aorta with bicuspid aortic valve: preliminary results. *J Thorac Cardiovasc Surg.* 2005;130:504-11.

4. Iliopoulos DC, Kritharis EP, Giagini AT, Papadodima SA, Sokolis DP. Ascending thoracic aortic aneurysms are associated with compositional remodeling and vessel stiffening but not weakening in age-matched subjects. *J Thorac Cardiovasc Surg.* 2009;137:101-9.
5. Wang M, Zhao D, Spinetti G, Zhang J, Jiang LQ, Pintus G, et al. Matrix metalloproteinase 2 activation of transforming growth factor- β 1 (TGF- β 1) and TGF- β 1-type II receptor signaling within the aged arterial wall. *Arterioscler Thromb Vasc Biol.* 2006;26:1503-9.

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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.

TABLE 1. Additional characteristics of the study population

Characteristic	TA (n = 11)	TAD (n = 12)	BA (n = 17)	BAD (n = 19)
Specimen obtained	Post mortem, LUMC	During elective repair of ascending aorta, LUMC	During stentless root replacement, collected residue material from proximal anastomosis, LUMC and 6 biopsies, EMC	During elective repair of ascending aorta, LUMC
Age (y, mean $\pm$ SD)	64.5 $\pm$ 9.0	72.3 $\pm$ 11.2	55.8 $\pm$ 9.8	60.7 $\pm$ 7.8
Male (%)	54.5	33.3	70.1	84.2
Female (%)	45.5	66.7	29.4	15.8
Ascending aortic diameter (mm, mean $\pm$ SD)	*	55.0 $\pm$ 10.7	36.5 $\pm$ 7.4 [†]	52.7 $\pm$ 6.2
Commissure position			Unicuspid, n = 1; RCC/LCC, n = 8; RCC/NCC, n = 4; LCC/NCC, n = 1; unknown, n = 3	RCC/LCC, n = 15; unknown, n = 4

TA, Nondilated tricuspid aortic valve; TAD, dilated tricuspid aortic valve; BA, nondilated bicuspid aortic valve; BAD, dilated bicuspid aortic valve; LUMC, Leiden University Medical Center; EMC, Erasmus Medical Center; RCC/LCC, fusion of the right and left coronary cusps; RCC/NCC, fusion of the right coronary and noncoronary cusps; LCC/NCC, fusion of the left coronary and noncoronary cusps; SD, standard deviation. *Data unavailable, clinically defined as nondilated by pathologist. [†]Data unavailable for 5 patients, clinically defined as nondilated by pathologist.

On basis of these observations and additional arguments provided here, we cannot endorse the concluding remarks of Drs Forte and Della Corte: “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, a 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.” In this respect, the definition and detection of aging of the vascular wall are an issue. Loss of aortic wall distensibility, which is based on the increase of collagen and loss of elastin, is considered by some to represent a measure of vascular wall aging⁵ and used not only for the TAV models but also for BAV.¹ We have not specifically studied the collagen content, but we do confirm the diminished elastin structure in BAV.² Additionally, we have introduced a new set of aging markers encompassing the balance between lamin A/C and

progerin.^{2,10} Even physiologic aging with increasing calendar 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 aging in TAV on the basis of an increase of progerin and accompanying apoptosis resulting in cytolytic necrosis, although this finding 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 aging in BAV. In our study we had the relatively unique opportunity to show that the structural immaturity was present in both nondilated 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. We postulate that secondarily hemodynamic influences, additionally triggered by the specific BAV aortic valve pathology, might have a different impact on the immature

BAV wall as opposed to the aging TAV aortic wall.

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References

1. Forte A, Della Corte A, Grossi M, Bancone C, Provenzano R, Finicelli M, et al. Early cell changes and TGF β pathway alterations in the aortopathy associated with bicuspid aortic valve stenosis. *Clin Sci (Lond)*. 2013;124:97-108.
2. Grewal N, Gittenberger-de Groot AC, Poelmann RE, Klautz RJ, Lindeman JH, Goumans MJ, et al. Ascending aorta dilation in association with bicuspid aortic valve: A maturation defect of the aortic wall. *J Thorac Cardiovasc Surg*. 2014;148:1583-90.
3. Owens GK, Kumar MS, Wamhoff BR. Molecular regulation of vascular smooth muscle cell differentiation in development and disease. *Physiol Rev*. 2004;84:767-801.
4. Deruiter MC, Rensen SS, Coolen GP, Hierck BP, Bergwerff M, Debie WM, et al. Smoothelin

expression during chicken embryogenesis: detection of an embryonic isoform. *Dev Dyn*. 2001;221:460-3.

5. Jones JA, Beck C, Barbour JR, Zavadzkas JA, Mukherjee R, Spinale FG, et al. Alterations in aortic cellular constituents during thoracic aortic aneurysm development: myofibroblast-mediated vascular remodeling. *Am J Pathol*. 2009;175:1746-56.
6. Slomp J, Gittenberger-de Groot AC, Glukhova MA, van Munsteren JC, Kockx MM, Schwartz SM, et al. Differentiation, dedifferentiation, and apoptosis of smooth muscle cells during the development of the human ductus arteriosus. *Arterioscler Thromb Vasc Biol*. 1997;17:1003-9.
7. Grewal N, Gittenberger-de-Groot AC, DeRuiter MC, Klautz RJM, Poelmann RE, Duim SN, et al. Bicuspid aortic valve: phosphorylation of c-Kit and downstream targets are prognostic for future aortopathy. *Eur J Card Thor Surg*. August 26, 2014 [Epub ahead of print].
8. Cotrufo M, Della CA, De Santo LS, Quarto C, De Feo M, Romano G, et al. Different patterns of extracellular matrix protein expression in the convexity and the concavity of the dilated aorta with bicuspid aortic valve: preliminary results. *J Thorac Cardiovasc Surg*. 2005;130:504-11.
9. Mohamed SA, Noack F, Schoellermann K, Karluss A, Radtke A, Schult-Badusche D, et al. Elevation of matrix metalloproteinases in different areas of ascending aortic aneurysms in patients with bicuspid and tricuspid aortic valves. *ScientificWorldJournal*. 2012;2012:806261.
10. Bökenkamp R, Raz V, Venema A, DeRuiter MC, van Munsteren C, Olive M, et al. Differential temporal and spatial progerin expression during closure of the ductus arteriosus in neonates. *PLoS One*. 2011;6:e23975.
11. Olive M, Harten I, Mitchell R, Beers JK, Djabali K, Cao K, et al. Cardiovascular pathology in Hutchinson-Gilford progeria: correlation with the vascular pathology of aging. *Arterioscler Thromb Vasc Biol*. 2010;30:2301-9.
12. Ragnauth CD, Warren DT, Liu Y, McNair R, Tajsic T, Figg N, et al. Prelamin A acts to accelerate smooth muscle cell senescence and is a novel biomarker of human vascular aging. *Circulation*. 2010;121:2200-10.

<http://dx.doi.org/10.1016/j.jtcvs.2014.08.027>

MINIMALLY INVASIVE FULL BIATRIAL COX MAZE IV: WE ARE GOING IN THE RIGHT DIRECTION

To the Editor:

I read with great interest the article by Lawrance and colleagues,¹ and I congratulate them on this very interesting and well-written article. They have shown that the Cox maze IV procedure, with its inherent variations, can be performed by means

of a less invasive right anterolateral minithoracotomy with excellent outcome. My personal preference is for the classic standard “cut-and-sew” Cox maze III procedure. Once the surgeon has acquired technical expertise, this procedure is both easy and safe to do. What is truly important is not the complexity of the procedure, but rather the aortic crossclamp time. This is the rub, and this is why alternative energy sources for atrial fibrillation surgery have mushroomed in recent years. Since 2002, this has been termed as Cox maze IV procedure. Damiano and his working group² have been pioneers in this technology. The idea proposed by Lawrance and colleagues¹ looks promising. In addition to the minimally invasive surgery, they used the only 2 energy sources that have been proved to be successful achieving full transmural lesions in the atria, bipolar radiofrequency and cryoablation. This great effort by Lawrance and colleagues¹ in this article highlights that the trend is now toward the idea conceived by Cox³ 11 years ago. He stated that surgery for atrial fibrillation should meet the following conditions: (1) the procedure should preferably be epicardial by nature; (2) the energy source should be capable of penetrating epicardial fat and ablating all types of atrial fibrillation; (3) cardiopulmonary bypass must be avoided; (4) the procedure should be amenable to endoscopic or minimally invasive techniques; (5) it should be performed in less than 1 hour; and (6) hospital discharge should be possible on the first postoperative day. Although it is true that not all these objectives have been achieved, we must recognize that we are on the right track. Novel devices are being developed^{4,5}; as yet, however, transmural lesions have not been safely produced on the beating heart by epicardial ablation. Unfortunately, cardiopulmonary bypass remains a crucial aspect to perform this kind of procedure. The

most important point is that we are going on the right direction, each moment getting closer to the goal. I really congratulate Lawrance and colleagues¹ for this fine and great effort.

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References

1. Lawrance CP, Henn MC, Miller J, Sinn LA, Schuessler RB, Maniar HS, et al. A minimally invasive Cox-Maze IV is as effective as sternotomy while decreasing major morbidity and hospital stay. *J Thorac Cardiovasc Surg*. June 6, 2014 [Epub ahead of print].
2. Damiano RJ Jr, Badhwar V, Acker MA, Veeragandham RS, Kress DC, Robertson JO, et al. The CURE-AF trial: a prospective, multicenter trial of irrigated radiofrequency ablation for the treatment of persistent atrial fibrillation during concomitant cardiac surgery. *Heart Rhythm*. 2014;11:39-45.
3. Cox JL. Atrial fibrillation II: rationale for surgical treatment. *J Thorac Cardiovasc Surg*. 2003;126:1693-9.
4. Sakamoto S, Voeller RK, Melby SJ, Lall SC, Chang N, Schuessler RB, et al. Surgical ablation for atrial fibrillation: The efficacy of a novel bipolar pen device in the cardiologically arrested and beating heart. *J Thorac Cardiovasc Surg*. 2008;136:1295-301.
5. Watanabe Y, Weimar T, Kazui T, Lee U, Schuessler RB, Damiano RJ Jr. Epicardial ablation performance of a novel radiofrequency device on the beating heart in pigs. *Ann Thorac Surg*. 2014;97:673-8.

<http://dx.doi.org/10.1016/j.jtcvs.2014.07.017>

RUPTURE OF EXPANDED POLYTETRAFLUOROETHYLENE NEOCHORDAE USED FOR MITRAL VALVE REPAIR: DOES SIZE MATTER?

To the Editor:

In a report published in another journal in 2007,¹ we reported 2 cases of rupture of synthetic chordae tendinae (expanded polytetrafluoroethylene [ePTFE]). We also analyzed the possible causes of what was then considered an extremely rare finding, which had first been reported by Buttany and