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Pulse Wave Imaging (PWI) in Normal, Hypertensive and Aneurysmal Human Aortas *In Vivo*: A Feasibility Study

Ronny X. Li¹, Jianwen Luo¹, Sandhya K. Balaram², Farooq A. Chaudhry², Danial Shahmirzadi¹, and Elisa. E. Konofagou^{1,3}

Elisa. E. Konofagou: ek2191@columbia.edu

¹Department of Biomedical Engineering, Columbia University, New York, NY, USA

²St. Luke's-Roosevelt Hospital Center, New York, NY, USA

³Department of Radiology, Columbia University, New York, NY, USA

Abstract

Arterial stiffness is a well-established biomarker for cardiovascular risk, especially in the case of hypertension. The progressive stages of an abdominal aortic aneurysm (AAA) have also been associated with varying arterial stiffness. Pulse Wave Imaging (PWI) is a noninvasive, ultrasound imaging-based technique that uses the pulse wave-induced arterial wall motion to map the propagation of the pulse wave and measure the regional pulse wave velocity (PWV) as an index of arterial stiffness. In this study, the clinical feasibility of PWI was evaluated in normal, hypertensive, and aneurysmal human aortas. Radiofrequency-based speckle tracking was used to estimate the pulse wave-induced displacements in the abdominal aortic walls of normal ($N = 15$, mean age $32.5 \text{ years} \pm 10.2$), hypertensive ($N = 13$, mean age $60.8 \text{ years} \pm 15.8$), and aneurysmal ($N = 5$, mean age $71.6 \text{ years} \pm 11.8$) human subjects. Linear regression of the spatio-temporal variation of the displacement waveform in the anterior aortic wall over a single cardiac cycle yielded the slope as the PWV and the coefficient of determination r^2 as an approximate measure of the pulse wave propagation uniformity. The aortic PWV measurements in all normal, hypertensive, and AAA subjects were 6.03 ± 1.68 , 6.69 ± 2.80 , and $10.54 \pm 6.52 \text{ m/s}$, respectively. There was no significant difference ($p = 0.15$) between the PWVs of the normal and hypertensive subjects while the PWVs of the AAA subjects were significantly higher ($p < 0.001$) compared to those of the other two groups. Also, the average r^2 in the AAA subjects was significantly lower ($p < 0.001$) than that in the normal and hypertensive subjects. These preliminary results suggest that the regional PWV and the pulse wave propagation uniformity (r^2) obtained using PWI, in addition to the PWI images and spatio-temporal maps that provide qualitative visualization of the pulse wave, may potentially provide valuable information for the clinical characterization of aneurysms and other vascular pathologies that regionally alter the arterial wall mechanics.

Keywords

Abdominal aorta; abdominal aortic aneurysm; aortic stiffness; hypertension; pulse wave velocity (PWV); pulse wave imaging (PWI); speckle tracking

1. Introduction

The relationship between arterial stiffness and cardiovascular risk has been well-documented by numerous clinical longitudinal studies. Stiffening of large arteries such as the aorta has been shown to be a strong predictor of coronary heart disease, congestive heart failure, and stroke in well-functioning older adults (Sutton-Tyrrell *et al* 2005), all-cause and cardiovascular mortality in end-stage renal disease (Blacher *et al* 1999), and all-cause and cardiovascular mortality, fatal stroke, and primary coronary events in hypertensive patients (Laurent *et al* 2001; Laurent *et al* 2003; Boutouyrie *et al* 2002). Thus, the accurate and reliable quantification of arterial stiffness may have a widespread impact on the early detection, diagnosis, and prognosis of cardiovascular risk.

Each ejection of the left ventricle sends a pulse wave through the arterial tree that propagates as a pressure wave, inducing displacements in the vascular wall (i.e. diameter wave) and giving rise to the natural pulsation of the arteries (Fung, Springer-Verlag 1997). The traveling speed of this wave (i.e. pulse wave velocity, or PWV) is widely regarded as the most robust index for quantification of arterial stiffness (O'Rourke *et al* 2002; Nichols and O'Rourke, Hodder Arnold Publication 2005; Willum-Hansen *et al* 2006; Hirata *et al* 2006) and can be directly and quantitatively related to the Young's modulus of the vessel by the established Moens-Korteweg equation (Moens 1878; Korteweg 1878).

The PWV values reported in virtually all large-scale longitudinal studies have been obtained via implementation of the foot-to-foot method (Sutton-Tyrrell *et al* 2005; Laurent *et al* 2001; Laurent *et al* 2003; Boutouyrie *et al* 2002), which entails measurement of the travel time and distance of the pressure waveform between two remote sites, commonly the carotid and femoral arteries. Such a technique suffers from major limitations, primarily arising from the fact that vascular elastic properties are changing throughout the arterial tree due to its varying geometry, surrounding environment, and composition of the vessel wall constituents (Nichols and O'Rourke, Hodder Arnold Publication 2005; Fung, Springer-Verlag 1993). The carotid-femoral foot-to-foot method produces a global estimate of the PWV averaged across the entire circulation, thus inherently lacking the sensitivity to detect variations in the *regional* arterial stiffness. This is a major pitfall because several vascular diseases such as atherosclerosis and aneurysms only affect localized regions in the arterial tree (Vorp 2007; Kleinstreuer *et al* 2007; Bleasdale *et al* 2003). In addition, the foot-to-foot technique is prone to sizeable errors in the distance measurement (Davies *et al* 2003; Mookerjee *et al* 2010), which is performed extracorporeally. For these reasons, the PWV is currently not widely used as a diagnostic index despite its promise.

Pulse Wave Imaging (PWI) is a noninvasive, ultrasound-based technique to visualize and map the estimated pulse wave-induced vessel wall displacement waveforms in 3D (2D + time), allowing for assessment of the regional (i.e. within the imaged segment) PWV and

wave propagation uniformity r^2 (Fujikura *et al* 2007; Luo *et al* 2009; Vappou *et al* 2010). Until now, all *in vivo* applications of PWI in humans have been in healthy subjects with no previous history of cardiovascular disease (Vappou *et al* 2010; Vappou *et al* 2011; Luo *et al* 2012). PWI typically yields PWV measurements of 4 to 7 m/s with $r^2 > 0.95$ in normal aortas (Vappou *et al* 2010; Vappou *et al* 2011; Li *et al* 2011). By comparison, the carotid-femoral PWV typically varies between 6 and 7.5 m/s in healthy, middle-aged populations (Vermeersch *et al* 2008) and may correlate with the regional PWV measured by PWI (Vappou *et al* 2011). While the mechanical properties are expected to remain mostly uniform over short segments in normal aortas, this may not be the case in pathological aortas.

Hypertension is a highly prevalent cardiovascular risk condition that may affect up to 90% of individuals in their lifetime (Wang and Vasan 2005). Although the exact mechanisms of hypertension are largely unknown, it is firmly believed that the pulse pressure in large arteries is a key determinant of the degenerative changes that characterize hypertension (Savage *et al* 2002). Thus, assessment of the aortic elasticity may be of great clinical interest for the general understanding of hypertension. From a physiological perspective, the mechanical integrity of the aortic wall is mainly determined by its matrix constituents, namely elastin, collagen, and smooth muscle (Fung, Springer-Verlag 1997). Elastin is highly distensible and load-bearing at low pressures, while collagen is 1000 times stiffer and load-bearing at high pressures. We can expect an increase in the intraluminal pressure to exert a greater force on the wall, engaging more collagen fibers and theoretically increasing the stiffness and associated PWV of the aorta.

The abdominal aortic aneurysm (AAA) is responsible for 15,000 fatalities annually in the United States and is the 10th leading cause of death (Maldonado, Long Island Press 2010). An AAA is a focal dilation of an abdominal aortic segment that may asymptotically progress for several years (Vorp 2007). If undetected or left untreated, AAA rupture carries a 75–90% mortality rate (Kleinstreuer *et al* 2007). In addition, only six countries in the world (Stather, Dattani *et al.* 2013) have implemented a standard clinical screening procedure for AAAs, which are mostly discovered incidentally during routine physical or radiographic exams performed for unrelated reasons (Kleinstreuer *et al* 2007). Clinical observations show that the formation, expansion, and rupture phases of an AAA are each associated with changes in arterial stiffness, mainly driven by elastin and collagen degradation (Kleinstreuer *et al* 2007; Vorp *et al* 1998; Raghavan *et al* 2000). In terms of PWV, the Moens-Korteweg equation does not apply in aneurysmal cases because the equation is based on the assumption that the vessel has a uniform radius. However, the biomechanical and geometric changes associated with an AAA will undoubtedly alter the pulse wave propagation behavior. Due to its ability to directly visualize and spatio-temporally map the pulse wave, PWI can potentially serve as a valuable clinical tool for noninvasive characterization of AAAs *in vivo*.

The purpose of this study is to assess the clinical feasibility of PWI in hypertensive and aneurysmal human abdominal aortas. The results were compared to those in normal human aortas.

2. Methods and Methods

2.1. Clinical Study Design

In vivo imaging studies approved by the Institutional Review Boards of St. Luke's-Roosevelt Hospital Center and Columbia University were conducted on patients who had been diagnosed with hypertension (systolic blood pressure ≥ 140 mmHg recorded 0–2 days prior to imaging) and/or untreated AAAs. Patients who were on anti-hypertension medication at the time but had a previous history of hypertension were also regarded as hypertensive subjects. Out of the 29 total hypertensive and 11 total AAA patients imaged, 11 hypertensives and 3 AAAs were excluded due to poor B-mode image quality. The remaining hypertensive subjects (10 F, 8 M) had an average age of 65.4 ± 18.3 years. The remaining AAA subjects (3 F, 5 M) had an average age of 69.2 ± 14.7 years. In addition, 15 healthy volunteers (mean age 32.5 years ± 10.2) were imaged as a control group.

2.2. Data Acquisition

The targeted imaging region was the infrarenal abdominal aorta, which is where nearly 90% of aortic aneurysms occur (Kleinstreuer *et al* 2007). Ultrasound RF signals were acquired from each patient in the supine position using a Sonix RP system (Ultrasonix Medical Corporation, Burnaby, Canada) with a 3.3 MHz curvilinear transducer in the long-axis orientation, as shown in figure 1. To standardize the data acquisition across subjects, the transducer was positioned such that the pulse wave propagated from right to left in the ultrasonic image plane (figure 1). RF signals were collected in 2.5-second acquisitions and digitized at 20 MHz to ensure capture of at least one full cardiac cycle per acquisition. For each subject, 5–8 acquisitions were performed so that the PWV measurements could be averaged over multiple cardiac cycles. To minimize rigid motion, the subjects were requested to perform breath-holding for the duration of each acquisition.

The imaging depth was set at the minimum depth required to visualize both the anterior and posterior aortic walls. Since an increase in depth leads to a decrease in frame rate, the beam density and/or the ultrasonic image plane size was reduced in subjects with deeper aortas in order to ensure a high frame rate. The image plane size was also reduced for subjects in which abdominal gas or artifacts obstructed the full view of the aorta. Consequently, the imaging depth varied from 7–15 cm, the beam density varied from 16–32 beams, and the image plane size varied from 60–100% of the full field of view. This resulted in frame rates between 242 and 462 Hz.

For reliable PWV estimation, the frame rate must be sufficiently high so that the pulse wave can be captured by at least two frames (i.e. Nyquist rate) before it travels the length of the imaged aortic segment. Thus, the upper limit of the measureable PWV (PWV_{max}) was expressed as follows:

$$PWV_{max} = (L * FR) / 2 \quad (1)$$

where L is the length of the aortic segment and FR is the frame rate. Equation 1 was used to verify whether the measured PWV was valid given the associated frame rate, as described in the next section.

2.3. Data Processing

The incremental (i.e., inter-frame), axial (i.e., parallel to the ultrasound beams) displacements in the aortic walls were estimated offline using a fast normalized 1D cross-correlation method on the RF signals (Luo *et al* 2010) with a 3.5-mm window size and 80% overlap. In order to normalize the units of motion by the frame rate, the axial displacements were multiplied by the frame rate to obtain axial velocities, which were color-coded and overlaid onto the corresponding 2D B-Mode images reconstructed from the RF signals.

Since the posterior aortic wall exhibits little motion *in vivo* due to its close proximity to the spine, manual segmentation of the inner anterior aortic wall was performed in the first frame of each acquisition sequence and updated automatically in subsequent frames based on the incremental axial displacements. The temporal incremental axial velocities in the segmented region were used to generate a 3D spatio-temporal map depicting the anterior wall velocity waveform at each beam location in the imaged segment over time. In order to estimate the PWV, the waveforms in normal subjects were observed to identify a tracking feature that would best distinguish the waveforms at each consecutive beam location. The 50% upstroke was selected as the fiduciary point for waveform tracking and subsequent PWV estimation based on the observation that in normal subjects, the 50% upstroke of the waveforms exhibited the greatest separation. To remain consistent across all subjects, the 50% upstroke was used for waveform tracking in the hypertensive and AAA cases as well. From the spatio-temporal map, the 50% upstroke of the wall velocity waveform at each beam location over a single cardiac cycle was automatically detected by traversing the waveform to locate its peak and foot values, then finding the point in the waveform exactly halfway between its peak and foot.

Linear regression of the relationship between the 50% upstroke arrival time and the beam location along the anterior wall yielded the slope as the apparent PWV and the r^2 as an approximate index of the wave propagation uniformity. If the apparent PWV exceeded its PWV_{max} (equation 1), the measurement was deemed unreliable, since PWV_{max} is the theoretical upper limit on the PWV that can be measured at the given frame rate. Since the beam sweeping induces delays in the acquisition of each RF line (and hence the motion estimation), the real PWV was obtained by compensating for the beam sweeping-induced delays in the pulse wave arrival times as described by Luo *et al* (2012).

3. Results

Figure 2 shows consecutive PWI frames (B-Mode overlaid with pulse wave-induced wall velocities) illustrating the propagation of the pulse wave in one representative normal (2a), hypertensive (2b), and aneurysmal (2c) subject. The wave propagation over all frames acquired during a single cardiac cycle for each case in figure 2 is shown as ciné-loops in Supplemental movies 1, 2, and 3. The arrival of the pulse wave induces an upward (i.e. towards the transducer) motion (shown in red) in the anterior wall. The arrows indicate the apparent position of the 50% upstroke of the waveform as it propagates from proximal (closest to the heart) to distal (closest to the iliac bifurcation) across the imaged segment. In the normal aorta (figure 2a), the wave propagation could be clearly visualized and appeared to be mostly uniform. In the hypertensive case (figure 2b), the propagation of the wavefront

was still apparent. However, unlike in the normal case, the pulse wave-induced anterior wall motion near the proximal end began to deteriorate during the wave propagation, as can be seen in the rightmost frame in 2b. This could indicate a peak narrowing of the wall velocity waveform. The highly non-uniform nature of the wall velocity distribution in the aneurysmal aorta (figure 2c) rendered it difficult to distinguish the pulse wave propagation.

Figure 3 shows the spatio-temporal maps of the anterior aortic wall velocity in three normal subjects, ages (a) 27, (c) 31, and (e) 55. Figure 4 shows the spatio-temporal maps of the wall velocity in three hypertensive subjects, ages (a) 45, (c) 53, and (e) 77. Figure 5 shows the spatio-temporal maps of the wall velocity in three AAA subjects, ages (a) 74 (3.3 cm AAA), (c) 66 (4.6 cm AAA), and (e) 68 (3.4 cm AAA). In figures 3–5, the wall velocity waveforms at five locations along the imaged segment corresponding to (a), (c), and (e) are shown in (b), (d), and (f), respectively. In the aneurysmal cases, the brown lines indicate the beginning and end of the dilated aneurysmal segment as qualitatively approximated from the B-Mode images. The normal case shown in 3c is the same as that shown in figure 2a, the hypertensive case shown in 4c is the same as that shown in figure 2b, and the AAA case shown in 5e is the same as that shown in figure 2c.

In all normal and hypertensive cases shown, the waveform propagated in a uniform fashion ($r^2 = 0.89$). However, the hypertensive waveforms appeared to be more variable over the cardiac cycle compared normals. For example, the waveforms in the normal aortas shown in figures 3b and 3d maintained virtually the same amplitude and morphology throughout its propagation, while the normal waveform shown in figure 3f steadily decreased in amplitude but still appeared to maintain the same shape. However, in the hypertensive cases shown in Figures 4b and 4d, both the amplitude and morphology of the waveform varied noticeably throughout its propagation. Compared to the normal cases (3b, 3d, 3f), the hypertensive case shown in figure 4d exhibits peak narrowing. In the hypertensive case shown in Figure 4f, the peak of the waveform was wider and far less pronounced compared to the normal and other hypertensive cases shown.

In all AAA cases shown, the waveform propagation was highly non-uniform ($r^2 = 0.60$) and the wall motion began to decrease past the initial dilation. Also, a downward motion (i.e. away from the transducer) occurred in the anterior wall within the duration of the pulse wave as indicated by a blue region on the spatio-temporal map near the distal end of the imaged segment. In contrast, the pulse wave induced only upward motion of the anterior wall in the normal and hypertensive cases shown.

Five hypertensive and three AAA subjects exhibited a negative PWV and were excluded from the results presented in this study. Due to branching and vascular inhomogeneities, the waveform at each beam location is a combination of the incident wave originating from the heart and possibly multiple reflected waves originating from the downstream periphery (Fung, Springer-Verlag 1997; Nichols and O'Rourke, Hodder Arnold Publication 2005). Observation of a negative PWV may likely have arisen from the inability to distinguish the forward wave from the reflected wave(s) due to insufficient frame rate and/or complex waveform mixing. The PWV measurements averaged over at least five cardiac cycles for each remaining subject are shown in figure 6. The PWVs in the hypertensive and AAA

subjects were more variable than those in the normal subjects as indicated by the error bars. The average PWV in all normal, hypertensive, and AAA subjects was 6.03 ± 1.68 , 6.69 ± 2.80 , and 10.54 ± 6.52 m/s, respectively (figure 7a). There was no significant difference ($p = 0.15$) between the PWVs in the normal and hypertensive subjects. However, the PWVs in the AAA subjects were significantly higher ($p < 0.001$) compared to those in the other two groups. The average r^2 in all normal, hypertensive, and AAA subjects was 0.93 ± 0.05 , 0.88 ± 0.11 , and 0.46 ± 0.23 , respectively (figure 7b). Although the r^2 of the normal and hypertensive aortas were not significantly different ($p = 0.04$), that of the AAA subjects was significantly lower ($p < 0.001$) than that of the other two subject groups.

4. Discussion

This study demonstrated the capability of PWI to spatio-temporally map the propagation of the pulse wave as a wall velocity wave in the infrarenal abdominal aortas of normal, hypertensive, and aneurysmal human subjects. The PWV was estimated in all subjects via linear regression of the spatio-temporal variation of the waveform upstroke, and the linear coefficient of determination r^2 was obtained as an approximate measure of the wave propagation uniformity. Compared to other imaging methods for estimating PWV based on MRI (Kraft *et al* 2001; Macgowan *et al* 2002; Boese *et al* 2000) and Doppler imaging (Eriksson *et al* 2002; Rabben *et al* 2004; Hartley *et al* 1997), the high temporal resolution of PWI allows for the acquisition of multiple waveforms (i.e. equal to the beam density) along short aortic segments over a single cardiac cycle, thus providing many temporal and spatial samples for PWV estimation as well as fused functional and anatomical images at high frame rates showing simultaneously the vessel structure and wall motion (figure 3).

It is worth noting that there existed an angle-dependence in the motion estimation arising from the use of a curvilinear probe and the fact that anatomically, the aorta may have been oriented such that the direction of wall motion was not exactly parallel to the ultrasound beams. This may have resulted in estimated axial displacements that were only an off-angle component of the true displacement magnitude. Since this study focused on measuring the pulse wave velocity, the arrival time of the waveform at each beam location was of primary importance rather than the waveform magnitudes themselves. Since the same field of view was maintained for the duration of each acquisition, the direction of wall motion at each beam location maintained the same angle with the beam. Thus, although the estimated axial displacements may have been smaller than the true displacements, the estimated displacement waveform at each beam location maintained the same morphology as the true displacement waveform. This would not have affected the waveform tracking, since the 50% upstroke was identified relative to the peak and the foot in each waveform.

In addition to pulse wave-induced radial expansion, the abdominal aorta also experiences longitudinal motion (Cinthio, Ahlgren *et al.* 2006). Since the pulse wave propagates by inducing radial displacements in the vessel wall, only the axial component of wall motion was estimated in this study while the longitudinal motion was neglected. Future studies will be aimed at using 2D motion estimation methods to estimate the lateral wall displacement for more complete wall motion analysis.

Qualitatively, the wave propagation in normal aortas was the most uniform, whereas the amplitude and morphology of the successive waveforms over the cardiac cycle appeared to be more variable in hypertensive aortas. In all AAA cases, the dilated vascular wall resulted in highly variable waveform morphologies, decreased wall motion within the aneurysm, and a downward motion of the anterior wall at the distal end of the imaged segment. Quantitatively, the significantly higher [lower] PWV [r^2] estimates in the AAA subjects suggested greater aortic stiffness and less uniform pulse wave propagation compared to the normal and hypertensive subjects.

The *regional* aortic PWVs measured using PWI in the normal aortas were consistent with values found in literature obtained using MRI (Kraft *et al* 2001; Macgowan *et al* 2002; Boese *et al* 2000), which varied between 4 and 7 m/s. However, most clinical studies that have investigated the *in vivo* relationship between PWV and various pathologies such as hypertension have utilized some form of the foot-to-foot method (Sutton-Tyrrell *et al* 2005; Laurent *et al* 2001; Laurent *et al* 2003; Blacher *et al* 1999; Blacher *et al* 2001) and thus reported the *global* PWV, which may differ from the *regional* PWV at various sites in the arterial tree. Thus, there is a shortage of existing literature against which to compare the hypertensive and aneurysmal PWV measurements obtained in this study.

4.1 Aging and gender

In clinical studies, the principal factors modulating the PWV in the absence of disease are age, blood pressure, and to a lesser extent, gender (Safar *et al* 2002). In AAA cases, the risk of rupture is four times greater in women than in men (Kleinstreuer *et al* 2007). In this study, the normal subjects were significantly younger than the pathological subjects ($p < 0.001$), but both genders were well-represented in all subject groups. However, since the subjects were categorized by pathology, the factors of aging and gender on the aortic properties were not reflected.

4.2 Hypertensive subjects

While previous longitudinal studies reported a positive correlation between the carotid-femoral (i.e. *global*) PWV and cardiovascular events in hypertensive patients (Laurent *et al* 2001; Laurent *et al* 2003; Boutouyrie *et al* 2002; Blacher *et al* 2001), the results from our study indicated that there was no significant difference in the *regional* aortic PWVs between normal and hypertensive subjects. Since aging and hypertension are both assumed to increase arterial stiffness and the hypertensive subjects in this study were significantly older than the normal controls, this raises the question of why the hypertensive subjects did not exhibit a significantly higher PWV. This could be attributed to a number of factors.

In vivo arteries exhibit tapering, branching, and geometrical non-uniformity throughout the arterial tree, resulting in multiple reflection sites (Fung, Springer-Verlag 1997; Nichols and O'Rourke, Hodder Arnold Publication 2005; Bleasdale *et al* 2003) such as the iliac bifurcation, which is located immediately downstream from the infrarenal abdominal aorta. The mixing of the forward wave and possibly multiple reflected waves at a given site (Fung, Springer-Verlag 1997) is a phenomenon that becomes augmented by aging and some pathologies (Mitchell *et al* 2004; Segers *et al* 2009). Hence, the PWV measured using PWI

was obtained by tracking the resultant of the forward and reflected waves, which travel in opposite directions. Along these lines, it is possible that the arterial stiffening that is presumed to occur due to aging and hypertension may have caused both the forward and reflected waves to travel faster, resulting in more frequent mixing an apparently slower forward wave. This may also contribute to the greater intra-subject variability in PWV and waveform morphology observed in the hypertensive group. On the other hand, the normal aortas in this study were much younger and less affected by reflections.

Two additional factors in the hypertensive subjects that were not extensively considered in this study were the effects of smoking and response to medication, both of which may affect vascular mechanical properties (Mahmud and Feely 2003; Tomiyama *et al* 2011). Finally, nearly all hypertensive patients in this study had been diagnosed with at least one other pathology such as renal disease, heart disease, or diabetes. Not only can such diseases affect arterial elasticity, they also require the patient to take additional medications which may affect the arterial wall properties.

Considering all the factors indicated above, the complexity of the hypertensive subject group becomes apparent. Since it is virtually impossible to distinguish the individual effects of each confounding factor, the resultant pulse wave propagation patterns and measured PWVs represent the combined effect of each confounding factor on top of the hypertensive conditions.

4.3 AAA subjects

In two of the AAA cases shown (figures 5c and 5e), the waveforms maintain enough upstroke (blue dots) for reliable waveform tracking along the entire length of the imaged segment despite the decreased wall motion in the dilated region. In the other AAA case shown (figure 5a), the wall motion decreases to the extent where the 50% upstroke is not apparent, thus limiting the ability to determine the arrival time of the upstroke at every position over the entire imaged segment.

In AAA cases, the effects of aging, wave reflection, medication, smoking, and confounding pathologies also apply. The problem is further complicated by the complex geometry of the aneurysmal aorta, which can lead to turbulent flow within and near the aneurysm (Kleinstreuer *et al* 2007). The drastic variations in the morphology of the successive waveforms due to an aneurysm significantly limit the tracking of a consistent fiduciary point in each waveform, which may explain the high variability of the PWV estimations in AAA subjects. However, the significantly lower r^2 values found in the AAA subjects compared with normal and hypertensive subjects were consistent with previous *in vivo* PWI results on AAA murine models (Luo *et al* 2009), which also showed a decreased r^2 in the presence of an aneurysm.

As previously stated, the presence of the dilated aneurysm sac invalidates the use of the Moens-Korteweg equation to derive the arterial Young's modulus from the PWV. In addition, the change in waveform morphology in AAA subjects may likely depend on augmented reflected waves, geometrical non-uniformity, and inhomogeneous wall mechanics. Thus, changes in waveform morphology and magnitude may not have

necessarily been correlated with changes in vascular stiffness. However, due to the positive correlation between arterial stiffness and PWV, future studies will be aimed at incorporating the geometry of the aneurysm to supplement the measurement of PWV as a surrogate of arterial stiffness. The ability of PWI to obtain the actual morphologies of the wall motion waveforms across the aneurysmal segment enables more indepth analysis of the arterial mechanical properties.

4.4 Conclusions

PWI is a promising technique that enables both visual and computational evaluation of the *regional* pulse wave propagation, which could aid in the early detection and characterization of many vascular diseases. The results from this feasibility study demonstrate the potential of PWI to differentiate between normal and pathological arteries through evaluating various features of the pulse wave over complete cardiac cycles. As the sample size increases in this ongoing clinical study, we plan to further categorize the pathological subjects based on parameters such as blood pressure, age, gender, and AAA diameter in order to optimize the diagnostic capability of PWI.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.

Schematic for subject scanning. The curvilinear ultrasound transducer was placed in the long-axis orientation on the stomach of the subject lying in the supine position. To standardize the data acquisition across subjects, the transducer was orientated such that the pulse wave propagated from right to left in the ultrasonic imaging field of view (in the same direction as blood flow).

The black dotted lines indicate the boundaries of the field of view.

Figure 2.

Consecutive PWI frames (B-Mode image overlaid with pulse wave-induced wall motion) showing the propagation of the pulse wave along the aortic wall in (a) a normal (age 31), (b) a hypertensive (age 46), and (c) an aneurysmal (age 66, 3.4 cm-diameter AAA) subject. In all frames, the transducer was oriented such that blood flows from right to left (i.e. proximal to distal as labeled in the first frame of (a)) in the ultrasonic image plane. The time stamp represents the approximate time elapsed after the systolic phase of the cardiac cycle. In each frame, the arrow indicates the apparent position along the anterior wall of the 50% upstroke of the pulse wave that was used as the fiduciary point for PWV estimation. In the aneurysmal case (c), the propagation of the wave upstroke is not as distinct as it is in the other two cases.

Figure 3.

(a, c, e) Spatio-temporal maps of anterior aortic wall velocity in three normal subjects, ages (a) 27, (c) 31, and (e) 55. Subfigures (b), (d), and (f) show the wall velocity waveforms at five locations along the imaged segment corresponding to the spatio-temporal maps in (a), (c), and (e), respectively. The blue squares represent the 50% upstroke in each waveform as it propagates along the wall. The PWV and r^2 values were obtained from the linear regression of the spatio-temporal variation of the 50% upstroke, represented by the purple line in (a), (c), and (e). Subfigures (c) and (d) correspond to the same subject shown in figure 2a.

Figure 4.

(a, c, e) Spatio-temporal maps of anterior aortic wall velocity in three hypertensive subjects, ages (a) 45, (c) 53, and (e) 77. Subfigures (b), (d), and (f) show the wall velocity waveforms at five locations along the imaged segment corresponding to the spatio-temporal maps in (a), (c), and (e), respectively. The blue squares represent the 50% upstroke in each waveform as it propagates along the wall. The PWV and r^2 values were obtained from the linear regression of the spatio-temporal variation of the 50% upstroke, represented by the purple line in (a), (c), and (e). Subfigures (c) and (d) correspond to the same subject shown in figure 2b.

Figure 5.

(a, c, e) Spatio-temporal maps of anterior aortic wall velocity in three AAA subjects, ages (a) 74 (3.3 cm AAA), (c) 66 (4.6 cm AAA), and (e) 68 (3.4 cm AAA). Subfigures (b), (d), and (f) show the wall velocity waveforms at five locations along the imaged segment corresponding to the spatio-temporal maps in (a), (c), and (e), respectively. The blue squares represent the 50% upstroke in each waveform as it propagates along the wall. The PWV and r^2 values were obtained from the linear regression of the spatio-temporal variation of the 50% upstroke, represented by the purple line in (a), (c), and (e). In (a), (c), and (e), the brown lines indicate the beginning and end of the dilated aneurysmal segment as qualitatively approximated from the B-Mode images. Subfigures (e) and (f) correspond to the same subject shown in figure 2c.

Figure 6.

PWV measurements averaged over at least five cardiac cycles for each subject. Standard deviations are shown as black error bars.

Figure 7.

(a) PWV and (b) r^2 averaged over all subjects for each of the three subject groups. Standard deviations are shown as black error bars. The average PWV in all normal, hypertensive, and AAA subjects was 6.03 ± 1.68 , 6.69 ± 2.80 , and 10.54 ± 6.52 m/s, respectively. The average r^2 in all normal, hypertensive, and AAA subjects was 0.93 ± 0.05 , 0.88 ± 0.11 , and 0.46 ± 0.23 , respectively. The star denotes statistical significance with $p < 0.001$.