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CLINICAL IMPLICATIONS

Aortas reveal the myth of male privilege

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The commonest congenital heart defect in adults is the bicuspid aortic valve. It affects 1.3 % of the population worldwide and is responsible for more deaths and complications than all the other congenital heart defects combined (Fig. 1). Fusion of aortic valve leaflets occurs most commonly (≈80 %) between the right coronary and left coronary leaflets (RL), which are the anterior leaflets of the aortic valve. Fusion also occurs between the right coronary and noncoronary leaflets (RN; ≈17 %), and least commonly between the noncoronary and left coronary leaflets (LN; ≈2 %). Verma and Siu recently provided an overview of the basic principles, recent advances, and recommendations for the treatment of adults with bicuspid aortopathy [1]. Aortic stenosis and insufficiency are the hallmarks of a bicuspid aortic valve; however, dilatation of any or all proximal aortic segments extending from the aortic root to the aortic arch, namely, bicuspid aortopathy, is also present in at least half of affected persons (Fig. 2). A heterogeneous pattern of aortic dilatation develops in an affected person, probably reflecting heterogeneity in molecular, rheologic, and clinical features [2].

In this issue, Lee et al. [3] suggest that aortic remodeling in patients with bicuspid aortic valve-associated thoracic aneurysms is sex-dependent. They studied the structural remodeling in patients with bicuspid aortic valves and compared molecular alterations in men and women by investigating aortic aneurysmal tissue samples. Women had smaller aortic aneurysms than men, but the size difference disappeared when the data were normalized for body surface area. Elastin fibers were disorganized and reduced in men and women. However, only men exhibited disarrayed collagen fibers and reduced protein. The mRNA levels were similar in both groups,

suggesting post-translational degradation of proteins, more prominent in men compared to women. The enzymatic elastase activity was elevated in both men and women, while the membrane-anchored collagenase membrane type 1 matrix metalloprotease (MT1-MMP) was more increased in men than in women. Furthermore, matrix metalloprotease (MMP)-8 and MMP-13 were lower, while MMP-2 was higher in women than men. Tissue-inhibitor of metalloprotease (TIMP)-3 and TIMP-4 were similarly decreased in both sexes, while TIMP-2 was increased in women. The vascular smooth muscle cell density in the media of dilated aortas from men corresponded to an increase in caspase-3 cleavage, compared to women. The authors suggest a sex-dependent MMP/TIMP axis, including collagen remodeling and vascular smooth muscle cell survival, could protect women from aortic rupture.

Lee et al. [3] claim that sex-related effects have not been explored in thoracic aortic aneurysms associated with bicuspid aortic valve disease. Predictors of bicuspid aortopathy progression include older age, male sex, elevated systolic blood pressure, coexisting aortic valve stenosis or regurgitation, and morphologic features of the valve, namely, right or left cusp fusion [4]. It is important to distinguish between bicuspid valve disease and aortopathy when evaluating series, although the two are closely related. Systolic blood pressure, male sex, and valve disease severity were identified in earlier studies, although age was considered to be the most important factor [5, 6]. Verma and Siu provide a decision-making algorithm in their review [1]. Aortic root diameter is the most important variable upon which decisions are based in terms of further imaging or intervention. A reanalysis of earlier patient series should reveal whether or not less women arrive at a given aortic root diameter across age groups.

Chromosomes XX or XY genetically determine female or male sex. Bicuspid aortic valves are twice as common in men,

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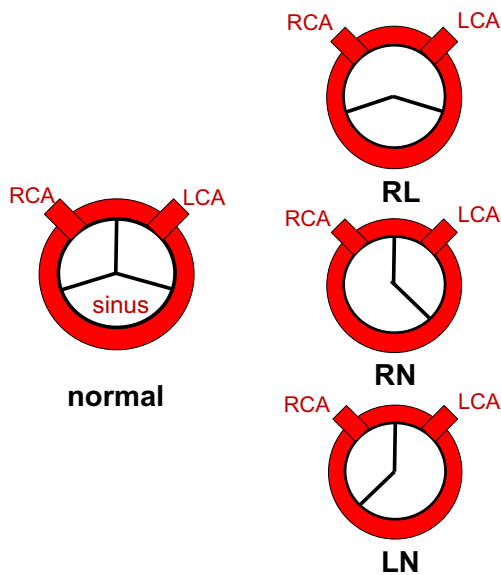e-mail: luft@charite.de

Fig. 1 Scheme of morphologic valve fusion patterns: Shown are a normal configuration of three aortic valve cusps at the sinuses of the right and left coronary arteries and the noncoronary sinus (of Valsalva). Fusion of the right and left cusps results in a bicuspid valve termed RL, the commonest variant. Fusion also occurs between the right and noncoronary leaflets (RN). Least common is a fusion between left and noncoronary leaflets (LN)

than in women [4]. The anomaly is said to have a genetic variance of about 90 % [7]. Both familial clustering and isolated valve defects have been documented. The incidence of bicuspid aortic valve can be as high as 10 % in families affected with the valve problem. Recent studies suggest that bicuspid aortic valve could be an autosomal dominant condition with incomplete penetrance. More importantly perhaps is the fact that other congenital heart defects are associated with bicuspid aortic valve at various frequencies, particularly coarctation of the aorta, which must always be ruled out. A strong genetic association has been claimed for the notch homolog 1 (*NOTCH1*) [8].

A wise policy is to stay away from politics, particularly related to gender disparities. Women live longer than men, have less heart disease, perhaps related to more sensible living and more attention to health issues than men. Preventing cardiovascular disease in women is receiving deservedly increased attention [9]. A worthwhile pursuit, as Lee et al. show [3], is identifying mechanisms of sexual dimorphism that call to attention differences leading to better decision-making and treatments for both women and men. Nonetheless, the decision-making tree suggested by Verma and Siu [1] should
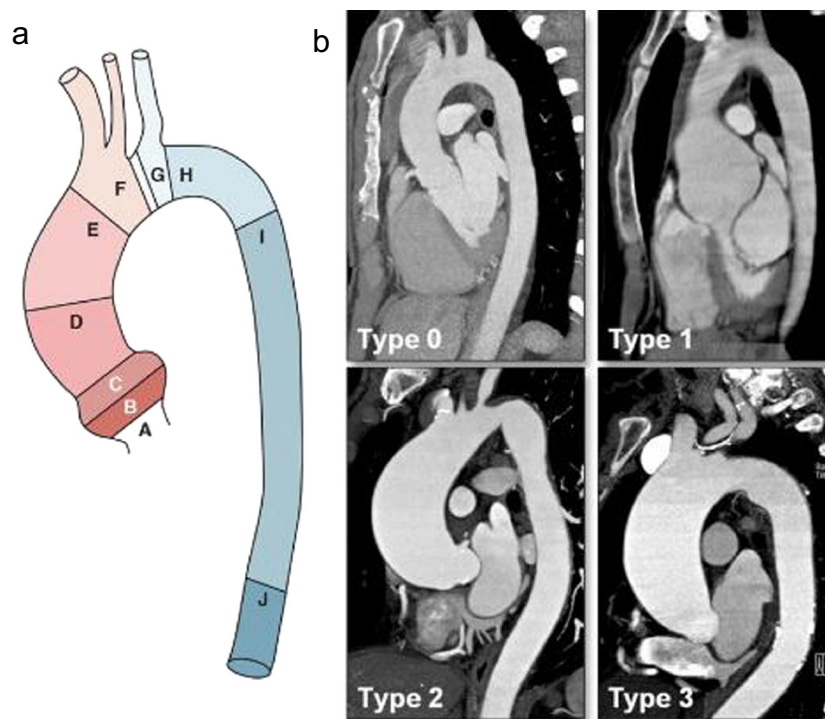

Fig. 2 The resultant outflow blood stream leads to differing forms of aortopathy dependent upon the type of bicuspid valve. Aortopathy occurs in over half the patients. The 10 levels used in aortic dimension measurements (*A–J*) with representative MDCT images of bicuspid aortopathy phenotypes are shown (published in Kang et al. [2] and permission provided by courtesy of Elsevier Publisher). **a** Scheme of the 10 levels used in aortic dimension measurements (*A–J*) with **b** representative MDCT images of bicuspid aortopathy phenotypes is shown. *Type 0* is a normal aorta; *type 1* is characterized by dilated aortic root. If the aortic enlargement involves the tubular portion of the ascending aorta, it is classified as *type 2*, whereas in *type 3*, there is diffuse involvement of the entire ascending aorta and the transverse aortic arch. *A* aortic annulus, *B* sinuses of Valsalva, *C* sinotubular junction, *D* tubular portion of the ascending aorta, *E* proximal to the innominate artery (or common trunk in case of a bovine arch), *F* distal to the innominate artery (or common trunk), *G* proximal to the left subclavian artery, *H* distal to the left subclavian artery, *I* proximal descending aorta, *J* distal descending thoracic aorta at the level of the diaphragmatic hiatus, *MDCT* multidetector computed tomography

remain unaltered until epidemiological observational and co-hort studies verify the new information.

Respectfully,

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