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Influence of Beta-Blocker Therapy on Aortic Blood Flow in Patients with Bicuspid Aortic Valve

Bradley D. Allen¹, Michael Markl^{1,2}, Alex J. Barker¹, Pim van Ooij¹, James C. Carr¹, S Chris Malaisrie³, Patrick McCarthy³, Robert O. Bonow⁴, and Preeti Kansal⁴

¹Department of Radiology, Feinberg School of Medicine, Northwestern University, Chicago, USA

²Department Biomedical Engineering, McCormick School of Engineering, Northwestern University, Chicago, USA

³Division of Cardiothoracic Surgery, Northwestern University, Chicago, USA

⁴Department of Medicine - Cardiology, Feinberg School of Medicine, Northwestern University, Chicago, USA

Abstract

Purpose—In patients with bicuspid aortic valve (BAV), beta-blockers (BB) are assumed to slow ascending aorta (AAo) dilation by reducing wall shear stress (WSS) on the aneurysmal segment. The aim of this study was to assess differences in AAo peak velocity and WSS in BAV patients with and without BB therapy.

Methods—BAV patients receiving BB (BB+, n=30, age:47±11 years) or not on BB (BB–, n=30, age:46±13 years) and healthy controls (n=15, age:43±11 years) underwent 4D flow MRI for the assessment of in-vivo aortic 3D blood flow. Peak systolic velocities and 3D WSS were calculated at the anterior and posterior walls of the AAo.

Results—Both patient groups had higher maximum and mean WSS relative to the control group (p=0.001 to p=0.04). WSS was not reduced in the BB+ group compared to BB– patients in the anterior AAo (maximum: 1.49±0.47N/m² vs. 1.38±0.49N/m², p=0.99, mean: 0.76±0.2N/m² vs. 0.74±0.18N/m², p=1.00) or posterior AAo (maximum: 1.45±0.42N/m² vs. 1.39±0.58N/m², p=1.00; mean: 0.65±0.16N/m² vs. 0.63±0.16N/m², p=1.00). AAo peak velocity was elevated in patients compared to controls (p<0.01) but similar for BB+ and BB– groups (p=0.42). Linear models identified significant relationships between aortic stenosis severity and increased maximum WSS (β=0.186, p=0.007) and between diameter at the sinus of Valsalva and reduced mean WSS (β=–0.151, p=0.045).

Conclusions—Peak velocity and systolic WSS were similar for BAV patients irrespective of BB therapy. Further prospective studies are needed to investigate the impact of dosage and duration of BB therapy on aortic hemodynamics and development of aortopathy.

Corresponding author: Michael Markl, Ph.D., Department of Radiology, Northwestern University, 737 N. Michigan Avenue Suite 1600, Chicago, Illinois 60611, USA, Phone: +1 312-695-1799, mmarkl@northwestern.edu.

All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation

Conflicts of Interest: None

Keywords

bicuspid aortic valve; beta blocker; 4D flow MRI; aortic dilatation

INTRODUCTION

Bicuspid aortic valve (BAV), the most common congenital heart defect, is associated with progressive ascending aorta (AAo) dilation and aneurysm formation. [1,2] [3] A study by age quintile showed a high prevalence of aortic dilatation in 56% of those aged <30 years and up to 88% of those aged >80 years. [4] Aortic dilation is a result of medial degeneration of the aortic wall which is likely related to a genetic defect in BAV patients. [3,5] However, controversy exists over the relative contribution of changes in aortic blood flow patterns resulting from valve pathology versus underlying connective tissue abnormalities in aneurysm evolution in these patients. [6–9] Alterations in aortic blood flow characteristics such as elevated peak velocities and significant regional increases in aortic wall shear stress (WSS) have been found secondary to BAV.[6,10–14] In particular, WSS, a measure of tangential flow-induced forces experienced at the aortic wall, is of interest given that abnormal values have been associated with extracellular matrix remodeling and aneurysm progression. [15–17]

As a result of studies in Marfan syndrome patients, medical therapy in BAV patients with an enlarged or rapidly growing aorta frequently includes the use of beta-adrenergic receptor antagonist (beta-blocker, BB). [18,19,3] The hypothesized mechanism of beta-blocker effectiveness is the decrease of the rate of change of arterial pressure (dP/dt) and thus force on the aneurysmal segment of the aorta.[20,21] In addition, changes in aortic hemodynamics can affect endothelial cell function by reducing WSS which is assumed to alter the path of aortic remodeling and dilatation[13]. The use of beta-blockers has been shown to slow aneurysm growth rates and reduce the risk of adverse events in aneurysm patients with Marfan syndrome. [18,22,19,23] However, data on the effectiveness of beta-blocker use in BAV patients are lacking[24] and the potential mechanism of action for a therapeutic benefit remains unclear.

4D flow magnetic resonance imaging (MRI) provides *in-vivo* blood flow visualization and quantification, and can be used to calculate regional WSS in the thoracic aorta.[25,26] In this retrospective cross-sectional study, we used 4D flow MRI to assess the impact of beta-blocker treatment on AAo peak velocity and WSS in two matched groups of BAV patients with and without BB treatment and compared to control subjects. We hypothesized that beta-blocker therapy in BAV patients will result in reduced aortic peak velocity and WSS compared to BAV patients without BB therapy thus suggesting a potential hemodynamic benefit in slowing aortic dilation.

MATERIALS AND METHODS

Cross-Sectional Study

BAV patients receiving beta-blockers (BB+: n=30, M:F=23:7, age: 47±11 years) and those not on beta-blockers (BB-: n=30, M:F=23:7, age: 46 ±13 years) underwent 4D flow MRI as a part of clinician ordered cardiovascular MRI assessment. Beta-blocker treatment status at the time of imaging was determined based on retrospective review of the clinical chart of BAV patients who had undergone 4D flow MRI. A group of age-matched healthy controls (n=15, M:F=12:3, age: 43±11 years) were also studied. BAV patients were matched for systolic blood pressure (BB+: 125±17 mmHg, BB -: 127±18 mmHg, p=0.66), degree of aortic stenosis (7 patients in each group with at least moderate stenosis based off of qualitative assessment of cine images as described in the clinical MRI report), and sinus of Valsava diameter (BB+: 3.9±0.5cm, BB-: 3.9±0.5cm, p=0.89) and mid-AAo diameter (BB +: 3.9±0.7cm, BB-: 4.0±0.6cm, p=0.70). To control for the potential influence of differences in BAV fusion patterns on aortic blood flow and WSS[6,10,13,2], only patients with right-left (RL) valve fusion pattern based on Siever's classification were included. [27] Eight patients in each BAV group were treated with angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARB). Data on reason for beta-blocker treatment initiation, duration of therapy, exact dose, and medication adherence were not available in all patients and not included in the matching algorithm. Institutional Review Board (IRB) approval was obtained for this HIPAA compliant study. Subjects were included in the study according to procedures approved by the IRB.

Magnetic Resonance Imaging

Cardiac MRI scans were performed using routine 1.5 T systems (MAGNETOM Avanto or Aera, Siemens, Germany). Free-breathing, electrocardiographic and respiratory navigator gated 4D flow MRI data were acquired with full volumetric coverage of the entire thoracic aorta and three-directional velocity encoding.[28] Data were acquired at each cardiac time frame as a set of anatomically-weighted magnitude data and three separate phase contrast acquisitions (encoding flow velocity along all three spatial dimensions). The result is a fully characterized 3D velocity field within the acquired 3D data volume. 4D flow imaging parameters were as follows: spatial resolution = 2.88–3.36 × 2.13–2.38 × 2.5–3.2 mm³, temporal resolution = 36.8–38.4 ms, TE/TR/flip angle = 2.17–2.41ms/ 4.6–4.8ms/15°, and velocity sensitivity (venc) = 150–375cm/s. Additional standard balanced steady state free precession (SSFP) images in standard cardiovascular views were prescribed as appropriate for the assessment of patients with aortic valve disease.

Data Processing and Analysis

All 4D flow data were corrected for Maxwell terms, velocity aliasing, and eddy currents using Matlab-based in-house software (Mathworks, MA). A 3D phase-contrast magnetic resonance angiogram (PC-MRA) was generated from the corrected data and a 3D segmentation of the thoracic aorta was performed (Mimics, Materialise, Belgium). Based on the 3D segmentation, time-resolved 3D WSS along the entire aorta vessel wall was calculated using a previously reported approach.[26,25] Briefly, WSS was derived from 1D smoothing splines fitted through the tangential wall velocities at each pixel along the wall

then multiplied by the dynamic viscosity of blood ($3.2 \times 10^{-3} \text{Pa s}$). Peak systole was defined by averaging velocities over the total segmented aorta for each cardiac time frame and identifying the time with highest average velocity. Time-averaged systolic values for absolute WSS and velocity were then generated using the average over the five cardiac time frames centered on the peak systolic time frame. WSS maximum intensity projections (MIP) were mapped onto a sagittal view of each aorta for qualitative review and regional analysis as shown in Figure 1.

Next, the AAo was isolated by dividing lines drawn orthogonal to the sinus of Valsalva and proximal to the brachiocephalic trunk and further subdivided into anterior and posterior regions (Figure 1). Maximum and mean WSS were calculated within each region, while peak velocity was calculated for the entire AAo. The maximum WSS and peak velocity values were defined as the average of the top 5% of all values in a region.

Statistical Analysis

All continuous data are presented as mean $\pm$ standard deviation. Comparisons between the three groups were performed using one-way analysis of variance (ANOVA). An intergroup comparison of differences in anterior and posterior WSS was performed using a paired t-test. Linear modelling was also performed to identify factors contributing to hemodynamic variations. Initial modelling included the following parameters: age, ejection fraction, aortic stenosis, aortic insufficiency, sinus of Valsalva diameter, mid-AAo diameter, systolic blood pressure, beta-blocker treatment, and ACE-inhibitor or ARB treatment. A $p < 0.05$ was considered significant.

RESULTS

Cardiac MRI including 4D flow, post-processing, and quantification was completed in all 75 subjects. Heart rate was the only demographic variable that differed between BB+ and BB- groups (62 ± 10 vs. 68 ± 12 , $p = 0.03$) (table 1). Figure 2 shows a comparison of resulting systolic WSS MIPs in BAV patients with no, moderate, and severe aortic stenosis from the BB+ and BB- groups compared to a representative control subject. Elevated WSS in BAV patients compared to controls and the impact of increasing stenosis grade on higher aortic WSS can clearly be appreciated.

Regional Wall Shear Stress and Peak Velocity

Results of WSS and peak velocity analysis are summarized in figure 3 and table 2. Systolic maximum WSS was similar for the BB+ and BB- patients for both the anterior AAo ($1.49 \pm 0.47 \text{N/m}^2$ vs. $1.38 \pm 0.49 \text{N/m}^2$, $p = 0.99$) and posterior AAo ($1.45 \pm 0.42 \text{N/m}^2$ vs. $1.39 \pm 0.58 \text{N/m}^2$, $p = 1.00$). Both groups had higher maximum WSS relative to the control group [anterior: $0.98 \pm 0.12 \text{N/m}^2$, $p = 0.001$ (BB+) and $p = 0.01$ (BB-); posterior: $1.02 \pm 0.15 \text{N/m}^2$, $p = 0.01$ (BB+) and $p = 0.04$ (BB-)]. Likewise, mean WSS was not different between BB+ and BB- groups (anterior: $0.76 \pm 0.2 \text{N/m}^2$ vs. $0.74 \pm 0.18 \text{N/m}^2$, $p = 1.00$; posterior: $0.65 \pm 0.16 \text{N/m}^2$ vs. $0.63 \pm 0.16 \text{N/m}^2$, $p = 1.00$), but elevated compared to controls in the anterior AAo [$0.52 \pm 0.08 \text{N/m}^2$, $p < 0.001$ (BB+), $p = 0.001$ (BB-)]. Peak velocity was also not significantly different in BB+ and BB- groups ($2.76 \pm 0.87 \text{m/s}$ vs. $2.44 \pm 0.77 \text{m/s}$,

$p=0.42$). The peak velocity in each group was significantly higher than controls [1.65 ± 0.23 m/s, $p<0.001$ (BB+), $p=0.008$ (BB-)].

Anterior/posterior comparisons within groups revealed higher anterior mean WSS in both the BB+ ($p<0.001$) and BB- ($p<0.001$) groups, but no difference in maximum WSS in either group. In controls there was no difference between mean or maximum anterior and posterior WSS.

Relationships between Aortic WSS and Patient Characteristics

As summarized in table 3, modeling was performed for maximum WSS, mean WSS, and peak velocity. In all three models, beta-blocker use did not correlate with systolic blood pressure, nor did ACE-inhibitor/ARB use. Models for both maximum WSS ($R^2=0.42$, $p=0.02$) and mean WSS ($R^2=0.38$, $p=0.04$) identified significant relationships. Aortic stenosis severity was the only parameter that was significantly correlated with increasing maximum WSS ($\beta=0.186$, $p=0.007$). Aortic diameter at the sinus of Valsalva was inversely correlated with mean WSS ($\beta=-0.151$, $p=0.045$), and showed a trend toward an inverse correlation with maximum WSS ($\beta=-0.374$, $p=0.07$).

DISCUSSION

The findings of this cross-sectional study indicate that BAV patients matched for age, gender, valve morphology, valve disease severity, blood pressure, and aortic diameter, AAO WSS and peak velocity were not different between patients receiving beta-blocker therapy compared to those without. Both patient groups (BB+ and BB-) exhibited similar and significantly elevated WSS and peak velocity compared to healthy controls, regardless of BB therapy. Our findings are consistent with previous reports demonstrating that WSS is elevated in BAV patients relative to normal controls and has an asymmetric distribution within the AAO.[6,10,13,14] Linear modeling demonstrated that aortic stenosis severity and aortic diameter at the sinus of Valsalva both correlate with changes in WSS, while treatment with beta-blockers, mid-ascending aortic diameter, and systolic blood pressure had no significant association. These findings are also evident from the examples shown in figure 2 which show that aortic stenosis grade is associated with WSS elevation while beta blocker treatment had no visible impact based on WSS MIPs.

The proposed mechanism of action of beta-blocker therapy for potentially slowing AAO dilation is to reduce WSS on the aneurysmal segment of the aorta by reducing the rate of pressure change in aorta (dP/dt). It is hypothesized that beta-blockers might be beneficial via this mechanism for reducing the rate of aortic dilatation. [20] Any reduction in pressure (static or dynamic) or change in wall compliance as a result of beta-blocker therapy should have an impact on WSS, as changes in these hemodynamic and tissue parameters will alter both velocity and velocity gradients at the aortic wall. However, the results of the current study do not show evidence of a change in peak systolic velocity or WSS between groups, and suggest that beta-blocker therapy may not impact these parameters in BAV patients. Before drawing a strong conclusion, it is important to note the potentially significant limitation introduced by the retrospective nature of our study and the associated potential for selection bias in our cohort. For example, it is possible that patients on beta-blockers may

have had even higher levels of WSS and corresponding aortic growth prior to treatment, and beta-blocker therapy “normalized” WSS to levels of BAV patients in whom the AAo was not dilated. Longitudinal assessments or studies in patients before and after treatment would be needed to address this question.

It is well documented that outflow patterns and WSS are different depending on BAV morphology.[13,6] While BAV morphology has not been shown to correspond with risk of aneurysm formation, it has been demonstrated that aortopathy phenotype does correlate with BAV morphology and related hemodynamics.[13] One potential process by which treatment with beta-blockers may slow aortic dilation could be a normalization of the asymmetric WSS distribution that is related to valve morphology. In our cross-sectional study of BAV patients with right-left fusion, there was a trend toward an anterior elevation of WSS which is consistent with previous reports. This finding was the same regardless of beta-blocker treatment, suggesting the beta-blockers did not change outflow asymmetry associated with valve morphology. Our data also demonstrate an inverse relationship between aortic diameter at the sinus of Valsalva and WSS which has been reported previously.[15]

While there was no difference in average WSS between the BB+ and BB– BAV patients, the BB+ group had a much wider range of WSS and peak velocity values, as compared to both the BB– and control group. This finding suggests that patients respond differently to treatment with beta-blockers and with different degrees of effect on aortic WSS and peak systolic velocity. If this finding is supported in longitudinal studies, hemodynamic monitoring with 4D flow MRI could identify patients who will respond favorably to treatment and better stratify patients who need alternative forms of therapy or surgical intervention.

It is important to recognize that WSS may not be the driver of aortic dilation and thus not the best quantitative measure of effectiveness. As discussed, there is considerable debate as to the relative roles of hemodynamics vs. intrinsic genetic defects in aneurysm formation. If hemodynamics plays a minimal role, WSS measure will be less relevant but treatment with beta-blockers also should have little impact on aortic growth. Nevertheless, a number of recent studies[13,15,14] provide evidence that 4D flow MRI with full volumetric coverage of the thoracic aorta can assess wall shear stress to quantify the impact of altered flow patterns on shear forces acting on the aortic wall. However, assessment of wall shear stress can be technically challenging and care has to be taken to accurately describe the underlying methodology to ensure reproducibility of the technique across clinical settings. Additionally, other hemodynamic measures may be useful to capture the hemodynamic impact of BAV in the aorta. Recent work by Hope et al in a small group of BAV patients with longitudinal 4D flow MRI assessment found that outflow displacement was a good marker.[12] Moreover, the underlying molecular mechanisms associated with mechano-sensing and transduction of the vascular endothelium are complex with at least ten membrane-bound proteins identified as potential mechanical sensors.[29] These proteins are sensitive not only to wall shear stress, but also perpendicularly-oriented pressure and circumferential-stretch forces at the vessel wall. [29] The relative contribution of each of these forces in aneurysm formation is not fully understood and it is possible that beta-blockers act through changes in these forces

or intrinsically in the mechano-transduction pathways in endothelial cells to slow aortic dilation.

Study Limitations

The current study is subject to several limitations. First, the retrospective nature of this study limits our ability to control for potential confounders relative to a prospective pre/post-treatment study. The BAV groups were very well matched to minimize this effect, but it is still not ideal. A longitudinal study observing the aortic growth patterns, additional hemodynamic parameters such as pressure gradient or blood pressure, and medication use would help further elucidate the value of beta-blocker treatment on aortic dilation in BAV patients. We have hypothesized that beta-blocker use acts through a reduction in WSS, but their benefit may manifest through a combination of these other mechanisms. Further studies are thus needed to confirm our results and to clarify the impact of dose and duration of BB therapy on aortopathy.

A further limitation is related to the potential variability in beta blocker dosage and duration of beta blocker treatment for individual patients which was not available for analysis in our cross-sectional patient study. In addition, no data were available for compliance and adherence to medication which can be crucial during BB therapy and may have influenced our findings. However, to date no systemic evaluation of the impact of beta blocker dose and duration of therapy on aortic hemodynamics or progressive aortic dilatation has been reported in the literature. While the near immediate effect of beta-blocker therapy on blood pressure reduction is known, the long term implication of beta-blocker therapy on vessel wall protein expression, changes in compliance, and response to mechanical stimuli is not known, and, by not matching patients for dose or duration of treatment, is not controlled for in the current study. It is accepted practice to prescribe beta blockers in order to retard aortic dilatation and prevent aortic dissection and rupture in patients with Marfan syndrome. However, this practice is based on limited evidence and the influence of aortopathy development in BAV patients is still unclear. Further longitudinal studies are thus urgently needed to clarify the impact of beta blocker dose and duration of therapy on patient outcome. 4D flow MRI may be ideally suited to monitor changes in both aortic hemodynamics and geometry over the course of the treatment and identify changes in wall shear or other forces and their associations with dose, duration of therapy and development of aortic pathology.

Lastly, the methodology for quantifying WSS is dependent on several assumptions that may introduce variability in WSS measurements. Most importantly, manual segmentation of the aorta wall was performed at one time point, so aortic motion during systole was not accounted for in the segmentation. If the wall was incorrectly defined as a result of the relatively low ($\sim 2.5 \text{ mm}^3$ voxel size) spatial resolution or inaccurate segmentation technique, or if there was significant motion, the calculated WSS will not actually reflect the stress on the wall in that region.

CONCLUSIONS

BAV patients with right-left valve fusion pattern subjected to beta-blocker therapy did not demonstrate differences in AAO peak velocity and WSS compared to patients without beta-blocker treatment. Future work should confirm these results in longitudinal studies and determine the added value of 4D flow MRI in identifying potential medication responders to aid in treatment planning and risk stratification in BAV patients.

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Figure 1.

Distribution of wall shear stress (WSS) based on a systolic WSS maximum intensity projections (MIP) mapped onto a sagittal view of the thoracic aorta. Quantification of mean and maximum systolic WSS in anterior and posterior regions of the the ascending aorta (AAo, from the sinus of Valsalva and the aortic arch proximal to the brachiocephalic trunk) is illustrated by the solid and dashed lines.

Figure 2.

Systolic wall shear stress (WSS) maximum intensity projections (MIPs) in BAV patients with A: no aortic stenosis (AS), B: moderate AS, and C: severe AS from the BB+ and BB- group compared to a representative control subject (D).

Figure 3.

Group wise comparisons of ascending aortic mean WSS (A), maximum WSS (B) and peak velocity between the BB+, BB- and control groups. The individual box plots illustrate the median and the 25th and 75th percentiles (edges), the whiskers extend to the most extreme data points not considered outliers, and outliers are plotted individually as 'o'. Significant differences are indicated by * < 0.05, ** - <= 0.01, ***<0.001.

Table 1

Bicuspid aortic valve patient characteristics.

	BB+ (n=30)	BB- (n=30)	p-value
Age	47.1±11.2	46.0±13.1	0.73
Gender (M:F)	23:7	23:7	1.00
Systolic Blood Pressure (mmHg)	125±18	128±18	0.66
Heart Rate (beats per minute)	68±12	62±10	0.03 *
Aortic Stenosis(no. of subjects)			0.80
None	23	23	
Trace	0	0	
Mild	3	4	
Moderate	2	1	
Severe	2	2	
Aortic Insufficiency (no. of subjects)			0.28
None	15	14	
Trace	5	3	
Mild	3	9	
Moderate	5	3	
Severe	2	1	
Aortic Diameter (cm)			
Sinus of Valsalva	3.9±0.5	3.9±0.5	0.89
Mid-Ascending Aorta	3.9±0.7	4.0±0.6	0.70
Medication (no. of subjects)			
Beta-blocker	30	0	--
ACE-inhibitor	3	5	0.46
Angiotensin Receptor Blocker	5	3	0.46
Statin	12	9	0.43
Calcium Channel Blocker	5	2	0.23

* indicates statistically significant differences.

Table 2

Regional Wall Shear Stress and Peak Velocity Data.

	BB-	BB+	Controls	(BB- vs. BB+)	(BB- vs. Controls)	(BB+ vs. Controls)
Max Ant. AAo WSS (N/m ²)	1.38±0.49	1.49±0.47	0.98±0.12	0.99	0.01	0.001
Max Post. AAo WSS (N/m ²)	1.39±0.58	1.45±0.42	1.02±0.15	1.00	0.04	0.01
Mean Ant. AAo WSS (N/m ²)	0.74±0.18	0.76±0.2	0.52±0.08	1.00	0.001	<0.001
Mean Post. AAo WSS (N/m ²)	0.63±0.16	0.65±0.16	0.52±0.10	1.00	0.07	0.02
Peak AAo velocity (m/s)	2.44±0.77	2.76±0.88	1.65±0.23	0.42	0.008	<0.001

AAo=ascending aorta; Ant=anterior; BB=beta adrenergic blocking agent; Post=posterior; WSS = wall shear stress.

Table 3

Linear modeling of parameters for ascending aorta wall shear stress and peak velocity in the patient-only cohort.

	Max WSS (R ² =0.42, p=0.02)		Mean WSS (R ² =0.38, p=0.04)		Peak Velocity (R ² =0.36, p=0.14)	
	Beta	p-value	Beta	p-value	Beta	p-value
Beta-Blocker	-0.049	0.709	-0.019	0.691	-0.317	0.423
ACE-inhibitor or ARB	-0.044	0.802	-0.002	0.978	-0.734	0.143
Ejection Fraction	0.013	0.310	0.004	0.382	0.027	0.416
Aortic Stenosis	0.186	0.007	0.048	0.051	0.291	0.122
Aortic Insufficiency	-0.009	0.886	0.004	0.848	-0.076	0.623
Sinus of Valsalva Diameter	-0.374	0.066	-0.151	0.045	-0.332	0.515
Mid-AAo Diameter	0.016	0.908	-0.014	0.774	-0.142	0.729
Age	0.002	0.783	-0.003	0.147	-0.015	0.396
Systolic blood pressure	-0.003	0.513	0.000	0.857	-0.002	0.882

AAo=ascending aorta; ACE=angiotensin converting enzyme; ARB=angiotensin receptor blocker; WS =wall shear stress.