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Reply to Editorial: The aortic wall with bicuspid aortic valve: immature or prematurely ageing?

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Modified after
Dear Editor:

We thank dr. Della Corte for his insightful comments and the opportunity to clarify a number of points from our work and you as an Editor to give us this opportunity. We agree with authors of the letter that the mechanisms driving aortic dilation in bicuspid aortic valve (BAV) and tricuspid aortic valve (TAV) are different but not explained as yet. Following 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. Haemodynamic 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 non-dilation (< 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 non- and dilated BAV and dilated TAV varied from either stenosis or no stenosis, with or without regurgitation. In dilated BAV and TAV in some cases only an ascending aorta replacement was performed as there was no aortic root pathology that needed surgical correction. All biopsy specimen were taken from the ascending aortic wall adjoining the surgical transverse aortotomy site. In case of post-mortem or transplantation material the tissue was taken at identical sites. The results of the Forte paper (1) and our publication (2) can in part be appreciated as complementary. Some differences need an additional explanation from our side as provided below. The described results in expression of alpha-smooth muscle actin in the Forte paper (1) and our study do indeed not correlate. This is most probably due to a difference of technique in which mRNA expression based on RT-PCR analysis of the vascular wall (1) was compared to our immunohistochemistry of the three vessel wall layers (2). In case of increased mRNA detection a lowered translation into protein cannot be excluded. Dr Della Corte is correct that almost absent smoothelin expression cannot be detected by immunohistochemistry, so we agree with their results that smoothelin expression is lowered, which correlates with an immature smooth muscle cell (SMC) 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 SMC population by myofibroblasts as indicated by Jones et al (5) and adopted by the Della Corte group (1). In our studies it suffices to have a mature contractile SMC 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 non-dilated as well as the dilated BAV (data unpublished). Apoptosis was however detected (not shown) in the media of the dilated TAV.
and was in our study (2) linked to the increased expression of progerin. On this aspect we will have further comments when discussing the aspect of ageing. As described above, 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 non- and dilated aortic wall, 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 paper (7) 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 co-authors that have adopted the selection technique as described before (8). We did not disclaim the earlier published differences (8, 9) in the structure of the wall and the expression of markers between the convex and concave site of the aorta. We performed, however, an additional analysis on these specimen with Transforming-Growth-Factorβ and endothelial nitric oxide and found no difference in expression between the convex and concave sites (7). Haemodynamic 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.

On basis of the above observations and additional arguments provided below we cannot endorse the concluding remarks of Dr Della Corte: ‘Functionally, one of the early signs of arterial ageing is impaired wall distensibility, which is known to occur in the BAV 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 ageing of the aortic wall, prompted by altered biomechanical environment could be drawn as well’. In this respect the definition and detection of ageing of the vascular wall is an issue. Loss of aortic wall distensibility, based on the increase of collagen and loss of elastin is adapted by some as a measure of vascular wall ageing (5) and used not only for the TAV models but also for BAV (1). We have not specifically studied the collagen content but confirm the diminished elastin structure in BAV (2). Additionally we have introduced a new set of ageing markers being the balance between lamin A/C and progerin (2, 10). Even physiologic ageing with increasing age has been correlated with the increased expression of progerin (10-12). We are excited about the fact that in this way we could differentiate
between TAV and BAV, showing increased physiologic ageing in TAV based on an increase of progerin and accompanying apoptosis resulting in cytolytic necrosis, while this was lacking in BAV. The decrease of distensibility as described (1, 5) might still hold for the aortopathy in both BAV and TAV but should in our opinion not be translated as an indication of premature ageing in BAV. In our study we had the relatively unique opportunity to show that the structural immaturity was present in both non- and dilated BAVs independent of the degree and type of underlying aortic valve pathology. In conclusion we demonstrated that a different mechanism underlies aortic dilation in BAV and TAV patients. We postulate that secondarily haemodynamic influences, additionally triggered by the specific BAV aortic valve pathology, might have a different impact on the immature BAV wall as compared to the ageing TAV aortic wall.
REFERENCES


