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Voxel-by-Voxel 4D Flow MRI Based Assessment of Regional Reverse Flow in the Aorta

Xin Shen, MS¹, Susanne Schnell, PhD², Alex J. Barker, PhD², Kenichiro Suwa, MD², Lingzi Tashakkor, MS¹, Kelly Jarvis, PhD¹, James C. Carr, MD², Jeremy D Collins, MD², Shyam Prabhakaran, MD³, and Michael Markl, PhD^{1,2}

¹Department of Biomedical Engineering, McCormick School of Engineering, Northwestern University

²Department of Radiology, Feinberg School of Medicine, Northwestern University

³Department of Neurology, Northwestern University

Abstract

Background—Complex and reverse flow in the aorta which has been implicated in aneurysm development and stroke via retrograde embolization.

Purpose—To evaluate global and regional differences between standard 2D plane-based and volumetric voxel-based quantification of regional forward/reverse flow, and reverse flow fraction (RFF) in the aorta.

Study Type—Retrospective

Subjects—35 subjects: 10 healthy controls (age: 57±7 years, 9 male), 9 patients without aortic valve regurgitation (AR) (age: 63±10 years, 7 male), 6 patients with mild AR (age: 66±6 years, 5 male), and 10 with moderate or severe AR (age: 60±16 years, 8 male).

Field Strength/Sequence—4D flow MRI (3T and 1.5T) was employed to acquire 3D blood flow velocities with entire thoracic aorta in all subjects.

Assessment—Data analysis included standard 2D plane-based quantification of forward/reverse flow, and RFF-plane. In addition, a new semi-automatic workflow based on 3D segmentation and extraction of an aorta centerline was developed for voxel-by-voxel visualization (forward/reverse flow and RFF-voxel maps) and quantification of regional voxel-by-voxel forward/reverse flow in the entire thoracic aorta.

Statistical Tests—Kruskal Wallis tests were performed to test for differences between groups. A two-sample t-test or Wilcoxon rank sum test was used to compare voxel-based and plane-based results.

Results—Semi-automatic plane-based analysis showed excellent agreement with standard manual plane-based analysis for net flow and RFF-plane (RFF-plane: $y=0.99x-0.0$, net flow:

$y=1.00x-0.21$, $R > 0.99$, $P < 0.0001$). Voxel-by-voxel maps demonstrated marked regional flow reversal in the ascending aorta in all patients and RFF-voxel was significantly increased ($P < 0.001$) compared to RFF-plane for all 4 groups with most pronounced differences for mild AR ($18.0 \pm 15.2\%$ vs. $4.7 \pm 5.4\%$). Voxel-based flow and RFF-voxel along the aorta showed areas with marked regional flow reversal (e.g. vortex flow) compared to plane-based analysis.

Data Conclusion—Voxel-based analysis demonstrated regional flow reversal which was not detected by plane-based analysis.

Keywords

flow; quantification; 4D flow MRI; flow reversal

Introduction

It has been previously shown that vortex flow in the ascending aorta (AAo) and flow reversal in the descending aorta (DAo) are related to complications such as increased AAo diameter (aneurysm), aortic valve regurgitation (AR), and stroke (1–6). Therefore, the visualization of aortic flow patterns as well as the quantification of reverse flow along the entire aorta could aid in the assessment of aortic diseases.

Current methods for the evaluation of aortic flow reversal and quantification of reverse flow fraction (RFF) include Doppler echocardiography (7), and 2D phase contrast MRI (8). Doppler echocardiography provides detailed anatomic and functional information (7) and is the main non-invasive clinical tool due to its low cost, wide availability, and ease of use (9). However, standard Doppler echocardiography is an inherently 2D technique with velocity encoded in a single direction (parallel to the beamline), which limits the ability to detect complex flow patterns (10). In addition, Doppler echocardiography is user dependent and thus has limited reproducibility (11).

The degree of vascular flow reversal can also be assessed using 2D phase contrast MRI (2D PC MRI) based on acquired 2D slices at several locations orthogonal to the aorta. RFF-plane is calculated at each location by dividing net forward flow by the net reverse flow of the entire cardiac cycle for each slice (12). While this method is used as the standard tool for the diagnosis of RFF-plane, the acquisition slice locations are positioned manually and only one velocity encoding direction (orthogonal to slice) is acquired.

4D flow MRI measures three-directional blood flow velocities (13) and allows for the visualization and quantification of complex flow patterns (14) with full volumetric coverage of the cardiovascular region of interest, providing the opportunity for a more complete evaluation of flow reversal (15,16). However, current flow quantification methods use plane-based analysis, similar to 2D PC MRI, and can thus miss important regional flow information. For instance, flow recirculation next to forward flow jets or vortex flow in the ascending and descending aorta (1,2) may lead to considerable regional flow reversal that may not be captured when using the standard plane-based calculation of forward and reverse flow. As a result, standard quantification of reverse flow and RFF-plane can yield small or non-existent RFF-plane although marked regional flow reversal may be present. This

standard approach may thus contribute to the known underestimation of RFF by 2D PC MRI compared to Doppler echocardiography. In addition, flow reversal assessment based on plane-based analysis may miss important regions with regional flow reversal. For example, recent studies have shown that reverse flow from high risk plaques in the descending aorta may constitute risk for cerebral stroke via retrograde embolization (6).

The aim of this study was to develop a 4D flow MRI based semi-automatic analysis of forward flow, reverse flow, RFF-plane, and RFF-voxel with full volumetric coverage of the aorta using both plane-based and voxel-based methods. We hypothesized that voxel-based analysis and mean reverse flow and RFF-voxel maps can visualize and quantify regional flow reversal, which are not detected by planar analysis of reverse flow.

Materials and Methods

This study was approved by the Institutional Review Board (IRB). Patients were enrolled via an IRB-approved retrospective chart review and waiver of consent. Control subjects were enrolled with written informed consent to participate in the study.

Study Cohort and MR Imaging

A total of 35 subjects (29 male, age = 61 ± 11 years) with suspected aortic disease underwent standard-of care cardiothoracic MRI on 1.5T MR systems (Espree, Aera, Avanto, Siemens) or 3T MR system (Skyra, Siemens). The aortic valve function was visually assessed by a cardiologist (K.S) with 5 years of experience using 2D cine balanced steady-state free precession (bSSFP) images through the aortic valve plane. Patients with normal aortic valve function based on visual assessment by 2D cine bSSFP images were classified as patients without AR (No AR group). Otherwise, the degree of AR was quantified by 2D phase contrast MRI by placing 2D slices at and below the aortic valve. If the resulting regurgitant fraction was less than 30%, the patients were considered to have mild AR (17). Patients with $>30\%$ regurgitant fraction were assigned to the moderate or severe (MoS) AR group. As a result, 6 patients had mild AR (5 male, age = 66 ± 6 years), 10 patients had MoS AR (8 male, age = 60 ± 16 years), and 9 patients had No AR (7 male, age = 63 ± 10 years). In addition, 10 healthy controls (9 male, age = 57 ± 7 years) were included in the study. For all subjects, the diameters of the aortic root at the Sinus of Valsalva (SOV) and the mid ascending aorta (MAA) were determined.

4D Flow MRI – Data Acquisition

All subjects underwent prospectively ECG gated 4D flow MRI with respiratory navigator gating and full coverage of the thoracic aorta (18). 4D flow imaging parameters were as follows: Repetition time(TR)/Echo time(TE)/Flip angle= 4.7–5.4 ms/2.2–2.8 ms/7–20°, spatial resolution (row $\times$ column $\times$ slice)= 2.1–4.2 mm $\times$ 1.7–2.8 mm $\times$ 1.9–3.4 mm, temporal resolution=37.6–43.2 ms, field of view (FOV) =320–450 mm $\times$ 240–366 mm, bandwidth =445–460 Hz/Pixel, velocity sensitivity (Venc) = 150–200 cm/s along all three velocity encoding directions. The 4D flow MRI pulse sequence parameters were selected according to a recently reported consensus statement for the use of 4D flow MRI for aortic applications (spatial resolution on the order of (2.5 mm)³ to provide a sufficient number of

voxels across the aortic diameter for accurate flow quantification, temporal resolution on the order around 40 ms, Venc 10% higher than the expected maximum aortic velocity) (19).

4D flow Data Analysis – Preprocessing

4D flow data analysis included corrections for velocity noise (20), Maxwell terms (21), eddy currents induced phase offset errors (22), and velocity aliasing (23). A 3D phase contrast MR angiogram (PC-MRA) was derived from the 4D flow data based on the multiplication of the phase contrast magnitude images with the absolute velocity images as describe previously (18) and used to generate a 3D segmentation of the aorta (Fig. 1A–C) to constrain the measured 4D flow velocity vector field within vessel boundaries (Mimics, Materialise).

4D flow Data Analysis – 3D Flow Visualization and Standard Manual 2D Planar Flow Quantification

The 3D segmentation of the vessel lumen (Fig. 1C) and the 4D flow data were loaded into commercial 3D visualization software (Enlight, CEI, USA). Aortic blood flow was visualized using time-resolved 3D pathlines throughout the entire thoracic aorta (see supplemental video 1). In addition, regional flow quantification was performed by manually positioning nine analysis planes orthogonal to the aorta at the following anatomic landmarks: aortic root (ROOT), proximal, mid and distal ascending aorta (AAo1, AAo2, AAo3), proximal, mid and distal arch (Arch1, Arch2, Arch3), and proximal and distal descending aorta (DAo1, DAo2) as shown in Fig. 1D. For each analysis plane, flow at each time point in the cardiac cycle was calculated by the standard flow quantification approach: Calculation of the average flow Q_j across the entire plane for each time point j in the cardiac cycle and quantification of forward ($Q_{forward}$) and reverse flow ($Q_{reverse}$) by summation of all positive or negative Q_j over time, respectively. RFF-plane was defined as the ratio of the absolute value of reverse flow to forward flow ($RFF - plane = \left| \frac{Q_{reverse}}{Q_{forward}} \right|$).

4D flow Data Analysis – Centerline-Based Flow Analysis

The workflow for semi-automatic plane-based and voxel-based assessment of flow and reverse flow fraction (Matlab, The Mathworks, USA) is illustrated in Fig. 1E–J. As a first step, a 3D aorta skeleton was derived which included supra-aortic branches (Fig. 1E). For ease of data manipulation, a 2D skeleton based on the 2D projection of the 3D aorta segmentation along the left-right direction was used to delete supra-aortic branches in the 2D skeleton (the skeleton without branches will be called centerline) and to order the centerline points from ROOT to DAo2 manually. Next, point-matching was applied between the 2D centerline and 3D skeleton by comparing point locations along the left-right direction. For each point in 2D, the closest point in 3D was considered the same point to the point in 2D (distance < 1mm) and at least 95% of points in 2D had matched points in 3D. The third coordinate of matched points in 3D was added to the ordered 2D centerline (Fig. 1F). For each point along the 3D centerline, normal vectors were determined and 150–200 planes (distances between centers of planes were < 3mm) orthogonal to the centerline were automatically generated (Fig. 1G). Voxels inside the aorta were considered members of a plane if their distance was < 1mm to each plane (voxels can be members of multi-planes). Based on the normal directions of the planes, velocity vectors of member-voxels on the

plane, and voxel size, the flow for each voxel was calculated (Q_{ij} : flow value in voxel i at time point j). Next, standard planar and voxel-based forward and reverse flow were calculated as follows:

1. **Standard plane-based analysis** (calculating average flow across the plane prior to determining total forward and reverse flow along the cardiac cycle). Summation of flow information for all voxels on the plane ($Q_j = \sum_{i=1}^n Q_{ij}$ with Q_{ij} : flow value in voxel i at time point j , n : total number of voxels on the analysis plane) and subsequent quantification of forward ($Q_{forward}$) and reverse flow ($Q_{reverse}$) by summation of all positive or negative Q_j over time
2. **Voxel-based analysis** (identifying regional forward and reverse flow for each plane prior to calculating total forward and reverse flow along the cardiac cycle). For each plane, the voxels with forward and reverse flow were identified and used to calculate with $Q_{j, forward} = \sum_{i=1}^{n1} Q_{ij, forward}$ and ($Q_{j, reverse} = \sum_{i=1}^{n2} Q_{ij, reverse}$ for each time point j , and $n1$: total number of voxels showing forward flow on the analysis plane, $n2$: total number of voxels showing reverse flow on the analysis plane. Total forward flow and reverse flow were subsequently calculated by summation of all $Q_{j, forward}$ and $Q_{j, reverse}$ over time, respectively. (Note: The voxel-based reverse flow analysis did not apply connectivity constraints and each voxel was treated independently for the quantification of forward flow, reverse flow, and RFF.)

Based on the obtained forward and reverse flow values, RFF-plane and RFF-voxel were calculated for each of the 2 methods. A detailed illustration of the differences in calculating plane-based and voxel-based flow reversal is provided in Fig. 2. For validation purposes, nine planes at identical anatomical locations were selected by visual inspection (Fig. 1D, 1H) to compare the semi-automatic plane-based analysis with standard manual 2D planar flow quantification.

In addition, using forward flow, reverse flow, and RFF-voxel of each voxel, aortic flow and RFF maps were generated by projecting the mean forward and reverse flow or RFF-voxel onto the aorta in oblique sagittal orientation to visualize the regions with flow reversal (examples in Fig. 4).

Plane-based vs. Voxel-based Flow Quantification

To account for inter-individual differences in aortic dimensions, flow quantification locations were interpolated onto 200 continuous planes (50 ascending aorta planes from ROOT to AAo3, 50 arch planes from AAo3 to Arch3, and 100 descending aorta planes from Arch3 to DAo2) for each of the 35 subjects included in the study (see Fig. 1I). This strategy allowed for averaging of flow parameters across subjects in each patient group and for consistent display of forward flow, reverse flow, RFF-plane, and RFF-voxel as a function of location in the thoracic aorta (see Fig. 1J). The mean and standard deviation of differences between plane-based and voxel-based analysis could then be calculated. The differences in $Q_{forward}$, $Q_{reverse}$, and RFF between plane-based and voxel-based analysis were calculated

for each of 200 planes, and the average differences of each region (AAo, arch, and DAo) in each subject were also calculated.

Statistical Analysis

Kruskal Wallis tests were performed to test for differences of demographic information - age, height, weight, ejection fraction (EF), and stroke volume (SV) between the four subject groups. Agreement of flow parameters between standard and semi-automatic plane-based analysis was assessed using Bland-Altman (BA) analysis to calculate mean difference (MD), and limits of agreement (LOA). In addition, Pearson correlation coefficients (R) were calculated. A Lilliefors test was used to assess normal distribution of hemodynamic parameters. If the data from plane-based vs. voxel-based analysis followed a normal distribution, a two-sample t-test was performed. Otherwise, a Wilcoxon rank sum test was chosen. For all analysis, a p-value < 0.05 was considered statistically significant.

Results

Study Cohort

Patient demographics are summarized in table 1 and showed no statistically significant differences between subgroups except for stroke volume (SV, $P < 0.05$) and aortic dimensions (SOV and MAA). The SV was statistically significantly increased for MoS AR patients compared to healthy controls (116 ± 32 vs 78 ± 15 ml, $P < 0.01$), and for MoS AR patients compared to patients without AR (116 ± 32 vs 76 ± 26 ml, $P < 0.01$). In addition, healthy controls had smaller SOV ($P < 0.02$) and MAA ($P < 0.01$) diameters compared to all patients while aortic dimensions were similar between patient groups.

Standard manual 2D Planar Flow Quantification vs. Semi-automatic Plane-based analysis

The results of Bland-Altman and correlation analysis for all 35 subjects are shown in Fig. 3 and table 2. Correlation analysis demonstrated statistically significant relationships (RFF-plane: $y = 0.99x - 0.0$, net flow Q_{net} : $y = 1.00x - 0.21$, $R > 0.99$, $P < 0.0001$) between standard manual 2D planar flow quantification and flow quantification results derived from the semi-automatic plane-based workflow (figure 3A. RFF-plane, figure 3B. net flow Q_{net}). Table 2 summarizes the results of correlation analysis for all subgroups, which showed similar agreement.

Bland-Altman (BA) plots including data of all 35 subjects are shown in Fig. 3 (C. RFF-plane, D. net flow Q_{net}). Compared to average RFF-plane (6.4%) and net flow Q_{net} (72.4 ml/cycle) over the entire cohort, the bias between standard manual 2D planar and semi-automatic plane-based flow quantification was negligible (Mean Difference (MD): 0.1% in RFF-plane plot, 0.4 ml/cycle in net flow Q_{net} plot). The limits of agreement (LOA) (RFF-plane: 1.01%, net flow: 2.25 ml/cycle) indicated overall very good agreement between two methods (RFF-plane: 16% of the average, net flow: 3% of the average). The most pronounced differences were seen for Mild AR or MoS AR subgroups (blue and magenta data points in Fig. 3C, 3D). The Bland-Altman analysis of subgroups from table 2 showed similar results.

Voxel-based vs. Plane-based analysis – Flow Maps

Examples of forward flow, reverse flow, and RFF-voxel maps for each subgroup are shown in Fig. 4. All subjects demonstrated regional reverse flow in the AAo which was most pronounced in patients (indicated by the red arrows in Fig. 4). Visually observable regional reverse flow in the inner curvature of AAo decreased in the order of: Mild AR $\approx$ MoS AR $>$ No AR $>$ Control. The inner curvature of AAo always showed low forward flow, which resulted in high RFF-voxel values in this region. In addition, there was subtle but notable regional flow reversal near the inner curvature of the proximal descending aorta (yellow arrows in Fig. 4).

Voxel-based vs. Plane-based analysis – Flow Quantification

Fig. 5 summarizes the comparisons between plane-based and voxel-based flow quantifications at the 9 analysis planes. Reverse flow was significantly increased ($P<0.0001$) for voxel-based analysis for all 4 groups ranging from 5.5 to 17.3 ml/cycle with the largest differences seen for the mild AR group (3.8 ± 4.6 vs. 21.1 ± 23.0 ml/cycle, $P<0.0001$). RFF-voxel was significantly elevated ($P<0.0001$) compare to RFF-plane for all 4 groups with most pronounced differences seen for the mild AR group ($4.7\pm5.4\%$ vs. $18.0\pm15.2\%$, $P<0.0001$). Forward flow was only significantly different in the mild AR ($P=0.013$) and MoS AR groups ($P<0.01$).

Results for plane-based vs. voxel-based flow analysis along the entire aorta are shown in Fig. 6 ($Q_{forward}$, $Q_{reverse}$) and Fig. 7 (RFF-plane, RFF-voxel). Each flow or RFF curve represents mean (thick solid lines) and $\pm$ SD region (thinner solid or dash lines) across each sub-group as a function of distance along the aorta. Gray stars indicated statistically significant difference between the two analysis methods. Compared to plane-based analysis curves, reverse flow curves by voxel-based analysis consistently showed larger reverse flow and RFF along entire aorta. The largest differences were seen in the mid AAo. Voxel-based analysis resulted in larger regional reverse flow (as indicated by voxel-based minus plane-based reverse flow) in the following order (the numbers in the parentheses indicate the maximum difference along entire aorta): Mild AR (55 ml/cycle) $>$ MoS AR (50 ml/cycle) $>$ No AR (40 ml/cycle) $>$ Control (20 ml/cycle) (see Fig. 6). The RFF maximum difference in the following order: Mild AR (30%) $\approx$ No AR (30%) $>$ MoS AR (20%) $>$ Control (15%) (see Fig. 7).

The mean $\pm$ SD of differences of plane-based versus voxel-based flow and RFF evaluation in each region (AAo, Arch, DAo, and entire aorta) and in each subgroup (Control, No AR, Mild AR, and MoS AR) are summarized in table 3. Note that net flow (Q_{net}) (calculated by $Q_{ne} = Q_{forward} - |Q_{reverse}|$) remained same between 2 analysis methods (details in Fig. 2), indicated that the difference of $Q_{forward}$ by voxel-based analysis was equal to the difference of $Q_{reverse}$ and only flow differences were reported. The average differences of both flow and RFF were found to be statistically significantly larger in AAo region of patient groups (mild AR, MoS AR, and No AR, more than 30.8 ± 18.3 ml/cycle flow difference and more than $17.6\pm8.9\%$ RFF difference) compared to other regions (arch and DAo, flow difference: less than 8.5 ± 8.4 ml/cycle, $P<0.0001$, RFF difference: less than $8.7\pm6.7\%$, $P<0.0001$) or all

regions of healthy controls (flow difference: less than 10.0 ± 6.3 ml/cycle flow, $P < 0.0001$, RFF difference: less than $9.8 \pm 5.5\%$, $P < 0.0001$).

Discussion

Voxel-based analysis clearly demonstrated regional flow reversal, which was not detected by plane-based analysis. Mean reverse flow and RFF-voxel maps can visualize the region with most pronounced flow reversal. Based on these developments, we found regional flow reversal using the new voxel-based approach even in healthy controls not detected by plane-based analysis. Voxel-based analysis can thus quantify overall flow reversal while plane-based analysis may only indicate global flow reversal. Statistically significant differences of forward flow between voxel-based and plane-based methods indicated the region with most pronounced region flow reversal.

From mean reverse flow and RFF-voxel maps, flow reversal regions were found for all subjects in the AAo and to a lesser extent in the DAo. Similar flow patterns were found using mean reverse flow maps in patient groups (Mild AR, MoS AR, and No AR), which were different to the patterns of healthy controls. By visually inspecting the reverse flow maps, higher AR severity tended to result in more pronounced AAo regional flow reversal (MoS AR $\approx$ Mild AR $>$ No AR $>$ Controls). By subtracting plane-based analysis from the voxel-based quantification results, regional flow reversal was detected and this also showed general agreement that as AR severity increased so did AAo region flow reversal.

Based on these findings, we speculate that plane-based analysis underestimates flow reversal. Previous studies (2–4) investigating aberrant vortex or regional flow reversal mostly used flow patterns instead of plane-based analysis which did not detect significant flow reversal associates with vortex or helix flow. These findings and the results from our study suggest that 2D PC MRI may be suboptimal for the quantification of AR. In addition, there is significant debate about appropriate location of plane placement and the effects of other associated flow characteristics such as turbulent/post-stenotic and vortex flow patterns on AR quantification. Moving towards a 4D and voxel-based approach may help address some of these issues. Our study demonstrated that the voxel-based approach resulted in higher RFFs compared to the plane-based approach, compatible with the generally observed underestimation of MRI derived AR compared to Doppler echocardiography.

It should be noted, that plane-based analysis of $Q_{reverse}$ in our study cohort resulted in generally low reverse flow (less than 10 ml/cycle except MoS AR patients). This would result in a statistically significant difference of $Q_{reverse}$ from voxel-based compared to plane-based analysis even if the difference was not high (less than 3 ml/cycle in $Q_{reverse}$). However, we were able to obtain pronounced regional flow reversal indirectly by checking for statistically significant differences in forward flow ($Q_{forward}$). Since the values from plane-based analysis were high for $Q_{forward}$ (> 50 ml/cycle), a statistically significant difference was only seen when the flow difference was substantial (more than 25 ml/cycle). From these results, the pronounced regional flow reversal was found to occur mostly in the AAo region, and as expected the regional flow reversal decreased with the severity of AR (MoS AR $\approx$ Mild AR $>$ No AR $>$ Control).

Previous studies have found aberrant aortic flow patterns for patients (e.g. dilated aorta, aortic aneurysm, and coronary artery disease) compared to healthy controls (13,24,25), which agreed with the results we found from mean reverse flow and RFF-voxel maps. For reverse flow quantification, standard manual 2D planar analysis has also been widely used. However, previous methods only focused on several discrete planes, which might miss regions with marked reverse flow along the entire aorta. The new analysis workflow presented in this study allowed for the quantification of flow reversal and RFF (plane and voxel) from continuous planes by both plane-based and voxel-based analysis along the entire aorta.

The quantification of regional voxel-by-voxel flow reversal in the AAo has been evaluated in previous studies (26,27) using 2D PC MRI. Similar to our study, global flow curves were separated into forward and reverse flow curves based on the velocity sign of pixels within the analysis plane. In a study by Bensalah et al (27), a total number of 102 healthy subjects without cardiovascular disease were included and the ratio of reverse flow to forward flow was about 10–15% which is close to results of the healthy controls in our study. However, because of the limited spatial coverage provided by 2D PC MRI, flow quantification was only performed in several planes and no flow reversal was detected at the beginning of cardiac cycle. In our study, we found flow reversal for the entire cardiac cycle likely related to the three-directional velocity encoding of 4D flow MRI.

As an additional finding, voxel based flow analysis identified regional flow reversal at the proximal DAo. Compared to flow reversal in the AAo, this effect was much smaller. Nonetheless, the detection of flow reversal in the proximal descending aorta is in line with recent studies which have provided evidence that DAo flow reversal is a common epiphenomenon, even in the absence of aortic valve insufficiency which are in line with our findings (28) (29). For example, a recent Doppler echocardiography study in 296 hypertension patients by Hashimoto et al (28) demonstrated that aortic stiffening causes aortic flow reversal, which was found in all subjects (reverse/forward flow ratio, $35\pm 10\%$) and was positively correlated with parameters of aortic stiffness such as pulse wave velocity, independent of age, aortic diameter, and aortic pressure. Further, the detection of the presence, location, and extent of DAo flow reversal by 4D flow MRI may aid in the identification of patients at risk for stroke via retrograde embolization from high risk plaques in the descending aorta (6). Future studies are warranted to further investigate the diagnostic value of reverse flow maps for the reliable identification of flow reversal at the proximal DAo and its correlation with risk for cerebral embolism.

This study has limitations. The patient cohort was small which influenced the statistical analysis between groups and underlines the feasibility character of this study. A further drawback of our study is related to the variability of the spatial resolution and thus voxel sizes across the patient and volunteer cohort. A reduction in spatial resolution (i.e. increased voxel size) may have led to an underestimation of peak forward or reverse flow in these subjects. Nonetheless, comparison of planar and voxel-based flow reversal is based on relative intra-subject differences and thus less dependent on spatial resolution.

The new analysis workflow required manual interaction to create centerlines, which increased the quantification process duration. In addition, the manual definition of start and end planes and regions for the semi-automatic analysis could lead to inter-observer errors. The reproducibility and observer variability were not analyzed neither. Because of the relative dense planes along the centerline, many planes may contain the same flow information. This would help to make the results line in figures smooth. In addition, the impact of spatial and temporal resolution of flow and RFF quantification was not analyzed. 4D flow MRI data with improved spatial resolution may lead to a more accurate quantification results. Further, stroke volume (SV) was statistically significantly different between subgroups which was expected as SV often increases during aortic insufficiency, which is related to AR severity (30). Therefore, we cannot exclude SV as a factor to influence results between sub-groups. Another limitation is that echocardiography is still the standard of care and is widely used in hospitals, which means the new method for flow measurement would be expected to compare with echocardiography which was not been done in this study.

The standard deviations of reverse flow and RFF-voxel in voxel-based analysis of each subgroup were much larger than for the plane-based analysis, indicating that even in the same subgroup, different subjects may have different regional flow reversal, and subjects from different subgroups may have the same amount of regional reverse flow. Interestingly, voxel-based analysis resulted in similar regional flow reversal and RFF for both MoS AR and mild AR patient groups. It should be noted, that the degree of aortic AR in our study cohort was quantified by 2D PC MRI which relies on plane-based analysis of flow reversal. As a result, this analysis may have underestimated regurgitant fraction which was used to separate the patients into different AR severity groups. In contrast, the voxel-based analysis for AR severity placed these subjects in the same AR severity group, which might be better suited for the classification of AR severity.

Future studies should include larger cohorts stratified by aortic disease to systematically investigate the relationships between elevated voxel-based RFF-voxel and metrics aortic pathology and disease progression and compare these findings to the clinical reference standard (2D PC MRI and Doppler echocardiography). These studies could assess the value of voxel-based reverse flow maps for the easy identification of regions with most pronounced flow to guide definition of most optimal regions for RFF quantification. Further, longitudinal studies are warranted to evaluate the prognostic value of 4D flow based analysis of regional flow reversal and RFF related to patient outcome (e.g. referral to aortic valve surgery, progressive aortic dilatation).

In conclusion, the newly developed voxel-based analysis workflow can evaluate overall flow reversal and detect regional flow reversal which was missed or significantly underestimated by standard plane-based analysis. Mean reverse flow and RFF-voxel maps provide useful tools for the identification of regions with the most pronounced flow reversal. Regional reverse flow was detected mostly in the ascending aorta and less prominently in the descending aorta. Future research will focus on quantitative analysis to identify connections between regional flow reversal and physiological dysfunction.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Schematic illustration of the standard (A–D) and newly developed (E–K) data analysis workflows. Standard 4D flow analysis included data pre-processing of the original 4D flow data (A. Magnitude B. Velocity), 3D segmentation (C), and placement of 2D analysis planes for flow quantification (D). The new workflow for both plane-based and voxel-based analysis included: (E) 3D skeleton of aorta, (F) smooth 3D center line. Black stars show centerline points and red dots show the anatomy of aorta, (G) 20% of the auto-generated planes (only show 20% for better display), (H) Planes identical to standard manual 2D planar method for comparison. Assessment the difference: (I) Boundaries of each region and number of planes after interpolating. (J) Forward flow map based on locations of black stars in (I). Blue stars mean the interpolated plane locations with same distance.

Figure 2.

Illustration of plane-based versus voxel-based analysis of forward/reverse flow and reverse flow fraction (RFF-plane and RFF-voxel) for three time points in the cardiac cycle ($t=1,2,3$). Schematic flow patterns resembling flow profiles in the mid ascending aorta (white circles) for each of these time points are shown on the left side. For illustration purposes, simplified flow velocity profiles are shown as 5 velocity vectors (blue arrows) across the plane (5 voxels across the plane) with unit length for forward/reverse flow. Q_i represents the flow value in voxel i , $Q_j/Q_{j,forward}/Q_{j,reverse}$ is the overall net/forward/reverse flow in the plane at time point j , $Q_{forward}/Q_{reverse}$ is the forward/reverse flow for cardiac cycle, RFF is the reverse flow fraction, and Q is the net flow. For standard plane-based analysis, the net sum of all voxels (Q_j) is independently calculated for each of time points $t=1,2,3$. Next, flow (Q_j) is separated into $Q_{forward}$ and $Q_{reverse}$ and RFF-plane is calculated. For voxel-based analysis, all voxels (Q_i) were separated into $Q_{j,forward}$ or $Q_{j,reverse}$ for each voxel at each time point $t=1,2,3$. Next, $Q_{forward}$ and $Q_{reverse}$ separately calculated as the sum of $Q_{j,forward}$ or $Q_{j,reverse}$ over all time points and RFF-voxel was calculated. Note that both methods result in identical net flow but RFF-voxel result compared to RFF-plane is markedly different (67% compared to 25% in the example).

Figure 3.

Agreement between standard manual 2D planar flow quantification and semi-automatic plane-based quantification. A) Reverse flow fraction (RFF-plane) correlation analysis. B) Net flow correlation analysis. C) Reverse flow fraction (RFF-plane) Bland Altman (BA) analysis. D) Net flow Bland-Altman (BA) analysis.

Figure 4.

Representative flow and RFF-voxel maps examples from each group. A) Forward flow maps for 4 groups. B) Reverse flow maps for 4 groups. C) RFF-voxel maps for 4 groups. The red/yellow arrows in (B) indicate regions with marked regional reverse flow and elevated regional RFF-voxel.

Figure 5. Flow quantification results by both plane-based and voxel-based analysis in each subgroup. (A) Reverse flow fraction. (B) Reverse flow. (C) Forward flow.

Figure 6.

Forward (curves above horizontal zero line) and reverse (curves below zero line) flow comparison of plane-based (red) vs. voxel-based (blue) quantification. The solid thick lines indicate the mean value across the entire cohort of for each sub-groups. The solid and/or dash thin lines showed the standard deviation (SD). The black vertical lines mark the boundaries of ascending aorta, arch, and descending aorta. The gray stars on the top or bottom indicate statistically significant differences between plane-based and voxel-based results. A) Control group. B) Patients without AR group. C) Mild AR group. D) MoS AR group. E) All groups.

Figure 7.

Reverse flow fraction (RFF-plane and RFF-voxel) comparison for plane-based vs. voxel-based quantification. The solid thick lines indicate the mean value across the entire cohort of for each sub-group. The solid and/or dash thinner lines showed the standard deviation (SD). The black vertical lines mark the boundaries of ascending aorta, arch, and descending aorta. The gray stars indicate statistically significant differences between plane-based and voxel-based results. A) Control group. B) Patients without AR group. C) Mild AR group. D) MoS AR group. E) All groups.

Patient demographics including age, gender, height (Ht), weight (Wt), ejection fraction (EF), and stroke volume (SV) as mean $\pm$ standard deviation (SD) except for gender in the format of male and female numbers. The p-value calculated by Kruskal Wallis test showed the statistical difference between subgroups.

Table 1

Group	Age	Gender	Ht(cm)	Wt(kg)	EF(%)	SV(ml)	SOV (mm)	MAA(mm)
Control	57 $\pm$ 7	9M1F	173 $\pm$ 7	94 $\pm$ 17	59 $\pm$ 6	78 $\pm$ 15	33.4 $\pm$ 2.6	32.9 $\pm$ 3.0
No AR	63 $\pm$ 10	7M2F	173 $\pm$ 13	84 $\pm$ 22	58 $\pm$ 6	76 $\pm$ 26	40.4 $\pm$ 5.3	43.1 $\pm$ 3.7
Mild AR	66 $\pm$ 6	5M1F	172 $\pm$ 9	80 $\pm$ 9	61 $\pm$ 4	92 $\pm$ 10	45.3 $\pm$ 4.9	42.8 $\pm$ 5.0
MoS AR	60 $\pm$ 16	8M2F	176 $\pm$ 13	83 $\pm$ 16	57 $\pm$ 8	116 $\pm$ 32	44.3 $\pm$ 4.7	40.9 $\pm$ 5.1
P-value	0.32	N/A	0.65	0.32	0.45	0.04	<0.02	<0.01

Table 2

Results of correlation and Bland-Altman (BA) analysis for reverse flow fraction (RFF-plane) and net flow between manual and semi-automatic plane based methods. R=correlation coefficient, MD=mean difference, LOA=limits of agreement.

		Correlation		Bland Altman	
Groups		r	P-value	MD	LOA
Controls	RFF-plane	0.98	<0.0001	-0.08%	0.57%
	Net Flow	>0.99	<0.0001	-0.44 ml/cycle	2.15 ml/cycle
No AR	RFF-plane	0.98	<0.0001	-0.05%	0.82%
	Net Flow	>0.99	<0.0001	-0.15 ml/cycle	1.64 ml/cycle
Mild AR	RFF-plane	0.99	<0.0001	-0.28%	1.58%
	Net Flow	>0.99	<0.0001	-0.44 ml/cycle	2.16 ml/cycle
MoS AR	RFF-plane	>0.99	<0.0001	-0.05%	1.38%
	Net Flow	>0.99	<0.0001	-0.57 ml/cycle	3.73 ml/cycle
All Data	RFF-plane	>0.99	<0.0001	-0.1%	1.12%
	Net Flow	>0.99	<0.0001	-0.4 ml/cycle	2.61 ml/cycle

Table 3

Flow and reverse flow fraction (RFF) differences between plane-based and voxel-based analysis in each region (AAo, Arch, DAo, and entire aorta) and subgroup (Control, No AR, Mild AR, MoS AR, and all groups). The voxel-based analysis always results in higher value than plane-based analysis which means the differences shown in figure were made by voxel-based results subtracted plane-based results.

		AAo	Arch	DAo	Entire Aorta
Control	Flow-difference (ml/cycle)	10.0 ± 6.3	3.9 ± 2.2	1.9 ± 1.4	4.4 ± 4.8
	RFF-difference (%)	9.8 ± 5.5	5.9 ± 2.5	3.4 ± 2.1	5.6 ± 4.3
No AR	Flow-difference (ml/cycle)	30.8 ± 18.3	7.6 ± 8.5	3.2 ± 2.5	11.2 ± 15.4
	RFF-difference (%)	23.9 ± 9.7	8.7 ± 6.7	5.4 ± 3.1	10.8 ± 9.9
Mild AR	Flow-difference (ml/cycle)	39.4 ± 19.9	6.6 ± 5.4	3.8 ± 3.2	13.4 ± 18.4
	RFF-difference (%)	26.5 ± 10.8	7.1 ± 4.7	6.1 ± 4.3	11.4 ± 11.0
MoS AR	Flow-difference (ml/cycle)	34.4 ± 19.4	8.5 ± 8.4	3.5 ± 2.5	12.5 ± 16.7
	RFF-difference (%)	17.6 ± 8.9	6.9 ± 5.9	4.4 ± 3.0	8.3 ± 7.9
All Groups	Flow-difference (ml/cycle)	27.3 ± 20.0	6.6 ± 6.9	3.0 ± 2.5	10.0 ± 14.8
	RFF-difference (%)	18.5 ± 10.8	7.1 ± 5.3	4.6 ± 3.2	8.7 ± 8.6