Reviewer’s report

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

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Reviewer: Thais Coutinho

Reviewer’s report:

Warner colleagues hypothesized that patients with bicuspid aortic valves (BAV) have greater arterial stiffness than individuals with tricuspid aortic valves, and sought to evaluate this hypothesis in a case control study. They found that measures of central (Zc and cfPWV) and peripheral (cbPWV and crPWV) arterial stiffness were similar between cases and controls, but patients with BAV had greater peripheral wave reflection compared to controls. After carefully reviewing the manuscript, I would like to offer the following comments and suggestions:

MAJOR COMPULSORY REVISIONS:

1) The finding of elevated AIx 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 AIx and therefore AIx 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 AIx. Models should also be adjusted for beta blocker use. I would be interested in seeing whether the differences in AIx between groups remain after adjustment for these variables (in addition to height).

2) The N of the study is so small that the possibility of type II error is not trivial.

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.
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.

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.

DISCRETIONARY REVISIONS:
None.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
I declare that I have no competing interests.