Two-minute k-t accelerated aortic 4D flow MRI:

Dual-center study of feasibility and impact on velocity and wall shear stress quantification

Article type: Original Research

Keywords: 4D flow MRI; aorta; wall shear stress; k-t acceleration; dual center

Abbreviations

4D flow MRI: three-dimensional (3D) cine (time-resolved) phase-contrast MRI with three-directional velocity-encoding

AA: ascending aorta

AS: aortic valve stenosis

BAV: bicuspid aortic valve

DA: descending aorta

HTN: hypertension

PWV: pulse wave velocity

WSS: wall shear stress

Summary statement: We show the feasibility in a clinical setting of 2-minute aortic 4D flow MRI in 68 healthy volunteers and patients from 2 centers, providing reproducible velocity and wall shear stress indices sensitive to expected aging- and disease-related aortic hemodynamic alterations.

Implications for Patient Care: Our work aims at accelerating 4D flow MRI, whose clinical use is currently limited by long scan times while evidence for its potential value in diagnosis and patient

management has been growing. Such efforts are needed to allow 4D flow MRI longitudinal, larger multi-center studies to investigate its prognostic value.

Abstract

Purpose: To 1) investigate the two-center feasibility of highly k-t accelerated 2-minute aortic 4D flow MRI; 2) evaluate its performance for the quantification of aortic velocities and wall shear stress (WSS).

Methods: This cross-sectional study prospectively included 68 subjects (Center I: 11 healthy volunteers [age=61±15years], 16 patients with aortic disease [age=60±10years]; Center II: 14 healthy volunteers [age=38±13years], 27 patients with aortic or cardiac disease [age=78±18years]). All subjects underwent highly accelerated 4D flow MRI (k-t acceleration with R=5) of the thoracic aorta. For comparison, conventional 4D flow MRI (R=2) was acquired in the n=27 subjects at Center I. Data analysis included the quantification of regional peak systolic velocities and 3D WSS in the aorta.

Results: k-t accelerated scan times (Center I: 2:03±0:29min, Center II: 2:06±0:20min) were significantly reduced compared to conventional 4D flow (Center I: 12:38±2:25min, $p<0.0001$). Overall good agreement was found between the two techniques (absolute differences≤15%) but proximal aortic WSS was significantly underestimated in patients by k-t accelerated when compared to conventional 4D flow ($p\leq0.03$). k-t accelerated 4D flow MRI was reproducible (intra- and inter-observer intraclass correlation coefficient≥0.98) and identified significantly increased peak velocities and WSS in patients with stenotic ($p\leq0.003$) or bicuspid ($p\leq0.04$) aortic valves compared to healthy volunteers. In addition, k-t accelerated-derived velocities and WSS were inversely related to age ($r\geq-0.53$, $p\leq0.03$) for all healthy volunteers.

Conclusion: k-t accelerated aortic 4D flow MRI providing 2-minute scan times was feasible and reproducible at 2 centers. Although WSS can be underestimated in patients, consistent healthy ageing- and disease-related changes in aortic hemodynamics were observed.

Introduction

Three-dimensional cine phase-contrast magnetic resonance imaging with three-directional velocity encoding, known as 4D flow MRI (1), has proven to be a useful tool for the visualization and quantification of cardiovascular hemodynamics in cardiothoracic diseases, such as congenital heart disease (2), valvular heart disease (3), or aortic abnormalities (4). However, its use in clinical routine is still hampered by lengthy scan prescription including navigator placement for respiration control, and long scan times ranging from 5 to 15 minutes for aortic applications.

Recently developed highly accelerated 4D flow MRI allows for total scan times in the order of 2 minutes. Significant scan time reduction was achieved by k-t acceleration and free breathing without respiratory navigator control, combined with a dedicated k-space sampling to minimize breathing artifacts (5). A pilot study at a single center demonstrated its technical feasibility in in-vitro flow phantom experiments, 10 healthy volunteers and 10 patients with aortic disease (5). Findings of this pilot study revealed that 2-minute 4D flow MRI could reliably quantify hemodynamic indices such as velocity and flow in close agreement with conventional respiratory navigator-gated 4D flow MRI (5).

The initial application of this technique, however, was limited to MRI studies at a single center and did not assess the impact of k-t-acceleration combined with dedicated k-space sampling on more advanced derived hemodynamics metrics, such as wall shear stress (WSS) (4,6–9), or arterial stiffness indices, such as pulse wave velocity (PWV) (10,11). WSS is defined as the viscous force applied by blood flow parallel to vessel walls, and has been shown to be involved in the regulation of endothelial cell function and vessel wall remodeling via endothelial mechanotransduction (12). 4D flow MRI-based assessment of WSS has recently gained increased interest for the characterization of aortic valve disease and associated changes in aortic hemodynamics. Regionally elevated WSS has been implicated in aortic wall tissue degradation (6,13), suggesting its ability to non-invasively detect tissue disease. PWV, which is defined as the speed of the arterial blood pressure wave to travel along an artery, is inversely related to the vessel elasticity. Aortic PWV was shown to strongly and independently predict cardiovascular mortality in elderly subjects (10),

and several imaging studies have reported the usefulness of MRI to provide an accurate non-invasive measurement of aortic PWV (11).

The objective of this study was to build on the previously developed 2-minute 4D flow MRI protocol and to 1) prospectively investigate the feasibility of 2-minute aortic 4D flow MRI in larger volunteer and patient cohorts at two centers; and 2) evaluate its performance for the quantification of 3D regional WSS and pulse wave velocity (PWV).

Materials and Methods

Study cohort

Healthy volunteers with no history of cardiovascular disease and patients scheduled for standard-of-care cardiothoracic MRI were prospectively recruited between July 2016 and December 2017. Approval of the local Institutional Review Boards, HIPAA compliance and informed consent from all participants were obtained. Patient recruitment at Center I targeted consecutive patients with aorta and/or aortic valve disease, while recruitment at Center II targeted all patients, due to a lower proportion of aortic disease. Center I subjects underwent both conventional respiration-controlled and k-t accelerated free breathing 4D flow MRI, while Center II subjects underwent k-t accelerated free breathing 4D flow MRI only due to time constraints. Of note, 20 out of the 71 subjects included in the present study have been previously reported (5). While the prior study investigated conventional aortic flow hemodynamic indices at a single center, in this manuscript we included more patients at the initial center, extended to another inclusion center and investigated quantification of more advanced parameters such as aortic wall shear stress and pulse wave velocity.

MRI acquisitions

4D flow MRI was acquired in a sagittal oblique volume which included the thoracic aorta on 1.5T MRI systems (Center I: Aera or Avanto; Center II: Aera, Siemens, Germany), except for 4 Center II patients (3T Prisma, Siemens). Standard-of-care cardiothoracic MRI included the administration of Gadolinium-based contrast agent (Center I patients: Gadavist, Bayer, Leverkusen, Germany; all Center II subjects: Dotarem, Guerbet, Villepinte, France) prior to 4D flow data acquisition, except for Center I healthy volunteers who were recruited for a non-contrast research MRI. Conventional respiration-controlled aortic 4D flow MRI was acquired at Center I according to current consensus recommendations (1) using the acquisition parameters summarized in Table 1. Briefly, navigator gating of the lung-liver interface with a fixed 16-mm acceptance window size (14), and parallel imaging GRAPPA (15) along the phase-encoding direction k_y with an acceleration factor R=2 and 24 reference lines were employed. k-t accelerated free breathing aortic 4D flow MRI was acquired at both centers using similar acquisition parameters, with k-t PEAK GRAPPA (16) with R=5 and no respiration control to keep the acquisition even shorter (Table 1). To minimize respiration-related artifacts, an optimized Cartesian k_y-k_z-space filling pattern was used as described previously (5): corners were filled initially followed by a centric reordering, to prioritize k-space center acquisition and thus favor contrast over as few respiratory cycles as possible once stable patient physiological and respiratory conditions are reached. Scan time was recorded for all 4D flow MRI scans.

Standard cine balanced steady-state free precession (bSSFP) short-axis images covering the left ventricle (LV) were also acquired to compute LV stroke volume (SV) as a reference standard in subjects from Center II.

4D flow MRI data analysis

The same analysis workflow which is illustrated in Figure 1 was applied to aortic 4D flow MRI datasets acquired at both centers. 4D flow MRI data pre-processing included corrections for Maxwell terms, eddy currents, velocity aliasing and noise, as well as the computation of a 3D phase-contrast MR angiogram

(PC-MRA), using a previously described software developed in Matlab (R2017b version, The Mathworks, Natick, MA, USA) (Figure 1.a) (17). Next, a segmentation of the 3D aortic volume was generated (Mimics, Materialise NV, Louvain, Belgium) and used to mask blood flow velocities inside the thoracic aorta. Peak systole was automatically defined as the cardiac time frame with the highest velocity as averaged over the entire volume. Hemodynamic quantification included the calculation of peak systolic velocity and WSS as shown in Figure 1.b. The 3D aorta segmentation was used to calculate a systolic velocity maximal intensity projection (MIP), and volumetric peak systolic velocities were extracted in consecutive contiguous regions of interest covering the ascending aorta (AA), aortic arch, and descending aorta (DA) (18) , as defined by the following anatomic landmarks: AA: aortic valve to the most proximal supra-aortic branch (brachiocephalic trunk), arch: brachiocephalic trunk to the most distal subclavian artery, DA: subclavian artery to the level of the aortic valve. Finally, peak systolic 3D WSS on the aortic surface was calculated using a previously published 3D algorithm (19). Regional maximum WSS (defined as the mean of the absolute WSS top 2% to reduce the effect of noise, as previously proposed (7)) was extracted in 6 manually defined regions of interest covering the inner and outer wall of the AA, aortic arch and DA.

In addition, global aortic PWV was quantified from all conventional and k-t accelerated 4D flow MRI datasets collected at Center I using a previously described strategy (20,21). Briefly, a centerline of the 3D segmented aortic volume was first generated to allow automated positioning of cross-sectional planes every 4 mm along the aorta (22). Time-resolved flow rate waveforms were then computed within each 2D plane using masked velocities, and the time delay between the first most proximal aortic plane and each subsequent plane was calculated using maximal cross-correlation between the two flow rate waveforms (23). Finally, PWV was defined as the inverse slope of the linear regression on each time delay plotted according to the distance to the most proximal plane along the aortic centerline.

Stroke volume in the AA was computed from k-t accelerated 4D flow data in Center II healthy volunteers (17). First, a 2D cross-sectional plane was positioned on the 3D segmented volume at the level of the

pulmonary artery using EnSight (10.1.4 version, CEI, USA), in which AA borders were then delineated for each time frame of the cardiac cycle using a custom software (Matlab, MathWorks, USA). Finally net flow volume was obtained by time-integrating the flow rate waveform.

Intra- and inter-observer variability of k-t accelerated 4D flow MRI-derived hemodynamic indices

Reproducibility of the regional aortic peak systolic maximal velocity and WSS quantification was assessed by blinded repeated analysis by the first observer and by a second independent observer, for 20 randomly selected k-t accelerated 4D flow MRI datasets from both Center I and Center II (5 healthy volunteers and 5 patients from each Center).

Statistical methods

Statistical analyses were performed using Matlab (MathWorks, USA). The Lilliefors test was used to test for normal distribution of subjects' basic characteristics, scan times, as well as aortic hemodynamic and stiffness parameters, which were provided as mean ± standard deviation. Comparisons between conventional and k-t accelerated 4D flow MRI acquired in the same subjects at Center I, as well as between cine bSSFP- and k-t accelerated 4D flow-derived LV SV at Center II, were performed using Wilcoxon signed-rank tests, Bland-Altman analyses and intraclass correlation coefficients (ICC). Mean biases, limits of agreement (± 1.96 x standard deviations) and absolute differences between the 2 techniques, expressed as the percentage of the reference standard, were calculated. Bland-Altman analyses and ICC were further used to study intra- and inter-observer variability. Differences in k-t accelerated 4D flow scan times between Center I and Center II, as well as differences between patients and healthy volunteers, were evaluated using a Wilcoxon rank sum test. Finally, the relationship with age of k-t accelerated 4D flow MRI-derived aortic velocity and WSS indices was investigated using linear regressions and pooling of Centers I and II data. Spearman's rank correlation coefficients r were calculated. A p value <0.05 was considered statistically significant.

Results

Study cohort

A total number of 71 subjects were recruited from both centers. One patient dataset from Center I and 2 patient datasets from Center II were excluded, due to complete signal loss in the 4D flow images in the DA as a result of previous stented aortic coarctation and volume orientation mispositioning, respectively. Basic characteristics of the resulting 68 subjects (n=25 healthy volunteers, n=43 patients) are summarized in Table 2. Patients recruited at Center I had various concomitant diseases: 9 had aortic dilation or aneurysm, 8 had a bicuspid aortic valve (BAV), 4 had aortic valve stenosis (AS), one had aortic valve regurgitation (AR), 3 had previously undergone surgery (two underwent aortic valve replacement (AVR), including one with aortic repair, and one underwent repair of type A aortic dissection). Patients recruited at Center II were referred for aortic disease (n=6), cardiac disease (n=20) and type II diabetes with dyspnea (n=1). Among patients with aortic disease, one had aortic dilation with AR, 4 had AS, one had had concomitant AVR and dissection repair. Cardiac disease ranged from coronary artery disease (n=5) including myocardial infarction (n=2), heart failure (n=7), hypertensive disease (n=3), dilated cardiomyopathy (n=2), dilation of all cardiac chambers (n=1), myocarditis (n=1) and cardiac mass (n=1).

Conventional vs. k-t accelerated aortic 4D flow MRI at Center I

Scan times are provided in Table 2, confirming significantly shorter k-t accelerated 4D flow MRI acquisitions when compared to conventional 4D flow MRI in the n=27 subjects recruited at Center I ($p<0.0001$).

Figure 2.a illustrates aortic peak systolic velocity MIPs and 3D aortic systolic WSS magnitude in representative examples of a healthy volunteer and patients from Center I, obtained using conventional and k-t accelerated 4D flow MRI. Similar aortic velocity and WSS patterns were observed between the two techniques. The corresponding quantitative regional aortic hemodynamic indices as obtained using conventional and k-t accelerated 4D flow MRI are summarized in Table 3 and Figure 3 (Bland-Altman

diagrams). Discrepancies between both methods were overall higher for WSS (absolute differences averaged over the whole group and ICC in the inner AA: 12±14% and ICC=0.87; outer AA: 13±8.9% and ICC=0.89; inner arch: 14±15% and ICC=0.91; outer arch: 15±12% and ICC=0.92; inner DA: 13±13% and ICC=0.71; outer DA: 11±13% and ICC=0.74) than for velocity (AA: 5.2±4.3% and ICC=0.98; arch: 10±15% and ICC=0.95; DA: 9.6±10% and ICC=0.77). Only AA WSS in patients was significantly underestimated by k-t accelerated 4D flow when compared to the conventional approach (p=0.03 and p=0.02 on the inner and outer curvature, respectively).

Finally, after exclusion of a 71-yo outlier in which we obtained non-physiological values including using conventional 4D flow data, global aortic PWV was significantly different between conventional and k-t accelerated techniques (11.0±3.3 m/s vs. 9.7±2.8 m/s, p=0.003; mean bias [limits of agreement] = 1.3 [-2.5;5.1] m/s; absolute difference = 15±21%; ICC = 0.73).

k-t accelerated 4D flow MRI at Center II

k-t accelerated 4D flow scan times in the order of 2 minutes were also achieved for the n=41 subjects recruited at Center II (Table 2). Representative examples of peak systolic aortic velocity MIP and 3D WSS magnitude from subjects recruited at Center II are provided in Figure 2.b. Quantitative values in healthy volunteers and patients are provided in Table 4.

LV SV obtained in healthy volunteers (n=14) was 98±23 and 84±18 mL using cine bSSFP and k-t accelerated 4D flow data (p=0.0002), respectively, resulting in mean bias [limits of agreement] = -14 [-35;6.3] mL, absolute difference = -14±9.1% and ICC = 0.70.

k-t accelerated 4D flow MRI - full cohort

Significant inverse relationships were obtained between healthy volunteers' age and k-t accelerated 4D flow MRI-derived systolic peak velocities (aortic arch: r=-0.64, p=0.0005; DA: r=-0.75, p<0.0001) as well as maximum WSS (inner arch: r=-0.57, p=0.003; outer arch: r=-0.53, p=0.007; inner DA: r=-0.81, p<0.0001; outer DA: r=-0.80, p<0.0001), across the entire cohort of 25 controls recruited at both centers (Figure 4).

In patients, as illustrated in Figure 2, k-t accelerated 4D flow was able to reproduce the expected disease-related changes in aortic hemodynamics when compared to healthy volunteers at both centers: regionally elevated systolic WSS and velocity in the AA of patients with AS, reduced WSS in patients with hypertension or dilated aorta and no AS, altered AA flow following surgery. Differences compared to healthy volunteers were significant for the following subgroups (Figure 5): AS (AA velocity: 98% increase, p<0.0001; inner AA WSS: 54% increase, p=0.003; outer AA WSS: 51% increase, p=0.001), BAV (AA velocity: 47% increase, p=0.01; outer AA WSS: 29% increase, p=0.04) and hypertension (inner AA WSS: 19% decrease, p=0.04; outer AA WSS: 24% decrease, p=0.05). The WSS decrease in patients with a dilated aorta and no aortic valve disease when compared to healthy volunteers did not reach statistical significance (inner AA: 12% decrease, p=0.08; outer AA: 10% decrease, p=0.29).

Finally, good intra- and inter-observer reproducibility at both Centers was found for the estimation of aortic hemodynamic indices provided by k-t accelerated 4D flow MRI (Table 5).

Discussion

The purpose of this work was to assess the two-center feasibility of a recently proposed k-t accelerated free breathing aortic 4D flow MRI sequence under 2 minutes, as well as its ability to quantify reliable velocity and WSS indices. Our main findings were: 1) k-t accelerated aortic 4D flow MRI was feasible with short scan time and without the need for respiratory navigator placement, in prospectively recruited healthy volunteers and patients at two centers, 2) on average, two minute-scan time was achieved in study

cohorts at both centers, which was significantly shorter than conventional navigator-gated 4D flow, 3) peak systolic velocities in all regions as well as distal aortic systolic maximum WSS were equivalent in both healthy volunteers and patients, 4) in patients, proximal aortic WSS was significantly underestimated compared to conventional 4D flow-derived WSS, 5) aortic hemodynamic indices provided by k-t accelerated 4D flow were reproducible and reflected the expected age- and disease-related alterations.

While the k-t accelerated aortic 4D flow MRI sequence was successfully acquired in the 71 prospective healthy volunteers and patients at both centers, three datasets had to be excluded from the analysis because of either acquisition volume mispositioning or signal loss, which was easily explained by the presence of a stent (24). In agreement with a pilot study (5), we found that scan times were in the order of 2 minutes and thus on average 6 times shorter compared to navigator-gated aortic 4D flow MRI.

The findings of this study demonstrated that accelerated 4D flow MRI was able to provide reliable velocities when compared to conventional 4D flow MRI in the AA, aortic arch and DA. This is in agreement with recent works investigating various ways to accelerate 4D flow MRI, from k-t acceleration (5), self-gated ultra-short echo time (25), low-rank matrix structure and Hadamard sparsity (26), echo-planar imaging (27), pseudo-random variable-density Cartesian undersampling combined with k-t SPARSE-SENSE (28), to hybrid one- and two-sided flow encodings only (29). Other recent studies have focused on reducing 4D flow scan times down to a single breath-hold based on spiral sampling combined with dynamic compressed sensing (30) or Bayesian imaging approach (31), which allows to avoid both respiratory motion and the use of lengthy navigator. This growing literature on the application of acceleration techniques to 4D flow MRI suggests the opportunity to foster its clinical use, which is today often limited by long scan times.

Previous work also demonstrated the agreement between k-t accelerated and conventional 4D flow MRI in the estimation of aortic net volume (5). In the present study, due to the lack of a 4D flow reference at the second Center, we compared k-t accelerated flow volume to standard-of-care bSSFP-derived LV SV in healthy volunteers and found reasonable relationship, with values and mean bias which were similar to

previously reported findings (18 healthy volunteers; 4D flow-derived aortic flow volume = 81±24 mL vs. LV SV = 97±14 mL, resulting in mean bias = -15±44 mL) (32).

We further investigated aortic 3D WSS and found increased discrepancies between k-t accelerated and conventional 4D flow MRI. The underestimation of k-t accelerated-derived WSS was significant in patients with aortic disease for both the AA inner and outer curvature walls, and we observed heteroscedastic Bland-Altman plots with higher discrepancy obtained for higher WSS values. This could be explained by several factors, including respiratory motion and differences in spatial and temporal resolutions that could underestimate complex hemodynamic alterations, as well as between the two imaging acceleration techniques (standard GRAPPA vs. k-t acceleration). Indeed, in agreement with our findings, significant differences were previously shown in aortic WSS estimated using k-t GRAPPA accelerated 4D flow with an acceleration factor R=5 when compared to GRAPPA with R=2, with the same spatial and temporal resolutions (33). Another study on a realistic thoracic aortic phantom reported a significant underestimation of WSS using 4D flow when reducing spatial and temporal resolutions, with a higher sensitivity to the former (34). A 70% difference in WSS was found when reducing resolutions from 1.5x1.5x2.0mm^3 and 20ms to 2.5x2.5x4.0mm^3 and 40ms, respectively (34). Future studies should investigate their separate effects and subsequently define optimized spatial and temporal resolutions as well as acceleration.

Nonetheless, aortic velocity and WSS provided by k-t accelerated 4D flow were able to characterize expected age- and disease-related alterations. First, we found that both indices significantly decreased with age in healthy volunteers, as previously described (8,35,36). We further obtained correlation coefficients similar to those previously reported using aortic 4D flow MRI ($r=0.57$, $p<0.001$ for velocity and $r=0.62$, $p<0.001$ for WSS in 56 controls aged from 19 to 78 years (36); $r=0.58$, $p=0.012$ for circumferential WSS and $r=0.71$, $p<0.0001$ for axial WSS in 24 controls aged from 21 to 74 years (8)). Furthermore, our indices were able to characterize the known increase in proximal aortic velocity (37) and WSS (38,39) in patients with AS when compared to healthy volunteers. In accordance with the literature, patients with a BAV also

demonstrated a significant increase in peak velocity (40) along with asymmetrically increased WSS on the AA outer wall (41). Conversely, we observed the previously reported decrease in AA WSS in patients with hypertension (42) and in the 5 patients with a dilated aorta and no AS/BAV (37,39,43), although the latter was not significant. Finally, post-surgery 4D flow MRI data revealed various aortic hemodynamic changes (4,7); however, due to the low number of patients and heterogeneity of procedures, we did not find any significant differences compared to healthy volunteers. Importantly, observed significant differences in aortic valve disease patients compared to healthy volunteers were larger than WSS underestimation vs. conventional 4D flow, and similar to previous findings reported in a large cohort of 571 patients using a conventional 4D flow MRI technique: patients with AS had increased regional AA WSS by 16-177%, and patients with a BAV had an increased outer AA WSS by 9-34% (39). In addition, the intra- and inter-observer variability of k-t accelerated 4D flow MRI-derived WSS was much lower than these physiologic WSS differences, and similar to previously reported conventional 4D flow reproducibility (mean difference $\leq$ 0.09 [-0.3; 0.5] Pa for WSS (7) and 0.01 m/s, ICC = 0.98 for velocity (18)).

Finally, we found significantly different global aortic pulse wave velocity between conventional and k-t accelerated 4D flow MRI data. We speculate that respiration control, spatial resolution, as well as temporal resolution may have contributed to the observed PWV differences as previously demonstrated (44). More studies are needed to further investigate the clinical value of k-t accelerated 4D flow-derived aortic PWV.

The main limitation of our study is the small and heterogeneous population, although we were able to retrieve statistically significant findings that were consistent with literature. Populations were also different between the 2 institutions, in terms of disease but also age and gender distributions, due to the prospective feature of our study. Different scanners were used, including different field strengths. However only 4/68 subjects were scanned at 3T while all the other 94% of subjects were scanned at 1.5T; moreover, such field strengths were previously shown to be of identical performance for the quantification

of aortic peak systolic velocity or WSS (45). An additional drawback is related to the lack of a gold standard for aortic hemodynamic measurements since invasive procedures could not be performed. Instead, we chose to define 4D flow MRI acquired according to the current consensus (1) at Center I and conventional cine bSSFP left ventricular stroke volume measurements at Center II, as a reference standard. Further interscan test-retest studies will be needed to demonstrate the reproducibility of this k-t accelerated 4D flow MRI technique. This preliminary multi-center effort should be extended to more institutions both with and without experience with cardiovascular MRI to confirm the feasibility of such sequence. Finally, a technical limitation is related to the lengthy image reconstruction time which could reach up to 12 minutes, which can be shortened by improved GPU-based implementation in future studies.

Conclusion

The findings of this study demonstrate the dual-center feasibility of 2-minute k-t accelerated aortic 4D flow MRI, which was able to characterize consistent healthy ageing- and disease-related changes in velocity and WSS, although the latter was significantly underestimated in the proximal aorta of patients when compared to conventional 4D flow. Such efforts in fostering 4D flow clinical use are crucial to allow longitudinal, larger multi-center studies needed to establish specific aortic hemodynamic indices reference normal ranges.

References

1. Dyverfeldt P, Bissell M, Barker AJ, et al. 4D flow cardiovascular magnetic resonance consensus statement. J Cardiovasc Magn Reson 2015;17(1):72. doi: 10.1186/s12968-015-0174-5

2. Driessen MMP, Schings MA, Sieswerda GT, et al. Tricuspid flow and regurgitation in congenital heart disease and pulmonary hypertension: comparison of 4D flow cardiovascular magnetic resonance and echocardiography. J Cardiovasc Magn Reson 2018;20(1):5. doi: 10.1186/s12968-017-0426-7

3. Binter C, Gotschy A, Sündermann SH, et al. Turbulent Kinetic Energy Assessed by Multipoint 4-Dimensional Flow Magnetic Resonance Imaging Provides Additional Information Relative to Echocardiography for the Determination of Aortic Stenosis Severity. Circ Cardiovasc Imaging 2017;10(6):e005486. doi: 10.1161/CIRCIMAGING.116.005486

4. Bissell MM, Loudon M, Hess AT, et al. Differential flow improvements after valve replacements in bicuspid aortic valve disease: a cardiovascular magnetic resonance assessment. J Cardiovasc Magn Reson 2018;20(1):10. doi: 10.1186/s12968-018-0431-5

5. Bollache E, Barker AJ, Dolan RS, et al. k-t accelerated aortic 4D flow MRI in under two minutes: Feasibility and impact of resolution, k-space sampling patterns, and respiratory navigator gating on hemodynamic measurements. Magn Reson Med 2018;79(1):195–207. doi: 10.1002/mrm.26661

6. Guzzardi DG, Barker AJ, van Ooij P, et al. Valve-Related Hemodynamics Mediate Human Bicuspid Aortopathy: Insights From Wall Shear Stress Mapping. J Am Coll Cardiol 2015;66(8):892–900. doi: 10.1016/j.jacc.2015.06.1310

7. Bollache E, Fedak PWM, van Ooij P, et al. Perioperative evaluation of regional aortic wall shear stress patterns in patients undergoing aortic valve and/or proximal thoracic aortic replacement. J Thorac Cardiovasc Surg 2018;155(6):2277-2286.e2. doi: 10.1016/j.jtcvs.2017.11.007

8. Kolipaka A, Illapani VSP, Kalra P, et al. Quantification and comparison of 4D-flow MRI-derived wall shear stress and MRE-derived wall stiffness of the abdominal aorta. J Magn Reson Imaging 2017;45(3):771–778. doi: 10.1002/jmri.25445

9. Sotelo J, Dux-Santoy L, Guala A, et al. 3D axial and circumferential wall shear stress from 4D flow MRI data using a finite element method and a laplacian approach. Magn Reson Med 2018;79(5):2816–2823. doi: 10.1002/mrm.26927

10. Meaume S, Benetos A, Henry OF, Rudnichi A, Safar ME. Aortic pulse wave velocity predicts cardiovascular mortality in subjects >70 years of age. Arterioscler Thromb Vasc Biol 2001;21(12):2046–2050.

11. Ohyama Y, Redheuil A, Kachenoura N, Ambale Venkatesh B, Lima JAC. Imaging Insights on the Aorta in Aging. Circ Cardiovasc Imaging 2018;11(4):e005617. doi: 10.1161/CIRCIMAGING.117.005617

12. Tanweer O, Wilson TA, Metaxa E, Riina HA, Meng H. A Comparative Review of the Hemodynamics and Pathogenesis of Cerebral and Abdominal Aortic Aneurysms: Lessons to Learn From Each Other. J Cerebrovasc Endovasc Neurosurg 2014;16(4):335–349. doi: 10.7461/jcen.2014.16.4.335

13. Bollache E, Guzzardi DG, Sattari S, et al. Aortic valve-mediated wall shear stress is heterogeneous and predicts regional aortic elastic fiber thinning in bicuspid aortic valve-associated aortopathy. J Thorac Cardiovasc Surg 2018;156(6):2112-2120.e2. doi: 10.1016/j.jtcvs.2018.05.095

14. Markl M, Harloff A, Bley TA, et al. Time-resolved 3D MR velocity mapping at 3T: improved navigator-gated assessment of vascular anatomy and blood flow. J Magn Reson Imaging 2007;25(4):824–831. doi: 10.1002/jmri.20871

15. Griswold MA, Jakob PM, Heidemann RM, et al. Generalized autocalibrating partially parallel acquisitions (GRAPPA). Magn Reson Med 2002;47(6):1202–1210. doi: 10.1002/mrm.10171

16. Jung B, Ullmann P, Honal M, Bauer S, Hennig J, Markl M. Parallel MRI with extended and averaged GRAPPA kernels (PEAK-GRAPPA): Optimized spatiotemporal dynamic imaging. J Magn Reson Imaging 2008;28(5):1226–1232. doi: 10.1002/jmri.21561

17. Schnell S, Entezari P, Mahadewia RJ, et al. Improved Semiautomated 4D Flow MRI Analysis in the Aorta in Patients With Congenital Aortic Valve Anomalies Versus Tricuspid Aortic Valves. J Comput Assist Tomogr 2016;40(1):102–108. doi: 10.1097/RCT.0000000000000312

18. Rose MJ, Jarvis K, Chowdhary V, et al. Efficient method for volumetric assessment of peak blood flow velocity using 4D flow MRI. J Magn Reson Imaging JMRI 2016;44(6):1673–1682. doi: 10.1002/jmri.25305

19. Potters WV, van Ooij P, Marquering H, vanBavel E, Nederveen AJ. Volumetric arterial wall shear stress calculation based on cine phase contrast MRI. J Magn Reson Imaging JMRI 2015;41(2):505–516. doi: 10.1002/jmri.24560

20. Markl M, Wallis W, Brendecke S, Simon J, Frydrychowicz A, Harloff A. Estimation of global aortic pulse wave velocity by flow-sensitive 4D MRI. Magn Reson Med 2010;63(6):1575–1582. doi: 10.1002/mrm.22353

21. Markl M, Wallis W, Strecker C, Gladstone BP, Vach W, Harloff A. Analysis of pulse wave velocity in the thoracic aorta by flow-sensitive four-dimensional MRI: Reproducibility and correlation with characteristics in patients with aortic atherosclerosis. J Magn Reson Imaging 2012;35(5):1162–1168. doi: 10.1002/jmri.22856

22. Vali A, Aristova M, Ansari SA, et al. Feasibility of Automated Analysis of Dual-Venc 4d Flow Mri to Assess Hemodynamics in Patients With Intracranial Atherosclerotic Disease. Stroke 2018;49(Suppl_1):ATP119.

23. Jarvis K, Vali A, Prabhakaran S, Collins JD, Markl M. 4D Flow MRI-Based Aortic Pulse Wave Velocity: Systematic Analysis of the Impact of Temporal Resolution on Estimation in Patients with Aortic Atherosclerosis and Age-matched Controls. Proc ISMRM 2018;2928.

24. Wang Y, Truong TN, Yen C, et al. Quantitative evaluation of susceptibility and shielding effects of nitinol, platinum, cobalt-alloy, and stainless steel stents. Magn Reson Med 2003;49(5):972–976. doi: 10.1002/mrm.10450

25. Krämer M, Motaal AG, Herrmann K-H, et al. Cardiac 4D phase-contrast CMR at 9.4 T using self-gated ultra-short echo time (UTE) imaging. J Cardiovasc Magn Reson 2017;19(1):39. doi: 10.1186/s12968-017-0351-9

26. Valvano G, Martini N, Huber A, et al. Accelerating 4D flow MRI by exploiting low-rank matrix structure and hadamard sparsity: Accelerating 4D Flow MRI by Low-Rank Sparse Decomposition. Magn Reson Med 2017;78(4):1330–1341. doi: 10.1002/mrm.26508

27. Garg P, Westenberg JJM, van den Boogaard PJ, et al. Comparison of fast acquisition strategies in whole-heart four-dimensional flow cardiac MR: Two-center, 1.5 Tesla, phantom and in vivo validation study: Whole Heart 4D Flow Validation Study. J Magn Reson Imaging 2018;47(1):272–281. doi: 10.1002/jmri.25746

28. Liu J, Koskas L, Faraji F, et al. Highly accelerated intracranial 4D flow MRI: evaluation of healthy volunteers and patients with intracranial aneurysms. Magn Reson Mater Phys Biol Med 2018;31(2):295–307. doi: 10.1007/s10334-017-0646-8

29. Wang D, Chien A, Shao J, Ali FA, Hu P. Accelerated phase contrast MRI using hybrid one- and two-sided flow encodings only (HOTFEO). NMR Biomed 2018;e3904. doi: 10.1002/nbm.3904

30. Dyvorne H, Knight-Greenfield A, Jajamovich G, et al. Abdominal 4D Flow MR Imaging in a Breath Hold: Combination of Spiral Sampling and Dynamic Compressed Sensing for Highly Accelerated Acquisition. Radiology 2015;275(1):245–254. doi: 10.1148/radiol.14140973

31. Rich A, Potter LC, Jin N, Liu Y, Simonetti OP, Ahmad R. A Bayesian approach for 4D flow imaging of aortic valve in a single breath-hold. Magn Reson Med 2019;81(2):811–824. doi: 10.1002/mrm.27386

32. Frydrychowicz A, Wieben O, Niespodzany E, Reeder SB, Johnson KM, François CJ. Quantification of thoracic blood flow using volumetric magnetic resonance imaging with radial velocity encoding: in vivo validation. Invest Radiol 2013;48(12):819–825. doi: 10.1097/RLI.0b013e31829a4f2f

33. Schnell S, Markl M, Entezari P, et al. *k-t* GRAPPA accelerated four-dimensional flow MRI in the aorta: Effect on scan time, image quality, and quantification of flow and wall shear stress: *k-t* GRAPPA Acceleration and Hemodynamics. Magn Reson Med 2014;72(2):522–533. doi: 10.1002/mrm.24925

34. Montalba C, Urbina J, Sotelo J, et al. Variability of 4D flow parameters when subjected to changes in MRI acquisition parameters using a realistic thoracic aortic phantom: Variability of 4D Flow Parameters Using a Realistic Thoracic Aortic Phantom. Magn Reson Med 2018;79(4):1882–1892. doi: 10.1002/mrm.26834

35. Lantz J, Renner J, Länne T, Karlsson M. Is aortic wall shear stress affected by aging? An image-based numerical study with two age groups. Med Eng Phys 2015;37(3):265–271. doi: 10.1016/j.medengphy.2014.12.011

36. van Ooij P, Garcia J, Potters WV, et al. Age-related changes in aortic 3D blood flow velocities and wall shear stress: Implications for the identification of altered hemodynamics in patients with aortic valve disease: Age-Related Changes in 3D Velocity and WSS. J Magn Reson Imaging 2016;43(5):1239–1249. doi: 10.1002/jmri.25081

37. Masutani EM, Contijoch F, Kyubwa E, et al. Volumetric segmentation-free method for rapid visualization of vascular wall shear stress using 4D flow MRI. Magn Reson Med 2018;80(2):748–755. doi: 10.1002/mrm.27159

38. von Knobelsdorff-Brenkenhoff F, Karunaharamoorthy A, Trauzeddel RF, et al. Evaluation of Aortic Blood Flow and Wall Shear Stress in Aortic Stenosis and Its Association With Left Ventricular Remodeling. Circ Cardiovasc Imaging 2016;9(3):e004038. doi: 10.1161/CIRCIMAGING.115.004038

39. van Ooij P, Markl M, Collins JD, et al. Aortic Valve Stenosis Alters Expression of Regional Aortic Wall Shear Stress: New Insights From a 4-Dimensional Flow Magnetic Resonance Imaging Study of 571 Subjects. J Am Heart Assoc 2017;6(9):e005959. doi: 10.1161/JAHA.117.005959

40. Farag ES, van Ooij P, Planken RN, et al. Aortic valve stenosis and aortic diameters determine the extent of increased wall shear stress in bicuspid aortic valve disease: AS and Aortic Diameters Determine WSS in BAV. J Magn Reson Imaging 2018;48(2):522–530. doi: 10.1002/jmri.25956

41. Barker AJ, Markl M, Burk J, et al. Bicuspid Aortic Valve Is Associated With Altered Wall Shear Stress in the Ascending Aorta. Circ Cardiovasc Imaging 2012;5(4):457–466. doi: 10.1161/CIRCIMAGING.112.973370

42. Vasava P, Jalali P, Dabagh M, Kolari PJ. Finite Element Modelling of Pulsatile Blood Flow in Idealized Model of Human Aortic Arch: Study of Hypotension and Hypertension. Comput Math Methods Med 2012;2012:1–14. doi: 10.1155/2012/861837

43. Bürk J, Blanke P, Stankovic Z, et al. Evaluation of 3D blood flow patterns and wall shear stress in the normal and dilated thoracic aorta using flow-sensitive 4D CMR. J Cardiovasc Magn Reson 2012;14(1):84. doi: 10.1186/1532-429X-14-84

44. Bargiotas I, Mousseaux E, Yu W-C, et al. Estimation of aortic pulse wave transit time in cardiovascular magnetic resonance using complex wavelet cross-spectrum analysis. J Cardiovasc Magn Reson 2015;17(1):65. doi: 10.1186/s12968-015-0164-7

45. Strecker C, Harloff A, Wallis W, Markl M. Flow-sensitive 4D MRI of the thoracic aorta: Comparison of image quality, quantitative flow, and wall parameters at 1.5 T and 3 T. J Magn Reson Imaging 2012;36(5):1097–1103. doi: 10.1002/jmri.23735

Tables

Table 1. Acquisition parameters used for aortic 4D flow MRI exams according to the inclusion center.

	Center I		**Center II**
	Conventional	*k-t accelerated*	*k-t accelerated*
ECG gating	Prospective		Prospective
Respiration control	Navigator (16-mm window)	None	None
TR (ms)	4.8±0.1	4.2±0.1	4.2±0.1
TE (ms)	2.4±0.1	2.2±0.1	2.2±0.1
Flip angle (°)	Healthy volunteers: 7; patients: 15		15
Acq. matrix	160x84-100	160x70-80	160x80
FOV (mm^2)	340-400x270-325	360-400x270-300	280-440x270-330
SRes (mm^3)	3.1-3.7x2.1-2.5x2.4-3.2	3.4-3.9x2.3-2.5x2.6-3.3	3.4-4.1x2.3-2.8x2.4-2.8
N_{Seg}	2	4	4
TRes (ms)	38.5±0.7	66.4±1.3	66.9±1.0
Slices (n)	27±3	26±5	24±2
Venc (cm/s)	150-250 depending on stenosis presence/severity		150-450
Parallel imaging	GRAPPA (y) R=2	PEAK GRAPPA (y-z-t) R=5	PEAK GRAPPA (y-z-t) R=5
rBW (Hz/pixel)	455-460	650	650

Both conventional and k-t accelerated aortic 4D flow were acquired at Center I, while only k-t accelerated 4D flow was acquired at Center II. ECG: electrocardiogram; TR: repetition time; TE: echo time; FOV: field of view; SRes: spatial resolution; N_{Seg}: number of k-space segments per cardiac time frame; TRes: temporal resolution; Venc: encoding sensitivity; R: acceleration factor; rBW: receiver bandwidth.

Table 2. Subject characteristics and conventional and k-t accelerated 4D flow MRI scan times.

	Center I		Center II	
	Healthy volunteers	*Patients*	*Healthy volunteers*	*Patients*
	n=11	*n=16*	*n=14*	*n=27*
Subject characteristics				
Gender	4 women	3 women	11 women	14 women
Age (years)	61±15 [31-77]	60±10 [40-74]	38±13 [25-70]	58±16 [31-81]
Weight (kg)	86±20	89±12	77±15	79±18
Heart rate (bpm)	67±10	71±12	66±11	62±10
4D flow MRI scan time (min)				
Conventional	11:47±1:30	13:17±2:49	-	-
k-t accelerated	1:56±0:14*	2:07±0:36*	1:59±0:18	2:09±0:20

*: $p<0.05$ for comparison between conventional and k-t accelerated 4D flow MRI within subject groups.

Table 3. Comparison between conventional and k-t accelerated 4D flow regional aortic hemodynamic indices: systolic velocity and WSS.

	Center I			
	Healthy volunteers		*Patients*	
	n=11		*n=16*	
	Conventional	*k-t accelerated*	*Conventional*	*k-t accelerated*
Peak systolic maximal velocity				
AA	1.66±0.31 m/s	1.63±0.24 m/s	2.10±0.73 m/s	2.03±0.73 m/s
arch	0.83±0.16 m/s	0.89±0.17 m/s	1.18±0.54 m/s	1.13±0.53 m/s
DA	0.97±0.21 m/s	0.99±0.20 m/s	0.97±0.22 m/s	0.93±0.19 m/s
Systolic maximum WSS				
inner AA	1.36±0.25 Pa	1.44±0.21 Pa	1.58±0.55 Pa	1.49±0.53 Pa*
outer AA	1.29±0.23 Pa	1.39±0.23 Pa	1.70±0.60 Pa	1.55±0.55 Pa*
inner arch	0.86±0.16 Pa	0.97±0.21 Pa	1.12±0.50 Pa	1.11±0.51 Pa
outer arch	0.81±0.19 Pa	0.89±0.24 Pa	1.15±0.64 Pa	1.09±0.67 Pa
inner DA	0.92±0.20 Pa	0.99±0.17 Pa	0.94±0.20 Pa	0.91±0.27 Pa
outer DA	0.89±0.22 Pa	0.94±0.20 Pa	0.88±0.24 Pa	0.83±0.22 Pa

Velocity and WSS values are provided as mean ± standard deviation for each group and each 4D flow technique. AA: ascending and DA: descending aorta; WSS: wall shear stress. *: $p<0.05$ between conventional and k-t accelerated 4D flow.

Table 4. k-t accelerated 4D flow regional aortic systolic velocity and WSS at Center II.

	Center II	
	Healthy volunteers	*Patients*
	n=14	*n=27*
	k-t accelerated	
Peak systolic maximal velocity		
AA	1.44±0.23 m/s	1.73±0.68 m/s
arch	1.09±0.17 m/s	1.00±0.27 m/s
DA	1.26±0.29 m/s	0.93±0.24 m/s
Systolic maximum WSS		
inner AA	1.23±0.24 Pa	1.25±0.50 Pa
outer AA	1.22±0.18 Pa	1.20±0.50 Pa
inner arch	1.10±0.19 Pa	0.94±0.22 Pa
outer arch	1.00±0.19 Pa	0.94±0.35 Pa
inner DA	1.29±0.30 Pa	0.91±0.24 Pa
outer DA	1.27±0.36 Pa	0.86±0.25 Pa

Velocity and WSS values are provided as mean ± standard deviation for each group.

AA: ascending and DA: descending aorta; WSS: wall shear stress.

Table 5. Intra- and inter-observer variability of k-t accelerated 4D flow MRI-derived aortic peak systolic maximal velocity and wall shear stress according to the inclusion Center.

	Peak systolic maximal velocity		**Systolic maximum WSS**	
	Bias [LOA] (m/s)	*ICC*	*Bias [LOA] (Pa)*	*ICC*
Center I (n=10)				
Intra-observer	0.03 [-0.15;0.20]	0.99	0.01 [-0.11;0.13]	0.98
Inter-observer	0.03 [-0.18;0.24]	0.98	0.01 [-0.11;0.14]	0.98
Center II (n=10)				
Intra-observer	0.01 [-0.13;0.15]	0.99	-0.002 [-0.18;0.17]	0.98
Inter-observer	0.03 [-0.18;0.23]	0.98	0.01 [-0.11;0.14]	0.99

WSS: wall shear stress; LOA: limits of agreement = mean bias ± 1.96 x standard deviation; ICC: intraclass correlation coefficient..

Figures legends

Figure 1. Analysis workflow of 4D flow MRI data: a. Preprocessing including correction for eddy currents, noise as well as velocity aliasing, calculation of a 3D phase-contrast MR angiogram (PC-MRA), 3D segmentation of the aortic volume and automated detection of the peak systolic phase. b. Quantification of peak systolic maximal velocity in 3 aortic regions using maximal intensity projections (MIPs), and 3D peak systolic maximal wall shear stress (WSS) in 6 regions of interest throughout the aortic surface.

Figure 2. 4D flow-derived aortic velocity and WSS map examples according to the sequence and inclusion center: a. Peak systolic velocity volumetric maximal intensity projections in sagittal orientation (MIPs, top rows) and 3D WSS maps in right-anterior view (bottom rows) obtained in representative Center I healthy volunteer (top left corner) and three patients, using conventional (on the left for each pair) and k-t accelerated (on the right for each pair) 4D flow MRI. b. Peak systolic velocity MIP (top row) and 3D WSS maps (bottom row) obtained using k-t accelerated 4D flow MRI in representative Center II healthy volunteer (left column) and three patients with aortic disease or hypertension (HTN). Of note, velocity MIPs were eroded by one pixel to suppress border noise.

Figure 3. Bland-Altman diagrams for comparison between conventional and k-t accelerated 4D flow aortic hemodynamic indices: Comparison between k-t accelerated and conventional 4D flow-derived peak systolic velocity and WSS in n=27 subjects recruited at Center I. a: peak velocity in the ascending aorta (AA), aortic arch and descending aorta (DA) of healthy volunteers (circles) and patients (squares); b. peak systolic maximum WSS at the inner and outer regions of the AA, aortic arch and DA of healthy volunteers (circles) and patients (squares).

Figure 4. Linear regressions for association of k-t accelerated 4D flow MRI-derived regional aortic hemodynamic indices with age in healthy volunteers from both Centers (n=25). a: peak systolic maximal velocity in the aortic arch and descending aorta (DA); b: peak systolic maximum wall shear

stress (WSS) along the inner and outer wall of the aortic arch and DA. Spearman's rank correlation coefficients and p values are provided.

Figure 5. Ascending aortic peak velocity and WSS obtained using k-t accelerated 4D flow according to disease: Averaged peak systolic velocity (left) and WSS (right) of healthy volunteers (left bars) and patients with aortic valve stenosis, aortic aneurysm, bicuspid aortic valve, after aortic surgery or hypertension, while pooling subjects from both centers.