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Various Phenotypic Expressions of the Bicuspid Aortic Valve

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ABSTRACT

The phenotypic expressions of the bicuspid aortic valve (BAV) are unpredictable and difficult to compartmentalize. In the modern era, BAV has been reported to account for approximately 50% of the cases with severe aortic stenosis requiring surgery and has also been associated with aortic regurgitation, bacterial endocarditis, and aortic dissection. Echocardiography is the diagnostic tool used to identify BAV. The clinical associations and high prevalence rate of BAV have added to the importance of this clinical inquiry. The present study aimed to explore the multifaceted challenges associated with BAV, as well as the current knowledge on this complex entity.

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Introduction

The phenotypic expressions of the bicuspid aortic valve (BAV) are unpredictable and difficult to compartmentalize. In the modern era, BAV has been reported to account for approximately 50% of the cases with severe aortic stenosis requiring surgery and has also been associated with aortic regurgitation, bacterial endocarditis, and aortic dissection (1,2). Echocardiography is the diagnostic tool used to identify BAV (3). The clinical associations and high prevalence of BAV have added to the importance of this clinical inquiry.

Some of the main factors that make BAV an enigmatic clinical challenge even to expert clinician are the heterogeneous clinical presentations, varied valvulo aortopathies with a wide range of phenotypes and unpredictable outcomes, uncertain natural history, and ambiguity as to whether it is an innocent bystander or a primary disease (2).

The present study aimed to explore the multifaceted challenges associated with BAV, as well as the current knowledge regarding this complex entity.

Heterogeneous Clinical Presentations

The clinical presentations and effects of BAV are diverse, with few clinical or genetic indicators to predict the outcomes or associated complications. BAV could be diagnosed at stages in life, including in neonates and octogenarians, and might be associated with inconstant clinical circumstances (4). The spectrum of identification is vast, ranging from a heart murmur in an asymptomatic patient to severe aortic valve disease manifesting as heart failure. The life-threatening associations of BAV include bacterial endocarditis and thoracic aortic aneurysm dissection (5,6). The variable clinical presentations and phenotypic expressions of BAV make its diagnosis and management challenging for physicians.

BAV: A Valvulo Aortopathy with Diverse Phenotypic Expressions and Arbitrary Outcomes

The high incidence and prevalence of BAV requiring surgical intervention, as well as the high incidence rate of the associated thoracic aortic

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aneurysm formation mandates that this condition be considered a valvulo aortopathy to determine the orderly associations between the phenotypic expressions of the disease.

BAV has various phenotypic expressions (7), which are classified, as follows:

• Type I (right and left coronary cusp fusion): commissures at 10 and 5 o'clock;
• Type II (right non-coronary cusp fusion): commissures at 1 and 7 o'clock;
• Type III (left non-coronary cusp fusion): commissures at 2 and 8 o'clock .

The two cusps of most BAVs exhibit asymmetrical systolic excursion and eccentric systolic flow pattern. The ascending aorta displays a spectrum of aneurysmal phenotypes, the most common of which is tubular ascending aorta dilatation (60-70%) exhibiting the fastest growth rate (0.4-0.6 mm/year). Furthermore, there is a sinus of valsalva dilatation phenotype (approximately 25% of the dilated aortas), which is associated with type I BAV and male gender (8-11). The aortic phenotypes encountered in BAV are as follows:

• Tubular ascending aorta (most common);
• The entire ascending aorta may be affected, including the valsalva sinus and tubular aorta with sinotubular junction effacement;
• Dilation of the valsalva sinus preferentially associated with type I BAVs.

The principal mechanisms involved in the varied BAV-related valvular aortic phenotypes remain unclear. There is a major knowledge gap regarding the reason for BAV to be stenotic and/or regurgitant, as well as another that is linked to the thoracic aortic aneurysm (TAA), and yet another remains working without being stenotic or regurgitant. The most perplexing issue in this regard is the lack of insight into the reason for the small number of the patients with BAV incurring aortic dissection and the fact that aortic diameters are only modestly predictive (12).

BAV: The Epitome of Genotype-to-Phenotype Variability

BAV is associated with congenital and genetic syndromes, as well as cardiovascular manifestations, such as Shone's complex, coarctation, ventricular septal defect, anomalous pulmonary veins, and syndromic conditions (e.g., familial TAA, Loeys-Dietz syndrome, Turner's syndrome, and aortic dissection) due to the alpha-smooth muscle actin (ACTA2) gene mutation. The Notch1 and GATA5 genes have been identified in the families with BAV (13-16). However, the genomic causes and their clinical manifestations remain unknown. There may be varied genomic substrates that lead to more complex conditions in children and isolated BAV or BAV-associated aortopathy in adults. The reason for children to have severe BAV dysfunction remains unknown. Adults may have moderate BAV and develop aortic dissection. For instance, a 91-year-old patient was incidentally diagnosed with BAV despite the normal function. Evidently, genetic and environmental factors play a pivotal role in this regard, and pathogenetic economy does not occur.

Approaching Adult BAV Patients

Expert consensus suggests that the following management principles provide the optimal available evidence-based therapeutic measures for BAV:

• Coarctation must be evaluated via echocardiography, computed tomography (CT)-scan or magnetic resonance imaging (MRI);
• Surveillance should follow the current valvular and echocardiography appropriateness criteria (17);
• Surgical interventions should be in accordance with valvular guidelines (18);
• If the aortic root or ascending aorta is dilated to ≥40 millimeters by echocardiography, it should be confirmed by CT-scan/MRI follow-up within six months and annual imaging if stable;
• Dental hygiene is imperative to the prevention of endocarditis;
• Echocardiographic screenING of all the first-degree family members is essential;
• Elective intervention is required for ascending aortic aneurysms with the aorta measures of >55 or >45 millimeters if aortic valve replacement (AVR) is performed or at the dilation rate of >0.5 cm/year (19);
• After the surgical intervention for the ascending aorta, the arch and descending thoracic aorta should be monitored every three years;
• In familial thoracic aortic disease, genetic counseling may be prudent.

The present study aimed to describe six cases of BAV with a succinct history, physical examination, multi-modality imaging, and clinical decision-making elucidating the aforementioned points.

Case One

Clinical Presentation

A 43-year-old male patient referred for the evaluation of fatigue. He had no chest pain, dyspnea, palpitation or syncope. The patient was referred for AVR due to severe aortic stenosis.

Clinical Examination

The blood pressure of the patient was 130/80 mmHg, and pulse rate was 80 bpm. In addition, the patient had normal jugular vein pressure (JVP),

normal carotid upstroke, normal S1 and S2, and 2/6 systolic ejection murmur at baseline.

Echocardiography

The echocardiographic features of the patient were as follows: normal left ventricular size and systolic function, BAV, peak average velocity (AV)=4.6 m/sec, mean AV gradient=43 mmHg, LVOT-tvi=23 cm, calculated continuity equation (AVA)=1 cm^2.

Genetics

The patient was negative for NOTCH1, ACTA2, KCNJ2, and GATTA5.

Clinical Decision-making

Echocardiography showed type II bicuspid AV (Figure 1), and the ascending aorta revealed a tubular phenotype (38 mm) (Figure 2). In addition, the Doppler data indicated the peak velocity of 4.6 m/sec (Figure 3). The valve area was measured using the continuity equation and estimated at one cubic centimeter. The planimetry of the AV revealed a normal valve area (Figure 3), and visualization showed normal valve excursion (Cine 1). However, the calculated valve area and visual appearance were discordant.

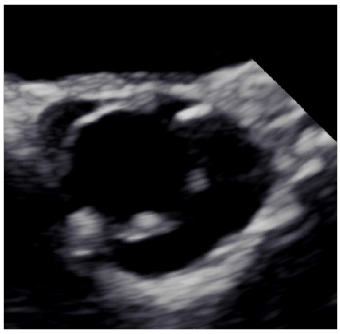

Figure 1. Phenotype Type 2 bicuspid AV still frame in systole demonstrating right and noncoronary cusp fusion

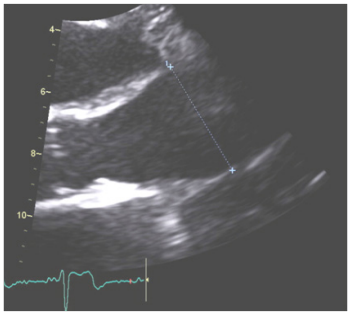

Figure 2. Ascending aorta with tubular phenotype that measures 38 mm.

Visualization of the AV showed no aortic stenosis. Therefore, we had to determine the cause of gradient elevation based on the following:

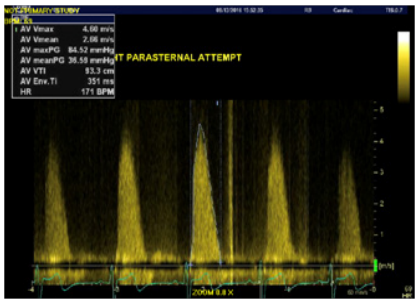

Figure 3. Continuous wave Doppler across the AV with the suprasternal position revealing a peak velocity of 4.6 m/sec and mean gradient of 36 mm Hg and calculated valve area if 1 cm2 using the continuity equation.

• The calculated stroke volume indicated that the gradient was not associated with the increased flow that occurred due to anemia, hyperthyroidism, aortic regurgitation, and hemodialysis.
• The other influential factors in the gradient were jet eccentricity and aortic root size.
• BAV often has eccentric jets that cause further pressure loss and lower pressure recovery, thereby leading to falsely elevated gradients. Moreover, marked jet eccentricity could increase the gradients by 25 mmHg. This case represented a classic example of falsely elevated gradients in BAV with eccentric flow. Planimetry is considered to be the 'gold standard' for BAV.

Case Two

Clinical Presentation

A 47-year-old male patient presented with exertional dyspnea and fatigue for approximately one year.

Clinical Examinations

The blood pressure of the patient was 140/60 mmHg, with the pulse rate of 75 bpm, rapid carotid upstroke with rapid collapse, normal JVP, blowing holodiastolic diastolic murmur (3/4), and brisk femoral pulses with systolic and diastolic sounds.

Echocardiography Findings

The patient had mild left ventricular (LV) dilation with preserved LV systolic function, type II BAV with leaflet prolapse and severe eccentric AV regurgitation and enlarged aorta involving the valsalva sinus and tubular aorta, along with the effacement of the sinotubular junction (43 mm).

Cardiac Catheterization

The patient had normal coronary arteries.

Genetic Findings

The patient was positive for G4.5 (tafazzin), while negative for NOTCH1, ACTA2, KCNJ2, and GATTA5.

Clinical Decision-making

The 47-year-old patient had type II BAV (Figure 5) and dilated ascending aorta involving the valsalva sinus and tubular aorta, along with sinotubular junction effacement (44 mm) (Figure 6). Furthermore, he had left ventricular non-compaction cardiomyopathy with normal systolic function (Cine 2). BAV prolapsed (Cine 3), revealing severe eccentric aortic regurgitation (Cine 4 & 5).

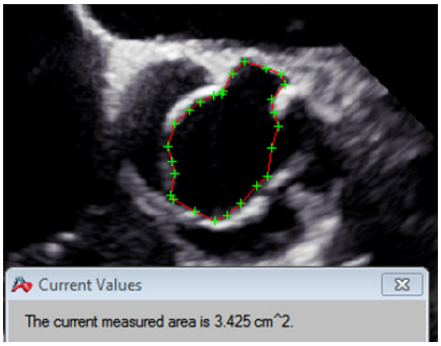

Figure 4. Planimetry of the AV with the AVA ~ 3.4 cm^2.

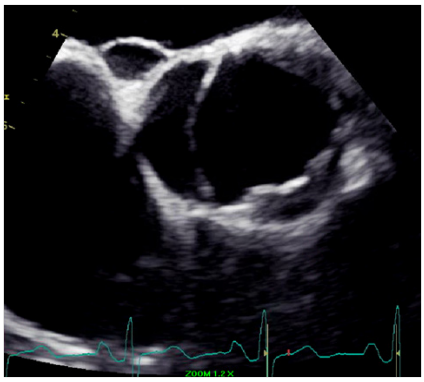

Figure 5. Phenotype Type 2 bicuspid AV still frame in systole demonstrating right and non-coronary cusp fusion.

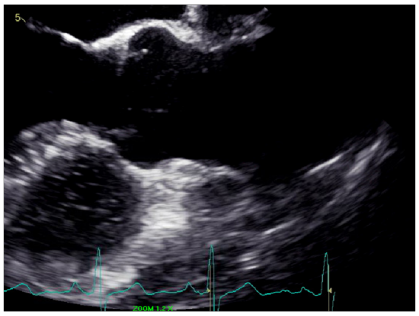

Figure 6. Dilated ascending aorta measuring 44 mm with a phenotype involving the entire ascending aorta: involving the sinus of Valsalva and tubular aorta with sinotubular effacement.

The debate was whether to proceed with the Bentall procedure or AVR with aortic wrapping. Transesophageal echocardiography suggested the maximum aortic dimension of 44 millimeters. In addition, CT-scan showed the maximum dimension of the ascending aorta to be 43 millimeters (Figure 7). The guidelines in this regard recommend aortic root replacement at 45 millimeters (or more). These guidelines are non-evidence-based and extrapolated from Marfan guidelines. With respect to type I BAV, data suggest that it is associated with rapid aortic root dilation. Considering that the valve in this patient was of type II, the debate persisted, and the decision was to be made upon surgery (Figure 8). The maximum dimension was 40 millimeters in surgery, and AVR with aortic root wrap was performed in accordance with the guidelines for the postoperative imaging of the aortic root.

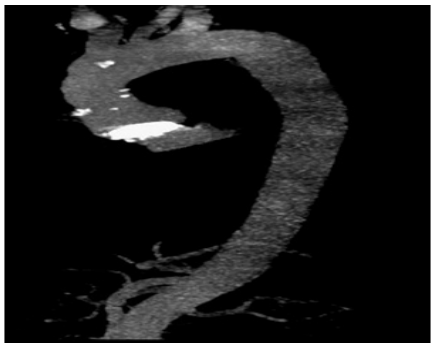

Figure 7. Cardiac tomography of the ascending aorta measuring 43 mm

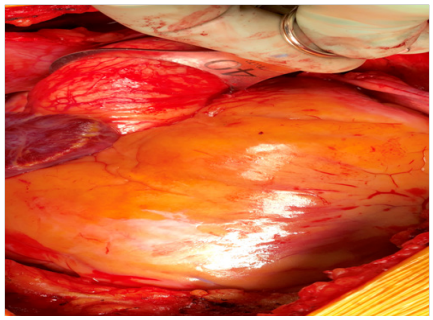

Figure 8. Intraoperative assessment of the ascending aorta with surgeon measuring 40 mm.

Case Three

Clinical Presentation

A 57-year-old female patient presented with the six-month history of dyspnea. In addition, she had a history of vasodepressor syncope, diabetes, and pulmonary sarcoidosis. The patient›s father also had a bicuspid valve.

Clinical Examinations

The blood pressure of the patient was 150/50 mmHg, with the pulse rate of 76 bpm, bounding carotid upstroke with rapid collapse, S1 S2 RRR with water hammer pulses, and diastolic murmur (2/4).

Echocardiography Findings

The patient had a Mildly dilated LV cavity (left

ventricular ejection fraction= 50%), elevated LV, filling pressure manifesting as the early closure of the mitral valve BAV, and eccentric aortic regurgitation.

Genetic Findings

The patient was negative for NOTCH1, ACTA2, KCNJ2, and GATTA5.

Cardiac Catheterization

The patient had normal coronary arteries.

Aortography

The patient had severe aortic regurgitation.

Clinical Decision-making

The 57-year-old female patient had type II BAV (Figure 9), tubular ascending aorta (45 mm) (Figure 10), and prolapsing AV (Cine 6) with eccentric AR (Cine 7 & 8). There was a difference of opinion regarding the severity of the AR based on the echocardiographic imaging. The clinical examination was indicative of severe AR, which was confirmed by aortography (Cine 9). The constellation of the findings regarding severe aortic regurgitation and the ascending aorta (45 mm) led to the recommendation of the Bentall procedure.

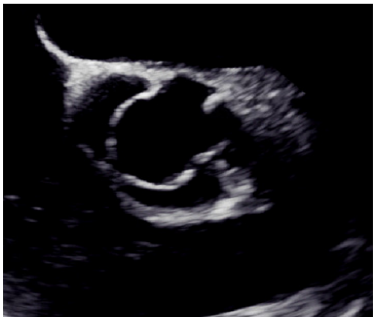

Figure 9. Phenotype Type 2 bicuspid AV still frame in systole demonstrating right and noncoronary cusp fusion.

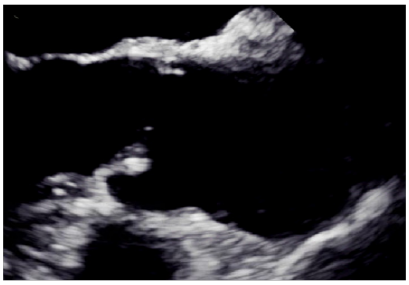

Figure 10. Ascending aorta is tubular phenotype with maximum dimension measuring 45 mm.

Case Four

Clinical Presentation

A 62-year-old male patient presented with increased fatigue, shortness of breath, and heart murmur. The patient's brother had an aortic valve replacement for BAV.

Clinical Examinations

The blood pressure of the patient was 130/85 mmHg, with the pulse rate of 85 bpm, normal JVP, normal carotid upstroke, S1 S2 RRR with normal pulse, and diastolic murmur (1/4) when he leaned forward in a seated position.

Echocardiography Findings

The patient had normal LV size and systolic function, type I BAV with trivial-to-mild aortic regurgitation, and dilated valsalva sinus (53 mm).

Genetic Findings

The patient was negative for NOTCH1, ACTA2, KCNJ2, and GATTA5.

Clinical Decision-making

The 62-year-old male patient had type I BAV (Figure 11), isolated dilation of the valsalva sinus (53 mm) (Figure 12), and mild aortic regurgitation (Cine 10-13). As such, repeated echocardiography was recommended for six months since the predominant valsalva sinus dilatation phenotype was associated with type I BAV and male gender. Furthermore, this root phenotype has been associated with faster tubular ascending root dilation.

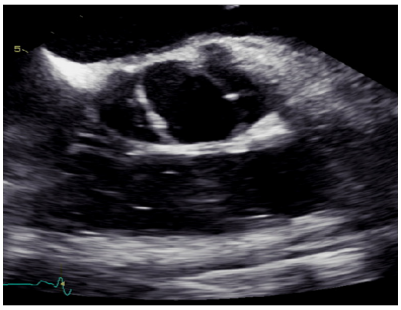

Figure 11. Phenotype Type 1 bicuspid AV still frame in systole demonstrating right and left cusp fusion.

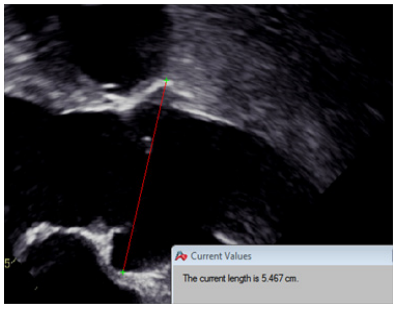

Figure 12. Ascending aorta phenotype isolated dilation of the Sinus of Valsalva.

Case Five

Clinical Presentation

A 65-year-old male patient referred for the evaluation of recalcitrant hypertension and exertional

shortness of breath. The systolic blood pressure of the patient was 160 mmHg despite treatment with dilacor XR (240 mg/day), toprol XL (100 mg/day), lisinopril (40 mg/day), and hydrodiuril (25 mg/day).

Clinical Examinations

The blood pressure of the patient was 170/88 mmHg, with the carotid pulse rate of 75 bpm, normal JVP, normal carotid upstroke, and S1 S2 S4 2/4 SEM, and pulses revealing brachial femoral delay.

Echocardiography Findings

The patient had normal LV size and systolic function, increased LV wall thickness (septum and posterior wall: 15 mm), BAV with mild aortic regurgitation, dilated valsalva sinus, and ascending aorta with the effacement of the sinotubular junction (maximum dimension of the aorta: 45 mm). In addition, the aortic arch was poorly visualized, and the pulsed wave Doppler of the abdominal aorta revealed decreased pulsatile flow and continuous flow in the diastole.

Cardiac Catheterization

The patient had mild coronary artery disease.

Genetic Findings

The patient was negative for NOTCH1, ACTA2, KCNJ2, and GATTA5.

Clinical Decision-making

The 65-year-old male patient had type III BAV (Figure 13) and dilated valsalva sinus, with the tubular ascending aorta and effacement of the sinotubular junction (Figure 14). Furthermore, he was resistant to medical therapy for hypertension, which raised concern for a secondary etiology. Transesophageal short and long axis imaging showed mild, eccentric aortic regurgitation (Cine 14 & 15). In addition, the pulsed wave Doppler of the abdominal aorta raised the suspicion of aortic coarctation of the aorta (Figure 15), while MRI showed coarctation (Figure 16). Therefore, examination for the repair of the coarctation by the interventional and surgical team was recommended.

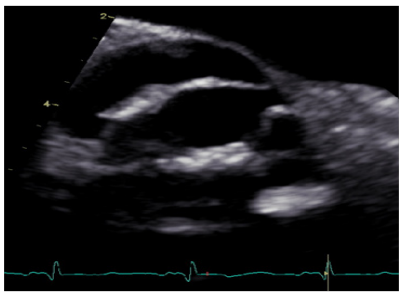

Figure 13. Phenotype Type 3 bicuspid AV still frame in systole demonstrating left and noncoronary cusp fusion.

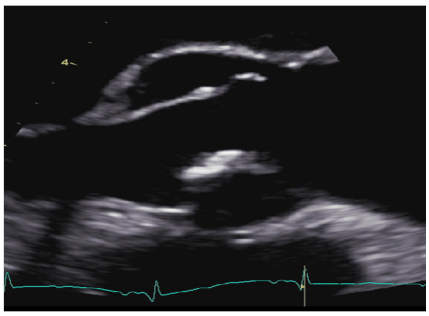

Figure 14. Phenotype of the dilated ascending aorta measuring 45 mm with a phenotype involving the entire ascending aorta: involving the sinus of Valsalva and tubular aorta with sinotubular effacement.

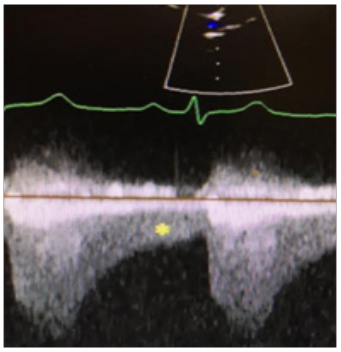

Figure 15. PW Doppler of the abdominal aorta with limited pulsatile flow and continuous flow in diastole.

Figure 16. MRI of the thoracic aorta.

Conclusion

The presented cases aimed to explore various phenotypic expressions of the BAV and identify the associated clinical presentations, physical examinations, and multi-modality imaging, which allowed the clinicians to make an accurate diagnosis for effective clinical decision-making regarding the required surgical treatment.

Acknowledgements

None.

Conflict of Interest

The authors declare no conflict of interest.

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