Author’s response to reviews

Title: Augmentation Index and Proximal Aortic Stiffness In Bicuspid Aortic Valve Patients with Non-Dilated Proximal Aortas

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Author’s response to reviews: see over
Dear Dr Manginas,

Thank you for inviting the resubmission of our manuscript entitled: **Augmentation Index and Aortic Stiffness In Bicuspid Aortic Valve Patients with Non-Dilated Proximal Aortas.**

We appreciate the care and attention paid by the two reviewers and we feel that the manuscript has been considerably strengthened by the changes motivated by their reviews.

Below are our point-by-point responses to the reviewer comments and we have resubmitted the manuscript in accordance to the instructions provided by BMC Cardiovascular Disorders.

Respectfully,

Gordon Huggins, MD

**MAJOR COMPULSORY REVISIONS:**

1) The finding of elevated Alx among BAV patients compared to controls was not initially expected and does not make as much sense from a pathophysiologic standpoint. Thus, I am highly suspicious this could have been due to confounding factors. The authors did well in adjusting the models for height, since shorter stature leads to higher peripheral wave reflection. However, 3 additional adjustments should be made: (1) The proportion of women among BAV patients was much higher than among controls (40% vs 23%). Female sex is known to be associated with higher augmentation index (See Cecelja M et al JACC 2009 and Coutinho T et al JACC 2012). Thus, models should also be adjusted for sex; (2) heart rate also influences Alx and therefore Alx models have been traditionally adjusted for HR as well; (3) The proportion of BAV taking beta blockers was also much higher than controls, and by slowing heart rate beta blockers are also associated with higher Alx. Models should also be adjusted for beta blocker use. I would be interested in seeing whether the differences in Alx between groups remain after adjustment for these variables (in addition to height).

Elevated Alx in BAV has been observed in two additional studies therefore elevated Alx in BAV, while unexpected, is a documented part of the phenotype. We provide a stronger physiological rationale for the observation of elevated Alx in BAV. Importantly, this is the first study to directly assess pressure from wave reflections (Alx) in patients with BAV. Previous studies estimated central/aortic pressure from a radial pressure
wave using a generalized transfer function. While the suitability of this approach in the general population is well recognized and accepted, use of a generalized transfer function to estimate central/aortic AIx has never been validated in patients with BAV.

To address the reviewer’s important points we have performed additional analyses. We now additionally adjust for sex, height, heart rate and beta-blocker use with ANCOVA, as suggested. This information is provided in the results section, and this new model continues to observe significant differences in AIx. It is well established that HR is inversely associated with AIx (pacing studies note that for every 10 beat increase in HR, you can expect to see a 5% reduction in AIx). Since our patients with BAV had a slightly higher HR (2 bpm), this would be expected to result in a lower AIx in BAV which was not the case. Adjusting for HR further exaggerated the differences in AIx. We also wish to point out that owing to sample size, the proportions may not be particularly revealing. Indeed we noted 5 patients with BAV taking beta blockers and 3 patients with TAV taking beta blockers. Although the proportions look large, absolute values are not. Additionally adjusting for BB use had no effect on group differences in AIx. We thank the reviewer for emphasizing this important point and we feel our additional analyses have strengthened the manuscript.

2) The N of the study is so small that the possibility of type II error is not trivial. We agree that sample size is a concern. In the limitations section of the Discussion we now report the partial eta-squared and retrospective observed power for multi-variable adjusted AIx. As can be seen, we had a moderately high effect size (eta-squared = 0.47) with adequate power (0.79) to sufficiently detect group differences in AIx. Therefore we are confident that we are not observing a statistical anomaly (i.e. type II error). We thank the reviewer for emphasizing this point and feel that this new information provides the reader better context for evaluating the strength of our findings within the context of our sample size.

3) In the second paragraph of the discussion the authors mention that a size mismatch between aortic root and ascending aorta may play a role in the higher augmentation index, and cite a reference to support this theory. Physiologically, this theory does not make sense. The reference cited talks about mismatch between proximal aorta and more peripheral vessels, not mismatch within the ascending aorta. Peripheral wave reflection (and thus, augmentation index) is not influenced by the size of the aortic root and ascending aorta, but by the impedance mismatch/size mismatch between the more proximal and more distal arteries in the arterial tree, especially at branching points.

We have removed the concept of central size mismatch from the paper. The references related to AIx and aortic geometry have been corrected. We also now state that elevated AIx in BAV may be related to altered distal/peripheral arterial impedance mismatches created by microvascular damage from higher central flow dynamics, which is in keeping with the reviewer’s suggestions above.

MINOR ESSENTIAL REVISIONS:
1) In the Discussion (first paragraph) the authors state that BAV is not associated
with abnormalities of the central aorta as previously suspected. This is not exactly true, because since the authors did not study patients with dilated aortas, we still do not know if arterial stiffness contributes to aortic dilation or not. A better statement would be to say that BAV patients without aortic dilation do not have higher aortic stiffness than controls.

We have made this correction.

2) In Table 1 we see that the peak velocity through the aortic valve was greater than 2 m/s among BAV patients. This may, to some degree, interfere with the non-invasive determination of Zc, if the LVOT pulse wave Doppler sample volume is placed too close to the aortic valve and therefore incorporates these higher aortic velocities into the LVOT TVI, which is then used for aortic flow calculation for Zc. I do not believe that this non-invasive technique has been validated in subjects with high aortic velocities.

We have removed Zc from the manuscript. We now include a measure of arterial elastance (derived solely from the contour of the pressure wave and echo-derived measures of stroke volume = vascular parameter independent of aortic flow data). Effective arterial elastance was originally shown by Dr. Kelley and Dr. Kass to be associated with measures of impedance (Circulation 1992;86:513-21). Similar to the results obtained with Zc, Ea (whether presented in absolute terms or indexed to BSA, Eai) does not differ between BAV and TAV supporting original findings with Zc.

Reviewer 2

1. The number of patients is too low (10 patients and 13 control)
We agree that this is a concern. In the limitations section of the Discussion we now include partial eta-squared and retrospective observed power for Alx. As can be seen, we had a moderately high effect size (eta-squared = 0.47) with adequate power (0.79) to sufficiently detect group differences in Alx. Therefore we are confident that we are not observing a statistical anomaly (i.e. type II error). We thank the reviewer for emphasizing this point and feel that this new information provides the reader better context for evaluating the strength of our findings within the context of our sample size.

2. Ascending aortic diameter was higher than control although it was not significant (p:0.07). This data makes it difficult to interpret the results of the study.

When ascending aortic diameter is properly scaled to body surface area (displayed as ascending aortic index in Table 1), there were no group differences in aortic geometry. Alx was not associated with ascending aortic diameter (r = 0.23, p = 0.15). Furthermore, adjusting for absolute ascending aortic diameter with Analysis of Covariance does not affect group differences in Alx (adjusted means: BAV = 16%; TAV = -2.5%, p = 0.015). Therefore, we do not believe that this specific aortic geometric
parameter affects interpretation of our findings. We now include the ANCOVA analysis in the Results section.

There are many studies investigating the arterial stiffness in patients with bicuspid aortic valve and aortic dilatation.

While many have investigated arterial stiffness in BAV, few have used the only currently recognized “gold standard” method for measuring stiffness – pulse wave velocity. Moreover, even fewer have investigated pressure from wave reflections (AIx, a very different hemodynamic risk factor than PWV). Although AIx and PWV are slightly related, they do not capture the same vascular physiology and are not equivocal predictors of CV risk and target organ damage (Circulation 2010 Feb 2;121(4):505-11).

This is the first study to directly assess pressure from wave reflections (AIx) in patients with BAV. Previous studies estimated central/aortic pressure from a radial pressure wave using a generalized transfer function. While the suitability of this approach in the general population is well recognized and accepted, use of a generalized transfer function to estimate central/aortic AIx has never been validated in patients with BAV. As correctly pointed out by the other reviewer, higher aortic flow velocity in BAV may compromise accuracy of some hemodynamic measures. We directly assessed central/carotid pressure to obtain AIx. We did not derive any measure. This is important as previous research has demonstrated that AIx estimated from radial artery correlates poorly to directly measured carotid AIx (American journal of hypertension. 2005;18:1168-1173).

This is the first study to note associations between AIx and vascular shear in patients with BAV suggesting a link between pulsatile pressure and flow hemodynamics. We believe our findings are novel and provide greater insight into the vascular abnormalities present with BAV.