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In Vivo Quantification of Aortic Stiffness Using Magnetic Resonance Elastography in Hypertensive Porcine Model

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Abstract

Purpose—Aortic stiffness plays an important role in evaluating and predicting the progression of systemic arterial hypertension (SAH). The aim of this study is to determine the stiffness of aortic wall using magnetic resonance elastography (MRE) in a hypertensive porcine model and compare it against invasive aortic pressure measurements.

Methods—Renal wrapping surgery was performed on eight pigs to induce SAH. Aortic MRE was performed at baseline and two months post-surgery using a retrospectively pulse-gated gradient-echo MRE sequence on a 1.5T scanner. Mechanical waves of 70Hz were introduced into the aorta. Invasive central aortic pressure measurements were obtained prior to each scan to calculate mean arterial pressure (MAP). MRE data were analyzed to obtain effective aortic stiffness. Spearman's rank correlation analysis was performed to assess the relationship between MAP and MRE-derived aortic stiffness.

Results—Significant increase in effective aortic stiffness was observed between baseline and two months post-surgery measurements (paired t-test; $p=0.004$). The average MAP by pooling all animals was 65.24 ± 9.42 mmHg at baseline and 92.57 ± 11.80 mmHg two months post-surgery with $p < 0.0001$. Moderate linear correlation was observed between MAP and effective aortic stiffness ($\rho=0.52$; $p=0.046$).

Conclusion—This study demonstrated that in SAH porcine model, MRE-derived aortic stiffness increased with increase in MAP.

Keywords

Aortic wall stiffness; mean arterial pressure; central aortic pressure; systemic arterial hypertension; MR elastography

INTRODUCTION

Systemic arterial hypertension (SAH) is a chronic cardiovascular condition characterized by elevation of arterial blood pressure (1). Although blood pressure increase is usually asymptomatic, long-term high blood pressure is a major risk factor for cerebrovascular, cardiovascular, renal, and retinal diseases, making SAH a leading contributor to the global burden of disease and premature death with mortality rate of 9.4 million each year (2–4). Currently, there are approximately 1 billion people affected by SAH worldwide and the total hypertensive population is predicted to reach 1.56 billion by 2025 (5).

Brachial artery blood pressure is widely measured in clinical practices; however, multiple factors such as the arm position, the cuff location and brachial artery diseases can cause significant discrepancies between brachial artery pressure and the central aortic pressure which truly reflects the general blood pressure experienced by the circulation system. Moreover, it is well known that brachial artery pressure will not reflect the true central aortic pressure (6,7) which is a more accurate predictor of cardiovascular events (8–10). On the other hand, approaches to estimating central aortic pressure are usually invasive, or if non-invasively acquired, the resulting arterial pulse pressure measurements may not provide complete information about aortic pressure. It is known that aortic compliance is altered with changes in arterial pressure (11). Additionally, aortic stiffness is also known to be closely associated with a variety of cardiovascular comorbidities such as atherosclerosis, aortic aneurysm, aging-related vascular degradation, etc. (12–15). It has been demonstrated that aortic stiffness is an important biomarker for SAH as the non-linear viscoelastic behavior of arterial wall results in increased stiffness with increased arterial pressure (16–18). Therefore, spatial estimation of aortic stiffness plays an indispensable role in better evaluating and predicting the progression of SAH without the need for invasive pressure measurements.

Pulse wave velocity (PWV) is the current gold standard for estimating the stiffness of the aorta (19). However, it has several major limitations. First, peripheral wave-based measurements such as the carotid-femoral PWV method measures pulse wave from peripheral arteries which is a poor reflection of the central aortic pulse wave (20). Second, it is challenging to obtain the true aortic wall thickness, diameter, and pulse wave pass length that are required to correctly derive aortic stiffness from PWV (21). In addition, PWV only provides a global measure of aortic stiffness and does not provide temporal and spatial estimates (22).

Magnetic resonance elastography (MRE) is a novel non-invasive phase-contrast (PC) MR imaging technique in which the shear stiffness of soft tissues can be spatially estimated by encoding the externally applied periodic motion with motion encoding gradients (MEGs) (23–25). Earlier studies have demonstrated the feasibility and reproducibility of aortic MRE

in healthy volunteers and its comparison against PWV methods (26). Furthermore, it has also been demonstrated that there was significant difference in MRE-derived effective aortic stiffness between normotensive volunteers and hypertensive patients (4). However, to the best of our knowledge, estimation of MRE-derived effective aortic stiffness using three-dimensional volumetric MRE data in hypertensive subjects and its correlation to invasive pressure measurements has not been demonstrated previously.

Therefore, the aim of this study is to estimate MRE-derived effective aortic stiffness in a hypertensive porcine animal model and compare it against mean arterial pressure obtained from invasive central aortic pressure measurements (22).

METHODS

In vivo aortic MRE was performed on 8 juvenile pigs (Yorkshire pigs; weight: ~70lbs) after obtaining the approval of institutional animal care and use committee (IACUC).

Hypertension Animal Model

The animals underwent renal wrapping surgery which is known to induce chronic SAH (27,28). The animals were placed in a supine position on the surgery table and pre-operative Bupivacaine (0.5%, dosage: 3–5 ml) was injected into the incision site. Renal wrapping surgery was performed via a midline abdominal incision. Both the kidneys were cleared of perinephric fat and wrapped firmly using sterile umbilical tape without constricting the renal vessel (29). The abdominal wall was then closed in multiple layers using absorbable sutures. Post-operative analgesia consisted of a dose of Buprenorphine (0.3 mg/ml, dosage: 0.005–0.02 mg/kg) and a fentanyl transdermal patch (100 mcg/hr/72hrs).

Experiment Setup

All MR imaging was performed on a 1.5T Siemens scanner (Avanto, Siemens Healthcare, Erlangen, Germany). The animals were positioned feet-first in the scanner. A custom-built pneumatic driver system was used to generate 70Hz mechanical waves in the abdominal region. The mechanical vibration frequency was chosen to achieve strong wave penetration as described in our earlier study which demonstrated its feasibility and reproducibility (22). The passive driver was placed on the posterior side of the animal as shown in Figure 1 and connected to the active component of the pneumatic system via a plastic tube to induce the mechanical vibrations. MRE was performed at baseline (i.e., prior to the surgery) and 2 months post-surgery (M2). Due to technical issues with the scanner, M2 data were not acquired in one of the eight animals, as the IACUC protocol did not allow us to scan on a different day once the animal was prepared for the study.

Central Aortic Pressure Measurement

Prior to each MRE measurement, a catheter pressure transducer (SPR-882, Millar, Inc., Houston, TX) was advanced through the femoral artery into the aorta under fluoroscopy (OEC 9800, GE Healthcare, Milwaukee, WI) to measure the central aortic pressure. Aortic pressure was recorded continuously by a bridge-amplifier (FE221, AD Instruments, Colorado Spring, CO) and Power Lab (PL3508, AD Instruments, Colorado Spring, CO).

Simultaneously, a Bio-amplifier (FE136, AD Instruments, Colorado Spring, CO) was also used to record the ECG signal.

Image Acquisition

A retrospectively pulse-gated gradient echo MRE sequence with flow compensation was employed to acquire MRE wave images of the aorta in sagittal view. To allow for performing the MRE inversion on a 3D volumetric MRE dataset, three 5mm slices covering the entire aorta were acquired with 2.5mm overlap between each slice. The imaging parameters included: echo time (TE)=11.04 ms; repetition time (TR)=14.28 ms; flip angle=15°; field of view (FOV)=384×384 mm²; acquisition matrix size=128×64; reconstructed matrix size=256×256; number of cardiac phases=8; slice thickness=5 mm with 2.5mm overlap; GRAPPA acceleration factor=2; four MRE phase offsets; and 120Hz motion encoding gradient was applied separately along x, y and z-axis to encode the in-plane and through-plane motion. The total acquisition time for each MRE scan was about 12–16 seconds depending on the heart rate of the animal. Breath hold was performed during image acquisition under suspended mechanical ventilation.

Image Analysis

The sagittal images were masked to delineate the abdominal aorta. Subsequently, the aortic MRE data were processed using MRElab (Mayo Clinic, Rochester, MN). As described earlier (30), the first harmonic displacement data were filtered using a fourth order Butterworth band-pass filter with cutoff values of 1–40 waves/FOV to eliminate noise and the longitudinal component, and directionally filtered in eight directions to remove the reflected waves. A local-frequency estimation (LFE) inversion (31) was performed on the 3D volumetric MRE dataset to obtain the spatial frequency from the filtered displacement data in each motion encoding direction. Assuming soft tissue density to be 1gm/cm³, the effective shear stiffness can then be calculated by

$$\mu = f_{mech}^2 / f_{sp}^2 \quad (\text{Eq. 1})$$

where f_{MECH} is the mechanical frequency and f_{sp} is the spatial frequency. The effective stiffness obtained using LFE is equivalent to solving the Helmholtz equation under the assumptions of infinite medium, incompressibility of the tissue, local homogeneity and no attenuation (25). The reported effective stiffness value in this study is a weighted combination of stiffness from all encoding directions.

Additionally, the mean arterial pressure was derived from the measured central aortic pressure using the following equation.

$$MAP = (2 \times P_{dia} + 1 \times P_{sys}) / 3 \quad (\text{Eq. 2})$$

where P_{dia} and P_{sys} are diastolic and systolic aortic pressure, respectively.

Statistical Analysis

Statistical analysis was performed using SAS 9.4 (SAS, Inc. Cary, NC). Spearman's rank correlation was used to assess the relationship between MAP and MRE-derived effective aortic stiffness. In addition, paired t-tests were conducted to examine the difference in MAP and effective aortic stiffness between baseline and M2 measurements. A p -value 0.05 was considered statistically significant.

RESULTS

Higher aortic stiffness was observed at M2 when compared to the baseline measurements. Figure 2 shows the magnitude, corresponding wave images and effective aortic stiffness maps of the same animal at baseline and M2, demonstrating stiffer post-operative aorta.

The mean effective aortic stiffness by pooling all animals is 3.06 ± 0.42 kPa and 3.75 ± 0.44 kPa for baseline and M2, respectively. Figure 3 shows the comparison of the stiffness measurements at baseline and M2 in all animals with $p=0.004$ (95% Confidence Interval (CI) for stiffness difference: [0.322, 1.062]), suggesting that the mean effective aortic stiffness was significantly higher at M2 compared to the baseline measurements.

Aortic stiffness changed cyclically across the cardiac cycle. Figure 4 shows the polynomial function used to fit the mean effective stiffness of eight animals across one cardiac cycle with a goodness of fit of $R^2=0.89$ at baseline, and $R^2=0.94$ at M2. The mean curves demonstrated that effective aortic stiffness increased from baseline (green line) to M2 (blue line) across the entire cardiac cycle.

The MAP for each animal at baseline and M2 are illustrated in Figure 5a. The average MAP was 65.24 ± 9.42 mmHg and 92.57 ± 11.80 mmHg for all animals at baseline and M2, respectively. A significant increase in MAP was observed at M2 ($p<0.0001$; 95% CI for pressure difference: [20.15, 34.50]) compared to the baseline measurements.

Significant moderate correlation was observed between MAP and MRE-derived effective aortic stiffness. Spearman's rank correlation coefficient was $\rho=0.52$ with $p=0.046$ as shown in Figure 5b.

DISCUSSION

This study has shown that MRE-derived effective aortic stiffness increased with increase in MAP in a hypertensive porcine model. Aortic stiffness significantly increased from baseline to M2 and also varied cyclically across the cardiac cycle. Significant moderate linear correlation was observed between aortic stiffness and MAP. Therefore, this work has demonstrated the potential of using MRE-derived aortic stiffness as a surrogate for central aortic pressure, and the influence of MAP on aortic compliance.

MRE-derived effective aortic stiffness and MAP demonstrated significant moderate linear correlation. In the aorta, the wall stiffness is affected by its geometry, intrinsic properties as well as loading condition experienced by the aorta, such as from blood pressure (11,32). Therefore, the effective aortic stiffness obtained in this study was influenced by the

combination of above-mentioned factors. When compared to the baseline measurement, the significantly stiffer aorta observed at M2 can be partially attributed to the substantial elevation in blood pressure induced by renal wrapping surgery. Elevated MAP applies a higher load on the aortic wall, directly leading to an increase in aortic stiffness as well as intrinsic extracellular matrix (ECM) remodeling of the wall which then alters the aortic compliance (33–35). Additionally, the aortic pressure measurements were obtained prior to MRE scan in this study and all MRE scans were performed under anesthesia, which may also influence the correlation between the effective aortic stiffness and MAP. Therefore, not accounting for geometry of the aorta and physiologic variations due to anesthesia partially explain the observed moderate correlation between the effective stiffness and MAP.

The effective stiffness of the aorta was evaluated at each cardiac phase in this work, providing a better understanding of temporal variation of aortic stiffness throughout the entire cardiac cycle. The changes in the stiffness during a cardiac cycle is critical in many diseases, such as aneurysm formation, because it provides the information on pressure loading during systolic and diastolic phase, which can eventually lead to aneurysmal rupture (36,37). In addition, the changes in compliance of the aorta due to different disease conditions such as atherosclerosis or Marfan syndrome can also alter the pressure within the aorta (38). Blood pressure and arterial stiffness are both interdependent being a cause and effect of one another. It is unclear whether the change in arterial compliance is a passive consequence of change in blood pressure or it is due to the changes in the arterial wall structure (11). Nevertheless, studies involving both human subjects and animal models have demonstrated that acute blood pressure variation can result in change in arterial stiffness (32,39). Thus, the observed stiffness variation pattern in this study can be explained by the cyclic fluctuation of central aortic blood pressure within a cardiac cycle, which also explains the consistent pattern observed at baseline and M2 despite the difference in mean effective stiffness.

The effective aortic stiffness values reported in this study are based on the already validated waveguide principle (40,41). The waves propagating both in the lumen and aortic wall are processed together at a given frequency of excitation to report the effective stiffness values. This principle provides the opportunity to avoid high spatial-resolution imaging just to demonstrate the aortic wall. This technique also reported robust stiffness values: 1) with good reproducibility in healthy human subjects (22); 2) in evaluating abdominal aortic aneurysms (37); 3) in showing significant difference between normotensive and hypertensive human subjects (4); and 4) with good correlation against PWV and increase in stiffness as a function of age (26).

The results observed in our study are in line with several studies reporting significant aortic stiffness increase with elevated pressure in the aorta (4,32,40,42–44). Using MRE method, Kolipaka et al. observed significantly higher aortic stiffness among subjects with SAH (4). However, the earlier study did not correlate the effective stiffness to any pressure measurements as the subjects had controlled SAH. Xu et al. reported elevated MRE-derived Young's modulus-wall thickness product (E^*t) with elevated static pressure increment within the aorta (44). Performing ex vivo MRE on an aorta harvested from hypertensive

porcine model, Woodrum et al. observed significantly higher Young's modulus-wall thickness product in hypertensive porcine aorta than in the control group (40).

The stiffness values reported in this work are in the range of previously published results (4,22,26,37,45). However, the stiffness values obtained in this study cannot be directly compared to previous results as those were from both human subjects (4,22,26,37) and ex vivo animal models (40,45) performed at different mechanical excitation frequencies. Moreover, Young's modulus-wall thickness product was studied in some of the earlier studies (40,44) instead of MRE-derived effective stiffness of the aorta which was reported in this work. Therefore, stiffness reported in this study cannot be compared to ex vivo animal models or adult human subjects' stiffness values. Furthermore, to the best of our knowledge, this is the first in vivo study reporting effective aortic stiffness in a hypertensive porcine model using MRE.

There are several limitations in this study. First, the geometry of the aorta was not considered in obtaining the aortic stiffness. Consequently, the measured aortic stiffness is considered to be an "effective" measurement. However, an earlier study has shown high correlation between stiffness values obtained with and without considering the geometry of the aorta (26). Second, the central aortic pressure was measured under anesthesia (isoflurane) before each baseline and M2 scan. Isoflurane is a well-accepted anesthetic agent for porcine research models. Although isoflurane can decrease heart rate, pressure, and cardiac output at higher concentrations, the depth of anesthesia in this study was closely monitored and adjusted to prevent spontaneous respiration during breath holds without depressing the heart rate or other physiological variables. Third, the temporal resolution of pressure measurement was higher (1ms) compared to MRE acquisition (171–200ms). Furthermore, the pressure measurements were collected 30 min prior to MRE acquisition. Therefore, it becomes challenging to exactly match the pressure measurements to stiffness values across the cardiac cycle. Hence, stiffness measurements were only correlated against MAP. Fourth, each encoding direction of external motion and multiple slices were acquired in separate breath holds and then processed to obtain stiffness maps. Nevertheless, the breath holds were consistent without any registration errors between scans as they were obtained under suspended mechanical ventilation. Future work will incorporate acquiring three-dimensional MRE data within a reasonable breath hold time. Finally, during the breath holds, the heart rate was closely monitored and controlled by the anesthesia. We acknowledge that prolonged breath hold can increase the heart rate, blood flow and blood pressure, which could potentially lead to biased estimation of the effective aortic stiffness. However, we anticipate that short burst of breath holds (i.e. 12 to 16 sec) may not significantly affect the aortic stiffness. Despite these limitations, it was demonstrated that MRE-derived effective aortic stiffness increased with disease progression and correlated with MAP.

CONCLUSION

In conclusion, this study has demonstrated that MRE-derived effective aortic stiffness increased with SAH in a porcine model. The effective aortic stiffness measurements are significantly higher and varied cyclically across one cardiac cycle two months after renal

wrapping surgery compared to baseline. Significant moderate correlation was observed between effective aortic stiffness and MAP derived from invasive aortic pressure measurements. Therefore, this study provides the potential of using MRE-derived aortic stiffness in understanding the pathophysiology of hypertension.

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Figure 1. Experiment Setup

Schematic of the experiment setup demonstrates that the passive driver was placed on the back of the animal and connected to the active driver located outside the scan room using a plastic tube. A 70Hz vibration was induced in the abdominal aorta.

Figure 2. Aortic MRE Data

The magnitude images of the same animal at baseline and M2 are displayed in the figure (a, g) with red contour delineating the aorta. Snapshots of propagating waves at four different time points in the abdominal aorta at baseline (b–e) and M2 (h–k) are demonstrated, and their corresponding stiffness maps at baseline (f) and M2 (l) are displayed. The demonstrated animal had the highest stiffness change among others. The mean aortic stiffness is 2.81 ± 0.63 kPa and 4.10 ± 1.04 kPa at baseline and M2, respectively.

Figure 3. Baseline and M2 Stiffness Measurements

The plot shows significant difference ($p=0.004$) in stiffness measurements at baseline and M2. The aorta data were not acquired for one of the animals indicated by the single blue circular marker in the figure at M2 due to technical difficulty with the scanner and IACUC regulations.

Figure 4. Aortic Stiffness and Cardiac Cycle

The plot displays the aortic stiffness values across cardiac cycle in all animals with colors representing different pigs, and different markers for baseline and M2 measurements. The green ($R^2=0.94$) and blue ($R^2=0.89$) curve shows the polynomial fit of mean stiffness values across cardiac cycle for all animals at baseline and M2, respectively. It can be observed that M2 has higher stiffness values compared to baseline with similar cyclic pattern across cardiac cycle.

Figure 5. Mean Arterial Pressure and Aortic Stiffness

a) shows significantly ($p < 0.0001$) higher MAP at M2 compared to baseline with a mean value of 92.57 ± 11.80 mmHg at M2 and 65.24 ± 9.42 mmHg at baseline. b) demonstrates the correlation between aortic stiffness and MAP with a significant ($p = 0.046$) Spearman's rank correlation coefficient of $\rho = 0.52$.