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Review Article

Sex differences in bicuspid aortic valve disease

William K.F. Kong [a,b], Jeroen J. Bax [a], Hector I. Michelena [c], Victoria Delgado [a,*]

[a] Department of Cardiology, Leiden University Medical Center, Leiden, the Netherlands
[b] Department of Cardiology, National University Heart Centre, National University Health System, Singapore
[c] Department of Cardiovascular Medicine, Mayo Clinic, Rochester, MN, USA

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A B S T R A C T

Bicuspid aortic valve (BAV), the most frequent congenital heart disease, is characterized by an uneven distribution between sexes. BAV is three to four times more frequent in men than in women which could be associated with a reduced dosage of X chromosome genes. In addition, BAV has a multifactorial inheritance, low penetrance and variable phenotypes that may lead to different form of valve degeneration and dysfunction over time as well as different incidence of aortic valve and vascular complications between men and women.

Definition of the phenotype is the first step in the evaluation of patients with BAV. Among the various phenotypes, BAV with a fusion raphe between the left and the right coronary cusp is the most frequent phenotype observed in men and women. It has been hypothesized that the valve and vascular related complications vary according to the BAV phenotype and this could explain differences in the clinical outcomes of men versus women. However, the evidence on the distribution of the various BAV phenotypes between sexes in not consistent and while some series have described differences between male and female, others have not confirmed those findings.

In terms of valvular complications, women present more frequently with aortic stenosis while aortic regurgitation is more frequently diagnosed in men. Furthermore, endocarditis is more frequently reported in men as compared to women. In terms of vascular complications, men show larger diameters of the various parts of the aortic root and ascending aorta and more frequently present complications in terms of aortic aneurysm and dissection as compared to women. Although there are no survival differences between men and women with BAV, compared to the general population some large series have shown that women have worse prognosis.

The present review article summarizes the differences between men and women in terms of BAV phenotype, type and incidence of aortic valve and vascular complications that will determine the differences in clinical outcomes.

Contents

Introduction

Bicuspid aortic valve (BAV) is the most common form of congenital heart valve disease and a major health care burden.[1,2] Patients with BAV are at high risk of developing aortic valve dysfunction [aortic

Abbreviations: AR, Aortic regurgitation; AS, Aortic stenosis; BAV, Bicuspid aortic valve.

* Corresponding author at: Department of Cardiology, Leiden University Medical Centre, Albinuusdreef 2, 2300 RC Leiden, the Netherlands.
E-mail address: V.Delgado@lumc.nl (V. Delgado).

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stenosis (AS),aortic regurgitation (AR) or both] and may undergo aortic valve replacement at an earlier age than patients with tricuspid aortic valves.[2,3] In addition to aortic valve dysfunction, bicuspid aortopathy, which comprises dilation of various segments of the aorta and aneurysm formation, is present in 40–50% of patients with BAV.[4,5] Despite this high incidence of aortopathy, aortic dissection is a rare complication (0.03% patient-years) for all patients with BAV although it occurs more frequently as compared with the general population.[6]

One of the characteristics of BAV is the uneven distribution between sexes: BAV is three to four times more prevalent in men as compared to women.[7,8] The prevalence of BAV according to sex has been found to be 7.1 cases per 1000 among male neonates, and 1.9 per 1000 among female neonates.[9] Non-syndromic BAV has been associated with multifactorial inheritance, low penetrance and variable phenotypes, however, it has been hypothesized that reduced dosage of X chromosome genes that escape X inactivation could explain the higher frequency of BAV in men.[10] In addition, the phenotypic characteristics of the BAV differ between men and women. This may lead to different form of valve degeneration and dysfunction over time as well as different incidence of aortic valve and vascular complications between men and women.

This review article summarizes the differences between men and women in terms of BAV phenotype, type and incidence of aortic valve and vascular complications that will determine the differences in clinical outcomes (Table 1).[11]

BAV phenotype

Several classifications of BAV phenotype have been proposed based on the number of cusps, presence and location of raphe and orientation of the commissures. The most frequently used classification is the one proposed by Sievers and Schmidtke based on 304 surgical specimens.[12] This classification considers type 0 BAV, when there are only two cusps and two commissures and there is no fusion raphe. Type 1 BAV is defined by the presence of a raphe fusing two cusps; and type 2 BAV is defined by the presence of two raphes (which could be considered unicuspid aortic valve).

Of the 3 different phenotypes, the fusion raphe between the left and the right coronary cusps is the most frequently observed. Of the 304 surgical specimens described by Sievers and Schmidtke, 78% were in men as compared to 22% in women.[12] However, the distribution of the various phenotypes of BAV in both sexes was not reported. The study by Kong et al. described the sex differences in BAV phenotype in 1992 individuals (72% and 28% female).[7] Type 1 BAV with fusion between the left and the right coronary cusps was the most frequent in male (69%) and female (68%). However, type 1 BAV with fusion between right and non-coronary cusps was slightly more frequently observed in male (17% vs 16%) while type 0 BAV was more frequently observed in female (12% vs 10%). These differences were not statistically significant. In contrast, Roman and colleagues reported that among 424 subjects with unoperated BAV from the GenTAC registry, men had more frequently type 1 BAV with fusion between the left and right coronary cusps than women (82% vs 69%, $P = .03$), whereas women more frequently presented with type 1 BAV with fusion between the right and noncoronary cusps (19% vs 31%, $P = .03$).[13] The evidence on the distribution of BAV phenotypes between sexes is not consistent and while some series have described differences between male and female,[13,14] others have not confirmed those findings.[7,15] Differences in sample size and selection of patients (i.e., ambulatory patients vs patients referred for surgery) may be important confounders that lead to controversial results.

The BAV phenotype is an important evaluation and its relation with aortic valvular and vascular complications is still the subject of ongoing research.

Table 1
Clinical outcomes in contemporary series of patients with bicuspid aortic valve according to sex.
Adapted with permission from Michelena et al.[11].

Study features and clinical outcomes	Contemporary studies evaluating sex differences in patients with BAV				
	Andrei et al[18]	Michelena et al[19]			Kong et al[7]
Publication year	2015	2016			2017
No. patients	628	416	2824	2242	1992
Clinical setting	AVR referral	Community population based	Tertiary referral	AVR referral	Tertiary referral
Men, n (%)	478 (76)	288 (69)	2089 (74)	1663 (74)	1424 (72)
Baseline age, years	♀ 61 ± 14 ♂ 56 ± 14	♀ 34 ± 21 ♂ 36 ± 21	♀ 49 ± 16 ♂ 52 ± 16	♀ 63 ± 14 ♂ 62 ± 13	♀ 47 ± 19 ♂ 47 ± 18
Association between sex and BAV phenotype	None	None	NA	NA	None
Aortic stenosis	More common in women as AVR indication	No differences between sexes at baseline, but more common in women as AVR indication	No differences between sexes at baseline	More common in women as AVR indication	More common in women at baseline
Aortic regurgitation	More common in men at baseline	More common in men at baseline	More common in men at baseline	More common in men at baseline	More common in men at baseline
Aortic root phenotype	NA	NA	NA	NA	More common in men at baseline
Aortic dissection	NA	More common in men	NA	NA	More common in men at follow-up
Endocarditis	NA	More common in men at follow-up	NA	More common in men as AVR indication	More common in men at follow-up
Survival comparison between sexes	Identical (propensity matched)	Identical	Identical	Identical	NA
Survival by sex compared with the general population	NA	Identical	Decreased for both but worse for women	Decreased for both but worse for women	NA
Independent predictors of morbidity and mortality	NA	BAV-related morbidity predicted by male sex Aortic regurgitation predictive of mortality only for women	Aortic regurgitation predictive of mortality only for women	Aortic regurgitation predictive of mortality only for women	NA

Abbreviations: AVR = aortic valve replacement; BAV = bicuspid aortic valve; NA = not applicable.

Types of BAV dysfunction

BAV is prone to calcium deposition, stiffening and premature fibrosis; AS and AR is accelerated and may appear one decade earlier than that of a tricuspid aortic valve.[16] Kong et al. have reported that AS was more frequently observed in women at first presentation (64.8% vs 51.8% in men; $P < .001$), whereas men were more likely to present with AR (62.4% vs 55.7% in women, $P < .001$) (Fig. 1).[7] In the Spanish registry including 852 patients referred for echocardiography at 8 tertiary hospitals, Evangelista et al. reported that women presented more frequently with normal valve function as compared to men (65% vs 50%; $P < .001$) and when BAV valve dysfunction was present, AR was more frequent among men (28% vs 13% in women; $P < .001$) whereas the frequency of AS was similar in men and women (21% vs 22%, respectively).[17] In a surgical series, Andrei et al. reported in 628 consecutive BAV patients that AR was more prevalent in men than in women (44% vs 29%, respectively, $P < .001$).[18] These results were also confirmed by Michelena et al. in a cohort of 2242 patients with BAV referred for aortic valve surgery: severe AR was more frequently observed in men (23% vs 10% in women, $P < .0001$) and severe AS in women at the time of aortic valve replacement (95% vs 86% in men, $P < .0001$).[19]

Underlying reasons for gender differences in prevalence of BAV type dysfunction have been suggested in various cohort studies.[7,19] One reason for the differences in prevalence of normal BAV function, AS or AR, is the type of patients included. While Kong et al.[7] and Evangelista et al.[17] included patients referred for echocardiography, Andrei et al.[18] and Michelena et al.[19] included patients referred for surgery, resulting in a selection bias that may explain the differences in prevalence of BAV dysfunction. Furthermore, independent factors associated with higher frequency of AR in BAV included male sex, the presence of aortopathy, fusion raphe and sigmoid prolapse (more frequently observed when there is fusion between the right and non-coronary cusps).[4,17] It has been shown that men with BAV have larger sinuses of Valsalva (root) dimensions than women with BAV, which may lead to insufficient coaptation of the aortic cusps with subsequent AR. Conversely, older age, female sex, and presence of raphe have been reported as independent correlates of BAV with AS.[4,17]

The association between BAV phenotype and type of valve dysfunction is more controversial. While type 0 BAV shows more frequently normal valve function in all series,[4,20,21] the location of the fusion raphe has not been consistently associated with AS or AR. Evangelista et al.[17] reported that the fusion between right and non-coronary cusps in type 1 BAV was more frequently associated with AS. In the series described by Ren et al.,[15] AR was more frequently observed among men aged 70 years or younger than age-matched women and, interestingly, the phenotype of BAV with anteroposterior orientation of the cusp (probably referring to fusion between the left and the non-coronary cusps) was more frequently observed in men. In contrast, AS and a phenotype of BAV with a septal-lateral orientation of the cusps (probably referring to fusion between the left and the right coronary cusps or between the right and the non-coronary cusps) were more frequently observed in women. However, the association between BAV phenotype and type of valve dysfunction has not been demonstrated in larger series.[4]

Sex differences in bicuspid aortopathy

Thoracic aorta dilation is a prominent feature of BAV, and increased aortic dimensions are already present in the paediatric BAV population. The underlying mechanisms associated with the presence of aortopathy include the altered flow patterns associated with the type of BAV and valve dysfunction as well as genetic factors.[22,23] Four-dimensional flow cardiovascular magnetic resonance studies have shown different flow patterns in the aortic root and ascending aorta for various phenotypes of BAV with normal function (Fig. 2).[24,25] The different helical blood flows may impact differently on the aortic wall leading to dilation of the different aortic segments. For example, Evangelista et al. showed that right-to-non coronary cusp fusion BAV was associated with smaller aortic root diameter than right-to-left coronary cusp fusion BAV (34.3 ± 5.3 mm vs 37.5 ± 5.6 mm; $p < .01$) and with larger arch diameter (33.3 ± 6.3 mm vs 30.9 ± 5.1 mm; $p < .01$).[17] When assessing the distribution of the aortic dilation phenotypes in relation to BAV phenotype and valve function, aortic root dilation was more frequently observed in patients with left-to-right coronary cusp fusion BAV than in patients with right-to-non coronary cusp fusion BAV. In the series of Kong et al., dilation of any segment of the aorta was more frequently observed in patients with raphe fusion between the left and right coronary cusps.[4] The presence of valve dysfunction further enhances the effects of the altered flow pattern on the aortic wall remodelling as shown by Evangelista et al.[17] The sex differences in terms of dimensions of the

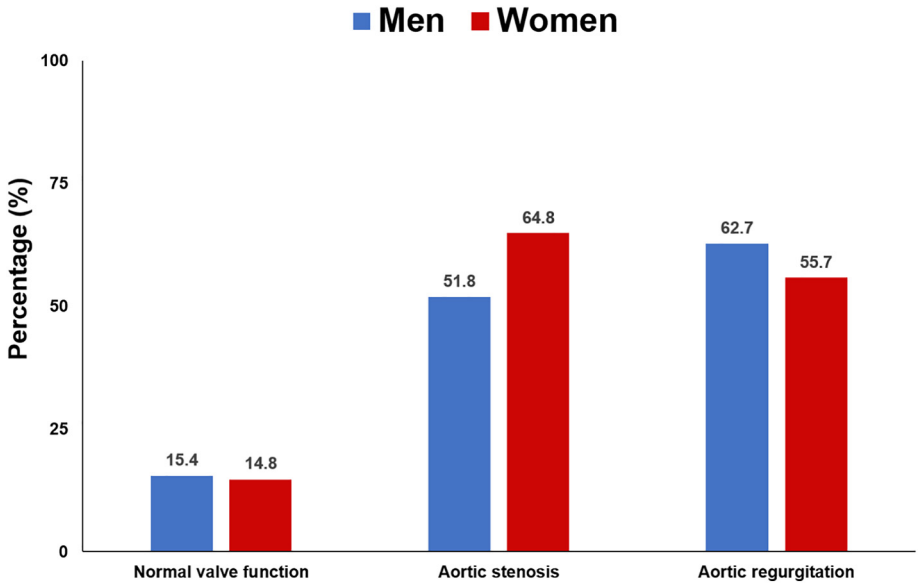

Fig. 1. Association between sex and types of aortic valve function in BAV population. This study by Kong et al. showed that men with BAV had more frequently aortic regurgitation at first presentation compared with women, whereas women presented more often with aortic stenosis compared to men.[7]

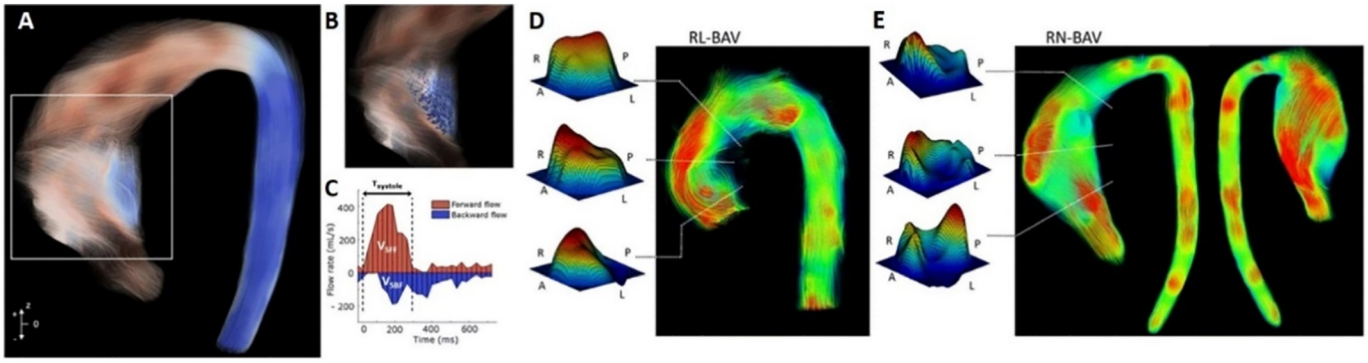

Fig. 2. Four-dimensional flow analysis with cardiovascular magnetic resonance in patients with BAV. Panels A, B, C. Systolic backward flow in a BAV patient. Red streamlines indicate forward flow in the ascending aorta, while blue streamlines indicate systolic backward flow. Panel D. Asymmetric outflow jet to the anterior wall in a right-to-left coronary cusp fusion BAV leading increasing shear stress and flow abnormality in the proximal (root) aorta. Panel E. Right-to-non coronary cusp fusion BAV with a posterior outflow jet shifting to the anterior wall at mid and distal ascending aorta leading to ascending aorta and arch dilation. Abbreviations: RL-BAV: right-left bicuspid aortic valve, RN-BAV: right-non coronary bicuspid aortic valve, VSBF: total systolic backward flow, VSFF: total systolic forward flow.
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various aortic segments and the presence of aortopathy have been described.[7] Women have smaller aortic annulus, root and sinotubular junction but not ascending aorta compared to men after adjustment for age, body surface area, hypertension, dyslipidaemia, smoking, diabetes mellitus, aortic valve dysfunction, and left ventricular ejection fraction (Fig. 3).[7] Michelena et al. also reported that men with BAV have larger absolute aortic dimensions and more frequently aortic aneurysm than women in their community, tertiary referral and surgical cohorts.[19] Similarly, Andrei et al. reported larger absolute aortic dimensions in men when compared to women (43.6 ± 7.9 mm versus 38.8 ± 9.3 mm, respectively; $P < .001$).[18] Furthermore, when describing the sex distribution of aortic dimensions according to established cut-off values into <40 mm, 40 to 44 mm, 45 to 49 mm, 50 to 54 mm, and ≥55 mm, Kong et al. reported that men had a significantly higher percentage of individuals with aortic dilation between 40 and 44 mm (24% versus 17%) and 45 to 49 mm (14% versus 9%) when compared to women ($P < .001$).[7]

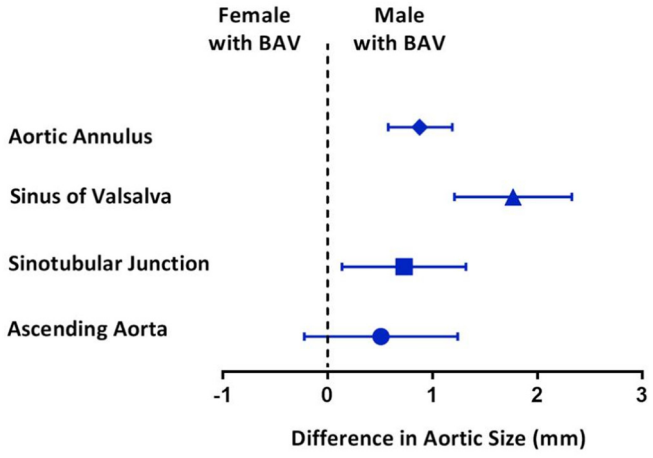

Fig. 3. Female patients with bicuspid aortic valve (BAV) have smaller aortic root dimensions. Absolute differences in various aortic dimensions between men and women with BAV after adjustment for age, body surface area, hypertension, dyslipidaemia, smoking, diabetes mellitus, aortic valve dysfunction, and left ventricular ejection fraction. Women have a smaller aortic annulus, sinus of Valsalva and sinotubular junction but not ascending aorta compared with male patients. Data are shown as mean with 95% confidence intervals.
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Some hypotheses have been proposed to explain why men with BAV show larger aortic dimensions and have more frequently aortic dilation as compared to women. First, the presence of undefined characteristics of the X chromosome that protect women from developing aortopathy has been shown.[26] For example, women with deficiency of X chromosome (Turner syndrome) have higher risk of BAV, aortic dilation, aneurysm and dissection than women with normal X chromosome.[27] Furthermore, Corbitt and colleagues reported the combined effect of a single copy of matrix metalloproteinases (TIMP) 1 and TIMP3 risk alleles further increased the risk of aortopathy in women with Turner syndrome (OR = 12.86, 95% CI = 2.57–99.39, $p = .004$).[28] The combination of X chromosome TIMP1 hemizygosity and variants of its autosomal paralogue TIMP3, significantly increase the risk of aortopathy in Turner syndrome.[28] There have been a few clinical and animal studies evaluating the contribution of sex hormones to the development of aortic dilation and aneurysm in the individuals with BAV.[29–31] There are some missing X-related factors that increase susceptibility to testosterone during early stages of development in an animal model.[31] Experimental models of aortic aneurysm indicated that administration of testosterone promotes aortic aneurysm formation, whereas estrogen could prevent this process through reducing extracellular matrix degrading enzymes.

Sex differences in endocarditis, dissection and mortality in BAV

Aortic valve endocarditis is ~17 times more prevalent in BAV patients as compared to the general population.[32] The frequency of BAV endocarditis has been estimated around 2%.[33,1,2,34]In a recent large BAV registry, the frequency of endocarditis among men and women was 4.5% and 2.5% respectively ($P = .037$).[4] Michelena et al. reported that 25-year rates of bicuspid endocarditis were 5 ± 2% for men and 0% for women ($P = .04$).[32] The reason of higher frequency of BAV endocarditis in men as compared to women remains unclear. It is important to acknowledge that, in general, endocarditis is also more frequently observed in men as compared to women and therefore individuals with BAV may not be an exception.[35]

Aortic dissection is the most critical and fatal complication in patients with BAV. In a previous study by Michelena et al., including 416 patients with BAV, aortic dissection occurred in 2 patients over a mean follow-up of 16 years, showing the low incidence of this complication but still significantly higher than in the general population.[6] However, there was no different rate of dissection between men and women. The study by Kong et al. reported a low incidence of aortic dissection and all cases occurred in men (0.6% vs. 0% for women $P < .001$).[7]

This could be explained by the sex differences in type of aortic dilation. Men show more frequently proximal ascending aorta dilation (root phenotype) which seems to be associated with higher risk of aortic dissection.[36,37] The root phenotype is associated with right-left cusp fusion, BAV-AR, and male sex, as well as possible higher risk of dissection. Therefore, careful adherence to current monitoring and referral guidelines is critical for (particularly male) BAV patients.[38]

In terms of overall survival, the direct comparison of three different cohorts of BAV population (community cohort, tertiary referral cohort and surgical referral cohort) showed no differences between men and women.[19] When the survival of those three cohorts was compared to the survival of the general population, women with BAV exhibited a significantly higher relative risk of mortality than men in both the tertiary and surgical referral cohorts. In addition, moderate and severe AR were independently associated with mortality in women of the community cohort whereas in the tertiary clinical referral cohort, lesser grades of AR were independently associated with mortality (particularly in women less than 45 years old). In the surgical referral cohort, severe AR and New York Heart Association class III-IV were independently associated with all-cause death after aortic valve replacement in women.[19] This new evidence should prompt early referral of BAV women with AR to specialized care with appropriate follow-up for timely referral for intervention.

Conclusions

There are still large gaps in understanding the pathophysiology of sex related bicuspid valvulopathy and aortopathy. Compared to women, men exhibited a higher risk of BAV related morbidity including AR, endocarditis, aortic dissection and aneurysm formation. AR was significantly more common in men whereas women presented more often with AS. There were no sex differences in aortic valve morphologies. Implementation of sex-specific treatment criteria for the BAV population should be encouraged to guarantee timely referral to treatment. Future research should emphasize sex-related differences since both sexes benefit from a tailored management with respect to timing of intervention and treatment modality.

Disclosures

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