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● *Original Contribution*

ENLARGED SIZE AND IMPAIRED ELASTIC PROPERTIES OF THE ASCENDING AORTA ARE ASSOCIATED WITH ENDOTHELIAL DYSFUNCTION AND ELEVATED PLASMA MATRIX METALLOPROTEINASE-2 LEVEL IN PATIENTS WITH BICUSPID AORTIC VALVE

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Abstract—The aim of this study was to test whether enlarged size and impaired elastic properties of the ascending aorta are associated with impaired endothelial function and increases in plasma matrix metalloproteinase (MMP)-2 concentrations in patients with bicuspid aortic valve (BAV) without significant valvular dysfunction. The size and the elasticity of the ascending aorta and the flow-mediated vasodilation (FMD) in the brachial artery in response to hyperemia were evaluated with 2-D echocardiography and high-frequency linear ultrasound in 42 patients with BAV without significant valvular dysfunction and 30 age- and sex-matched healthy controls. In the BAV group, diastolic ascending aortic diameter (AoD) (32.1 ± 8.1 mm vs. 25.3 ± 3.6 mm, $p < 0.001$) and aortic stiffness index (8.0 ± 5.3 vs. 4.0 ± 1.8, $p < 0.001$) were significantly higher, and aortic strain (7.4 ± 3.6% vs. 11.1 ± 3.0%, $p < 0.001$) and aortic distensibility (7.4 ± 4.1 × 10^{-6} cm^2/dyn vs. 11.1 ± 4.3 × 10^{-6} cm^2/dyn, $p < 0.001$) were significantly lower than those in the control group. The BAV group also had lower FMD (6.5 ± 2.2% vs. 11.9 ± 2.7%, $p < 0.001$) and higher plasma MMP-2 levels (226.7 ± 55.0 ng/mL vs. 177.0 ± 45.3 ng/mL, $p < 0.001$) compared with the control group. In the BAV group, AoD, aortic strain, aortic stiffness index and aortic distensibility significantly correlated with FMD and MMP-2 (all $p < 0.05$). The multivariable linear regression analysis further indicated that FMD and MMP-2 were independently associated with AoD ($\beta = -1.1$, $p = 0.005$, and $\beta = 0.09$, $p < 0.001$, respectively). These findings suggest that enlarged size and impaired elastic properties of the ascending aorta are associated with endothelial dysfunction and elevated plasma MMP-2 level in patients with BAV without significant valvular dysfunction. FMD and plasma MMP-2 level are the significant and independent predictors of dilation of the ascending aorta in patients with BAV. (E-mail: ybdeng2007@hotmail.com)

Key Words: **Endothelial function, Bicuspid aortic valve, Echocardiography, Nitric oxide.**

INTRODUCTION

Bicuspid aortic valve (BAV), the most common congenital heart defect, is recognized as a valvulo-aortopathy (Michelena et al. 2014). Apart from aortic stenosis or regurgitation, dilation of the ascending aorta is commonly observed in patients with BAV, and it is a risk factor associated with aortic dissection and rupture (Michelena et al. 2011). Controversy exists regarding the pathogenesis of dilation of the ascending aorta. Age and severity of valvular dysfunction were validated as two independent factors associated with dilated ascending aorta in patients with BAV (Kim et al. 2012). However, it was also observed that dilation of ascending aorta still occurred in BAV patients without significant valvular dysfunction or even several years after surgical correction of valvular dysfunction (Beroukhim et al. 2006; Hahn et al. 1992; Keane et al. 2000). Therefore, hemodynamic disturbance caused by valvular dysfunction cannot completely explain the BAV-associated aortopathy.

The genetic etiologies of BAV were observed in the past decades of investigation, and abnormalities of the gene encoding endothelial nitric oxide synthase (eNOS) were considered to be responsible for BAV and associated aortopathy (Fedak et al. 2002). Pre-clinical studies reported that endothelium-derived nitric oxide (NO) produced by eNOS was involved in cardiac valve morphogenesis,

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post-developmental vascular remodeling and angiogenesis, as well as in the formation of limb vasculature during embryogenesis (Gregg et al. 1998; Lee et al. 2000; Rudic et al. 1998). Deficiency in eNOS resulted in high incidences of BAV and formation of aortic aneurysm (Aicher et al. 2007; Lee et al. 2000). In addition, decreased bioactivity of endothelium-derived NO by downregulation of eNOS expression can increase basal secretion of promatrix metalloproteinase (MMP)-2 and activity of MMP-2 (Chen and Wang 2004; Matsunaga et al. 2002), which accelerates apoptosis of vascular smooth muscle cells and degradation of extracellular matrix, both leading to vascular remodeling and formation of aortic aneurysms (LeMaire et al. 2005). eNOS is known to maintain normal endothelial function by catalyzing the oxidative reaction to produce nitric oxide (NO) (Moncada and Higgs 1993). Recent clinical studies reported systemic endothelial dysfunction and elevated plasma levels of MMP-2 in patients with BAV (Ali et al. 2014; Tzemos et al. 2010). Therefore, the aim of this cross-sectional study was to test the hypothesis that enlarged size and impaired elastic properties of the ascending aorta are associated with impaired flow-mediated vasodilation (FMD) in response to hyperemia, a marker of endothelial dysfunction, and increases in plasma MMP-2 concentrations in patients with BAV without significant valvular dysfunction.

METHODS

Study population

Between January 2016 and May 2017, we identified 69 consecutive patients with BAV by echocardiography from the outpatients or inpatients in our hospital. The BAV was confirmed when only two valve leaflets were unequivocally identified, by two observers, at systole and diastole in the short-axis view with a clear fish-mouth appearance during systole (Brandenburg et al. 1983; Santarpia et al. 2012) (Fig. 1). Transesophageal echocardiography was performed when the transthoracic echocardiographic images were inadequate for making a diagnosis. One of the 69 patients with BAV was finally confirmed by transesophageal echocardiography. Exclusion criteria included the presence of moderate and/or severe aortic stenosis and/or regurgitation, history of cardiac surgery, hypertension or any other cardiovascular disease, dyslipidemia, diabetes mellitus and smoking. One patient with ischemic heart disease determined by coronary angiography, 2 patients with hypertension and 24 patients with moderate to severe aortic stenosis or regurgitation were excluded from the study population. Therefore, 42 patients (32 males, mean age: 34 ± 11 y, range: 13–55 y) were finally enrolled in the study. The healthy control group consisted of 30 age- and sex-matched volunteers (21 males, mean age: 30 ± 9 y, range: 15–50 y) with no evidence of hypertension or any other cardiovascular disease, dyslipidemia, diabetes mellitus and smoking by history, physical examination, laboratory testing, electrocardiography and echocardiographic examination.

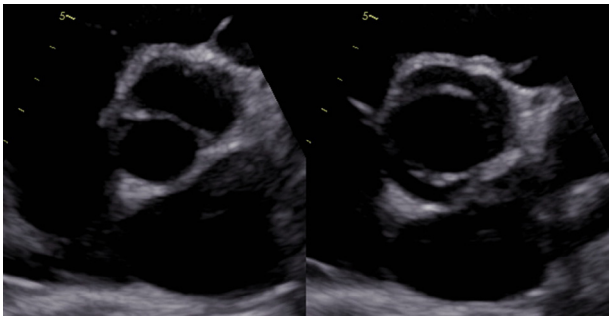

Fig. 1. Transthoracic echocardiographic image of bicuspid aortic valve in diastole (left) and in systole (right), revealing the clear fish-mouth appearance of the bicuspid aortic valve orifice.

This study protocol was approved by the institutional ethics committee, and informed consent was obtained from each patient before enrollment in the study.

Standard echocardiography

Two-dimensional echocardiography was performed using a Vivid E9 ultrasound system (GE Medical System, Horten, Norway) equipped with a 1.7- to 3.4-MHz M5 S phased array transducer. The biplane Simpson method was used to calculate left ventricular volume and ejection fraction (Lang et al. 2015). Left ventricular mass was calculated according to Devereux's formula (Devereux and Reichek 1977). Left ventricular volume and mass were indexed to body surface area. Transaortic systolic peak flow velocity was assessed using continuous wave Doppler, and aortic stenosis was considered mild when peak aortic velocity was <3 m/s (Bonow et al. 2008). The presence of aortic regurgitation was assessed on color and spectrum Doppler according to established criteria (Zoghbi et al. 2003).

Diastolic (AoD) and systolic (AoS) ascending aortic diameters were measured at 3 cm above the aortic valve using a 2-D-guided M-mode evaluation (Fig. 2) (Santarpia et al. 2012). AoD was measured at the peak of the R wave at the simultaneously recorded electrocardiogram, and AoS was measured at the maximal anterior motion of the anterior aortic wall. Brachial artery systolic (SBP) and diastolic (DBP) blood pressures were measured simultaneously using a properly sized cuff sphygmomanometer. Pulse pressure was calculated as SBP—DBP. The indices of aortic elasticity were calculated as follows: aortic strain (%) = 100 (AoS − AoD)/AoD; aortic stiffness index = ln(SBP/DBP)/[(AoS − AoD)/AoD]; aortic distensibility ($\times 10^{-6}$cm^2/dyn) = [2(AoS − AoD)/AoD (SBP—DBP)], as previously described by Nistri et al. (2008).

All images were digitally stored on the hard disk in the machine for offline analysis (EchoPac, GE Vingmed,