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THE AORTIC WALL WITH BICUSPID AORTIC VALVE: IMMATURE OR PREMATURELY AGING?

To the Editor:

We read with interest the study by Grewal and coworkers¹ suggesting a maturation defect of the aortic wall in patients with bicuspid aortic valve (BAV). A number of recent publications have addressed the pathobiology of BAV-associated aortopathy; however most of them just vaguely concluded that BAV and tricuspid aortic valve must have different mechanisms driving aortic dilatation. Grewal and coworkers¹ are commendable for their effort to define the nature of this difference.

Their data, however, are partially in contrast with previous studies, with which they failed to perform a critical comparison. We have reported² increased α -smooth muscle actin messenger RNA expression and only mildly and nonhomogeneously increased overall protein levels, with subintimal areas of α -smooth muscle

actin-positive cell loss. This relative stability of the amount of α -smooth muscle actin (in contrast with Grewal and coworkers' data¹), coupled with smoothelin decrease (not absence, unlike in Grewal and coworkers' results¹) was consistent with other studies both of samples from patients and of experimental models of aneurysm (discussed in our own article²) and suggests a loss of contractile-phenotype smooth muscle cells and the emergence of a differentiated myofibroblast line.

In our previously mentioned study,² we selected BAV and tricuspid aortic valve patients with aortic stenosis with a maximal diameter less than 4 cm and analyzed both the concavity and the convexity of the vessel to minimize confounding factors by distinguishing constitutive from stress-induced changes. Some of the authors among Grewal and coworkers have previously borrowed in their studies this protocol of sample retrieval from different sites of each aorta, first introduced by us,³ and confirmed that aortic wall changes are asymmetrically expressed with BAV, suggesting a role for long-standing flow and stress pattern alterations in their development. The change of smooth muscle cell orientation from circumferential to longitudinal direction that we observed in the convexity² is known to occur in vessels submitted to altered tensile strain. The undefined site of sampling in the study of Grewal and coworkers,¹ conversely, could explain these discrepancies.

Similarly, Grewal and coworkers¹ stated that the aortic wall specimens were obtained during full-root stentless implantation in patients with nondilated BAV,¹ suggesting that the BAV specimens were taken from the root (sinuses of Valsalva) instead of the ascending tubular tract proper. Where were the aortic specimens taken in the other patients, also considering that BAV aortopathy usually affects the ascending tract?

How was valve function in the 4 groups? Also, the mean diameters per subgroup were not listed.¹ Intimal thickness data¹ were at odds with previous investigations^{2,4}; could different diameters between BAV and tricuspid aortic valve subgroups explain this?

The paradigms of flow-induced remodeling share many mechanisms with the vascular aging process, including increased transforming growth factor- β receptor II signaling,⁵ which has been evidenced in aortopathies both with and without associated BAV.² Functionally, one of the early signs of arterial aging is impaired wall distensibility, which is known to occur in the BAV aorta, even before overt dilation. Thus with the currently available data, an hypothesis of defective wall maturation is hardly sustainable without ruling out the contribution of flow-induced remodeling. A conceptually opposite theory of premature aging of the aortic wall, prompted by altered biomechanical environment, could be drawn as well.

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Reply to the Editor:

We thank Drs Forte and Della Corte for their insightful comments and the opportunity to clarify a number of points from our work. We agree with the authors of the letter that the mechanisms driving aortic dilation in bicuspid aortic valve (BAV) and tricuspid aortic valve (TAV) are different but not as yet explained. Along that line, also based on the expertise of most of our authors, we hypothesized that a developmental background linking BAV and the accompanying aortic wall might provide new insights into the matter. Hemodynamic differences could still play a role in the developing pathobiology but might not be the primary insult.

This approach led to different selection criteria for our patient population. We did not primarily take into account the presence of aortic stenosis/regurgitation but focused on nondilation (<45 mm) and dilation of the aortic wall within the BAV and TAV groups. Additional characteristics of our study population are presented in Table 1, which also provides answers to a number of questions with regard to the material studied. The aortic valve pathology in nondilated and dilated BAV and dilated TAV varied between either stenosis or no stenosis, with or without regurgitation. In dilated BAV and TAV, in some cases only an

ascending aorta replacement was performed because there was no aortic root pathology that needed surgical correction. All biopsy specimens were taken from the ascending aortic wall adjoining the surgical transverse aortotomy site. In case of post mortem or transplant material, the tissue was taken at identical sites. The results of Forte and colleagues¹ and our publication² can in part be appreciated as complementary. Some differences need an additional explanation from our side, as provided here.

The described results in expression of α -smooth muscle actin in the article of Forte and colleagues¹ and our study do indeed not correlate. This is most probably due to a difference of technique in which messenger RNA expression based on reverse transcriptase polymerase chain reaction analysis of the vascular wall¹ was compared with our immunohistochemical examination of the 3 vessel wall layers.² In case of increased messenger RNA detection, a lowered translation into protein can not be excluded. Drs Forte and Della Corte are correct that almost absent smoothelin expression cannot be detected by immunohistochemical means, so we agree with their results that smoothelin expression is lowered, which correlates with an immature smooth muscle cell phenotype.^{3,4} With regard to the cellular composition of the media and intima of the aortic wall, we do not postulate a few resident fibroblasts to be present that, under experimental development of thoracic aortic dilation, replace the disappearing smooth muscle cell population by myofibroblasts, as indicated by Jones and associates⁵ and accepted by Forte and colleagues.¹ In our studies, it suffices to have a mature contractile smooth muscle cell phenotype that can switch to a synthetic (immature) phenotype that expresses most of the markers

also attributed to the myofibroblast phenotype, including the fibronectin splice variants.⁶ Our assumption is supported by less apoptosis (caspase-3) in the wall of the nondilated as well as the dilated BAV (unpublished data). Apoptosis was, however, detected (not shown) in the media of the dilated TAV and was in our study² linked to the increased expression of progerin. Regarding this aspect, we will have further comments when discussing the aspect of aging.

As described previously, our study population was primarily not selected on the valve pathology or on the difference in architecture of the convex versus concave site. The fact that our group consisted of patients with a nondilated versus a dilated aortic wall, with variable aortic valve pathology and commissure position, underlines that the observed differences between all BAVs and TAVs are intrinsic to the BAV wall morphology. This is further supported in a recently accepted article⁷ in which we did address the differences between the convex and concave aortic sites of patients with a dilated aortic wall, provided by our German coauthors who have adopted the selection technique described previously.⁸ We did not disclaim the earlier published differences^{8,9} in the structure of the wall and the expressions of markers between the convex and concave site of the aorta. We did, however, perform, an additional analysis on these specimens with transforming growth factor- β and endothelial nitric oxide and found no difference in expression between the convex and concave sites.⁷ Hemodynamic influences are therefore not excluded from having an important influence but according to our studies cannot be considered as the primary source for the observed differences in dilation formation between BAV and TAV.