Prevalence of Bicuspid Aortic Valve and Associated Aneurysmal Pathology in Patients Undergoing Echocardiography

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Abstract

Objective: Reports of prevalence and clinical significance of bicuspid aortic valve (BAV) disease are variable. We assessed our institutional echocardiography (ECHO) database to understand the reported prevalence of BAV and its potential association with thoracic aortic aneurysm disease (TAAD). Methods: All ECHOs of adult patients (>18 years) performed at a single institution between calendar year 2013 to 2018 were reviewed. BAV patients were categorized by age group (Young age:18-39 years; Middle age:40-65 years; Old age: >65years) to assess for aortic valvulopathy and TAAD. Logistic regression analysis was performed to understand association of BAV with TAAD. Results: Of 48,503 unique patient ECHOs, 245 (0.51%) described a diagnosis of BAV, with 93(40%) concomitant TAAD. Increased association with endocarditis (p=0.01) and severe aortic insufficiency (p=0.005) was seen in the Young group. Ascending aortic diameter was significantly higher in the Middle compared to the Young group (p<0.001), but similar to Old group. On multivariable regression, BSA(OR=7.31(2.27-23.57)) and age (OR=1.02(1.00-1.04)), but not BAV dysfunction (OR1.07(0.51-2.26)) were associated with TAAD. Conclusions: In this large cross-sectional ECHO study, reported BAV prevalence was 0.51%. We found high association of BAV with concomitant TAAD especially in patients greater than 40 years of age. This suggests that more frequent aortic surveillance may be warranted in the middle and old age BAV subjects.

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Running head: Bicuspid aortopathy; age prevalence

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Conclusions: In this large cross-sectional ECHO study, reported BAV prevalence was 0.51%. We found high association of BAV with concomitant TAAD especially in patients greater than 40 years of age. This suggests that more frequent aortic surveillance may be warranted in the middle and old age BAV subjects.

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INTRODUCTION

BAV is the most common congenital anomaly of the heart with a prevalence that ranges from 0.5% to 2%. (1-3) Its association with other congenital cardiac anomalies is well established and associated anomalies are often the cause of early disease diagnosis during childhood.(4) But when BAV is isolated, it has minimal progression during childhood (5) and usually presents later in life with either valvulopathy or aortopathy. The valvulopathy associated with BAV can present itself as insufficiency, stenosis or a mixed disease.(6, 7) Severity of valvulopathy varies between mild and non-significant to moderate or severe valve dysfunction.(3, 8) The associated aortopathy is variable in terms of the size of the aorta and it's a atomic location. Patients with BAV might have normal sized aorta or aneurysm/ectasia of the aortic root, ascending aorta, or both.(9, 10) The aim of this study was to assess the reported prevalence of BAV in a large Echocardiography (ECHO) database and to better understand the presentation of BAV in different age groups, the risk factors for thoracic aortic aneurysms and the surgical intervention stratified to each age group.

METHODS

Database and patient population . Yale-New Haven Hospital is a tertiary care center in the United States. Institutional electronic medical record system was queried to identify patients with age [?] 18 years old who had an ECHO for any indication from calendar year 2013 to 2018, either as an in inpatient, outpatient, or during an emergency department visit. ECHO reports were searched for a diagnosis of BAV. Patients were categorized according to their age at time of presentation: Young age group (18 to <40 years old), Middle age group (40 to 65 years old), and Old age group (>66 years old). Medical records of identified BAV patients were further reviewed for associated valve disease, aortic aneurysm disease and any surgical intervention offered for these problems. The Institutional Review Board at Yale University approved this study.

Patient characteristics . Age, height, and weight indicated values were recorded at the time of the ECHO. Race was categorized into Caucasian, African American, Asian, and other. Smoking was defined by more than 5 years of smoking. Comorbidities (hypertension, diabetes, dyslipidemia, congestive heart failure, chronic kidney disease, myocardial infarction, chronic obstructive pulmonary disease) were chosen

as commonly evaluated cardiovascular comorbidities and were defined using ICD-10 codes. To define aortic aneurysm, a 4 cm cut-off value was used for aortic root, ascending aorta and aortic arch.

Statistical analysis . Differences in the patient characteristics were compared with one-way ANOVA followed by Tukey test for continuous variables and Chi-square for trend test followed by pair-wise comparison when there was a difference for categorical variables. Multivariable logistic regression model was fitted to identify risk factors for aortic aneurysm or dilatation and the model included the following variables: age, sex, BSA, history of hypertension, diabetes, dyslipidemia, years of smoking, moderate or severe aortic valve stenosis and moderate or severe aortic insufficiency. P value of <0.05 and 95% confidence interval (CI)were used to define statistically significant difference. Analysis was conducted using Microsoft excel 2019 and Prism 8.2 (GraphPad Software, San Diego, CA) for simple analysis and SAS 9.4 (SAS Institute Inc, Cary, NC) for modelling.

RESULTS

Prevalence of BAV . In this cohort of 48,503 unique patients aged ^{3} 18 years who underwent ECHO for any clinical indications, BAV was present in 0.51% (n=245 patients). Of all the BAV patients identified, 17.1% (N=41) patients presented in a Young age group, 58% (N=143) in the Middle age group, and 24.5% (N=64) in the Old age group.

Demographics and comorbidities . Male sex (65-72%) and Caucasian race (71.4-85%) were predominant across all age groups. Other races were more likely to present in younger age. BMI and BSA were higher in middle age compared to the older age group. In general, comorbidities corresponded with age except for stroke (19.5 % versus 7% versus 13.3%, P=.3159) and CHF (4.8% versus 7% versus 13.3%, P=0.2191) which were not different across the age groups. (Table 1)

Valvulopathy . Endocarditis (9.5% versus 2.8% versus 0%) and severe AI (11.9% versus 4.2% versus 0%) trended towards higher incidence in young age group with a statically significant difference between young and older age groups. Moderate AI and moderate AS were not different across the age groups. Severe AS was higher in middle and older age group but not statistically different from younger age group (0% vs 9.8% vs 10%, P=0.0991). Combined AV dysfunction was not statistically different across the age groups (0% vs 7% vs 3.3%, P=0.6056). (Table 2)

Aortopathy . Aortic root size (3.1 ± 0.6 cm versus 3.5 ± 0.6 cm versus 3.6 ± 0.6 cm, P<0.0001) and ascending aorta size (3.5 ± 0.8cm versus 4.0 ± 0.7cm versus 4.1 ± 0.6cm, P=0.0008) were higher in the middle and older age groups compared to the younger age group but there was no difference in the root or ascending aortic size between the middle and older age groups. (Table 2) Plotting the root/height index against age showed gradual increase with age that slows down or stops in the older age group. Similar pattern was seen when ascending aorta/height index was plotted against age. (Figures 1 and 2)

To define independent risk factors for TAA and dilatations, a multivariable logistic regression analysis was performed. The model included patient's age, male sex, BSA, smoking, hypertension, hyperlipidemia, moderate or higher aortic valve stenosis, moderate or higher aortic valve insufficiency and left ventricular ejection fraction. Age (OR = 1.02 CI[1.00-1.04]) and BSA (OR = 7.31 [2.27-23.57]) were the only independent risk factors for TAA, while male sex, smoking, HTN, HLD, moderate or higher aortic valve stenosis, moderate or higher aortic valve insufficiency and left ventricular ejection fraction were not independent risk factors for TAA in this model. (Table 3)

Surgical intervention following diagnosis with BAV . 27% (N=66) had surgical intervention following ECHO diagnosis with BAV. 50% of the surgical intervention were aortic valve only. 12% of the patients had aortic (root or ascending) replacement only and 32% of patients had combined aorta and valve replacement. There was no statistically significant difference in the rates of intervention or types of intervention across age groups. (Table 2)

DISCUSSION

In this study of 48,503 patients aged [3] 18 years undergoing echocardiography,, we found the reported incidence of BAV to be 0.51%. In the literature, reported incidence of BAV incidence of BAV ranges between 0.4% to 2.25%. (11) Given the variability in BAV detection using current imaging techniques, autopsy studies can provide a reliable estimate of disease burden. In an autopsy study of 9966 cases from London Hospital published in 1938, incidence of BAV was 0.52%.(12) In a retrospective cohort study published in 2011 comprising of 41,687 cohorts undergoing echocardiography, Michelena et al., reported presence of BAV in 1% of the studied population.(13) In the same paper, published in JAMA, 20% of the diagnosed patients with BAV were less than 18 years of age. This was not a true population-based study as cohorts were chosen for echocardiography based on any cardiac disease history, or presence of positive auscultatory findings. In an echocardiographic survey of 817 apparently healthy primary school children, incidence of bicuspid aortic valve was 0.5%.(14) BAV runs a benign course during early life and most of the patients remain asymptomatic until their middle age, when abnormal shear stress due to altered valve geometry and inherent aortic wall defect likely starts to take its toll. We divided our study population in three groups namely, young age group (>18 and <40 years old), middle age group (>40 and <60 years old), and old age group (>60 years old). We used this stratification system based on the literature which suggests that most of the major events related to BAV occur between 40 and 60 years of age. In a study by Elefteriades group, in which they reported incidence of BAV in known patients of ascending aortic aneurysm being followed clinically.(15) Mean age at presentation in their study was 49 years. In an autopsy study of deceased with bicuspid aortic valve, mean age at the time of death was 46 years.(16) In a community based study, Michelena et al showed that 40% of cardiac events in a patient with BAV occur at a mean age of 52 years. (17) In our study, 58% of patients with BAV were first identified in the middle age group (40-65 years). We also found out that increased BSA was an independent risk factor for aneurysm formation. We know that increased BSA and BMI will demand increased flow across the BAV possibly leading to more shear stress on the valve leaflet and inherently deficient aortic wall. Theoretically this can confront us on two fronts. First, increased turbulence in the aorta and shear stress on the aortic wall could potentially lead to increased rate of aortic dilatation. Secondly, it can hasten the process of valvulopathy, and especially in the case of aortic stenosis, can give rise to higher gradient across the valve and hence potential early intervention.

In our study, 65-72% of patients with BAV, identified across all age groups, were of male sex. A cohort study from Toronto using echocardiography to identify patients with BAV reported that 64% to 80% of patients with BAV were of male sex.(18) Michelena et al., in their population-based study from Olmsted County, also reported that 69% of patients identified to have BAV were of male sex.(13)

Osler in 1886, first reported susceptibility of BAV for IE in his autopsy study of over 800 patients.(19) Incidence of endocarditis was 3.2% in our study group, with a significantly higher incidence in the young age group compared to the older age group (9.5% versus 0%), which could be related to IVDA in this age group. We also identified the same trend for severe AI, with significantly higher trend in young age group when compared with old age group (11.9% versus 0%).The risk of native valve endocarditis in patients with BAV is much higher than patients with tricuspid aortic valve,(20) and it tends to affect younger population, mostly undiagnosed BAV patients, and also runs a more aggressive course, with significantly more peri-annular abscess formation(21, 22).

17% of patients in our study had moderate or severe AI, with a significantly higher prevalence of severe AI in the young age group compared to the old age group. This is interesting because we know that one important contributing factor for AI in BAV is annular dilatation and effacement of sino-tubular junction. Since BAV is a progressive disease, one would anticipate that there would be higher incidence of severe AI in the old age group. This signifies the relevance of other factors like leaflet asymmetry and prolapse also impacting the progression of valvulopathy. In a database review of 158 young male (mean age of 18 years) diagnosed with BAV, 12.6% were found to have moderate to severe AI.(23) Same study also showed that those young males with AI had significantly enlarged aortic root and ascending aorta. In contrast to that, in our study we found that aortic root and ascending aortic diameter were significantly higher in the Middle and Old age group when compared with the Young age group. This is important because larger aorta at the baseline is a risk factor for progressive dilatation of the aorta.(24) In a retrospective study of 50 patients

with BAV, ascending aortic dimeter greater than 34 mm at baseline was a risk factor for significantly higher rate of aneurysm formation.(25) In Olmsted County study, during a follow up of 416 patients with BAV, risk of development of aortic aneurysm was 26% at 25 years, with baseline aortic diameter greater than 40 mm being a risk factor for aneurysm formation.(13) Same study also reported increased incidence of aortic dissection (0.5% per year) in patient with aortic aneurysm and BAV. In our study, 40% of patients diagnosed with BAV had concomitant ascending aortic aneurysm. However, distribution of patients with aortic root or ascending aortic aneurysm were not significantly different across the three defined age groups.

We also found that ascending aorta/height index and aortic root/height index increased with age especially in Middle age group, but this growth was not seen in the Old age group other than small number of outlier subjects. An echocardiography study of 280 BAV patients also reported that prevalence of ascending aorta dilatation across various age groups increased consistently till the age of 60 years followed by a decline.(26) This argues against aortic intervention for elderly patients with BAV and dilated aortas less than 5.5 cm as the rate of growth probably will slow down.

CONCLUSION

In this large single institution cross-sectional ECHO study, prevalence of BAV was 0.51%. There was a high association with concomitant ascending aortic aneurysm (40% of patients). 58% of patients at the time of diagnosis of BAV were between 40 and 60 years of age. Incidence of IE and severe AI in patients with BAV was significantly higher in young age group, whereas severe aortic stenosis had a higher incidence after age 40. Using multivariable logistic regression model, age and increased BSA were identified as risk factors for aortic aneurysm development.

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Table 1. patient characteristics

	Young age (18-<40 years old) N=42 (17.1%)	**Middle age (40-65 years old) N=143 (58.4%)**	**Old age (>=66 years old) N=60 (24.5%)**	**P**
Age (years)	31±5.7[2,3]	55±6.9[1,3]	75±7.8[1,2]	<.0001
Male sex (%)	29 (69)	103 (72)	39 (65)	0.5779
Race Caucasian (%)	30 (71.4)	112 (78.3)	51 (85)	0.0076*

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Race African American (%)	2 (4.8)	19 (13.3)	7 (11.7)	
Race Other(%)	10 (23.8)[2,3]	12 (8.4)	2 (3.3)	
BSA (m^2)	1.99±.33	2.05±.27[3]	1.91±.24	0.0046*
BMI (kg/m^2)	28±6.3	30±6.3[3]	26±5.5	0.0008*
Smoking (%)	6 (14.3)[3]	39 (27.3)	22 (36.7)	0.0133*
DM (%)	0[2,3]	25 (17.5)	14 (23.3)	0.005*
Hypertension (%)	11 (26.6)[2,3]	75 (52.4)[3,1]	51 (85)[1,2]	<0.0001*
Hyperlipidemia (%)	2 (4.8)[2,3]	39 (27.3)[3,1]	30 (50)[1,2]	<0.0001*
CKD (%)	0[3]	11 (7.7)[3]	11 (18.3)	0.0011*
Stroke (%)	4 (9.5)	10 (7)	8 (13.3)	0.3519
Atrial fibrillation (%)	2 (4.8)[3]	13 (9.1)[3]	15 (25)	0.0024*
CAD (%)	0[2,3]	25 (17.5)	19 (31.7)	0.0003*
COPD (%)	0[3]	9 (6.3)	8 (13.3)	0.0303*
PVD (%)	0	5 (3.5)	2 (3.3)	0.475
CHF (%)	2 (4.8)	10 (7)	8 (13.3)	0.2191
Ejection fraction (%)± SD	57.8±10.4[3]	58.6±11	54.6±11.8	0.0244*

BSA: Body Surface Area, BMI: Body Mass Index, DM: Diabetes Mellitus, CKD: Chronic Kidney Disease, CAD: Coronary Artery Disease, COPD: Chronic Obstructive Pulmonary Disease, PVD: Peripheral Vascular Disease, CHF: Congestive Heart Failure, *: statistically significant difference between the groups on post-hoc analysis, with [1]: young age group, [2]: middle age group and[3]: old age group.

Table 2. Clinical presentation of BAV patients in different age groups

	Young age (18-<40 years old) N=42 (17.1%)	**Middle age (40-65 years old) N=143 (58.4%)**	**Old age (>=66 years old) N=60 (24.5%)**	**P**
Root size ± SD (cm)	3.1 ± 0.6[2,3]	3.5 ± 0.6	3.6 ± 0.6	<0.0001*
Ascending size ± SD (cm)	3.5 ± 0.8[2,3]	4.0 ± 0.7	4.1 ± 0.6	0.0008*
Endocarditis (%)	4 (9.5)[3]	4 (2.8)	0 (0.0)	0.0101*
Moderate AI (%)	7 (16.7)	17 (11.9)	8 (13.3)	0.6895
Severe AI (%)	5 (11.9)[3]	6 (4.2)	0 (0.0)	0.0052*
Moderate AS (%)	4 (9.5)	24 (16.8)	6 (10.0)	0.8859
Severe AS (%)	0 (0.0)	14 (9.8)	6 (10.0)	0.0991

	Young age (18-<40 years old) N=42 (17.1%)	**Middle age (40-65 years old) N=143 (58.4%)**	**Old age (>=66 years old) N=60 (24.5%)**	**P**
Combined AV dysfunction (%)	0 (0.0)	10 (7.0)	2 (3.3)	0.6056
Root or ascending 4-5 cm (%)	10 (23.8)	61 (42.7)	22 (36.7)	0.2886
Root or ascending>=5 cm (%)	1 (2.4)	10 (7.0)	4 (6.7)	0.4301
Post-ECHO surgical intervention	**Post-ECHO surgical intervention**	**Post-ECHO surgical intervention**	**Post-ECHO surgical intervention**	**Post-ECHO surgical intervention**
All intervention (%)	11 (26.2)	44 (30.8)	11 (18.3)	0.276
Valve surgery only (%)	5 (11.9)	24 (16.8)	4 (6.7)	0.7017
Aorta surgery only (%)	1 (2.4)	6 (4.2)	1 (1.7)	0.7417
Valve and aorta surgery (%)	5 (11.9)	14 (9.8)	6 (10.0)	0.7829

SD: standard deviation, AI: aortic insufficiency, AS: aortic stenosis, AV: aortic valve.

*= post hoc analysis showing statistical significance between the groups: young age group[1], middle age group[2] and old age group[3].

Table 3. Predictors of ascending aortic or root diameter[?] 40 mm on multivariable logistic regression analysis

Effect	**OR**	**95% CI**	**P**
Male	1.57	0.80-3.08	0.1924
Smoking	0.92	0.48-1.74	0.7893
Aortic stenosis	1.01	0.53-1.92	0.9987
HTN	0.81	0.44-1.49	0.5009
DM	0.83	0.39-1.75	0.6255
HLD	0.92	0.49-1.75	0.8028
Aortic insufficiency	1.07	0.51-2.26	0.8587
BSA	7.31	2.27-23.57	0.0009
EF	0.99	0.96-1.01	0.2401
Age	1.02	1.00-1.04	0.0433

Figure Legends:

Figure 1. aortic root/height index plotted against age

Figure 2. ascending aorta/height index plotted against age