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Aortic Dilatation Associated with Bicuspid Aortic Valve: Relation to Sex, Hemodynamics, and Valve Morphology (The NHLBI GenTAC Registry)

Mary J. Roman, MD[a], **Norma L. Pugh, MS**[b], **Richard B. Devereux, MD**[a], **Kim A. Eagle, MD**[c], **Kathryn Holmes, MD, MPH**[d], **Scott A. LeMaire, MD**[e], **Rita K. Milewski, MD, PhD**[f], **Shaine A. Morris, MD, MPH**[g], **Siddharth K. Prakash, MD, PhD**[h], **Reed E. Pyeritz, MD, PhD**[i], **William J. Ravekes, MD**[j], **Ralph V. Shohet, MD**[k], **Howard K. Song, MD, PhD**[l], **Federico M. Asch, MD**[m], and **for the Investigators GenTAC**

[a]Division of Cardiology, Weill Cornell Medicine, New York, NY

[b]Biostatistics and Epidemiology Division, RTI International, Rockville, MD

[c]Division of Cardiology, University of Michigan Health System, Ann Arbor, MI

[d]Department of Pediatrics, Oregon Health & Sciences University, Portland, OR

[e]Division of Cardiothoracic Surgery, Baylor College of Medicine, and Department of Cardiovascular Surgery, Texas Heart Institute, Houston, TX

[f]Division of Cardiothoracic Surgery, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA

[g]Division of Pediatric Cardiology, Department of Pediatrics, Baylor College of Medicine, Houston, TX

[h]Department of Internal Medicine, McGovern Medical School, University of Texas Health Science Center, Houston, TX

[i]Department of Medicine, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA

[j]Department of Pediatrics, Johns Hopkins University School of Medicine, Baltimore, MD

[k]Department of Medicine, John A. Burns School of Medicine, Honolulu, HI

[l]Division of Cardiothoracic Surgery, Oregon Health & Sciences University, Portland, OR

[m]MedStar Health Research Institute, Washington, DC

Abstract

Corresponding author: Mary J. Roman, MD, Division of Cardiology, Weill Cornell Medicine, 520 East 70th Street, New York, NY, 10021. Telephone: 646-962-4733. FAX: 212-746-8561. mroman@med.cornell.edu.

This study analyzed the impact of sex, hemodynamic profile and valve fusion pattern on aortopathy associated with bicuspid aortic valve (BAV). The NHLBI GenTAC Registry provided comprehensive information on a large population of well-characterized patients with BAV. Of 969 enrolled patients with BAV, 551 (57%; 77% male) had already undergone valvular and/or aortic surgery. Echocardiographic imaging data were available on 339 unoperated or pre-operative participants who form the basis of this study. BAV function was normal in 45 (14%), with predominant regurgitation (AR) in 127 (41%), and predominant stenosis (AS) in 76 (22%). Moderate-severe AR was associated with larger sinuses of Valsalva (SOV) diameters compared to normal function and AS (all $p<0.01$). Moderate-severe AS was associated with larger AscAo diameter compared to normal function ($p=0.003$) but not to AR. SOV diameter was larger in men than women (3.7±0.7 vs. 3.3±0.6 cm, $p<0.0001$), whereas ascending aortic (AscAo) diameters were comparable (3.9±0.9 vs. 3.7±0.9 cm, $p=0.08$). Right-left commissural fusion was associated with larger SOV diameter (3.7±0.7 vs. 3.3±0.6 cm, $p<0.0001$) compared to right-noncoronary fusion pattern. Predominant AR was more common in men (45% vs. 27%, $p=0.004$) whereas AS was more common in women (29% vs. 18%, $p=0.04$). In conclusion, in the GenTAC Registry, AR was associated with diffuse (annular, SOV and AscAo) enlargement whereas moderate-severe AS was only associated with AscAo enlargement. Male sex and right-left cusp pattern of cusp fusion were associated with larger SOV diameters and greater likelihood of AR, whereas females had a higher prevalence of AS.

Keywords

bicuspid aortic valve; aortic aneurysm; aortic regurgitation; aortic stenosis

Bicuspid aortic valve (BAV) is the most common form of congenital heart disease, occurring in about 0.5-2% of all live births (1,2) and having a distinct male predominance (~3:1) (2-4). In about 9% of cases, there appears to be a genetic basis for BAV (5). Sex differences in BAV have been reported, primarily in surgical series (6,7), including higher prevalences of aortic regurgitation (AR) in men and of aortic stenosis (AS) in women. Aortic dilatation is a prominent feature of BAV and (8-12), and increases in aortic dimensions are already apparent in the pediatric population (2,4,13,14). The potential impacts of altered hemodynamics (6,9,11,15) and type of cusp fusion (6,16,17) on presence and location of aortic dilatation have been examined in several studies with inconsistent results. The NHLBI-sponsored National Registry of Genetically Triggered Thoracic Aortic Aneurysms and Cardiovascular Conditions (GenTAC) offers an opportunity to examine the effects of sex, hemodynamics and valve morphology on extent and location of aortic dilatation in BAV by providing comprehensive information on a large population of well-characterized patients.

Methods

The rationale and design of the GenTAC registry have been previously described (18). In brief, GenTAC was established as a longitudinal observational cohort study of individuals with genetically-triggered thoracic aortic aneurysm. Between 2006 and 2014, 3763 participants were enrolled in the original 6 centers (Johns Hopkins University, Baylor

College of Medicine, Oregon Health & Sciences University, University of Pennsylvania, University of Texas-Houston, Weill-Cornell Medical College) and in 2 additional centers (National Institute of Aging-Harbor Hospital, Queen's Medical Center) added in the second phase (19). Standardized data collection included clinical information, patient questionnaire, imaging studies, and details of surgical interventions. Institutional Review Board approval was obtained for this study at each of the 8 participating GenTAC clinical centers. Individual informed consent was obtained from each GenTAC Registry patient.

At the conclusion of registry enrollment (December 31, 2013), 969 patients with bicuspid aortic valve (BAV) and no syndromic diagnosis had been enrolled in GenTAC, including 738 (76%) males and 231 females. At time of enrollment, 551 (57%; 76% male) had already undergone surgery. Echocardiographic imaging data was available for 339 patients (267 unoperated and 72 [21%] pre-operative) who serve as the basis for the current analyses.

During the second phase of GenTAC (19), an imaging core lab (iCORE; MedStar Health Research Institute, Washington DC) was established (20). All available echocardiographic imaging studies were de-identified and analyzed by cardiologists using a standardized measurement protocol. Given the longitudinal nature of the registry and ongoing enrolment following establishment of the imaging core lab, studies may have been performed before, at time of, or following enrolment. Analyses at the iCORE was performed with Philips Xcelera or Digisonics DigiView workstations. Multiple imaging modalities (echocardiography, computed tomography, magnetic resonance) and both pediatric and adult studies were analyzed by the core lab. Given differences in measurement technique across modalities and pediatric vs. adult populations, the GenTAC Imaging Experts Committee made the prospective decision to analyze all aortic images according to a standard protocol, using an inner edge-to-inner edge technique at end systole at pre-specified locations, including the anulus, sinuses of Valsalva (SOV), and ascending aorta. Aortic dimensions were reported as absolute values and as Z scores (root and ascending aorta) after adjustment for differences in age, sex and body size, using published equations (21-23).

Aortic valve morphology was characterized as fusion of the right and left or right and non-coronary cusps; fusion of the left and non-coronary cusps was not encountered. Complete Doppler assessment was available in 312 patients. The severity of aortic regurgitation (AR) and aortic stenosis (AS) was quantified using established criteria (24,25). Predominant AR and AS were defined as AR or AS being either the sole hemodynamic abnormality or greater than the degree of the other abnormality, e.g., severe AS and mild AR would be categorized as predominant AS. When severity of AR and AS was identical, the hemodynamic profile was categorized as mixed AS/AR.

Demographic and phenotypic characteristics of males and females with BAV were compared using generalized linear models for continuous variables and chi-square tests for categorical variables. Data are presented as mean values with standard deviation as the index of dispersion. Generalized linear models to examine differences of least square means were used to determine associations of aortic dimensions with hemodynamic profile and/or valve morphology and in multivariable analyses.

Results

Demographics, aortic dimensions, and hemodynamics in 259 males and 80 females are compared in Table 1. The two groups were comparable in age, but males had significantly higher average systolic blood pressure and body size than females. Anular diameters and both absolute diameters and Z scores of the SOV were significantly larger in males than females, whereas dimensions of the ascending aorta were comparable. 36% of patients had dilated SOV (Z score≥2) with a higher prevalence of dilatation in males than females. 73% of patients had dilated ascending aortas (Z score≥2) with no sex difference in prevalence. Valvular function was normal in 14% of this largely-unoperated study population. AR was more common in males with BAV whereas AS was more common in women.

The association of altered aortic valve function with extent and location of aortic dilatation is examined in Table 2. Anular diameters were significantly larger in patients with AR compared to normal valve function and significantly higher in those with moderate-severe AR compared to both AS groups. SOV diameters were highest in those with AR and significantly higher than in those with AS, particularly when reported as Z scores. Ascending aortic diameters were likewise highest in those with AR but not larger than those with moderate-severe AS. These differences were lessened by comparison of Z scores (with wide standard deviations).

Because of the association of AR with larger diameters as well as with male sex, the sex comparisons in aortic root diameter were adjusted for the presence and severity of AR. The difference in absolute diameter of the SOV between males and females remained significant (3.75 vs. 3.35 cm, $p<0.0001$).

The predominant pattern of cusp fusion was right-left (77%), which was more common in males than females. SOV diameter, both absolute and expressed as a Z score, was significantly larger in those with right-left compared to right-noncoronary fusion, whereas diameters of the annulus and ascending aorta did not differ (Table 3). Although there were no significant differences in aortic valve function between the two patterns, there was a trend toward a higher percentage of predominant AS patients to have right-noncoronary fusion ($p=0.07$).

Discussion

The GenTAC Registry provides an opportunity to examine aspects of BAV-associated aortopathy in a large, geographically-diverse population of adults and children characterized using a standardized approach to phenotypic features and aortic imaging (18,19). The population includes varying hemodynamic profiles of aortic valve function and many unoperated patients, and is representative of the ~3:1 male predominance noted in other large studies.

Although aortic enlargement is now well-documented in large BAV populations through use of non-invasive imaging, the impact of superimposed valve dysfunction is thought to be an important factor in progressive dilatation. In the GenTAC population, AR was associated with markedly higher in annular, SOV and ascending aortic dimensions, even after adjustment for body size given the male predominance noted in AR. This observation has been reported in most previous echocardiographic studies (9,11,15).

A direct relation of aortic diameters to the severity of AR noted in this study is similar to that noted in some earlier studies (9,15) but not in others with lower prevalences of significant AR (11). The progressive increase in absolute left ventricular stroke volume needed to maintain net cardiac output in the presence of chronic, progressive AR, superimposed on underlying degenerative changes within the aortic wall (27), is thought to account for this phenomenon.

Aortic aneurysms associated with AS have traditionally been considered to be 'post-stenotic' due to the chronic impact of the high-velocity turbulent transaortic jet on the aortic wall. To the extent that BAV is a common cause of AS, the association of BAV with aortopathy unrelated to AS was not fully appreciated until non-invasive echocardiographic imaging in large samples demonstrated aortopathy independent of hemodynamic profile (8-12). Nevertheless, as with AR, the superimposed hemodynamics of AS may further impact the aorta, primarily the ascending aorta and only in the setting of moderate-severe AS, as noted in the GenTAC population. Support for this observation is provided by a recent 4D flow magnetic resonance imaging study of 20 BAV patients undergoing aneurysm resection wherein regional differences in wall shear stress correlated with extent of medial elastin degeneration (28). In contrast to our findings, two surgical series actually reported either no (15) or a negative (6) relation between AS severity and aortic dimensions.

In addition to the known male predominance of BAV, our study noted several striking sex differences in patients with BAV. SOV diameters were much larger in males, even after adjustment for differences in body size and for degree of AR. Larger diameters in males have been noted in previous studies, with significance either eliminated after adjustment for body size (6) or adjustment not performed (17,26). The higher prevalences of associated AR in males and AS in females noted in the current study has not been reported, to our knowledge, possibly due to lower prevalences of significant valve dysfunction in previous echocardiographic studies.

In surgical series with much higher prevalences of AS than AR compared to the present study, AR was noted to be more common in males than females (6,7). Males were also more likely to have fusion of the right and left coronary cusps than were females in our study, similar to earlier findings in 191 adult patients with BAV (16). By contrast, in a largely surgical Korean series, there were no sex differences in valve morphology (29).

The pattern of cusp fusion was right-left in 77%, similar to previous reports. In addition, we noted SOV, but not ascending aortic, diameters to be significantly larger in right-left fusion, even with correction for body size, given the male predominance in right-left fusion. Although the overall hemodynamic profile did not differ between the two cusp fusion morphologies, we noted a trend toward more AS in the right-noncoronary fusion pattern.

The relations of pattern of cusp fusion in BAV to hemodynamic profile and aortopathy has been examined in several reports. A surgical series of 334 patients noted more AR in the right-left fusion group (54 vs. 32% with right-noncoronary fusion) (6). Another largely surgical series noted more AR in the right-left fusion group (32 vs. 7%) and more AS in the right-noncoronary fusion group (66 vs. 46%). However, in a large pediatric series, Fernandes et al. noted both AS and AR to be more common in the right-noncoronary fusion pattern (odds ratio 2.4 for both) (3).

A potential limitation of the current study is the lack of native aortic imaging data on the GenTAC BAV participants who were enrolled after valve and/or aneurysmectomy surgery. However, the study does contain patients over a wide age range with a substantial minority of operated patients with pre-operative imaging, thus expanding the applicability beyond those studies that are exclusively under adult or pediatric clinical care or are exclusively surgical cohorts. In addition, standardized and blinded interpretation of all imaging studies by a central imaging core is a major strength of our multi-center cohort (20).

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Table 1

Comparison of Males and Females with Bicuspid Aortic Valve

Variable	Male (n=259 [76.4])	Female (n=80 [23.6])	P value
Enrollment Age (range; years)	42±21 (0.3 – 79)	38±21 (2 – 78)	0.11
Adult (≥18 years)	210 (81%)	60 (75%)	0.238
Enrollment systolic pressure (mmHg)	122±16	117±15	0.02
Enrollment diastolic pressure (mmHg)	71±12	71±10	0.65
Enrollment body surface area (m^2)	1.9±0.44	1.6±0.35	<0.0001
Annulus (cm)	2.65±0.53	2.38±48	<0.0001
Sinuses of Valsalva diameter (cm)	3.90±0.71	3.34±0.59	<0.0001
Ascending aorta diameter (cm)	4.01±0.88	3.86±0.91	0.11
Sinuses of Valsalva Z score	2.2±2.3	1.5±2.0	0.004
Sinuses of Valsalva Z score≥2	49%	34%	0.0083
Ascending aorta Z score	3.2±2.0	3.6±2.3	0.07
Ascending aorta Z score ≥2	76%	76%	0.9395
Hemodynamic Profile*			0.007
Normal	13%	18%	0.25
Predominant aortic regurgitation	45%	27%	0.004
Predominant aortic stenosis	19%	29%	0.04
Mixed aortic stenosis/aortic regurgitation	17%	13%	0.51
Aortic coarctation	6%	12%	0.05

*Predominant aortic regurgitation and aortic stenosis were defined as regurgitation or stenosis being either the sole hemodynamic abnormality or greater than the degree of the other abnormality.

Table 2

Comparison of Aortic Diameters Based on Hemodynamic Profile

Hemodynamic Profile**	Normal	Mild Stenosis	Moderate-Severe Stenosis	Mild Regurgitation	Moderate-Severe Regurgitation	P value
Age at image (years)	28±21	43±20	49±18†	39±18*	39±15*	<0.0001
Annulus (cm)	2.08 ± 0.43	2.20 ± 0.29	2.31 ± 0.42	2.45 ± 0.49†	2.62 ± 0.39†‡	<0.0001
Sinuses of Valsalva diameter (cm)	3.21 ± 0.84	3.33 ± 0.58	3.48 ±0.64	3.74 ± 0.67†	3.93 ± 0.54†‡	<0.0001
Ascending aorta diameter (cm)	3.23 ± 0.86	3.80 ± 0.71	3.96 ± 0.82†	3.90 ± 0.79†	4.10 ± 0.91†	<0.0001
Sinuses of Valsalva Z score	1.6 ± 1.8	0.4 ± 1.5	0.8 ± 1.5	1.9 ± 2.0‖	2.3 ± 1.9‡	0.0001
Ascending aorta Z score	2.6 ± 1.6	2.8 ± 1.6	3.1±1.6	3.2 ± 2.0	3.4 ± 2.2	0.16

** Predominant aortic regurgitation and aortic stenosis were defined as regurgitation or stenosis being either the sole hemodynamic abnormality or greater than the degree of the other abnormality.

* p=0.05 vs. normal;

† p<0.001 vs. normal;

‡ p<0.01 vs. both AS groups;

§ p<0.01 vs. normal;

‖ p<0.05 vs. moderate-severe aortic stenosis.

Table 3
Comparisons Based on Valve Morphology

Variable	Right-Left Fusion n=203	Right-Non Fusion n=57	P value
Male	76%	61%	0.03
Annulus (cm)	2.40 ± 0.42	2.34 ± 0.44	0.359
Sinuses of Valsalva diameter (cm)	3.68 ± 0.67	3.27 ± 0.58	<0.0001
Ascending aorta diameter (cm)	3.88 ± 0.92	3.69 ± 0.65	0.157
Sinuses of Valsalva Z score	1.7 ± 1.8	0.8±1.7	0.002
Ascending aorta Z score	3.0 ± 1.9	3.3 ± 1.7	0.262
Hemodynamic Profile *			0.52
Normal	86%	14%	
Predominant aortic regurgitation	82%	18%	
Predominant aortic stenosis	69%	31%	

* Predominant aortic regurgitation and aortic stenosis were defined as regurgitation or stenosis being either the sole hemodynamic abnormality or greater than the degree of the other abnormality.