, as with Doppler echocardiography, and large through-plane voxel resolutions (~6mm) can lead to underestimation of peak velocity due to the velocity component only being encoded normal to the plane orientation (single-direction velocity encoding) and partial volume errors. Furthermore, the misplacement of the 2D acquisition plane may miss the exact location of peak systolic velocity and can thus result in underestimation of systolic peak velocity.[9]

4D flow MRI (time-resolved 3D PCMRI with three-directional velocity encoding) has been used as an alternative to echocardiography and 2D PCMRI.[11-17] The inherent advantage of 4D flow MRI is related to its ability to provide full volumetric and temporal (3D + time) coverage of the vascular region of interest in combination with full access to the three-directional blood flow velocities. However, previous 4D flow MRI methods have been limited by long processing times and reliance on retrospectively positioned analysis planes for peak velocity assessment.[12-17]

In this study, we employ a new and facile approach based on systolic velocity maximum intensity projections (MIPs) and aortic region of interest (ROI) analysis to determine

regional peak velocity based on aortic 4D flow MRI data. The aim was to test the effectiveness of this approach to determine peak systolic velocity in the ascending aorta (AAo), aortic arch (arch) and descending aorta (DAo) of pediatric patients with BAV. We hypothesize that the volumetric velocity MIP based analysis of 4D flow MRI data can better accommodate complex aortic blood flow of BAV patients, will provide higher systolic peak velocities compared to Doppler echocardiography and 2D PCMRI, and will show good inter-observer variability and shorter analysis times than previous 4D flow MRI methods.

METHODS

Patient Selection & Characteristics

Patient characteristics are summarized in Table 1. Sixty-six pediatric patients with diagnosed BAV or unicuspid aortic valve underwent 4D flow MRI included in a physician-ordered cardiac MR assessment as part of this IRB-approved and HIPAA compliant study. Informed consent was obtained for performance of the 4D flow MRI sequence per IRB protocol.

The final cohort size was 51 patients (age = 14 ± 5 (min: 3 max: 24) years, male:female = 33:18) after a total of 15 patients were excluded for the following reasons: age < 3 years (n=3) due to inadequate spatial resolution in the 4D flow MRI to accommodate appropriate flow measurements, severe velocity aliasing present in the 4D flow MRI images (n=2) and the velocity MIP tool failing to detect the peak velocity due to significant noise within the 3D segmentation (n=10). Seventeen of the 51 patients underwent anesthesia for the MRI scan as per the institutional clinical protocol. The following aortic valve fusion patterns were included: n = 38 right/left coronary leaflet fusion, n = 10 right/noncoronary leaflet fusion, n = 3 right/left coronary & right/noncoronary leaflet fusion (unicuspid). Clinically indicated 2D PCMRI with aortic root peak velocity assessment was performed in 36 of 51 patients and spectral Doppler echocardiography was performed in the aorta in 34 of the 51 patients within 6 months of the MRI study (mean time difference between 4D flow MRI and echocardiography = 2.1 ±1.7 [0-5.8] months). Twenty-five patients had both 2D PCMRI and Doppler echocardiography data available.

Aortic root Z-scores (diameters normalized to body surface area) and AS severity grades were available for 51 and 34 patients, respectively, and used to test for correlation with peak velocities recorded by 4D flow MRI in the ascending aorta. EchoIMS (Merge Healthcare, Chicago, IL) was used to derive aortic root Z-scores from measurements made on systolic 3D gradient echo MRA or steady state free precession or gradient echo systolic phase cine imaging. AS severity grades were scored by a pediatric cardiologist on a scale of 0-4 in accordance with American Society of Echocardiography guidelines.[18]

MR Imaging

MRI studies were performed at 1.5 T (Avanto or Aera, Siemens, Erlangen, Germany) using either a 12-channel body matrix coil for the Avanto and an 18-channel body matrix coil for the Aera on larger patients or a 4-channel flex small or large coil on smaller patients for both the Avanto and the Aera. All 4D flow MRI studies were acquired in the sagittal plane with anterior to posterior phase direction and top to bottom read direction. 4D flow MRI data of

the thoracic aorta were acquired with 3-directional velocity encoding, prospective ECG gating and respiratory navigator gating. 4D flow MRI parameters were as follows: field of view = 250-320 × 156-260 mm^2, matrix size = 128-192 × 72-144, spatial resolution = 2.8 ± 0.43 (range 1.9-4.1) × 1.9 ± 0.20 (range 1.6-2.5) mm^2, slice thickness = 2.27 ± 0.47 (range 1.8-4) mm, 34 ± 10 slices, temporal resolution 39.7 ± 1.3 (range 37.6-42.4) ms, TE/TR/FA = 2.3-2.7 ms/4.6-5.0 ms/15° and velocity sensitivity (VENC) =120-400 cm/s. k-t GRAPPA[19] acceleration with R = 5, was available and used for 38 patients. For the other 13 patients' 4D flow MRI scans, standard GRAPPA parallel imaging with R = 2 was used. For patients who received 2D PCMRI, the 4D flow MRI VENC was set to 2/3 of the maximum velocity recorded by 2D PCMRI. For patients who did not receive 2D PCMRI, the 4D flow MRI VENC was set to 2/3 of the maximum velocity recorded by the most recent Doppler echocardiography. The 4D flow MRI VENC was set below the maximum velocity recorded by 2D PCMRI or Doppler echocardiography to ensure maximum signal throughout the 3D volume of interest. Velocity aliasing in the 4D flow MRI data due to velocities exceeding the VENC, could later be corrected during pre-processing as long as the velocities did not exceed twice the VENC. Scan times for 4D flow MRI ranged approximately between 6 and 12 min depending on if k-t GRAPPA was used.

2D PCMRI of the aortic root/AAo was acquired with single-directional velocity encoding in the through plane direction, either during free breathing (FB) (n=33, 2-3 signal averages) or breathheld (BH) (n=3) using retrospective ECG gating. 2D PCMRI parameters were as follows: field of view = 149-308 × 199-340 mm^2, spatial resolution = 1.3 ± 0.15 (range 1.0 – 1.7) × 1.3 ± 0.15 (range 1.0 – 1.7) mm^2, slice thickness = 5.2 ± 0.34 (range 5 – 6) mm, temporal resolution 22.7 ± 1.5 ms (range 20.3-26.7 ms), TE/TR/FA = 2.1-4.4 ms/5.7-5.8 ms/15-20° and VENC =150-400 cm/s. GRAPPA acceleration with R = 2 was used for all 2D PCMRI scans. Since Doppler echocardiography peak velocity was available for all patients scanned with 2D PCMRI, the VENC was chosen to be 10% below the most recent recorded Doppler echocardiography peak velocity. This convention is based on the knowledge that 2D PCMRI is known to underestimate Doppler echocardiography peak velocities. The 2D planes were placed at the level of the aortic valve leaflet tips in systole, perpendicular to the aortic vessel wall.

Data Analysis

4D flow MRI data was preprocessed to correct for noise, eddy currents, Maxwell terms, and velocity aliasing using an in-house tool (Matlab, MathWorks, MA). A time-averaged 3D phase contrast angiogram (PC-MRA) was computed as described previously[20] and used as an anatomical guide for 3D segmentation of the thoracic aorta (Mimics, Materialise, Belgium), which in turn was used to mask the 4D flow MRI velocity field (fig. 1).

Velocity Maximum Intensity plots—The time-resolved, masked aorta velocity field was imported into an in-house tool (Matlab, MathWorks, MA) and used to generate a velocity MIP that spans 3 time frames during peak systole in sagittal, coronal and axial views. The segmentation volume was eroded in all three dimensions by 1 voxel to offset segmentation errors. Additionally, the observer had the option to increase erosion to 2 voxels if segmentation errors were still visible. The maximum velocity within the entire segment was

automatically extracted (global maximum velocity). Next, 3D ROIs were manually drawn by two independent observers (MR and VC both with 1 year of experience in cardiac 4D flow MRI) for the AAo, arch and DAo in one view and then adjusted in the other two orthogonal views to exclude any unwanted anatomy if necessary. Care was taken to draw ROIs such that noisy areas near the aortic segmentation boundaries were excluded. In the context of this study, the term "noise" will refer to all artifacts, which are not considered legitimate velocities within the region of interest. The criteria for ROI selection are explained in Figure 2. Peak systolic velocities were then automatically extracted for each ROI. To account for false values due to residual velocity aliasing or noise voxels the following noise filter was applied:

$$D=\frac{dv}{dn}\left(vROI\left(0.99m{:}m\right)\right) \quad (1)$$

$$T=C*\mathrm{mean}\left(D\right) \quad \text{where} \quad C=10 \quad (2)$$

$$\mathrm{Noise}=D\left(n\right):D\left(m\right) \quad \textit{where} \quad D\left(n-1\right)\geq T \quad (3)$$

vROI is a vector containing the *n* voxel-wise velocity data enclosed by the ROI, sorted in ascending order by the velocity magnitude (*v*), where *m* is the final index. The filter was based on the calculation of the derivative *D* (Eq. 1) of the top 1% of *vROI*, which describes how velocity magnitudes vary from *n* to *n*+1. Assuming smoothly varying velocity magnitudes, any disproportionately large increase in magnitude relative to the mean increase was deemed to be an artifact of noise, aliasing or segmentation error. Therefore, all voxels with greater velocity magnitudes than *n* where the value of *D(n)* is *C* = 10 times greater than the mean of *D* were considered noise (Eq. 3) and excluded from peak velocity assessment (fig. 3). The constant multiplier (*C*) used in the threshold (*T*) (Eq. 2) was set to 10 after several iterations of the filter. Varying values of *C* were tested on cases with visible noise and compared to what was visually determined to be the peak velocity.

2D PCMRI post-processing—Post-processing of the 2D PCMRI data was performed using ROI analysis of the vessel. Similar to the 4D flow MRI a background subtraction was applied to correct for eddy currents. The analysis was performed using the QFlow software (Medis, Leiden, The Netherlands).

Doppler echocardiography post-processing—Clinically indicated echocardiography studies were performed on Philips IE33 ultrasound machines (Philips Healthcare, Best, The Netherlands) using the optimal transducer for patient size with single-directional velocity encoding. A single pediatric cardiologist retrospectively reviewed the echocardiography images (JR, 10 years of experience). The highest velocity was obtained by continuous wave Doppler, from the apical or suprasternal window.

Comparison with Echocardiography and 2D PCMRI and Inter-Observer Variability—For the 34 patients who had Doppler echocardiography within 6 months of the 4D flow MRI scan, the Doppler echocardiography peak velocity in the aortic root/AAo was compared to that of 4D flow MRI in the aortic root/AAo. In addition, the aortic root/AAo peak velocity derived from 2D PCMRI was compared to the 4D flow MRI derived peak velocities in the root/AAo for 36 patients. In a subgroup of patients who had both Doppler echocardiography and 2D PCMRI data available, aortic root/AAo peak velocity was compared between 4D flow MRI and 2D PCMRI, between Doppler echocardiography and 2D PCMRI, and between 4D flow MRI and Doppler echocardiography. To test for inter-observer variability, two independent observers, who were blinded to each other's results, performed the MIP analysis with the same segmentation and preprocessing settings for all 51 patients. The peak velocities from all 3 ROIs (AAo, arch, and DAo) were compared between observers.

Comparison of Single-Directional and 3-Directional Velocity Encoding—To understand the impact of 3-directional and single-directional velocity encoding on peak velocity measurements, 2D analysis planes were placed in the aortic root for 10 4D flow MRI datasets near the location of the corresponding 2D PCMRI analysis. Through-plane velocity (single-directional velocity) was compared to the velocity magnitude (3-directional velocity encoding).

Analysis Time and velocity aliasing correction—4D flow MRI data analysis times for using the velocity MIP tool post-processing for both users were recorded and averaged. The number of patients with aliasing that was corrected during post-processing was recorded.

Statistical analysis—Bland-Altman analysis was performed and mean percentage differences were calculated to compare peak velocity results between the three methods: 4D flow MRI versus Doppler echocardiography, 4D flow MRI versus 2D PCMRI and Doppler echocardiography versus 2D PCMRI. Inter-observer variability was tested with Bland-Altman analysis and by calculating intraclass correlation (ICC). The Wilcoxon signed-rank sum test was used to test the significance of the differences between peak velocities recorded by 4D flow MRI and Doppler echocardiography, and between 4D flow MRI and 2D PCMRI. To test for correlation between 4D flow MRI and Doppler echocardiography, 4D flow MRI and 2D PCMRI, and between 4D flow MRI peak velocities and aortic root Z-scores, Pearson's correlation coefficients and associated p-values were calculated. For testing correlation between AS severity grades and 4D flow MRI peak velocities, Spearman's rank correlation coefficient and associated p-value were calculated. The paired t-test was used to test if the temporal resolutions of 4D flow MRI and 2D PCMRI were significantly different.

RESULTS

4D flow MRI vs 2D PCMRI

The results of the comparison of peak velocity assessment in the AAo by 4D flow MRI and 2D PCMRI are summarized in Figure 4. As shown by the bar graphs, 4D flow MRI recorded significantly higher velocities compared to 2D PCMRI (2.04 ± 0.71 m/s vs 1.69 ± 0.79 m/s, 17.2% difference, $p < 0.001$) (fig. 4A). Bland-Altman analysis revealed a mean percentage difference between velocities recorded by each method of 22.9%. The two methods were strongly correlated ($r = 0.87$, $p <0.001$).

In addition, the paired t-test showed that the temporal resolution of 2D PCMRI was significantly higher ($p <0.001$) than 4D flow MRI.

4D flow MRI vs Doppler echocardiography

Figure 5 summarizes the results of the comparison of AAo peak velocities assessed by 4D flow MRI versus Doppler echocardiography. 4D flow MRI based peak velocity quantification resulted in similar velocities compared to Doppler echocardiography (2.05 ± 0.83 vs 2.03 ± 0.95 m/s, difference = 1.1%, $p = 0.2485$). Bland-Altman analysis demonstrated a mean percentage difference between velocities recorded by each method of 15.3%. There was strong correlation between 4D flow MRI and Doppler echocardiography ($r = 0.79$, $p<0.001$).

Subgroup analysis: Comparison of 4D flow MRI, 2D PCMRI and Doppler Echocardiography

The results of the comparison of peak velocity assessment in the AAo by 4D flow MRI and 2D PCMRI, 4D flow MRI and Doppler echocardiography, and 2D PCMRI and Doppler echocardiography for the subgroup of patients who had data from all 3 techniques available are summarized in Figure 6. Both Doppler echocardiography and 4D flow MRI recorded significantly higher velocities compared to 2D PCMRI (2.09 ± 1.03 m/s vs. 1.74 ± 0.93 m/s, 16.8% difference, $p < 0.005$, and 2.02 ± 0.79 m/s vs. 1.74 ± 0.93 m/s, 14.1 % difference, $p < 0.001$, respectively) (fig. 6A). 4D flow MRI and Doppler echocardiography recorded similar velocities (2.09 ± 1.03 m/s vs. 2.02 ± 0.79 m/s, 3.3% difference, $p = 0.64$). Bland-Altman analysis comparing 4D flow MRI and 2D PCMRI (fig. 6B), Doppler echocardiography and 2D PCMRI (fig. 6C), and 4D flow MRI and Doppler echocardiography (fig. 6D) revealed a mean percentage difference between velocities recorded by the two methods in each comparison of 19.8%, 23.5% and 13.8%, respectively. All three techniques were strongly correlated (4D flow MRI and 2D PCMRI: $r = 0.95$, $p <0.001$, Doppler echocardiography and 2D PCMRI: $r = 0.80$, $p <0.001$, 4D flow MRI and Doppler echocardiography: $r = 0.83$, $p <0.001$).

Comparison of Single-Directional and 3-Directional Velocity Encoding

Through-plane velocity significantly underestimated velocity magnitude by 6.6% (2.40 ± 0.58 vs. 2.57 ± 0.67 m/s, $p = 0.002$) compared to 3-directional velocity encoding.

Analysis Time and velocity aliasing correction

The average velocity MIP tool analysis time for both users was 92 ± 49 seconds. The exact analysis times for pre-processing and segmentation were not recorded, but were estimated to take approximately 15 min combined. The analysis time for processing the 2D PCMRI data was estimated to be 5 min per measured location.

Twenty six patients had velocity aliasing in their 4D flow MRI data that was later corrected during pre-processing.

Inter-observer variability

The results of Bland-Altman analysis for inter-observer variability are summarized in Figure 7. There was excellent agreement between both observers. The mean difference was 0.005 m/s with 0.192 m/s limits of agreement (95% CI). The average mean difference between observers was 2.0%. The ICC was found to be 0.98.

Correlation of 4D flow MRI peak velocities with aortic root Z-scores and AS severity grades

There was no correlation between 4D flow MRI peak velocities and aortic root z scores ($r = -0.11$, $p = 0.44$) and moderate correlation between 4D flow MRI peak velocities and AS severity grades ($r = 0.61$, $p<0.05$).

DISCUSSION

The findings of this study illustrate the potential of 4D flow MRI coupled with an efficient data analysis workflow to evaluate aortic hemodynamics in patients with bicuspid aortic valve disease. This is especially important given the knowledge that BAV subjects exhibit highly eccentric velocity jets. Supporting this concept, our method (henceforth referred to as 4D flow MIPs) demonstrated significantly higher velocities in the ascending aorta than 2D PCMRI in both the full cohort and the subgroup where all three imaging methods were available for analysis. This finding is in good agreement with previous studies, which reported a systematic underestimation of peak velocities by 2D PCMRI compared to 4D flow MRI.[11, 21] Additionally, the fact that 2D PCMRI underestimated peak velocities compared to the clinical reference standard, Doppler echocardiography, in our study as well as others[22, 23] supports the notion that 2D PCMRI underestimates true peak velocity rather than 4D flow MIPs overestimating it. The notion that 2D PCMRI underestimates 4D flow MRI velocities in part due to single-directional velocity encoding, which is supported by our findings of the comparison of peak velocity derived from the through-plane velocity component versus the 3-directional magnitude from the 4D flow MRI. The analysis at the aortic root showed that 1-directional through-plane encoding significantly underestimates the velocity magnitude. Peak velocity underestimation by 2D PCMRI can further be explained by its other inherent technical limitations: large slice thickness and thus largely anisotropic voxels, 2D planar analysis and operator dependence. The performance of 2D PCMRI may be further compromised in BAV patients due to the complex aortic outflow associated with BAV. 4D flow MIPs with 3-directional velocity encoding, and volumetric analysis directly address these short comings of 2D PCMRI. Doppler echocardiography is also limited by single-directional velocity encoding, 2D analysis and operator dependence.

Despite these limitations, there was no significant difference in velocities recorded by Doppler echocardiography and 4D flow MIPs. This is likely due to the superior temporal and spatial resolution of Doppler echocardiography negating the effects of intra-voxel dispersion, a limitation of both 2D PCMRI and 4D flow MRI. The percentage error of 4D flow MIPs compared to Doppler echocardiography was well within the clinically acceptable range for a new method, <30%.[24] There was also excellent agreement between observers in our method, further bolstering 4D flow MRI as a valid method for peak velocity assessment.

Numerous feasibility studies on 4D flow MRI peak velocity assessment have used 2D planar analysis instead of volumetric analysis, because it allows for comparisons with 2D PCMRI[13-15] and/or Doppler echocardiography[12, 14, 16, 17] to be at the exact same anatomical locations. Nordmeyer et al.[21] used the 4D flow MRI volumetric data set to visualize streamlines from which they identified the region of peak velocity and then placed 2D analysis planes accordingly. As with 2D PCMRI, improper post-processing plane position in 4D flow MRI can result in underestimation of peak velocity. Positioning and orienting analysis planes in 3-D space at one or more specific anatomical locations as an additional post-processing step can be time consuming and also result in poor reproducibility across subjects and between operators due to its operator dependence. Volumetric ROI analysis, as used in our study as well as others,[11, 25] can reduce operator dependence and the risk of missing the true systolic peak velocity. Systolic flow patterns, which can give a qualitative sense of hemodynamics, as has been shown in other work investigating the relationship between flow patterns and energy loss,[26] are readily apparent in 4D flow MIPs. Though previous methods[14, 16, 17, 21] have means of displaying flow patterns as well, they involve an additional step and result in longer processing times. Data and segmentation quality are also evident in the 4D flow MIPs.

Recent studies[11, 25] have implemented volumetric ROI analysis using commercially available 3D visualization software (EnSight, CEI, NC). In the study by Gabbour et al.[11], they compared 4D flow MRI using volumetric analysis to planar 4D flow MRI, while also comparing volumetric 4D flow MRI to echocardiography and 2D PCMRI in a heterogeneous cohort of 50 young adult and pediatric patients. Their volumetric method consisted of positioning a 3D cylinder to encompass the segment of interest while constraining it to avoid areas near the aortic walls. The peak velocity was found within the entire cylinder across all time frames. It was found that planar 4D flow MRI significantly underestimated volumetric 4D flow MRI peak systolic velocities in the AAo. Similar to our results, it was found that 2D PCMRI significantly underestimated volumetric 4D flow MRI velocities in the AAo. Their study differed from our study in that volumetric 4D flow MRI recorded significantly higher velocities than echocardiography in the AAo.. The underestimation of planar 4D flow MRI velocities compared to volumetric 4D flow MRI velocities supports the case to move from planar to volumetric analysis. Both studies suggest that volumetric 4D flow MRI is superior to 2D PCMRI for peak velocity detection. Different approaches in volumetric analysis may account for the differences in results between the studies for the volumetric 4D flow MRI and echocardiography comparison. Limitations of their volumetric peak velocity detection method are that it was only capable of eliminating noise near the segment walls and was dependent on the operator to determine which voxels were too close to the aortic wall. In our method, noise was automatically identified and

consequentially avoided via careful manipulation of ROI boundaries. Our method also used 3D segmentation of the aorta with erosion of the boundaries and noise filtering to further reduce any noise inside the ROI. Additionally, since our study focused specifically on patients with aortic valve disease, echocardiograms were performed with more intensive focus on obtaining the peak velocity, employing color flow mapping guidance and repeated measures from multiple acoustic windows and thus could have led more accurate peak velocity measurements. The increased susceptibility to noise in the study by Gabbour et al. and the emphasis on peak velocity assessment of our BAV cohort's Doppler echocardiograms may have accounted for the observed higher velocities of 4D flow MRI compared to Doppler echocardiography.

4D flow MRI is limited by long scan times compared to 2D PCMRI.[27] However, given the large anatomical coverage of 4D flow MRI, it may be faster to acquire 4D flow MRI than multiple 2D PCMRI acquisitions in the case of patients with complex heart disease.[11] At the cost of keeping scan times clinically feasible, 4D flow MRI suffers from lower temporal and spatial resolution relative to Doppler echocardiography and 2D PCMRI. Though the in-plane resolution of 4D flow MRI is lower than 2D PCMRI, 4D flow MRI has lower slice thickness resulting in close to isotropic voxels. Low resolution images are undesirable as this can lead to inadequate imaging of smaller vessels and intra-voxel dephasing, which could lead to inaccurate velocity measurements. Continued development of imaging acceleration techniques, such as k-t BLAST and k-t GRAPPA, will help improve spatial and temporal resolution.[28, 29] The advantages of 2D PCMRI over 4D flow MRI, the superior temporal and spatial resolution suggest 2D PCMRI should result in more accurate peak velocities than 4D flow MRI. However, 2D PCMRI underestimated velocities compared to Doppler echocardiography and 4D flow MRI. Therefore we hypothesize that the acquired single velocity direction is a key factor as well as the need to position the 2D plane at the correct location where the peak velocity presumably occurs.

Representing the 4D flow MRI data in the form of velocity MIPs results in the loss of the directional component of velocity data, which can aid assessing systolic flow patterns. Supplemental visualization techniques, such as particle traces[30], would be necessary to fully understand the directional component of blood flow velocity. The noise filter used was dependent on the number of voxels contained within the ROI and may be less effective when used on ROIs with low numbers of voxels. Further work would be needed to test and improve the noise filter's performance on smaller ROIs. Improvements in preprocessing techniques could potentially remove the need for the noise filter altogether.

Two different MRI scanners were used in this study. The different bore sizes and gradient performances of these scanners could lead to differences in field inhomogeneity. However, field inhomogeneity does not have a large effect at low field strengths, such as the 1.5 T scanners used in this study. Additionally, we did not compare 4D flow MRI velocities from one scanner to 2D PCMRI velocities from the other scanner for any of the patients and thus there was no bias due to scanner difference in our comparison of 4D flow MRI and 2D PCMRI.

Another study limitation is the difference between prospective ECG gating used in 4D flow MRI and the retrospective ECG gating used in 2D PCMRI, which primarily affects flow velocities during diastole. Since peak velocities in the aortic root and AAo occur during systole, any difference during diastole between 4D flow MRI and 2D PCMRI would not affect the results. In addition, 2D PCMRI was acquired either FB or BH. Previous studies[31, 32] have shown BH 2D PCMRI to record higher velocities and flow rates than FB 2D PCMRI. A study by Bauer et al.[33] found no significant difference in AAo flow velocities between FB and BH 2D PMCRI. However, they found FB 2D PCMRI to significantly underestimate myocardial tissue velocities, which are about 10 times slower than aortic velocities. Since we investigated peak systolic aortic velocities, we don't expect a difference between the velocities derived from FB versus BH in our study. The accuracy of the comparison of 4D flow MRI to Doppler echocardiography was limited by differences in scan dates between the exams, on the order of months, and by the reported effects of anesthesia, which was used per the clinical protocol for some MRI exams, but not for any Doppler echocardiography exams.[34] A more accurate comparison of 4D flow MRI and Doppler echocardiography would require the exams to be acquired on the same day under the same levels of anesthesia.

In conclusion, the use of 4D flow MIPs to measure peak systolic velocity in BAV patients agreed better with the clinical reference standard Doppler echocardiography when compared to 2D PCMRI. 4D flow MIPs employ rapid volumetric analysis with 3-directional velocity encoding and are thus better equipped to accommodate eccentric blood flow jets in the assessment of peak velocity than Doppler echocardiography or 2D PCMRI.

Acknowledgments

Marci Messina, RT(R)(MR), for her assistance with patient scanning and Ryan Kuhn and Paige Nelson for their help with data collection

Grants: NIH R01HL115828 and K25HL119608

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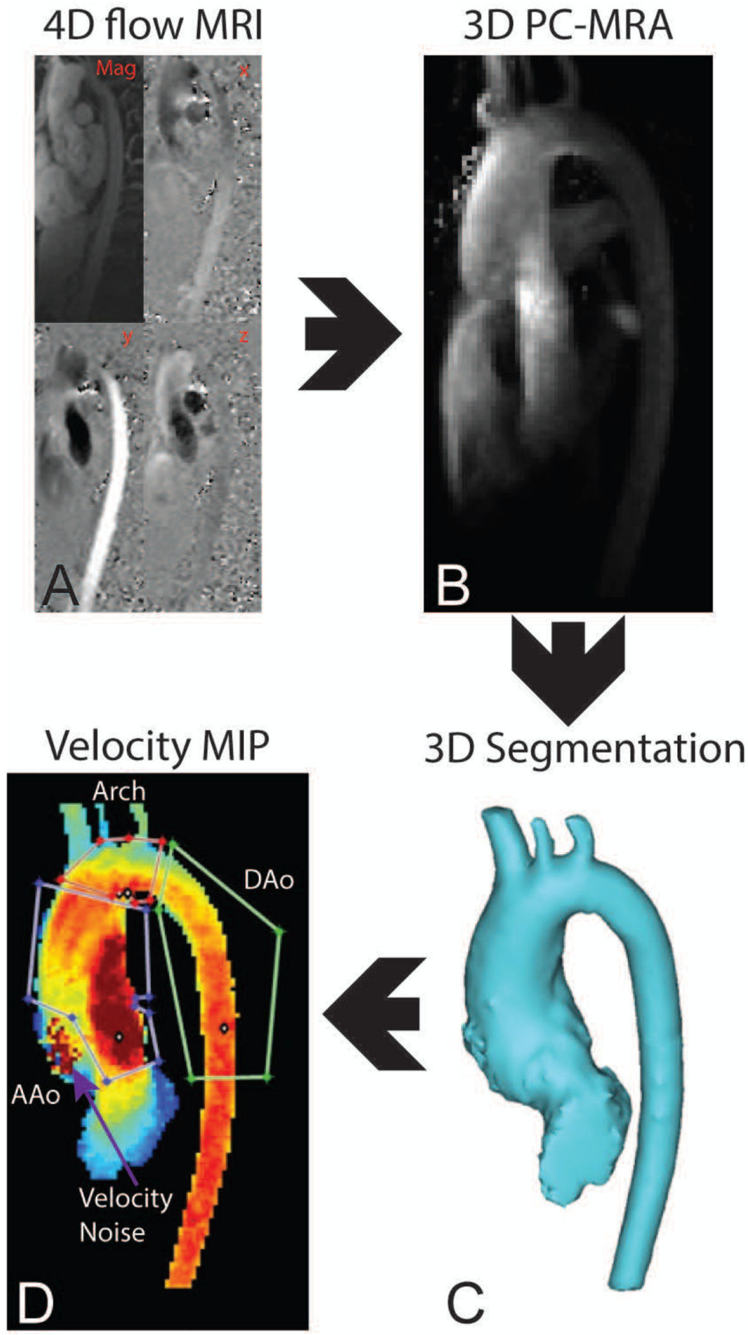

Figure 1.
Workflow starting with the 4D flow MRI data (A), which includes the magnitude data (mag), flow data in the 3 spatial directions x, y and z. The 4D flow MRI data is preprocessed and used to calculate a time-averaged 3D-PCMRA (B). The 3D-PCMRA is used as an anatomical reference for the 3D segmentation (C). Velocity MIPs (D) are generated by masking the preprocessed 4D flow MRI velocity field with the 3D segment. Note the noise excluded (purple arrow) from the ROI in the root. The white dot with the black outline refers to location of peak velocity

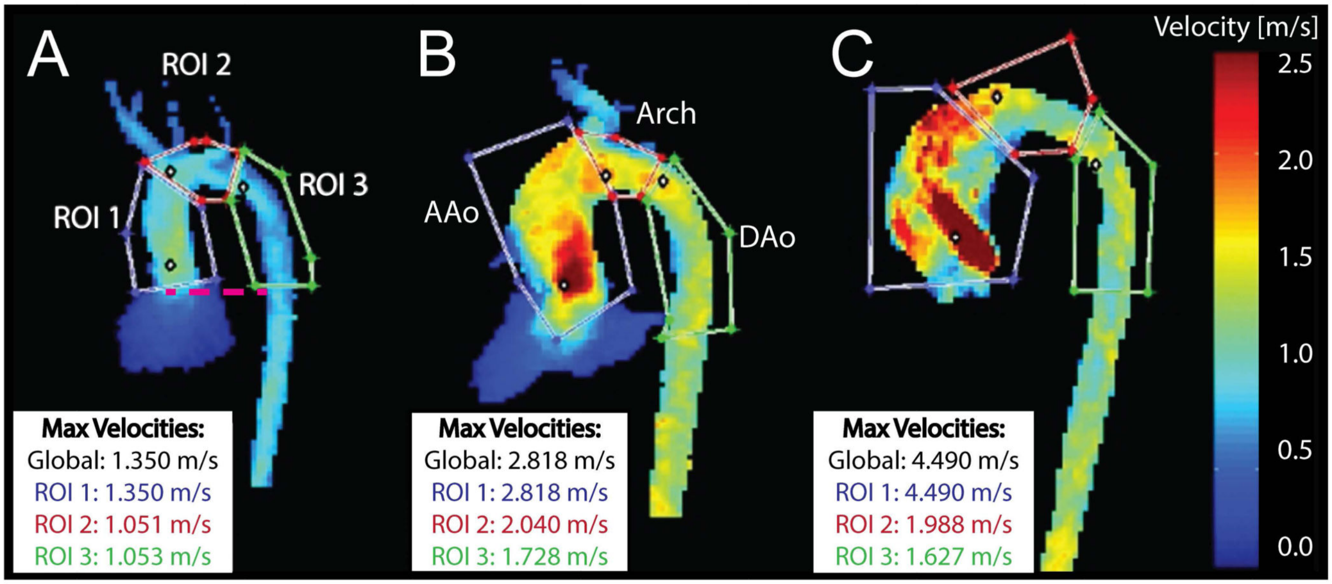

Figure 2.

Velocity MIP of patients with mild (A), moderate (B) and severe stenosis (C). The placement of ROI's can be seen in (A): ROI 1 captures the AAo, which is defined as the aortic segment from the aortic valve to the brachiocephalic trunk (BCT). The user visually identified the aortic valve by locating the origin of the systolic flow jet in the MIP and defined the ROI to start from just below the aortic valve and to end at BCT. ROI 2 captures the aortic arch, from the BCT to immediately distal of the left subclavian artery (LCA). ROI 3 captures the DAo from the distal part of the origin of LCA to the level of aortic valve. The dashed pink line in (A) denotes the level of the aortic valve extended to the bottom of ROI 3 in the DAo. The white dot with the black outline refers to the location of peak velocity in each ROI.

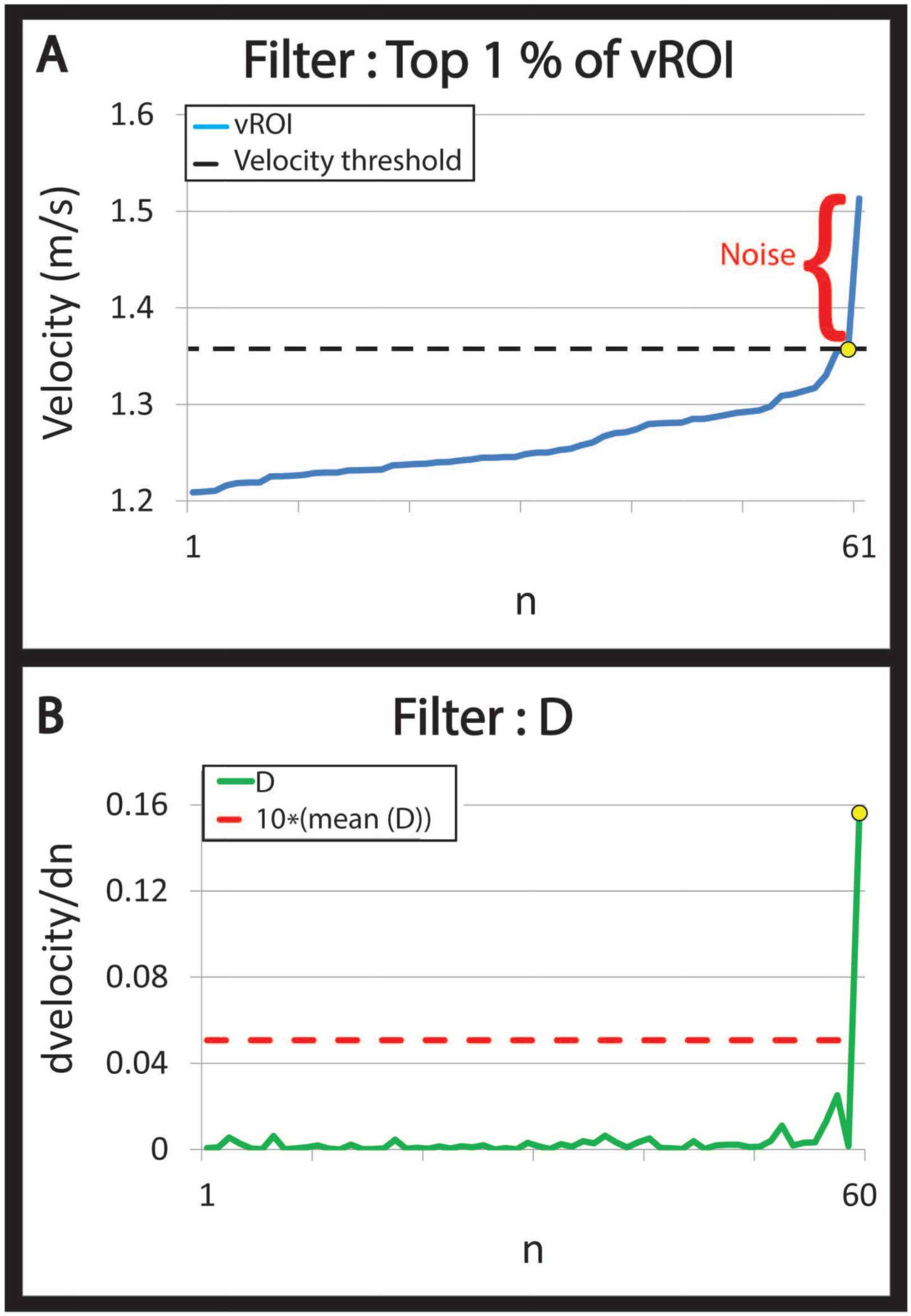

Figure 3.

An example of a plot of vROI (A), the top 1% highest velocities contained within a ROI sorted in ascending order, and the plot of D (B), the derivative of vROI with respect to n, for the same patient. The red dashed line in (B) represents the cutoff threshold for the filter and the yellow circle is a voxel with a D value greater than the threshold. All velocity magnitudes higher than the black dashed line are considered noise (A).

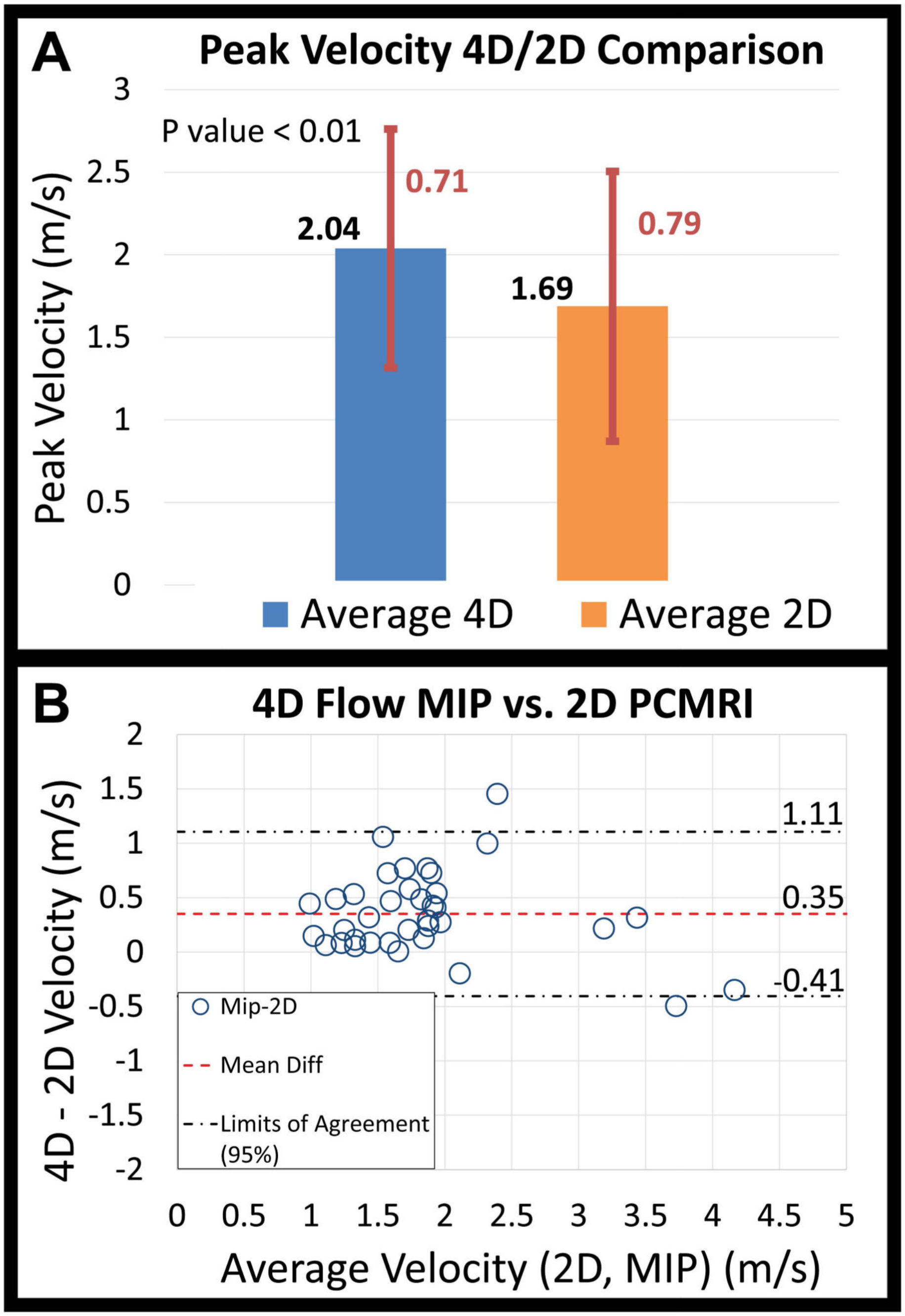

Figure 4.

Comparison of the average peak velocity recorded by 4D flow MRI and 2D PCMRI in the AAo as a bar graph (A). Bland-Altman comparing peak velocities recorded by 4D flow MRI and 2D PCMRI in the AAo for each patient (B).

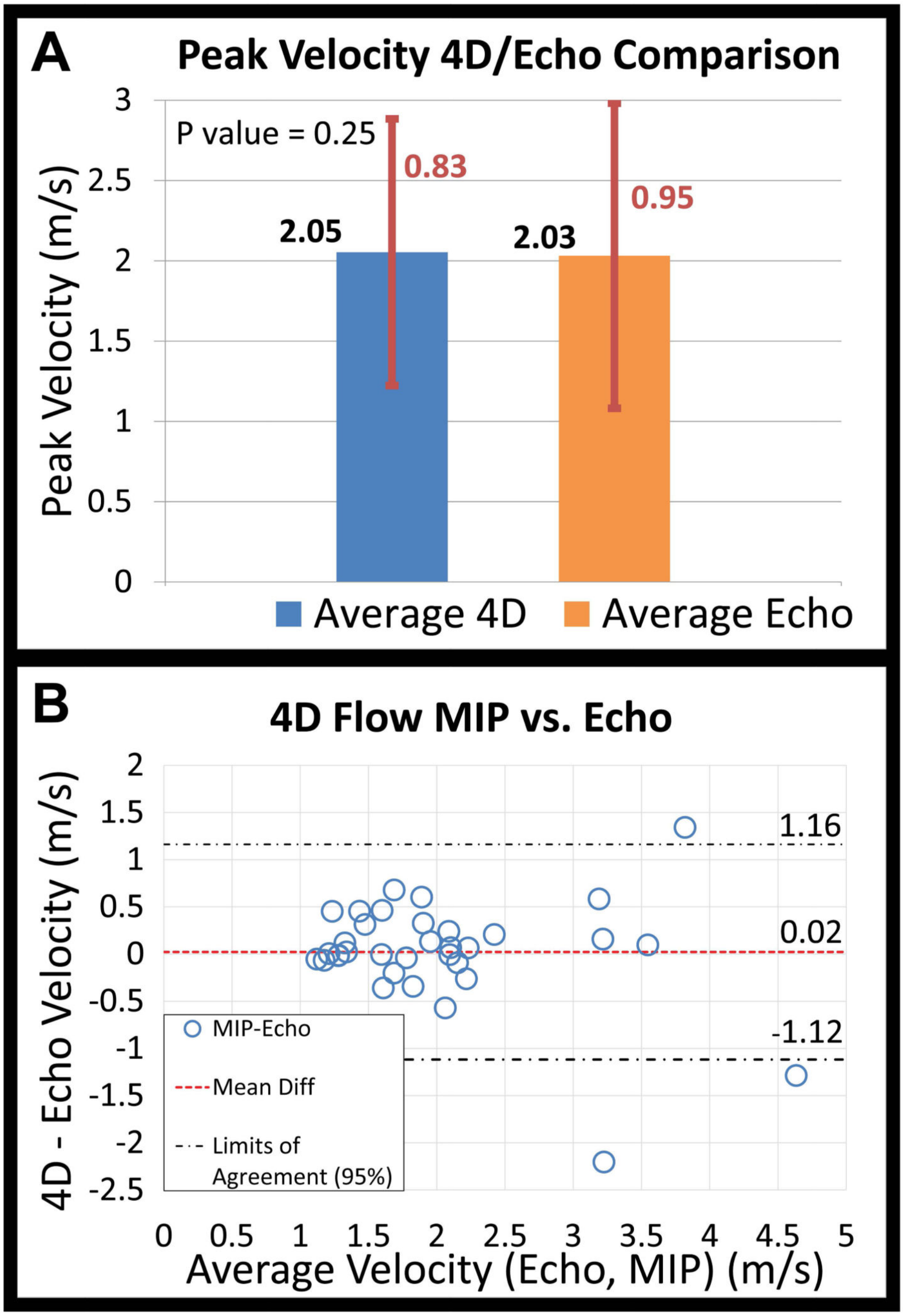

Figure 5.

Comparison of the average peak velocity recorded by 4D flow MRI and echocardiography in the AAo as a bar graph (A). Bland-Altman comparing velocities recorded by 4D flow MRI and echocardiography in the AAo for each patient (B).

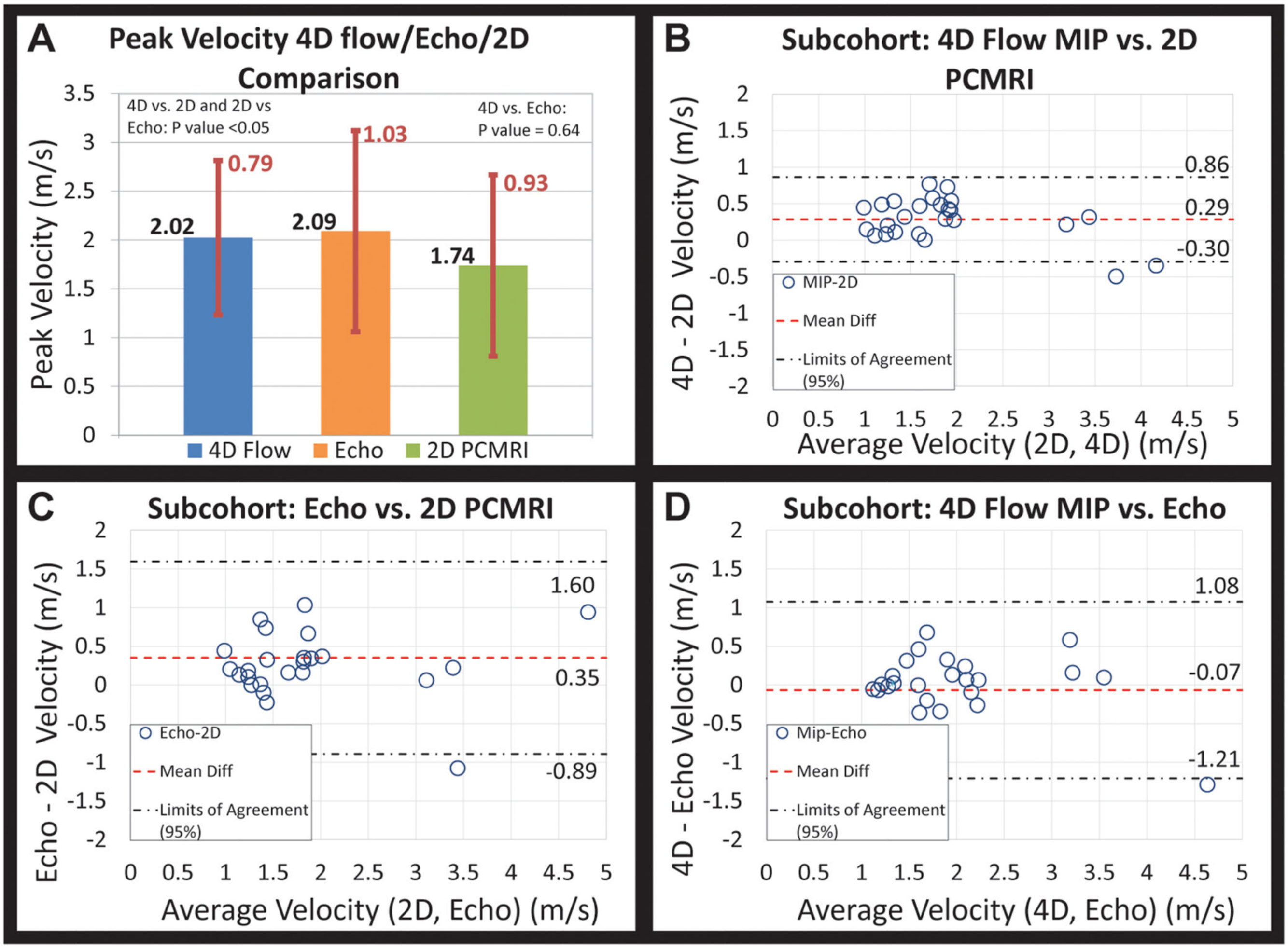

Figure 6.

Comparison of the average peak velocity recorded by 4D flow MRI, 2D PCMRI and Doppler echocardiography in the AAo as a bar graph for the subgroup of patients (n=25) who had data available from all three methods (A). Bland-Altman plots comparing peak velocities in the AAo of patients in the subgroup recorded by 4D flow MRI and 2D PCMRI (B), Doppler echocardiography and 2D PCMRI (C), and 4D flow MRI and Doppler echocardiography (D).

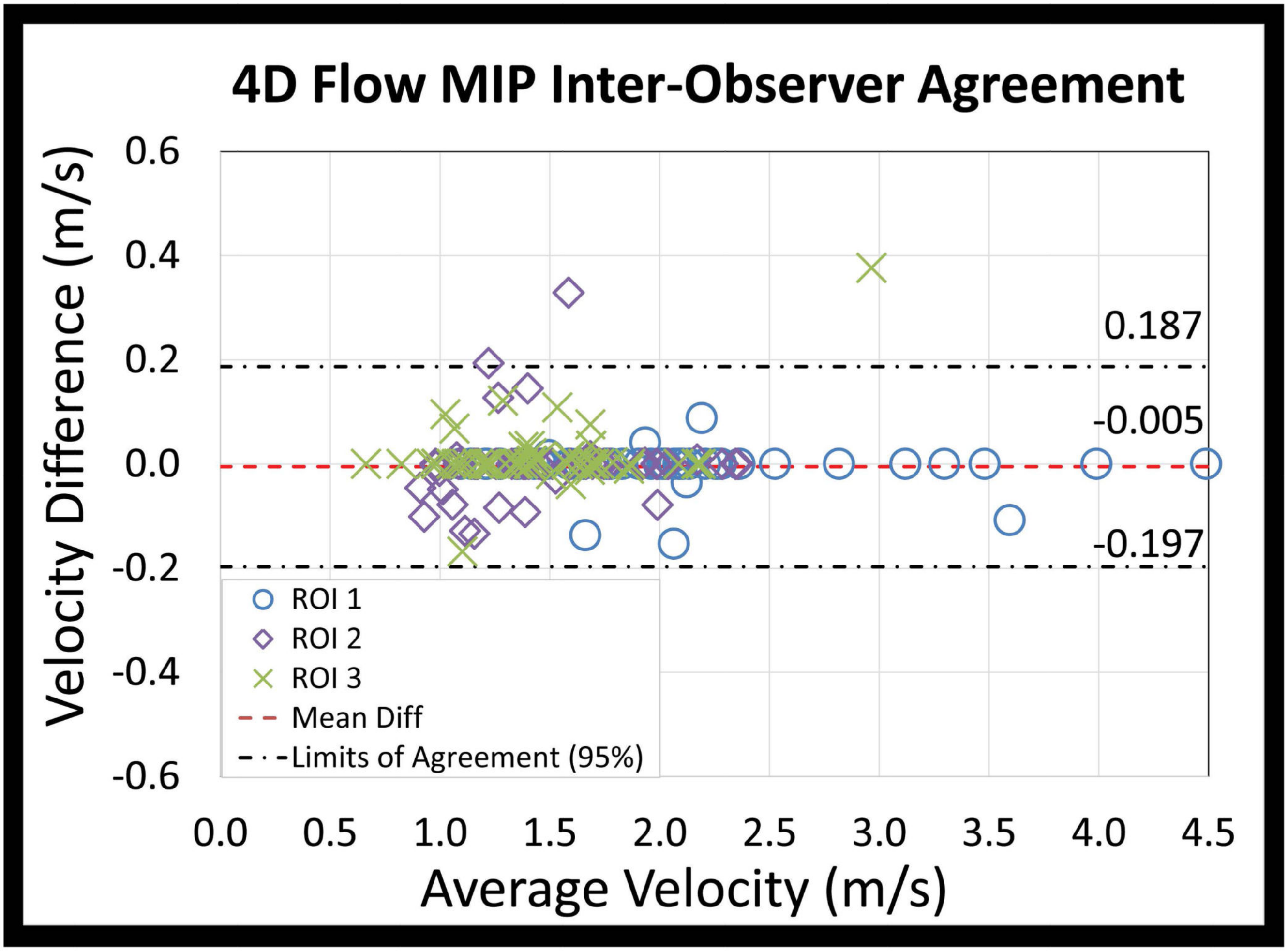

Figure 7.

Bland-Altman analysis comparing the two observers' 4D flow MIP velocity results in the AAo (ROI 1), arch (ROI 2) and the DAo (ROI 3).

Table 1

Patient characteristics for the entire cohort, a subgroup of patients who had Doppler echocardiography peak velocity data available, a subgroup of patients with 2D PCMRI data available and a subgroup of patients who had Doppler echocardiography and 2D PCMRI data avaible.

	Full Cohort	Doppler Echocardiography Vs. 4D flow MRI	2D PCMRI Vs. 4D flow MRI	2D PCMRI vs. 4D flow MRI vs. Doppler Echocardiography
Age (Mean ± std dev [Range]) / years	14.0 ± 4.7 [3.4-24.5]	14.1 ± 4.5 [3.4-21.8]	14.2 ± 4.7 [3.4-24.5]	14.4 ± 4.3 [3.4-20.3]
N	51	34	36	25
Gender (male:female)	33:18	21:13	24:12	16:10
BAV (# patients)	48	33	33	24
Unicuspid (# patients)	3	2	3	2
Right/left coronary leaflet fusion (# patients)	38	25	25	19
Right coronary/noncoronary leaflet fusion (# patients)	10	7	8	5
Stenosis grade by echocardiography (Mean ± std dev [Range])	0.76 ± 1.1 [0-4]	0.76 ± 1.1[0-4]	0.77 ± 1.1 [0-4][a]	0.77 ± 1.1 [0-4]
Aortic root Z-score (Mean ± std dev [Range])	2.7 ± 1.7 [-0.3-6]	2.6 ± 1.6 [0-6]	2.6 ± 1.5 [0.3-6]	2.7 ± 1.4 [0.7-6]

[a]Based on 25 of 36 patients with 2D PCMRI data available who also received a stenosis grade from echocardiography.