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Quantification and comparison of 4D-Flow MRI-derived wall shear stress and MRE-derived wall stiffness of the abdominal aorta

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Abstract

Purpose—Aortic wall shear stress (WSS_{Flow}) alters endothelial function, which in-turn changes aortic wall stiffness leading to remodeling in different disease states. Therefore, the aims of this study are to determine normal physiologic correlations between: 1) MRE-derived aortic wall stiffness (WS_{MRE}) and WSS_{Flow} ; 2) WS_{MRE} and mean velocity; 3) WS_{MRE} and pulse wave velocity (PWV); 4) WS_{MRE} and mean peak flow; and 5) WS_{MRE} , WSS_{Flow} and age using magnetic resonance elastography (MRE) and 4D-flow MRI in the abdominal aorta in healthy human subjects.

Methods—Cardiac-gated aortic MRE and 4D-flow MRI data were acquired in 24 healthy volunteers using a 3T scanner. For MRE, 70Hz external motion was applied to obtain wave images in all spatial directions in a separate breath-hold. Whereas, 4D-flow data was acquired under free-breathing. Wave images in all the directions were processed to obtain 3D-weighted stiffness map at end-systole (ES). WSS_{Flow} , mean velocity, PWV and mean peak flow were obtained using 4D-flow data. Pearson correlation was performed to determine association between all variables.

Results—A significant negative correlation was observed between: 1) ES WS_{MRE} and WSS_{Flow} in both axial ($r=-0.62$; $p=0.006$) and circumferential ($r=-0.52$; $p=0.016$) directions; 2) ES WS_{MRE} and mean velocity ($r=-0.58$; $p=0.012$); and 3) age and WSS_{Flow} in both axial ($r=-0.71$; $p<0.0001$) and circumferential ($r=-0.58$; $p=0.0012$) directions. A significant positive correlation was observed between: 1) ES WS_{MRE} and PWV ($r=0.69$; $p<0.0001$); 2) ES WS_{MRE} and mean peak flow ($r=0.53$; $p=0.016$); and 3) ES WS_{MRE} and age ($r=0.63$; $p=0.006$).

Conclusion—The negative significant correlation between aortic WSS_{Flow} and WS_{MRE} in normal volunteers demonstrates a relationship between WS_{MRE} and WSS_{Flow} .

Keywords

Wall shear stress; aortic wall stiffness; 4D-flow MRI; MR Elastography

INTRODUCTION

Changes in the biomechanical properties of the aorta, alter flow characteristics, and have an indirect effect on function of other organs such as heart, liver, and kidneys (1). Specifically in aortic aneurysms, characterization of the biomechanical behavior of the aortic wall is a potential tool for determining the rupture risk and help in timely repair of the aorta (2). Consequently, the biomechanical properties of the aorta (2–8) have been extensively studied to better understand the basis for aneurysm formation or development of dissection (2), as well as the effects from other conditions (6,9,10).

The commonly studied biomechanical properties of the aortic wall have included aortic wall stiffness and wall shear stress (WSS_{Flow}). Wall stiffness determines the compliance of the aorta, and has been shown to increase in many diseases (2,6,9,10). It has also been shown that wall stiffness increases with age (6).

On the other hand, aortic WSS_{Flow} is based on fluid (blood) shear velocity on the aortic wall, and any changes in blood shear velocity alter endothelial function of the aortic wall leading to remodeling (11). WSS_{Flow} has been shown to change in a variety of conditions (12–14).

Alteration of endothelial function by changing WSS_{Flow} in-turn changes aortic wall stiffness, leading to remodeling in different disease states (11). Similarly, the change in wall stiffness can alter flow characteristics of the aorta leading to a change in WSS_{Flow} . It might be important to determine both variables at an early stage of a disease process for appropriate treatment options; since one can be a causal and the other can be an effect or vice versa. Therefore, there is presumably a relationship between wall stiffness and WSS_{Flow} , which can provide important information regarding endothelial function and remodeling of the aorta. The ultimate utility of these measurements should provide improved understanding of the mechanical properties of the aorta and the mechanisms associated with different disease processes.

To date, there have been studies to measure aortic wall stiffness either invasively (15) or noninvasively (16). In addition, aortic WSS_{Flow} has been measured using fluid dynamics computational models (17), invasively using cardiac catheterization (18) and noninvasively using ultrasound (19). With the advent of MRI-based techniques, such as magnetic resonance elastography (MRE) and 4D-flow, both aortic wall stiffness and WSS_{Flow} can be noninvasively measured, both spatially and temporally. MRE is a noninvasive phase-contrast MRI based technique to estimate spatial stiffness of soft tissues (20–23); 4D-flow MRI is a phase contrast technique used to estimate WSS_{Flow} from time-resolved 3-dimensional velocity profiles (12,13).

Earlier studies have shown that MRE-derived aortic wall stiffness (WS_{MRE}) can be measured spatially and temporally across cardiac cycle and correlated with aging and pulse wave velocity (20,24,25). Similarly, WSS_{Flow} was measured spatially and temporally in different disease states (26,27); however, to the best of our knowledge none of the studies have correlated aortic WS_{MRE} against WSS_{Flow} noninvasively. The hypothesis of the study is that the WS_{MRE} and flow related parameters (i.e. WSS_{Flow} , mean velocity, pulse wave velocity (PWV) and peak velocity) will correlate against each other in normal subjects (i.e. normal physiologic conditions).

The aims of the study are to determine normal physiologic correlations in the abdominal aorta in healthy human subjects between: 1) aortic WS_{MRE} and WSS_{Flow} ; 2) aortic WS_{MRE} and mean velocity; 3) aortic WS_{MRE} and PWV; 4) aortic WS_{MRE} and mean peak flow using MRE and 4D-flow MRI; and 5) aortic WS_{MRE} , WSS_{Flow} and age.

METHODS

MRE and 4D-flow of the abdominal aorta were performed in 24 healthy volunteers of age ranging from 21 to 74 years after approval of Institutional Review Board and obtaining written informed consent.

Experimental Setup

All imaging was performed using a commercially available 3T MRI scanner (Tim Trio, Siemens Healthcare, Erlangen, Germany). The volunteers were placed head-first, in supine position, within the scanner. Using Velcro strap, a pneumatic driver was secured to the anterior abdominal wall below the xiphisternum of the volunteer for MRE acquisition as shown in figure 1. External mechanical vibrations of 70Hz were induced in the region of interest using the Resoundant driver system (Resoundant Inc., Rochester, MN). This Resoundant driver system has an active driver (i.e. acoustic speaker) placed outside the scan room, which was connected to the passive driver via a plastic tube to generate the required vibrations in the abdominal aorta.

Image Acquisition

MRE Acquisition—Retrospective cardiac-gated (pulse-gating) cine MRE (22,24,28,29) sequence was performed to obtain wave data in the sagittal plane of the abdominal aorta. The imaging parameters included: echo time (TE) = 9.52 ms; repetition time (TR) = 14.28 ms; slice thickness = 6 mm (3mm overlap with adjacent slices); number of slices = 3; acquisition matrix = 128 x 64; $\alpha = 25^\circ$; field of view (FOV) = 40 cm²; number of segments = 6 to 8 ($\pm$ motion encoding); MRE phase offsets = 4 (for tracking the wave); cardiac phases = 8; GRAPPA acceleration factor R = 2 (16 reference lines); and a motion encoding gradient (MEG) = 120Hz was applied separately in x, y and z directions for encoding the displacement field. The acquisition time for each slice and each encoding direction was ~16–22sec depending on the heart rate. Since MRE is pulse-gated, end-systolic (ES) phase from aortic MRE images was determined based on the aortic valve closure by obtaining trigger time from a standard cine balanced steady state free precession (bSSFP) sequence of the left ventricular outflow tract.

4D-Flow MRI Acquisition—Prospective cardiac-gated (ECG-gating) with a respiratory navigator 4D-flow MRI (30) (time resolved 3D PC-MRI with 3D velocity encoding) sequence was performed to obtain volumetric images of the entire aorta in the sagittal plane. The imaging parameters included: TE/TR = 2.6 ms/5.1 ms; flip angle = 7°; temporal resolution = 40.8 ms; spatial resolution = 1.7 x 2.0 x 2.2 mm³; velocity sensitivity along all three directions (venc) = 150 cm/s; GRAPPA acceleration factor R = 2 (24 reference lines). The acquisition time for 4D-flow MRI was ~11–15min. A separate 2D PC-MRI acquisition was performed with in-plane velocity encoding for PWV estimation. The imaging parameters included: TE/TR = 2.0 /9.0 ms; venc = 150 cm/s; acquisition matrix = 192x144; FOV = 30x40 cm²; slice thickness = 5 mm; flip angle = 15°; number of cardiac phases = 128; GRAPPA acceleration factor = 2 with 24 reference lines collected in the same scan; number of averages = 2 and lines per segment = 15. PC-MRI images were acquired under free breathing. The acquisition time for 2D-PC MRI was ~2min.

Data Analysis

MRE-Derived Aortic WS_{MRE} Estimation—Sagittal MRE waves images were masked to delineate abdominal aorta and processed using MRE-lab (Mayo clinic, Rochester, MN). The waves images were filtered using 2D Butterworth bandpass filter with cutoff values of 0.4m (1 wave/FOV) to 0.01m (40 waves/FOV) to remove longitudinal component of motion and directionally filtered in eight directions to remove the reflected waves. Then the first harmonic component of displacement fields in x, y and z directions were processed using local frequency estimation (LFE) algorithm to obtain a 3D-weighted stiffness map (24). The center-slice data from the resultant stiffness map was eroded by two pixels to account for the edge effects stemming from the LFE inversion algorithm. Finally, ES mean aortic WS_{MRE} was calculated and recorded using MATLAB (MathWorks, Natick, MA).

Wall Shear Stress, Mean Velocity, Peak Flow, PWV Estimation—4D-flow data was processed using in house custom built MATLAB program and EnSight (CEI, USA) as described elsewhere (8). The data underwent corrections for Maxwell terms, eddy currents and velocity aliasing (31) (figure 2b). In addition, a 3D phase MR angiogram was derived from the 4D-flow data and loaded to 3D-visualization software (EnSight 10, CEI, NC, USA) (figure 2c) for manual selection of region of interest (ROI) and placement of required planes across the abdominal aorta. Five 2D planes were manually placed and arranged throughout the length of the abdominal aorta approximately above renal arteries dividing the aorta into four sections as shown in figure 2d. All planes were positioned downstream constituting the descending aorta and placed normal to the flow direction i.e. orthogonal to the aorta. These planes were exported to the in-house custom built MATLAB tool and manually processed to obtain WSS_{Flow}, mean velocity and peak flow (31). Each plane was analyzed by manual drawing of the ROI's over the aortic lumen across the cardiac cycle and processed to report time-averaged WSS_{Flow} (figure 2e), mean velocity (from all phases and all planes) (figure 2e) and mean peak flow from all the planes (31). WSS_{Flow} estimation was based on the interpolation of the local velocity derivatives on the boundary of the segmented vessel lumen contour using b-splines as described earlier (31). PWV estimation was performed using a custom-built software in Matlab as described elsewhere (20) by tracking the foot of the velocity profile.

Statistical Analysis

Data analysis was performed by using SAS 9.4 software (SAS, Inc; Cary, NC). Pearson correlation coefficients were used to describe the association between i) mean ES aortic WS_{MRE} and WSS_{Flow} (circumferential and axial); ii) mean ES aortic WS_{MRE} and mean velocity; iii) mean ES aortic WS_{MRE} and PWV; iv) mean ES aortic WS_{MRE} and mean peak flow; and v) mean ES aortic WS_{MRE} , WSS_{Flow} (circumferential and axial) and age. The multiplicity was adjusted by performing Holm's Bonferroni step-down to control the type-1 error rate. A p -value < 0.05 is considered to be statistically significant.

RESULTS

All the volunteers were considered to be normal with no prior history of any cardiovascular diseases. There were 16 males in the age range of 24–71 years and 8 females between 21 to 74 years. In total there were 19 subjects with age < 40 years and 5 subjects > 50 years.

Figure 3 shows the magnitude image (A) with the red contour delineating the abdominal aorta, four snapshots of wave propagation (B–E) and the corresponding ES stiffness map (F) and the particle traces of flow through the aorta (G).

Mean ES aortic WS_{MRE} demonstrated a negative correlation to time-averaged WSS_{Flow} . Figure 4 shows a significant ($p=0.016$), moderate negative correlation ($r=0.52$) between ES aortic WS_{MRE} and circumferential WSS_{Flow} . Similarly, figure 5 shows a significant ($p=0.006$), moderate negative correlation ($r=0.62$) between ES aortic WS_{MRE} and axial WSS_{Flow} .

Mean ES aortic WS_{MRE} demonstrated a negative correlation to mean velocity. Figure 6 shows a significant ($p=0.012$), moderate negative correlation ($r=0.58$) between ES aortic WS_{MRE} and mean velocity.

Mean ES aortic WS_{MRE} demonstrated a positive correlation to PWV. Figure 7 shows a significant ($p<0.0001$), moderate positive correlation ($r=0.69$) between ES aortic WS_{MRE} and PWV.

Mean ES aortic WS_{MRE} demonstrated a positive trend to mean peak flow. Figure 8 shows a significant ($p=0.016$), moderate positive correlation ($r=0.53$) between ES aortic WS_{MRE} and mean peak velocity.

Mean ES aortic WS_{MRE} increased and WSS_{Flow} decreased with age. Figure 9A shows a significant ($p=0.012$), moderate negative correlation ($r=0.58$) between circumferential WSS_{Flow} and age; and similarly, figure 9b shows a significant ($P<0.0001$), good negative correlation ($r=0.71$) between axial WSS_{Flow} and age. Figure 9c shows a significant ($p=0.006$), moderate positive correlation ($r=0.63$) between Mean ES aortic WS_{MRE} and age.

DISCUSSION

This study demonstrated significant correlation between WS_{MRE} and WSS_{Flow} in both circumferential and axial directions and with other flow parameters (mean velocity and peak

flow) derived from 4D-flow MRI and as well as with age. Similarly, a significant correlation was determined between aortic WS_{MRE} and PWV. However, this initial feasibility study in normal subjects indicated a potential to further investigate these properties in different disease states.

Previous studies have shown that aortic WSS_{Flow} (3,13,14) and wall stiffness (10,25,32) were altered in variety of diseases. It has been shown that aortic WSS_{Flow} increases in patients with aortic valve stenosis (27) and/or associated aortic disease (bicuspid aortopathy) (26); while decreasing in the setting of atherosclerosis (18), aneurysm (33), hypertension (14,34), and increasing age (4). On the other hand, aortic wall stiffness increases in patients with atherosclerosis (10), aneurysm (2,25), hypertension (32,35), or advancing age (20,24). The decrease in aortic WSS_{Flow} and the increase aortic WS_{MRE} in similar disease states indicate that WSS_{Flow} and WS_{MRE} are inversely related (34). Therefore, this study also confirms that both WSS_{Flow} (axial, circumferential) and aortic WS_{MRE} demonstrated inverse significant correlation in normal subjects. However, the correlation is moderate, likely due to small sample size.

We anticipate that in specific disease states such as aneurysms, where the stiffness is higher and lower WSS_{Flow} the diagnosis might be completely different when compared to aneurysms with lower stiffness and WSS_{Flow} being lower or higher. In a recent study by Boyd et al (33), in contradiction to their hypothesis, they found out that rupture of the aneurysms occurred not at sites of high pressure (i.e. increased stiffness) and high WSS_{Flow} but rather at regions of low WSS_{Flow} . In another study (36), stiffness was positively correlated with WSS_{Flow} in unruptured aneurysms. In addition, during routine follow-up of aortic aneurysms every 3 to 6 months, any changes in WSS_{Flow} and WS_{MRE} compared to their earlier exam might be useful in determining the rupture potential. Therefore, these studies indicate that these variables together might provide even more valuable information regarding the rupture potential of the aneurysm and understanding the endothelial cell dysfunction and changes in amount of collagen and elastin which are directly related to WSS_{Flow} and stiffness.

Apart from WSS_{Flow} , mean velocity is other aortic physiologic parameter that is frequently reported in studies using 4D-flow MRI. Earlier studies have shown that mean velocity decreases with age (4) and also in patients with hypertension (14). However, it was shown that aortic WS_{MRE} increases with age (20) and hypertension (32). Therefore, based on the analogy and results described in earlier studies, aortic WS_{MRE} and mean velocity are inversely related, which is in agreement with our current findings.

A positive correlation was observed between mean peak flow and aortic WS_{MRE} . This positive correlation can be explained by the fact that peak blood velocity is subjected to elevated blood pressure, which affects the ES stiffness (37). It is also known that flow rate and velocity are dependent on geometry of the aorta and also with the disease conditions associated. Therefore, more studies are further warranted to understand the correlation between flow and aortic WS_{MRE} in different disease states.

A positive correlation was observed between WS_{MRE} and PWV. As already known PWV provides an indirect measure of aortic stiffness based on the pulse wave speed in the aorta; and we expect PWV and WS_{MRE} to be positively, linearly correlated, which the current results are in agreement with the results reported in previous studies (20,24). However, in some disease states, particularly in some aneurysms, the blood flow can be very slow and selecting appropriate velocity-encoding value to estimate PWV can become challenging. Additionally, in the abdominal aorta due to reflections of pulse waves, PWV estimates may not be accurate. Therefore, in these situations MRE can be a valuable tool to estimate time resolved (i.e. across cardiac cycle) spatial estimate stiffness of aorta.

Increase in WS_{MRE} and decrease in WSS_{Flow} was observed with increase in age. It is known that during aging, soft tissues undergo atrophy and an increase in the amount of fibrotic tissue and collagen in the aorta reflects in increased stiffness (38). Additionally, with increase in age the endothelial cell undergoes dysfunction causing decrease in WSS_{Flow} (39). These findings were in agreement with previous published results (4,20,24).

The WSS_{Flow} (3,13,14) and aortic WS_{MRE} (20,24,32) values reported in this study are in agreement with previously reported measurements. WSS_{Flow} values are mainly dependent on the drag force of the blood (gradient of blood flow velocities) at the boundaries that causes shear stress on the aortic wall. Whereas, aortic WS_{MRE} is based on the waveguide principle of propagation of external waves in the lumen, causing the aortic wall and adjacent blood vibrate with the same frequency as previously described (20,24,32,35). Hence, processing the waves in the lumen provides the stiffness map, which thus reflects the stiffness of the aortic wall. Using our approach, both WSS_{Flow} and aortic WS_{MRE} are obtained in-vivo at the same time in a single scan, which is advantageous compared to deriving WSS_{Flow} from a computational fluid dynamics measurements based on different aortic models. With WSS_{Flow} and aortic WS_{MRE} potentially important biomarkers in diagnosing various diseases, this combined acquisition is likely advantageous.

There are a few limitations to our study. First, the WSS_{Flow} measured in our study is dependent on the contours of lumen at the boundary of the wall (40); appropriate care was taken to draw the contours to avoid any bias. Second, the WSS_{Flow} measured is known to be underestimated because of lack of high spatial and temporal resolution (40). However, this effect is mitigated as long as the scans across subjects are performed with the same resolution. Third, the aortic WS_{MRE} measured is not absolute and termed to be “effective” as it does not consider geometry of the aorta. However, a previous study (20) demonstrated a strong correlation between inversions that incorporate measurements with and without the geometry of aorta. Therefore, our study adopted the same technique in estimating the 3D stiffness measurements. Fourth, the number of subjects in the old age group i.e. >50years are only 5. Our future studies will include more number of subjects in the older age group. Fifth, the inter-observer variability in drawing regions of interests (ROI's) was not taken into account. The ROI's drawn to derive the WS_{MRE} and the flow related measurements were outlined by the same observer to minimize bias from inter-observers. Additionally, the ROI's were checked by the experienced user (AK-12yrs) to minimize the errors. Finally, likely because of the small cohort and not a complete representation of normal subjects, the significant correlation between 4D-flow parameters and aortic WS_{MRE} needs to be further

investigated; and since only normal subjects are included in this study, the effect of disease on WSS_{Flow} and aortic WS_{MRE} and their relationship is still unknown. However, this is the first study to demonstrate a correlation between 4D-flow derived WSS_{Flow} and MRE-derived aortic WS_{MRE} .

In conclusion, this study demonstrates that there is a relationship between aortic WS_{MRE} and time-averaged WSS_{Flow} in the abdominal aorta. A moderate negative correlation was observed between both axial and circumferential WSS_{Flow} against ES aortic WS_{MRE} and as well as with age. Similarly, a moderate negative correlation was observed between ES aortic WS_{MRE} and mean velocity; and a moderate positive correlation between both ES aortic WS_{MRE} vs. PWV, ES aortic WS_{MRE} vs. peak flow, and ES aortic WS_{MRE} vs. age. However, more studies are warranted to understand the association between 4D-flow parameters and MRE-derived aortic WS_{MRE} in different disease states.

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Figure 1. Schematic of MRE driver system. As pneumatic active driver is placed outside the scan room and a passive driver (plastic drum) is placed on the abdomen is connected via a plastic tube to the active driver to induce 70Hz vibrations in the abdominal aorta.

Figure 2.

Shows the processing steps involved in analyzing 4D-flow MRI data in a volunteer. **A)** 3D-magnitude image of entire aorta and **B)** the corresponding flow images in the three encoding directions (v_i , v_j and v_k) which are processed for noise masking, anti-aliasing and eddy current corrections (post-processed); and the 3D reconstruction of the aorta. **C)** The 3D reconstructed aorta is then loaded in the Ensight (visualization software) and **D)** five planes (in ROI shown in A) were selected as the region of interest in the abdominal region which was then exported to custom built program in Matlab for **E)** calculating the velocity, flow and WSS_{Flow} measurements.

Figure 3.

A) Magnitude image with red contour delineating the abdominal aorta, **B–E)** 4 snap shot of wave images in the in-plane direction and **F)** the corresponding stiffness map. **G)** Shows the particle traces of the flow through the five planes selected in the abdominal aorta in the same volunteer.

Figure 4. Plot of ES aortic WS_{MRE} versus time averaged circumferential WSS_{Flow} . A negative Pearson correlation of $r=0.52$ ($p=0.016$) was observed.

Figure 5.
Plot of ES aortic WS_{MRE} versus time averaged axial WSS_{Flow} . A negative Pearson correlation of $r=0.62$ ($p=0.006$) was observed.

Figure 6. Plot of ES aortic WS_{MRE} versus mean velocity. A negative Pearson correlation of $r=0.58$ ($p=0.012$) was observed.

Figure 7.
Plot of ES aortic WS_{MRE} versus pulse wave velocity. A positive Pearson correlation of $r=0.69$ ($p<0.0001$) was observed.

Figure 8.
Plot of ES aortic WS_{MRE} versus mean peak flow. A positive Pearson correlation of $r=0.53$ ($p=0.016$) was observed.

Figure 9.

A) Plot showing circumferential WSS_{Flow} as a function of age with a negative Pearson correlation of $r=0.58$ ($p=0.0012$). **B)** Plot showing axial WSS_{Flow} as a function age with a negative Pearson correlation of $r=0.71$ ($p<0.0001$). **C)** Plot showing ES aortic WSS_{MRE} as a function age with a positive Pearson correlation of $r=0.63$ ($p=0.006$).