# Beta-Blocker Therapy Alters 3D Wall Shear Stress in the Ascending Aorta of Patients with Bicuspid Aortic Valve

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**Background:** Patients with bicuspid aortic valve (BAV) are at increased risk for ascending aorta (AAo) aneurysm development (1). Beta adrenergic receptor blockers (β-blockers) are the recommended medical treatment for slowing ascending aorta (AAo) dilation in BAV patients(2), and the effective use of β-blockers for this purpose has been demonstrated in longitudinal studies in patients with Marfan Syndrome. However, the mechanism of action that slows AAo dilatation as a result of treatment is not well understood. Changes in wall shear stress (WSS) have been shown to promote endothelial cell dysfunction (3) and may ultimately lead to vascular remodeling (4). Elevated AAo WSS resulting from high velocity and asymmetric outflow jets in BAV patients have been hypothesized to play a role in aneurysm growth and development in this cohort(5). β-blocker induced reduction of aortic WSS may thus be a potential mechanism to slow progression of aortopathy in these patients. Time-resolved 3D phase contrast (4D flow) MRI is a non-invasive technique that provides comprehensive hemodynamic assessment and allows for the quantification of 3D WSS regionally in the thoracic aorta. The aim of this study was to assess changes in AAo WSS associated with β-blocker therapy in BAV patients.

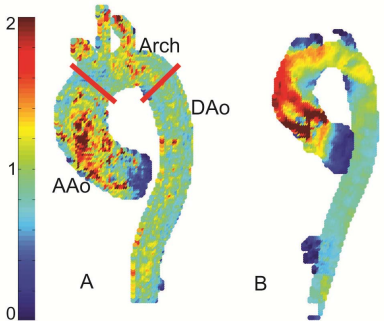


Figure 1: Wall Shear Stress Maximum Intensity Projections in a patient A) on β-blockers and B) not on β- blockers. Red line = aorta segments.

**Methods:** BAV patients on β-blockers (BB+) (n=10, M:F = 8:2, age: 53 ± 11 years) or not on β-blockers (BB-) (n=10, M:F = 9:1, age: 51 ± 15 years) underwent 4D flow MRI as part of this IRB-approved study. Groups were matched by BAV morphology (all right-left fusion), systolic blood pressure (BB+: 137 ± 12 mmHg, BB -: 132 ± 17 mmHg, p = 0.48), degree of aortic stenosis, and AAo diameter (BB+: 4.1 ± 0.7 cm, BB-: 3.6 ± 0.4 cm, p = 0.07). Five patients in each group were concurrently treated with ACE-inhibitors or angiotensin receptor blockers. MRI scans were performed at 1.5 T (MEGNETOM Avanto, Siemens, Germany) with spatial resolution = 2.88-3.36 x 2.13-2.38 x 2.5-3.2 $mm^3$, temporal resolution = 36.8-38.4 ms, TE/TR/ FA = 2.17-2.41 ms/ 4.6-4.8 ms/15°, and VENC = 150 – 375 cm/s. Data processing included correction for eddy currents and velocity aliasing, and 3D segmentation of the thoracic aorta was performed (MIMICS, Materlise, Belgium). 3D WSS along the entire aorta lumen surface was calculated using the method described by van Ooij(6) . Peak systole was defined as the cardiac phase with highest average velocity in the aorta, and systolic values for WSS ($WSS_{sys}$) and velocity ($vel_{sys}$) were defined as the average over five systolic phases centered on peak systole (peak systolic phase ± 2 phases). The aorta was divided into AAo, arch, and descending (DAo) regions (Figure 1A), and max and mean $WSS_{sys}$ and $vel_{sys}$ were calculated in each region. Max values were defined as the average of top 5% of all values in a region to account for noise within the data. $WSS_{sys}$ maximum intensity projections (MIP) were mapped onto a sagittal view of each aorta for visual comparison. In addition, histograms of AAo $WSS_{sys}$ distribution were generated for all patients and normalized by the total number of WSS values for each subject to permit comparison across subjects. Cohort-averaged histograms were calculated for BB+ and BB- patients. All results were compared using Student's t-test or Mann-Whitney U test as appropriate. Spearman ($r_S$) or Pearson (r) correlation was also performed. A $p<0.05$ was considered significant.

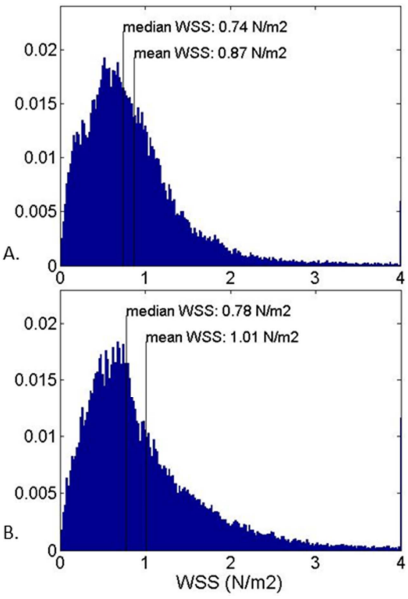


Figure 2: Cohort-averaged $WSS_{sys}$ histograms of patients A) on β-blocker treatment and B) not on β-blockers. It appears that $WSS_{sys}$ is more tightly clustered at low values of WSS in patients on β-blockers.

**Results:** The data shows a clear trend towards reduced $WSS_{sys}$ and peak $vel_{sys}$ in all aortic regions in BB+ patients , but the current study was underpowered (power = 19%) to detect a statistical difference between BB+ and BB- groups (Table). AAo max $WSS_{sys}$ showed a strong correlation with peak $vel_{sys}$ (r = 0.7, p = 0.001). $WSS_{sys}$ and $vel_{sys}$ in the AAo showed no correlation with mid-AAo diameter (r = 0.12, p = 0.61 and r = -0.28, p = 0.23) but did correlate with the degree of aortic stenosis ($r_S$ = 0.54, p = 0.01 and 0.51, p = 0.02). $WSS_{sys}$ MIPs for two subjects are visualized in Figure 1. Qualitatively, the regional distribution of $WSS_{sys}$ was highly variable between individuals for both groups and this observation was also noted on individual $WSS_{sys}$ histograms. On group histogram comparison in the AAo, group medians were 0.78 $N/m^2$ in the BB- group and 0.74 $N/m^2$ in the BB+ cohort. The root mean square difference between individual and group medians was 0.26 $N/m^2$ for BB- patients and 0.18 $N/m^2$ in BB+ patients, suggested a more tightly clustered $WSS_{sys}$ distribution in the BB+ group (Figure 2).

| | | Ascending Aorta | Arch | Descending Aorta |
|---|---|---|---|---|
| Max WSS ($N/m^2$) | BB+ | 2.3 ± 1.2 | 1.7 ± 0.5 | 1.6 ± 0.6 |
| | BB- | 2.8 ± 1.6 | 2.1 ± 1.6 | 1.7 ± 0.8 |
| | p-value | 0.46 | 0.27 | 0.74 |
| Mean WSS ($N/m^2$) | BB+ | 0.87 ± 0.3 | 0.89 ± 0.3 | 0.96 ± 0.3 |
| | BB- | 1.0 ± 0.4 | 1.1 ± 0.5 | 1.0 ± 0.4 |
| | p-value | 0.34 | 0.23 | 0.66 |
| Peak Velocity (m/s) | BB+ | 1.4 ± 0.5 | 0.8 ± 0.3 | 0.7 ± 0.2 |
| | BB- | 1.7 ± 0.5 | 1.0 ± 0.2 | 0.8 ± 0.4 |
| | p-value | 0.19 | 0.3 | 0.39 |

Table: WSS and velocity findings by aortic region.

**Conclusions:** Our results show that β-blocker therapy likely reduces WSS in the thoracic aorta, thus suggesting a mechanism for β-blocker effectiveness in slowing aortic dilation. However, in our cohort, it appears the treatment effect on individual patients is variable. The high inter-individual variability of 3D WSS highlights the potential diagnostic value of 4D flow MRI WSS quantification for individualized assessment β-blocker effectiveness in BAV aortopathy. A prospective study in a large number of patients pre- and post-treatment is required to better isolate the impact of β-blockers in this population.

**References: 1.**Tzemos et al. *JAMA*. (2008). **2.**Hiratzka et al. *J Am Coll Cardiol*. (2010). **3.**Reneman et al. *J Vasc Res*. (2006). **4.**Ben Driss et al. C*irculation*.(2000).**5.**Barker et al. *Circ Cardiovasc Imaging*. (2012). **6.**van Ooij et al. *J Magn Reson Imaging*. (2013).

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