Bicuspid Aortic Valve Disease Beyond the Aortic Root

Potential Prognostic Implications for Ascending Aortic Dilation*

S. Morteza Farasat, MD
Farmington, Connecticut

With an estimated incidence of 1% to 2% in the general population (1), bicuspid aortic valve (BAV) affects more patients than all other congenital heart anomalies combined (2). One-third of all patients with BAV experience one of the serious complications of BAV, including aortic stenosis, aortic regurgitation, infective endocarditis, and aortic dissection, in their lifetime (3).

Aortic root dilation is an important, potentially lethal complication of BAV (4) that substantially increases the risk of ascending aortic aneurysm, dissection, and rupture (3). Curiously, aortic valve replacement does not prevent progressive dilation of the ascending aorta (5), suggesting that mechanisms unrelated to hemodynamic factors, or to the valve per se, contribute to the aortopathy of BAV. Aortic root dilation occurs in nearly one-half of all patients with BAV (6–8). However, presently there are no prognostic factors to help identify the patients who are at an increased risk of developing ascending aortic dilation.

Given the strong heritability of BAV (9), genetic factors are thought to play a role in the pathogenesis of ascending aortic dilation in patients with BAV. Such a view gains support from a recent prospective study by Biner et al. (7), who discovered aortic root dilation in one-third of the first-degree relatives of BAV patients who had normal tricuspid aortic valves. Those investigators also found that indexes of aortic stiffness were higher in both BAV patients and their first-degree relatives compared with normal control subjects, irrespective of the presence of aortic root dilation or hypertension status (7). Genetic factors, especially those that regulate extracellular matrix turnover, have been implicated as putative mechanisms for these observations. Most notable among these are the genes that regulate the balance between various members of the matrix metalloproteinase (MMP) family and their tissue inhibitors (TIMPs).

Gene expression studies have documented increased expression of several MMPs, particularly MMP-2 and the ratio of MMP-2 to its tissue inhibitor, TIMP-1, in aortic tissues from BAV patients compared with subjects with a tricuspid aortic valve with or without aortic aneurysms (10–12). There is general agreement that this differential pattern of gene expression contributes to the classic pathological finding of aortic medial degeneration (4), characterized by loss of collagen and elastin fragmentation in the aortas of patients with BAV (10,11).

Another interesting observation is that deficiency of endothelium-derived nitric oxide, a key regulator of endothelium-dependent flow-mediated vasodilation, also seems to play a role in the defective valvulogenesis of BAV. In an experimental study, Lee et al. (13) showed that endothelium-derived nitric oxide synthase (eNOS) knockout mice had a significantly higher likelihood of developing BAV than control mice. This is corroborated by human studies documenting lower eNOS gene expression in the ascending aortas of BAV patients than in ascending aortas of control subjects with a tricuspid aortic valve (14).

The study by Tzemos et al. (15) in this issue of the Journal provides an integrating view of the aforementioned pathophysiological factors in BAV patients. In their observational study, Tzemos et al. (15) cross-sectionally evaluated 32 men with BAV, without significant aortic stenosis, who were classified as having nondilated or dilated ascending aortas. Brachial artery flow-mediated vasodilation, carotid-femoral pulse wave velocity (PWV), circulating plasma levels of MMP-2 and -9, as well as their respective tissue inhibitors, TIMP-1 and -2, were measured in the 2 BAV groups and in 16 healthy male control subjects. The investigators found that plasma levels of MMP-2 were higher in men with BAV and dilated aortas compared with both BAV subjects with nondilated aortas and normal control subjects. However, the plasma levels of MMP-9, TIMP-1, and TIMP-2 did not differ among the 3 study groups. Although plasma levels of MMPs do not necessarily mirror their tissue activity (16), the feasibility and ease of measuring plasma MMPs compared with in vivo determination of their activity in aortic tissue render plasma levels of MMPs an attractive candidate as a prognostic marker for future ascending aortic dilation in BAV patients.

The finding of impaired flow-mediated vasodilation, a hallmark of systemic endothelial dysfunction, in BAV patients with dilated aortas but not in those without dilated aortas suggests that endothelial dysfunction may represent a risk factor for the development of ascending aortic dilation. This finding provides a preliminary rationale for investigating whether statins, which are known to have salutary effects...
on endothelial function (17), can ameliorate BAV-related ascending aortic dilation.

Consistent with previous studies (7,18), Tzemos et al. (15) observed a higher PWV in BAV patients with dilated aortas compared with those with nondilated aortas and with normal control subjects. However, the PWV was similar in BAV patients with nondilated aortas and normal control subjects. According to the Moens-Korteweg equation: 

\[ \text{PWV} = \sqrt{\frac{Eh}{\rho D}} \]

where Eh is the aortic elastance–wall thickness product, \( \rho \) is the density of blood, and D is the vessel diameter, PWV is inversely related to the square root of the aortic diameter. Thus, for a given Eh, a larger vessel diameter would be expected to result in a lower PWV. However, in the study by Tzemos et al. (15), subjects with dilated aortas had a higher PWV than the other 2 groups, who had smaller aortic root diameters. This finding indicates that the lowering effect of the larger aortic root diameter on PWV in BAV patients with dilated aortas was counteracted by a more pronounced increase in the aortic elastance–wall thickness product, reflecting the pathological alterations in the aortic wall of BAV patients with dilated aortas.

The cross-sectional design and the exclusion of women from the study sample are the 2 most important limitations of the study by Tzemos et al. (15). Nonetheless, this study lays the groundwork for the future development of a risk stratification paradigm for predicting the development of ascending aortic dilation in patients with BAV. If the findings reported by Tzemos et al. (15) are corroborated in prospective studies, documenting that they pre-date ascending aortic dilation in patients with BAV, they may provide useful tools for risk stratification and thus guide surveillance and clinical management of patients with BAV.

Reprint requests and correspondence: Dr. S. Morteza Farasat, University of Connecticut School of Medicine, Division of Cardiology, 263 Farmington Avenue, Farmington, Connecticut 06030. E-mail: farasats@mail.nih.gov.

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