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Case Report

The Bicuspid Aortic Valve – Various Phenotypic Expressions

Timothy E Paterick

Department of Cardiology, Bay Care Clinic Green Bay, Wisconsin, USA

Corresponding Author: Timothy E Paterick, Department of Cardiology, and Bay Care Clinic Green Bay, Wisconsin, USA

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Abstract

The phenotypic expressions of the bicuspid aortic valve (BAV) are unpredictable, and difficult to compartmentalize. In current times the BAV is noted to represent approximately 50% of isolated severe aortic stenosis cases requiring surgery, and has been associated with aortic regurgitation, bacterial endocarditis and aortic dissection. Echocardiography is the diagnostic test to identify BAV. The clinical associations coupled with the high prevalence of BAV have made this an important area of clinical inquiry. We will explore the vast horizons and multifaceted challenges of the bicuspid aortic valve and our current understanding of this complex entity.

Key words: bicuspid aortic valve; aortopathy; coarctation; heterogeneity; genotype; phenotype

Introduction

The phenotypic expressions of the bicuspid aortic valve (BAV) are unpredictable, and challenging to compartmentalize. In contemporary times the BAV is noted to represent approximately 50% of isolated severe aortic stenosis cases requiring surgery, and has been associated with aortic regurgitation, bacterial endocarditis and aortic dissection [1, 2]. Echocardiography is the diagnostic test to identify BAV. [3] The clinical associations coupled with the high prevalence of BAV have made this an important area of clinical inquiry.

The heterogeneous clinical presentations, varied valvuloaortopathies with wide-ranging phenotypes and unpredictable outcomes, uncertain natural history, and ambiguity as to whether it is an innocent bystander or a primary disease make the bicuspid valve an enigmatic clinical challenge to even the expert clinician [2]. We will present five cases that attempt to explore the multifaceted faces of the bicuspid aortic valve and our current understanding of this complex entity.

Heterogeneous Clinical Presentations

The clinical presentations and effects of BAV are diverse with few clinical or genetic indicators to predict outcomes or associated complications. BAV can be diagnosed at any stage of life from newborn to octogenarian and may be related to 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. Life threatening associations include bacterial endocarditis and thoracic aortic aneurysm dissection [5, 6]. The variable clinical presentations and the various phenotypic expressions make the diagnosis and management of BAV a challenge for physicians.

Bav Is a Valvuloaortopathy with Diverse Phenotypic Expressions and Arbitrary Outcomes

The high incidence and prevalence of BAV requiring surgical intervention and the high incidence of associated thoracic aortic aneurysm formation mandates that it be viewed as a valvuloaortopathy for an orderly relationship among phenotypic disease expressions.

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

- Type 1 (right and left coronary cusp fusion): commissures at 10 and 5 o'clock
- Type 2 (right – noncoronary cusp fusion): commissures at 1 and 7 o'clock
- Type 3 (left – noncoronary 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, tubular ascending aorta dilatation being the most common (60-70%) and exhibiting the fastest growing rate (.4-.6 mm/year). There is also a sinus of Valsalva dilatation phenotype (approximately 25% of dilated aortas) and it associated with Type 1 BAV and male sex [8,9,19,11]. Aortic phenotypes encountered in BAV include:

- Tubular ascending aorta (most common)
- The entire ascending aorta may be affected, including the sinus of Valsalva and tubular aorta with sinotubular junction effacement

- Dilation of the Sinus of Valsalva preferentially associated with Type 1 BAVs

The underlying mechanisms responsible for such varied BAV associated valvuloaortic phenotypes remains enigmatic. There is a major knowledge deficit and it remains a mystery as to why a BAV becomes stenotic, another regurgitant, another associated with a TAA, and yet another remains functional. Most perplexing is the lack of insight into why a few BAV patients will incur aortic dissection and that aortic diameters are modestly predictive at best [12].

Bav: The Epitome of Genotype to Phenotype Variability

BAV is associated with congenital and genetic syndromes with cardiovascular manifestations such as ShoNes complex, coarctation, ventricular septal defect, anomalous pulmonary veins, and syndromic conditions such as familial TAA, Loeys- Dietz, Turner's and aortic dissection due to smooth muscle alpha actin (ACTA2) gene mutation. There has been identification of Notch1 and GATA5 gene in families with BAV [13, 14, 15, 16]. But the genomic causes and their clinical manifestations remain largely unknown. There may be very different genomic substrates that lead to more complex conditions in children and isolated BAV, or BAV associated aortopathy in adults. It is a mystery why some children have severe BAV dysfunction, an adult may have moderate BAV disease and develop aortic dissection, and a 91-year-old is incidentally found to have a BAV that functions essentially normal. It is clear that genetic and environmental factors play a role and that pathogenetic economy is not occurring.

Approaching the Adult BAV Patient

Expert consensus opinion suggests that the following management principles are the best available evidence - based medicine for BAV.

- Coarctation must to evaluated by echocardiography or CT/MRI
- Surveillance should follow current valvular and echocardiography appropriateness criteria (17)
- Surgical intervention should follow valvular guidelines (18)
- If aortic root or ascending aorta is dilated by echocardiography to 40 mm or greater then confirmation by computed tomography/magnetic resonance imaging with follow up in six months and if stable annual imaging.
- Dental hygiene is imperative to prevent endocarditis
- Echocardiographic screening of all first degree relatives
- Elective intervention for ascending aortic aneurysms if the aorta measures > 55 mm, or when > 45 mm if AVR is being performed, or dilation rate is > .5cm/year. (19)
- After surgical intervention of 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

Herein we present six cases of BAV with a succinct history, physical examination, multi-modality imaging and clinical decision making elucidating the points outlined above.

Case 1.

Clinical presentation:

43-year-old male presented for evaluation of fatigue. He denied chest pain, dyspnea, palpitation or syncope. The patient was referred for aortic valve replacement for severe aortic stenosis.

Examination:

Blood pressure 130/80 Pulse 80 bpm
Normal JVP, normal carotid upstroke, and normal S1 and S2, 2/6 systolic ejection murmur at the base.

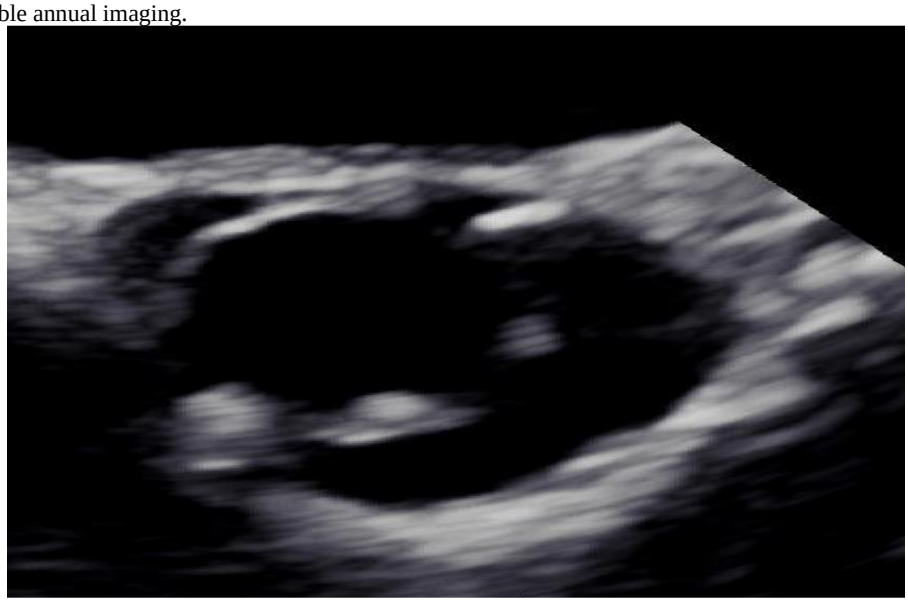
Echocardiography:

Normal LV size and systolic function
Bicuspid aortic valve
Peak AV velocity = 4.6 m/sec
AV mean gradient = 43 mm Hg
LVOT-tvi = 23 cm
Calculated AVA (continuity equation) = 1 cm2

Genetics: Negative for NOTCH1, ACTA2, KCNJ2, and GATTA5

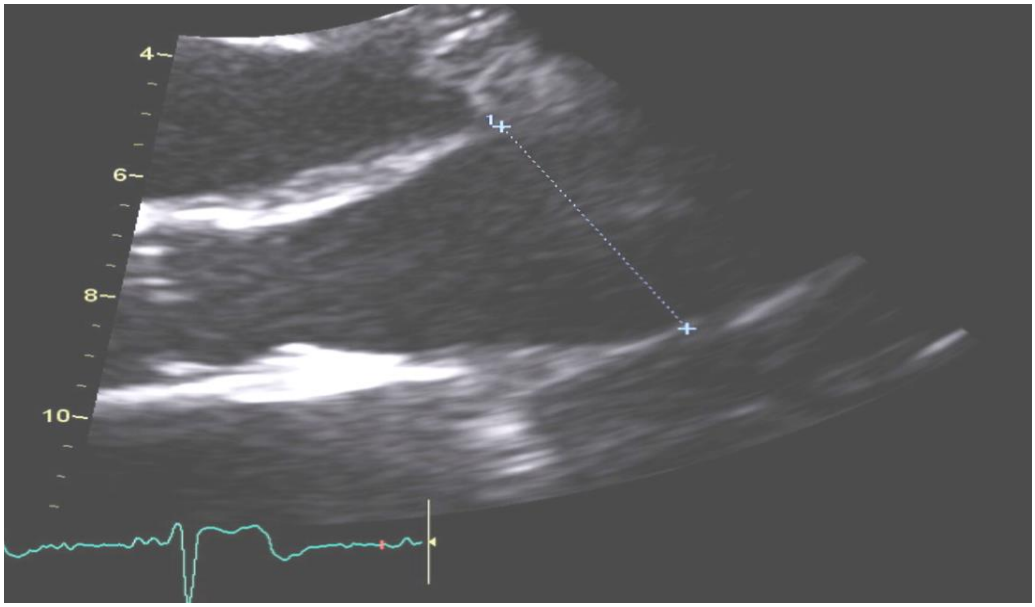
Clinical Decision-making:

The echo revealed a type 2 bicuspid AV (Figure 1) and the ascending aorta revealed a tubular phenotype that measured 38 mm (Figure 2).



Type 2 bicuspid aortic demonstrating the right and left coronary cusps

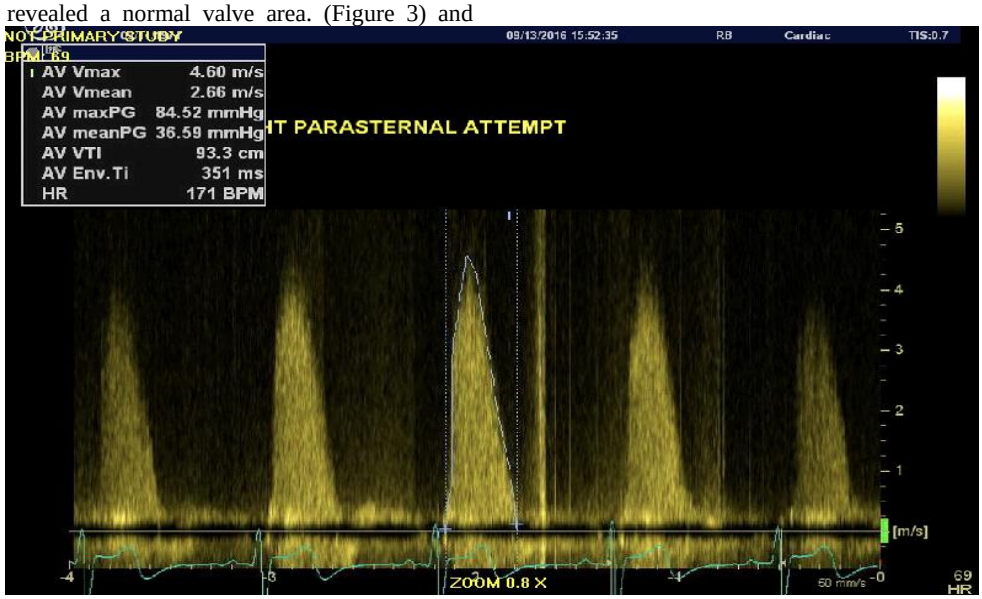
Figure 1: *Phenotype Type 2 bicuspid AV still frame in systole demonstrating right and noncoronary cusp fusion*



Ascending aorta measuring 38 mm

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

Doppler data revealed a peak velocity of 4.6 m/sec (Figure 3). The calculated valve area using the continuity equation was 1 cm2. The planimetry of the AV revealed a normal valve area. (Figure 3) and visualization revealed a normal valve excursion. (Cine 1) The calculated valve area and the visual appearance were discordant.



Continuous wave Doppler from the suprasternal notch across the AV

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 visualization of the AV reveals there is no aortic stenosis. So why is the gradient elevated?

- The calculated stroke volume reveals that the gradient is not related to increased flow that occurs with anemia, hyperthyroidism, aortic regurgitation, and hemodialysis.
- Other factors affecting the gradient are jet eccentricity and aortic root size.
- Bicuspid AV often has eccentric jets that result in more pressure loss, so less pressure recovery, resulting in falsely elevated gradients. Marked jet eccentricity can increase gradients by 25 mm Hg. This case represents a classic example of a falsely elevated gradient in a bicuspid aortic valve with eccentric flow. The gold standard for the bicuspid AVA is planimetry.

Case 2.

Clinical presentation:

47-year-old male presents with exertional dyspnea and fatigue for approximately one year.

Examination:

Blood pressure 140/60 Pulse 75 bpm
Carotid: rapid upstroke with rapid collapse Normal JVP
3/4 blowing holodiastolic diastolic murmur
Brisk femoral pulses with systolic and diastolic sounds

Echocardiography:

Mild LV dilation with preserved LV systolic function Type 2 bicuspid AV with leaflet prolapse and severe eccentric AV regurgitation and enlarged aorta involving the sinus of Valsalva and tubular aorta with effacement of the Sino tubular junction measuring 43 mm.

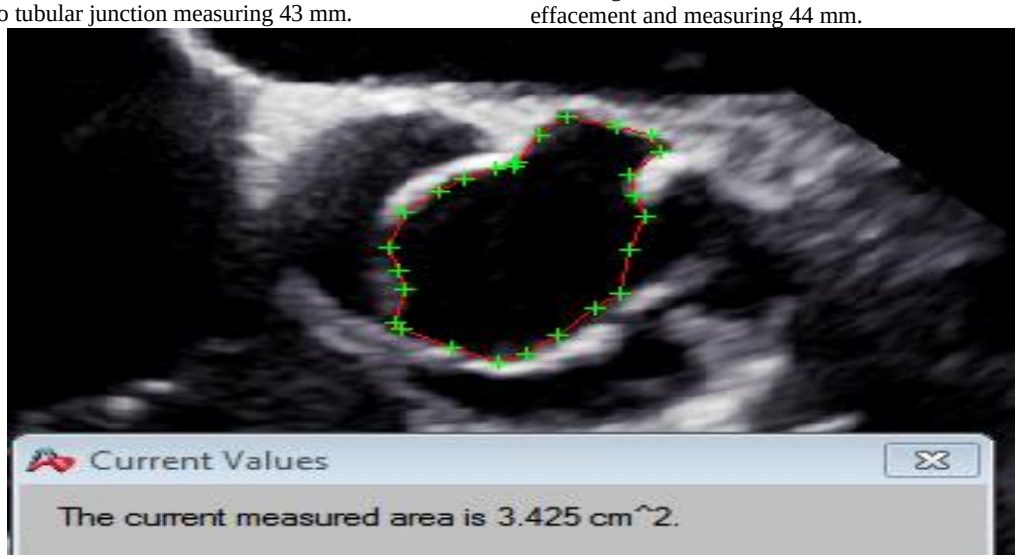
Cardiac catheterization:

Normal coronary arteries

Genetics: Positive for G4.5 (Tafazzin) Negative for NOTCH1, ACTA2, KCNJ2, and GATTA5

Clinical Decision-making:

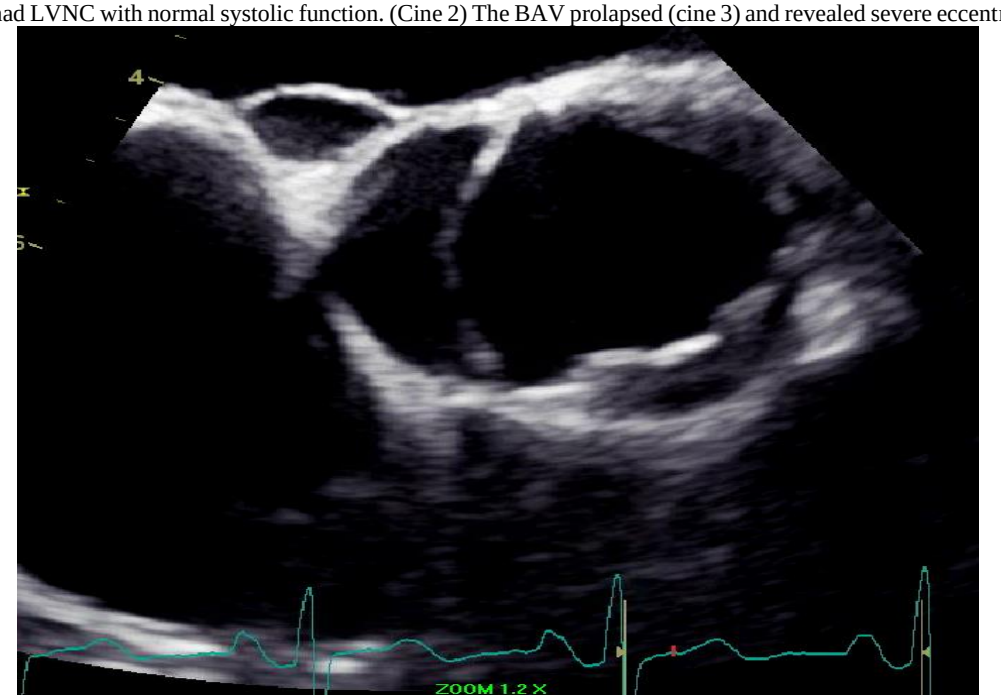
47-year-old with type 2 BAV (Figure 4) and dilated ascending aorta involving the sinus of Valsalva and tubular aorta with sinotubular junction effacement and measuring 44 mm.



Planimetry of the AV with AVA ~ 3.4 cm2

Figure 4: *Planimetry of the AV with the AVA ~ 3.4 cm2*

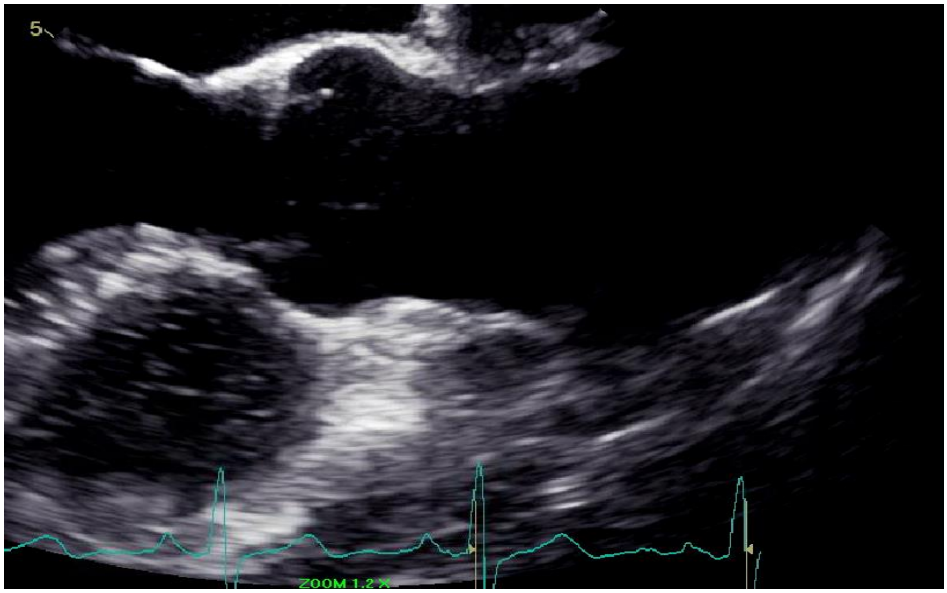
(Figure 5) The patient had LVNC with normal systolic function. (Cine 2) The BAV prolapsed (cine 3) and revealed severe eccentric aortic regurgitation.



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

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

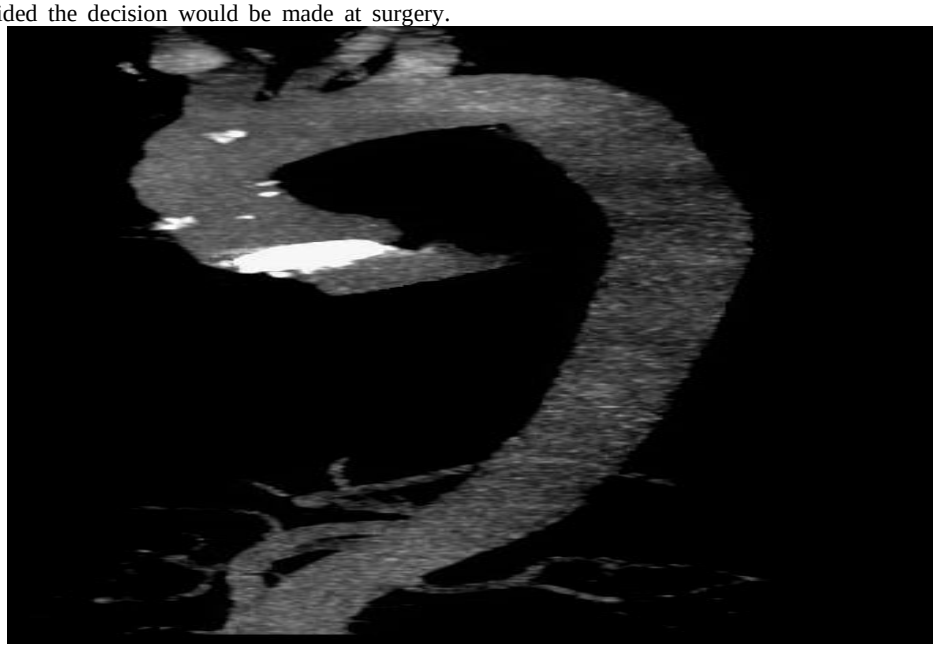
(Cine 4,5) The debate was whether to proceed with a Bentall operation or AVR with aortic wrapping. The TEE suggested a maximum aortic dimension of 44 mm. A CT scan was obtained and measured 43 mm as the maximum dimension of the ascending aorta. (Figure 6).



Dilated ascending aorta measuring 44 mm with a phenotype involving the entire ascending aorta: involving the sinus of Valsalva

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 Sino tubular effacement*

The guidelines recommend aortic root replacement at 45 mm or greater. These guidelines are non-evidenced based and extrapolated from the Marfan guidelines. In type 1 BAV there is data suggesting it is associated with rapid aortic root dilation. Since the valve was type 2 the debate persisted and it was decided the decision would be made at surgery. (Figure 7) The maximum dimension was 40 mm at surgery and according to guidelines an AVR with aortic root wrap was performed. The guidelines for post -operative imaging of the aortic root were recommended.



Cardiac tomography of the ascending aorta measuring 43 mm

Figure 7: *Cardiac tomography of the ascending aorta measuring 43 mm*

Case 3.

Clinical presentation:

57-year-old female presented with six-month history of dyspnea. She also had a history of vasodepressor syncope, diabetes and pulmonary sarcoidosis. Her father had a bicuspid valve.

Examination:

Blood pressure 150/50 Pulse 76 bpm
Carotid upstroke is bounding with rapid collapse
S1 S2 RRR with water hammer pulses
2/4 diastolic murmur

Echocardiography:

Mildly dilated LV cavity

LVEF = 50%
Elevated LV filling pressure manifest as early closure of the mitral valve
Bicuspid AV with eccentric aortic regurgitation

Genetics: Negative for NOTCH1, ACTA2, KCNJ2, and GATTA5

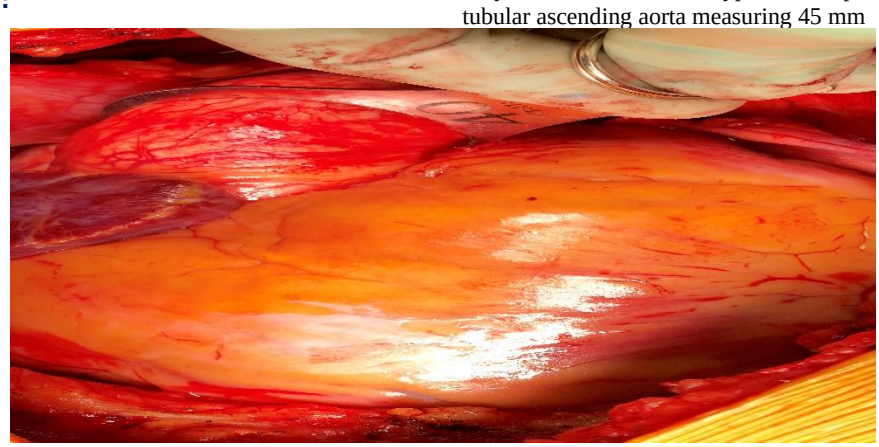
Cardiac catheterization:

Normal coronary arteries

Aortography: Severe aortic regurgitation

Clinical Decision-making:

57-year-old female with type 2 bicuspid aortic valve (Figure 8) and tubular ascending aorta measuring 45 mm

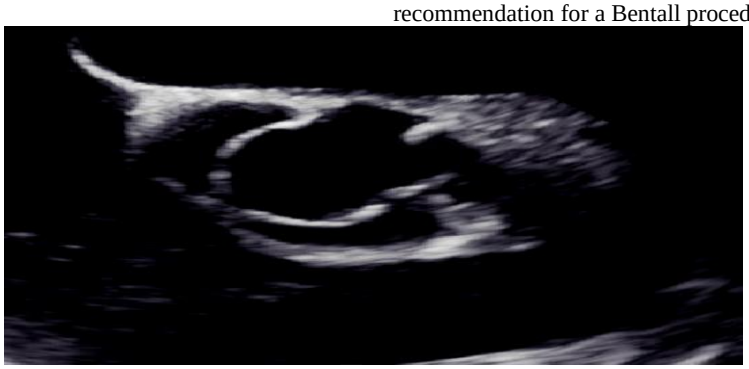


Intraoperative assessment of the ascending aorta measuring 40 mm

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

(Figure 9) and prolapsing AV (Cine 6) with eccentric AR. (Cine 7,8) There was a difference of opinion regarding the severity of the AR from echocardiographic imaging.

The clinical examination suggested severe AR and that was confirmed by aortography. (Cine9). The constellation of finding of severe aortic regurgitation and an ascending aorta measuring 45 mm led to a recommendation for a Bentall procedure.



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

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

Case 4.

Clinical presentation:

62-year-old male presented with increasing fatigue and shortness of breath and a heart murmur. He had a brother with an aortic valve replacement for bicuspid valve.

Examination:

Blood pressure 130/85 Pulse 85 bpm

JVP normal Carotid upstroke normal

S1 S2 RRR with normal pulse

1/4 diastolic murmur with the patient leaning forward from a sitting position

Echocardiogram:

Normal LV size and systolic function

Type 1 bicuspid AV with trivial to mild aortic regurgitation

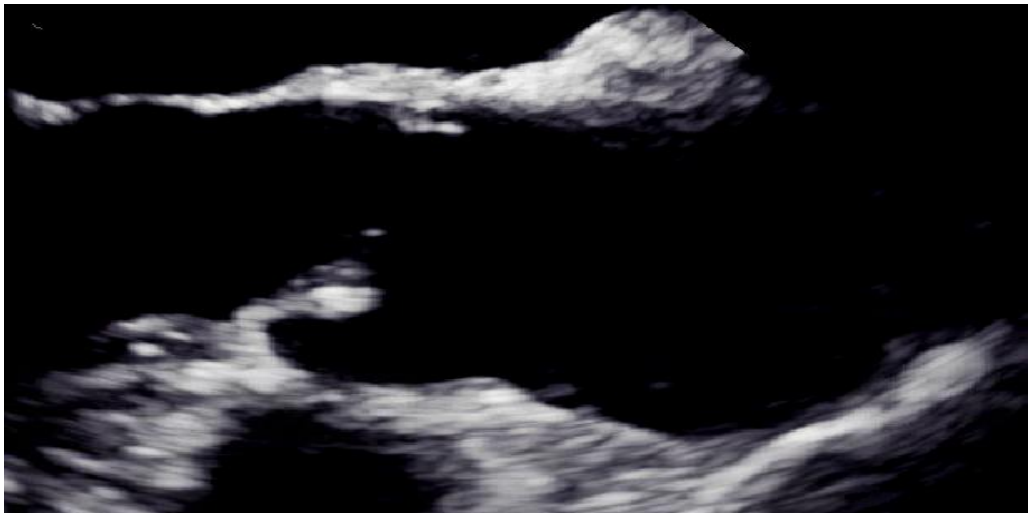
Dilated sinus of Valsalva measuring 53 m

Genetics:

Negative for NOTCH1, ACTA2, KCNJ2, and GATTA5

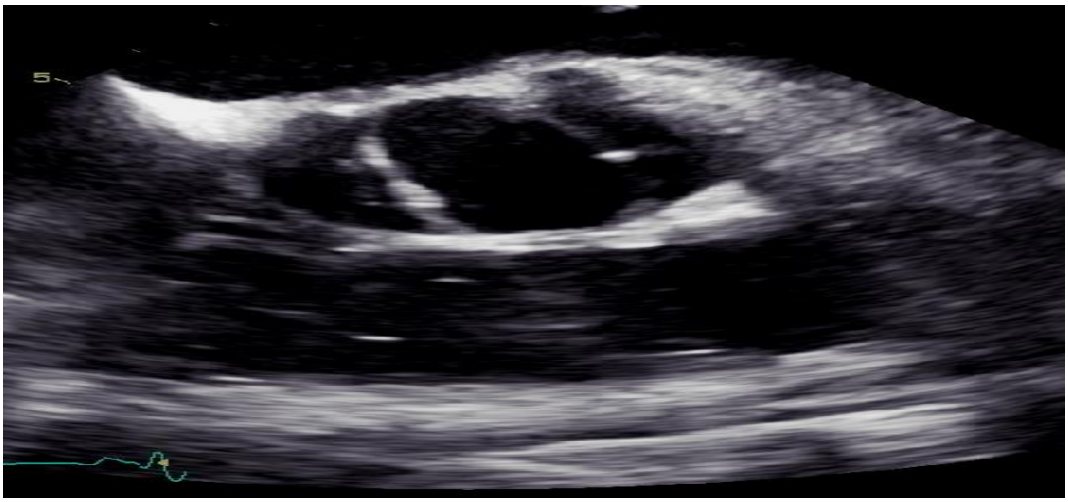
Clinical Decision-making:

62-year-old male with type 1 bicuspid aortic valve (Figure 10) and isolated dilation of the sinus of Valsalva measuring 53 mm (Figure 11) and mild aortic regurgitation. (Cine 10,11,12,13). The recommendation was repeat echocardiogram in 6 months because predominant sinus of Valsalva dilatation phenotype is associated with type 1 bicuspid aortic valves and male sex. This root phenotype has been associated with faster tubular ascending root dilation.



Ascending aorta is tubular phenotype with maximum dimension measuring 45 mm

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



Phenotype: Type 1 bicuspid AV still frame in systole demonstrating right and left cusp fusion

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

Case 5

Clinical presentation:

65-year-old male presented for evaluation of recalcitrant hypertension and exertional shortness of breath. His blood pressure was 160 systolic despite treatment with Dilacor XR 240 mg/day, Toprol XL 100 mg/day, Lisinopril 40 mg/day and Hydrodiuril 25 mg/day.

Examination:

Blood pressure 170/88 Pulse 75 bpm

Normal JVP Normal carotid upstroke

S1 S2 S4 2/4 SEM

Pulses revealed brachial femoral delay

Echocardiogram:

Normal LV size and systolic function

Increased LV wall thickness: septum and posterior wall measure 15 mm

Bicuspid aortic valve with mild aortic regurgitation

Dilated sinus of Valsalva and ascending aorta with effacement of the sinotubular junction – maximum dimension of the aorta is 45 mm

The aortic arch is poorly visualized

PW Doppler of the abdominal aorta revealed decreased pulsatile flow and continuous flow in diastole

Cardiac catheterization:

Mild coronary artery disease

Genetics:

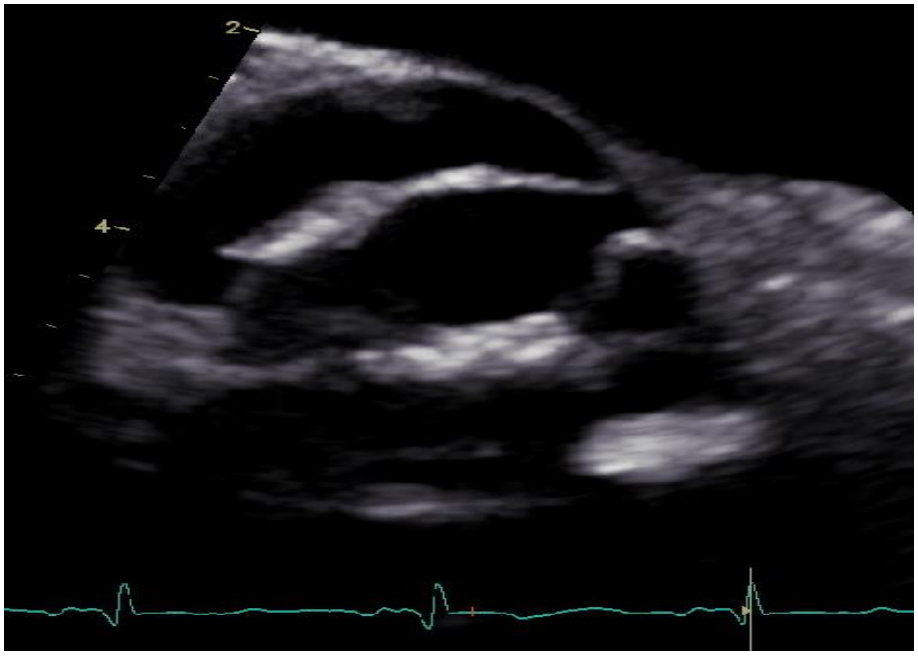
Negative for NOTCH1, ACTA2, KCNJ2, and GATTA5

Clinical Decision – making

65-year-old male with type 3 bicuspid aortic valve (Figure 12) and dilated sinus of Valsalva with tubular ascending aorta and effacement of the sinotubular junction (Figure 13).

Ascending aorta phenotype isolated dilation of the Sinus of Valsalva

Figure 12: *Ascending aorta phenotype isolated dilation of the Sinus of Valsalva*

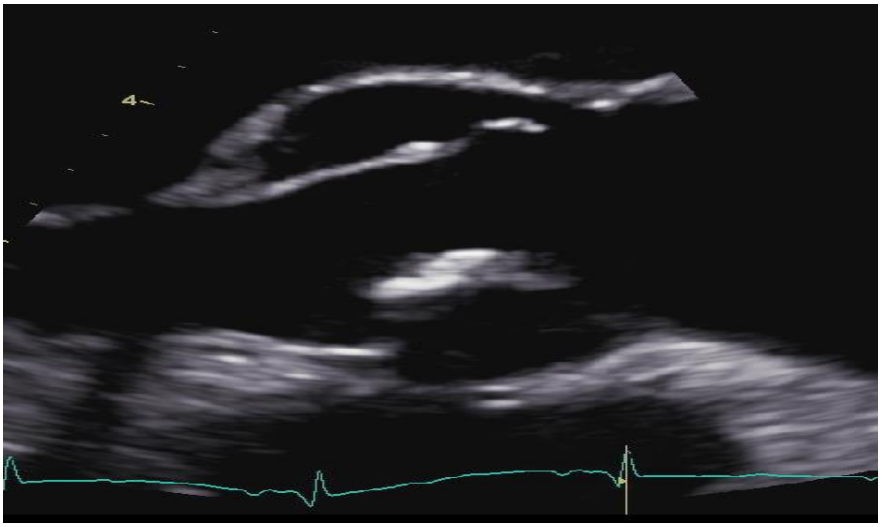


Phenotype: Type 3 bicuspid AV still frame in systole demonstrating left and noncoronary cusp fusion

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

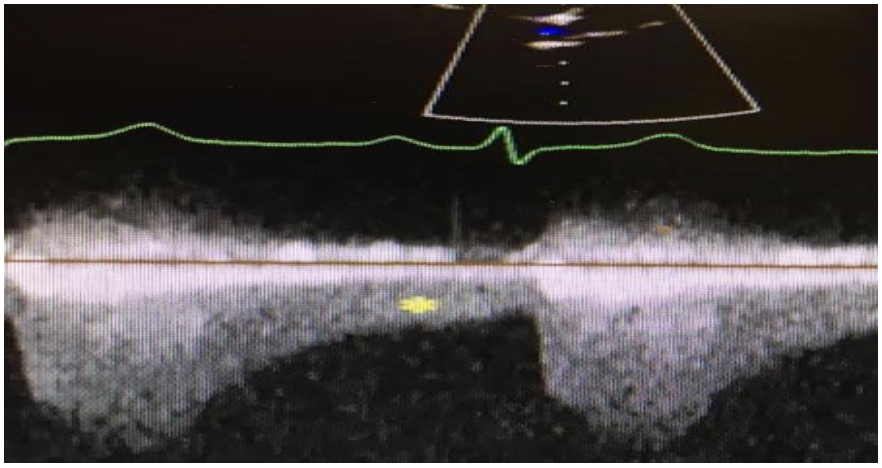
He had resistant to medical therapy hypertension prompting a concern for a secondary etiology. Transesophageal short axis and long axis imaging revealed mild, eccentric aortic regurgitation. (Cine 14, 15) PW Doppler in the abdominal aorta raised a suspicion of coarctation of the aorta. (Figure 14) MRI imaging revealed a coarctation. (Figure 15)

The recommendation was an evaluation by the interventional and surgical team for repair of the coarctation.



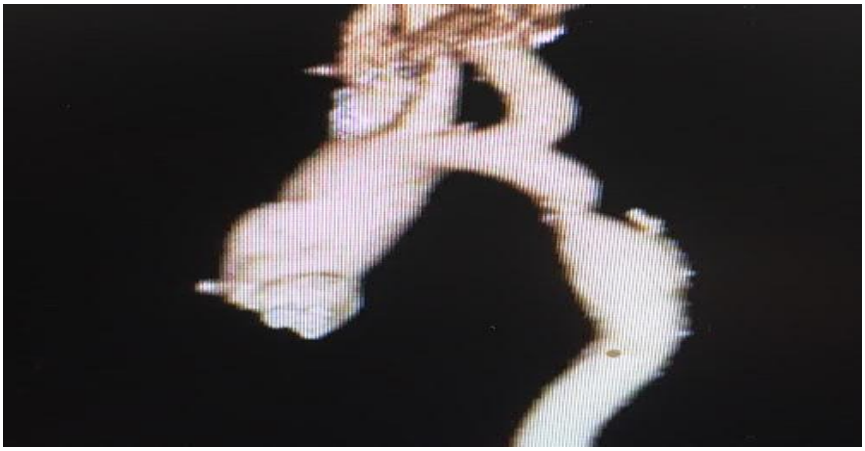
Phenotype of the dilated ascending aorta measuring 45 mm with a phenotype involving the entire ascending aorta: involving the sinus of Valsalva and tubular aorta

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*



PW Doppler of PW Doppler of the abdominal aorta limited pulsatile flow a continuous flow in diastole

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



MRI of the thoracic aorta demonstrating coarctation

Figure 16: *MRI of the thoracic aorta*

Conclusion

The presented case explores the various phenotypic expressions of the bicuspid aortic valve, The cases identify how the clinical presentation, physical examination and multi-modality imaging allow the clinician to make the diagnosis and enlightened clinical decisions regarding surgical treatment.

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