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Misclassification of Bicuspid Aortic Valves is Common and Varies by Imaging Modality and Patient Characteristics

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Abstract

Background: Bicuspid aortic valve (BAV) is the most prevalent adult congenital heart defect. BAV causes lifelong progressive disease that can be prevented by early diagnosis and long-term surveillance, but may be compromised by misclassification of valve morphology.

Methods: The study population was derived from the UTHealth Bicuspid Aortic Valve Registry, which includes serial images on more than 200 participants over a mean follow-up interval of 2.8 years. We abstracted descriptions of aortic valve morphology from transthoracic or transesophageal echocardiography, computed tomography angiography and magnetic resonance angiography reports. We used chi-square and t-tests to determine associations between reported valve morphologies (definitely bicuspid, possibly bicuspid, tricuspid, or uncertain) and clinical characteristics and assessed image quality using a validated tool.

Results: 40% of participants were misclassified in at least one imaging report. The mean interval between misclassification and correct diagnosis was 22 months. TEE, MR and CT were more sensitive than TTE and successfully reclassified 20% of participants, but were only used in 14% of patients. Misclassification was associated with age, the extent of valve calcification and image quality, but was not significantly associated with aortic regurgitation, gender, or cusp configuration.

Conclusion: Misclassification of BAV is prevalent, frequently leads to delayed diagnosis, and is more likely to occur in the most severely affected cases. TEE, CT and MR may increase diagnostic accuracy in up to half of BAV cases but are underutilized. Additional studies are needed to determine if misclassification of BAV patients leads to increased long-term morbidity and mortality.

Keywords

Bicuspid Aortic Valve; Adult; Congenital heart defect; Delayed diagnosis

Introduction

Bicuspid aortic valve (BAV) is the most prevalent adult congenital heart defect (Nistri et al: 2005; Roberts: 1970). BAV causes lifelong progressive disease that is responsible for more

than half of aortic valve replacement surgeries in adults and predisposes to a greatly increased prevalence of aortic aneurysms and acute aortic dissections (Borger et al: 2018). A transthoracic echocardiogram (TTE) should be performed at diagnosis to assess valve function and to screen for thoracic aortopathy or other congenital defects, such as coarctation, which frequently occur with BAV. Aortic magnetic resonance angiography or CT angiography is indicated in patients when valve morphology cannot be completely assessed by TTE (Alkadhi et al: 2010; Hope et al: 2012; Shenoy et al: 2014; Song: 2015). Serial evaluations are then recommended at various intervals as appropriate to monitor the progression of valve or aortic disease.

Adequate echocardiographic images are highly sensitive and accurate for the classification of aortic valve morphology (Chan et al: 1999). However, the initial diagnosis of BAV may be impeded by technical limitations, extensive calcification that may obscure the commissures, and the variable presentations of BAV disease. Early ascertainment and long-term surveillance of valve dysfunction may be compromised by these challenges (Michelen et al: 2011). Delayed recognition of BAV may also reduce opportunities for diagnosis and prophylactic treatment of thoracic aortic aneurysms, or for screening first-degree relatives. We therefore systematically evaluated imaging reports from our research registry to identify factors that may affect the diagnostic yield of screening and surveillance images.

Materials and Methods

The UTHealth Bicuspid Aortic Valve Registry (www.clinicaltrials.gov/ct2/show/NCT01823432) is an observational research registry that includes questionnaires, healthcare records and serial images from more than 400 participants who were enrolled at the University of Texas at Houston. Registry participants consent to be re-contacted for up to 15 years. The principal inclusion criterion is a confirmed diagnosis of BAV by expert review of images (S.P.) or operative reports. Valve morphology is adjudicated according to published standards (Murphy et al: 2017). Subjects are excluded if BAV cannot be confirmed, if they have syndromic or complex congenital heart disease, confirmed mutations in genes that cause familial aortopathy or congenital heart defects, or if they are unable to provide consent.

Subjects were included in this study if they had at least three imaging reports available for review. The images were obtained as part of routine clinical care at a total of 23 different clinical facilities, reflecting the diverse geographic origins of patients who are referred to our tertiary center. Data on aortic valve morphology and function were abstracted from TTE, transesophageal echocardiography (TEE, excluding perioperative studies), computed tomography angiography (CT) and magnetic resonance angiography (MR) reports. Aortic valves were classified as definitely bicuspid, possibly bicuspid, definitely tricuspid, or uncertain. Aortic valve calcification, aortic valve insufficiency and aortic valve stenosis were stratified as none, mild, moderate, or severe. For 74 participants in the study group who had available images, cusp orientation was determined by analysis of axial views. Chi-square and t-tests were used to determine associations between reported valve morphologies and clinical or patient characteristics.

The TTE image quality of subjects who were misclassified at least once, and age, BMI, and gender-matched individuals who were never misclassified, was compared using a standardized assessment tool (Picard et al: 2011) (Lopez: 2018). This metric includes an evaluation of brightness, resolution and focus in five distinct views (parasternal long axis, parasternal short axis, apical 4 chamber, subcostal sagittal, and suprasternal). The summed image quality scores range from 0 (poor quality) to 8 (ideal quality).

Results

Diagnostic Accuracy

Serial imaging reports were available for 204 UTHealth BAV Registry participants (2.4 +/- 1.4 reports per patient) with a mean follow up interval of 2.8 years. We observed that 40% (84/204) of study subjects were misclassified at least once: 27 as “possibly bicuspid”, 50 as “definitely tricuspid” and 26 as “uncertain.” 33 subjects were misclassified in more than one imaging report. The mean interval between misclassification and correct diagnosis was 22 months (1.6 images, Figure 1). TEE (78%), MR (75%) and CT (67%) were more sensitive than TTE (59%) for BAV diagnosis and successfully reclassified 20% (6/29) of participants, but only 14% (29/204) of subjects were imaged using any one of these alternative modalities prior to aortic valve intervention. TEE, MR, and CT more frequently included assessment of valve orientation (48%, 14/29) than TTE (36%, 74/203) and provided additional information about aortic dimensions (100%, 29/29).

Impact of Image Quality on Misclassification

108 TTE images for 44 misclassified subjects and for 30 correctly classified subjects were available for analysis. The mean quality score of images from subjects who were correctly classified was 6.2 (+/-1.6). The mean quality score of images from subjects who were misclassified was significantly lower (4.2 +/-2.6, $P < 0.0001$). The correctly classified reports included more adequate image orientations than the misclassified reports (4.2 versus 2.9). The principal driver of the discrepancy between the two groups was the quality of parasternal short axis views, which was more frequently inadequate in subjects who were misclassified (82%) than in correctly classified subjects (44%).

Impact of Patient Characteristics on Misclassification

Males (45%) and females (35%, $p=0.17$) were misclassified at similar rates, but males were more likely to be classified as ‘possibly bicuspid.’ Accurately classified subjects were younger (39 +/- 19 years) than misclassified subjects (52 +/- 11 years) ($p<0.0001$). The average BMI of ever-misclassified subjects (30.1 (7.1) kg/m²) was similar to accurately classified subjects (28.2 (7.3) kg/m²) ($p=0.06$). The prevalence of diabetes, hypertension, and smoking was not significantly more frequent in misclassified subjects. Individuals who were diagnosed due to clinical manifestations of valve disease ($n=160$, 41%) were misclassified as frequently as those who were diagnosed as an incidental finding (43%).

Impact of Valve Structure and Function on Misclassification

Subjects with mild, moderate, or severe valve calcification ($n=138$, 51%) were more frequently misclassified than subjects with minimal aortic valve calcification ($n=66$, 20%, p

< 0.0001) (Figure 2). Subjects with severe aortic stenosis (n=39, 59%) were misclassified more frequently than those without aortic stenosis (n=115, 34%, $p < 0.01$). Mild or moderate aortic stenosis or regurgitation was also significantly more prevalent in misclassified subjects (66%, 55/84, vs. 51%, 61/120, $p=0.037$). Valve orientation (L-R, n=53, vs. all others, n=21) or subsequent surgical valve replacement was not significantly associated with misclassification.

Discussion

Longitudinal studies show that BAV leads to substantial morbidity due to accelerated valve and aortic disease with a greatly increased lifetime risk for valve or aortic interventions and acute aortic dissection (Hardikar and Marwick: 2013). The current ACC/AHA guidelines for valvular heart disease support this approach by recommending lifelong surveillance of BAV patients (Nishimura et al: 2014). However, guideline-directed management is not possible without accurate imaging for timely diagnosis and treatment. Missed opportunities to identify BAV patients on routine surveillance images could delay diagnosis and lead to increased complications. We therefore evaluated clinical records and imaging reports from registry participants to determine the prevalence of and risk factors for BAV misclassification.

We found that misclassification of BAV is frequent and may lead to substantial delays in diagnosis, which are most pronounced in individuals with severe valvular disease. More than 40% of BAV patients in our cohort were misclassified at least once. The quality of misclassified TTE studies was frequently insufficient to evaluate aortic valve morphology. We also observed that inadequate or inconclusive studies did not always prompt a clinical response. At the end of the follow up period, 13% (26/204) of study subjects who had at least three serial images were still incorrectly classified (Figure 1). Only 17 of 27 (63%) subjects who were classified as 'possibly bicuspid' at least once and were available for long term follow up received additional imaging to clarify the diagnosis. We conclude that routine imaging substantially underestimates the prevalence and severity of BAV disease, even in academic hospitals with congenital heart disease specialists.

These findings highlight the importance of quality assessments by sonographers and cardiologists when BAV may be suspected in initial non-diagnostic images. Our results suggest that a stepwise approach may increase diagnostic accuracy: inadequate or non-diagnostic images should prompt clinicians to review previous reports and the clinical history, acquire additional sonographic views and/or refer patients for alternative imaging modalities. We found that TEE, CT or MR substantially improve the recognition of BAV and frequently provide additional prognostic information about the valve and aorta, but are underutilized. Standardized methods for imaging and reporting BAV may also improve diagnostic rates. The implications of this more rigorous approach for improved ascertainment of BAV and prevention of BAV-related complications through surveillance and surgical intervention should be assessed in prospective clinical trials.

Limitations

This was a retrospective study with the potential for substantial ascertainment bias. The study population (BAV cases at tertiary care centers) may not be representative of BAV patients who were diagnosed at other sites. Demographic and clinical variables were not uniformly available from the entire study cohort. The inclusion of some study subjects was based on subjective image interpretation and was not independently verified by surgical inspection or other methods. We were not always able to identify additional clinical factors that may have influenced the likelihood of BAV diagnosis. The sample size was insufficient to compare the efficacy of TEE, CT or MR to reclassify cases with difficult TTE images.

Conclusions

Routine imaging substantially underestimates the prevalence and severity of BAV and disproportionately affects the most severe cases. Abnormal aortic valve function or extensive valve calcification, especially in young adults, should raise clinical suspicion of BAV. If screening echocardiography is inconclusive, a stepwise approach that utilizes alternative imaging modalities can improve the diagnostic yield. Early ascertainment of BAV patients may reduce the long-term complications of aortic and valvular disease.

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Figure 1.

Reclassification of Bicuspid Aortic Valves in Serial Images. This diagram illustrates the reclassification of bicuspid aortic valve morphology over time in 204 registry participants who had at least three serial imaging reports available for review. Arrows represent reclassification of BAV cases into diagnostic categories (rows) across serial reports (columns).

Figure 2. Misclassification of bicuspid aortic valves is highly correlated with the extent of valve calcification. Scatterplot depicts the relationship between semi-quantitative valve calcification (*X*-axis, 0: none, 1: mild, 2: moderate, 3: severe) and the prevalence of misclassification (*Y*-axis)

Figure 3.

Representative images of accurately classified (A) and inaccurately classified (B, C) bicuspid aortic valves denoting commissures (arrows) and raphes (asterisks). A. Parasternal short axis transthoracic echocardiogram image of an accurately classified valve. B. Parasternal short axis transthoracic echocardiogram image of a valve that was repeatedly misclassified. C. Sagittal computed tomography angiogram image clearly delineates bicuspid morphology of B.

Table 1

Characteristics of the Study Cohort.

	Accurately Classified	1+ Misclassification
Total n	120	84
Male Sex (%)	70 (58.3)	57 (67.9)
Age at Diagnosis (Q1-Q3)	41 (25-52) *	55 (45-59)
BMI (kg/m², Q1-Q3)	27.2 (24-32)	28.7 (25-34)
Hypertension (%)	50 (41.7)	49 (58.3)
Diabetes (%)	15 (12.5)	11 (13.1)
Smoking (%)	44 (36.7)	42 (50.0)
Symptomatic at Diagnosis¹ (%)	95 (79.2)	65 (77.4)
Incidental Diagnosis² (%)	25 (20.8)	19 (22.6)
Calcified Aortic Valve³ (%)	67 (55.8) *	71 (84.5)
Severe Stenosis of Aortic Valve	16 (13.3) *	23 (27.4)
No or Minimal Valve Dysfunction⁴	59 (49.2) *	29 (34.5)
Documented Cusp Orientation⁵	54 (45.0) *	20 (23.8)
L-R Orientation⁵	41 (73.2)	12 (60.0)
Available TTE Images	30 (25.0)	44 (52.4)
Had CT, TEE, or MRI	13 (10.8)	16 (19.0)
Aortic Valve Surgery	46 (38.3)	39 (46.4)

¹ Symptomatic: documented cardiovascular symptoms at diagnosis;² Incidental: diagnosed as an incidental finding and was unrelated to clinical presentation;³ Includes mild, moderate or severe calcification;⁴ Includes aortic stenosis and aortic regurgitation;⁵ Cusp orientation was noted in image reports;

* significant at p<0.05.