Forme fruste or ‘Incomplete’ bicuspid aortic valves with very small raphes: The prevalence of bicuspid valve and its significance may be underestimated

Jason S. Sperling, Edward Lubat

A R T I C L E   I N F O
Article history:
Received 9 December 2014
Received in revised form 29 January 2015
Accepted 8 February 2015
Available online 10 February 2015

K E Y W O R D S
Bicuspid
Aortic
Anemia
Valve

A B S T R A C T
Background: Bicuspid aortic valve (BAV) comprises a broad spectrum of phenotypes. The importance of BAV in thoracic aortic aneurysm management has been debated. A subtle phenotype of BAV has been identified recently that could impact this debate.

Methods and results: 101 consecutive patients with intact aortic valves operated in the setting of ascending aneurysm between January 2011–January 2014 were retrospectively identified. 20 were excluded because of valve calcification. 91 of 81 remaining had aortic valve phenotype described in operative reports, including tri-leaflet, bicuspid, and diffuse-to-classic valves with small degrees of non-calcific fusion (raphes) at the commissures. Photographs of some three-leaflet valves with very small raphes were obtained. 18/79 (22.8%) had obvious BAVs and 61/79 (77.2%) were initially considered tri-leaflet valves. 18/61 (29.5%) of these had distinct but very small raphes and 12/18 (66.7%) involved the right/left commissure. Moderate or greater aortic insufficiency was found in 13/43 (30%) of patients with tri-leaflet valves, 8/18 (44.4%) with obvious BAVs, and in 9/18 (50%) three-leaflet valves with very small raphes. Retrospective review of computed tomographic, magnetic resonance imaging and trans-esophageal (but not trans-thoracic) echocardiography sometimes identified very small raphes.

Conclusions: Three-leaflet aortic valves exhibiting very small raphes occur in the setting of thoracic aortic aneurysm and aortic insufficiency and may represent forme fruste BAVs. They are sometimes identifiable with high-resolution valve imaging. Without accounting for forme fruste BAVs, the true prevalence and impact of BAV on aortic complications may have been historically underestimated.

1. Background

The diagnosis of bicuspid aortic valve (BAV) in patients with ascending aortic aneurysms has traditionally had implications for patient risk stratification and clinical management. Asymptomatic patients with ascending aneurysms but without identifiable genetic risk factors or family history generally undergo aortic intervention at an aortic diameter ≥ 5.5 cm. The 2010 AHA/ACC Guidelines for the Management of Thoracic Aortic Diseases recommended aortic intervention in the setting of BAV at an aortic diameter ≥ 5 cm (class I), or at sizes even smaller than 5 cm (class IIb) based on a risk ratio of relative aortic size (cross sectional area to height ratio ≥ 10 cm²/m) [1]. The more recently published 2014 AHA/ACC Guidelines for the Management of Patients With Valvular Heart Disease suggested a much more conservative approach with BAV-associated thoracic aneurysms, recommending aortic intervention at aortic sizes > 5.5 cm, just like tri-leaflet valves [2]. This seems to have been largely based on a study that cited a very low incidence of aortic dissection over a long period of observation in patients with aortic dilatation or aneurysm and BAV identified by trans-thoracic echocardiography (TTE) [3]. BAV is the most common genetic syndrome associated with ascending aneurysm, and is estimated to be present in 1–2% of the population of the United States [4]. BAV has also been shown to be significantly heritable, using sequential oligogenic linkage analysis routines [5]. This increases the importance of accurate diagnosis, since the patterns of inheritance are variable, with unpredictable manifestation of valvular or aneurysmal disease in patients and their relatives.

The so-called ‘normal’ tri-leaflet aortic valve has three symmetrical and distinct aortic valve leaflets. BAVs are often thought of as aortic valves that either have two large leaflets or three-leaflet valves with
extensive fusion (raphé) of two of the three leaflets, sometimes referred to as 'functionally' bicuspid valves (Fig. 1). The most common imaging modality used to detect BAV is surface echo, or TTE [6]. Echocardiographic criteria for the diagnosis of BAV have been well-established, and include identification of two large leaflets, leaflet asymmetry, a raphe, an oval-shaped valve orifice in systole, and valve doming in systole [7]. True two-leaflet BAVs represent a rare phenotype (only 7% of BAVs) [8]. In Sievers' series of over 300 patients with BAV identified during surgery, 88% exhibited what was described as type I phenotypes: three distinct aortic valve leaflets, with fusion (raphé) beginning at a single commissure, most often at the right/left commissure in two-thirds of the time [8]. Fig. 2 illustrates the Sievers classification system.

TTE has been known to miss the diagnosis of BAV in certain instances, at least in part due to inconsistent visualization of the aortic valve. A significantly more invasive test, trans-esophageal echocardiography (TEE), is known to have better accuracy for diagnosing BAV due to better overall image resolution [9]. Newer computed tomography (CT) and magnetic resonance (MR) imaging techniques have been reported to be able to identify BAV more reliably than echocardiography in certain patients using cine movies of the valve opening and closing [10–14]. Similar to TEE, these methods have largely depended on differentiating between an oval or fish-mouth shaped (bicuspid) versus a triangular shaped (tri-leaflet) valve opening when assessing the valve appearance in 'open' systole in valve short axis views.

Upon direct inspection of the aortic valve during routine ascending aortic surgery, we sometimes began to notice limited but distinct degrees of non-calcific commissural leaflet fusion (mini-raphé) despite intra-operative TEE and pre-operative imaging predicting purely tri-leaflet valve morphology (Fig. 3). We postulated that this could represent an 'incomplete' or forme fruste phenotype of BAV, whose clinical significance has not yet been defined. Epidemiologic studies describing the clinical impact of BAV on the incidence of aortic dissection and rupture that have not realized this entity could be unintentionally flawed.

2. Methods

We performed a retrospective analysis of 101 consecutive patients with intact aortic valves (no prior valve replacement) operated in the setting of ascending aortic aneurysm by a single surgeon at a single institution between January 2011 and January 2014. Patients with valve calcification or stenosis were excluded in order to eliminate any bias from calcific disease involving the commissures, leaving behind 81 patients for analysis. The aortic valve phenotype was specifically described in 79 of these 81 patients in the dictated operative reports. The Sievers classification system was used when BAV was identified, and the dictated operative reports specified valves with very limited leaflet fusion (raphé) when present. We were able to document the appearance of some of these valves using intra-operative photography (Fig. 3). In aortic valves with 3 leaflets, attention to subtle fusion among any of the 3 commissures was observed by physically lifting and attempting to separate the valve leaflets from one another usingatraumatic forceps to identify the presence of small raphes (Fig. 4). When available, TEE, MR and CT imaging was analyzed either retrospectively or prospectively in order to identify these very small raphes for correlation if possible (Fig. 5).

The Western Institutional Review Board waived the requirement of individual patient consent because of the low risk and retrospective nature of the analysis.

3. Results

Including patients with aortic valve calcification or stenosis, 35/101 (34.6%) had obvious BAVs and 66/101 (65.3%) were initially considered tri-leaflet by TEE in the OR. After excluding patients with valve calcification or aortic stenosis or in whom valve phenotype was not documented, 18/79 (22.8%) had obvious BAVs and 61/79 (77.2%) were regarded as tri-leaflet valves prior to surgery. In 18/61 (29.5%) of valves initially considered to be tri-leaflet, a very small raphe was identified (i.e. 3–6 mm in length), usually at a single commissure, and was dictated in the operative report as consistent with an 'incomplete' or forme fruste phenotype of BAV. When short axis systolic views of the aortic valve were available with CT, MRI or TEE, these valves almost always exhibited triangular-shaped valve orifices, consistent with normal tri-leaflet anatomy. Upon closer inspection of some of these imaging studies, sometimes, the very small raphe could actually be identified (Fig. 5).

Among the 18 non-calcified/non-stenotic three-leaflet valves with very small raphes, the Sievers nomenclature was used in the operative reports to describe the specific location of the raphe, and were regarded as forme fruste BAVs. 12/18 (66.7%) appeared to be type I forme fruste BAVs with limited fusion at a single commissure. Of these, fusion at the right/left commissure was most common, 6/12 (50%), followed by right/non fusion in 4/12 (33.3%) and left non fusion in 2/12 (16.7%). 6/18 (33.3%) of the forme fruste BAVs appeared to be subtle type II BAVs exhibiting fusion at 2 commissures, with all 6 (100%) involving the right/left commissure. Accounting for all of these three apparent forme fruste BAVs, 12/18 (66.7%) had small raphes at the right/left commissure.

Of these 79 non-stenotic valves, moderate (2+) or greater aortic insufficiency was found in 30/79 (38%). This degree of significant AI was found in 13/43 (30.2%) of patients with tri-leaflet valves, 8/18 (44.4%) of patients with obvious BAVs, and in 9/18 (50%) of patients found to have what appeared to be 'incomplete' or forme fruste BAVs. The mean age for all patients was 60.9 with a range of 35–82 years old. The mean age was 54.7 for obvious BAV and 63.1 for both tri-leaflet and forme fruste BAV patients.

---

**Fig. 1.** Commonly recognized aortic valve phenotypes: (a) Normal tri-leaflet valve; (b) 'naturally bicuspid' 2 leaflet BAV; (c) 'functionial' BAV with three leaflets and fusion (arrow) beginning at a commissure, close-up view.
4. Discussion

BAV represents a spectrum of aortic valve phenotypes with the great majority comprising 3-leaflet valves with some degree of commissural fusion (raphes), most often involving and beginning at the right-left commissure. While BAVs with well-developed raphes have been described extensively and studied, values that exhibit limited leaflet fusion (very small raphes) may represent a forme fruste of BAV that has been under-appreciated.

BAV has been debated as marker for aggressive aneurysm behavior [3]. While the 2010 AHA/ACC Guidelines for the Management of Patients With Thoracic Aortic Diseases regard BAV as an adverse risk factor [1], the more recently published 2014 AHA/ACC Guidelines for the Management of Patients With Valvular Heart Disease do not [2]. This more recent stance of benevolence seems to have been based on a lack of firm evidence of BAV as an adverse risk factor in general, and on a natural history study that showed a very low (0.3%) incidence of aortic dissection in patients followed with BAVs over a 25-year interval [3]. It is important to note that this study relied on TTE for the diagnosis of BAV. It is possible, however, that not recognizing the entity of forme fruste BAV (which seems to be very difficult with TTE alone) may have underestimated the true prevalence of BAV in patients with thoracic aneurysm who subsequently suffered aortic dissection or rupture in the community. Importantly, at the current time there is no scientific basis to support any notion that specific BAV phenotype or raphel length has any impact on the incidence of aortic complications. We have now noted forme fruste BAVs in two patients who suffered type A aortic dissection with aortic sizes smaller than 5 cm and no other genetic diagnosis. Initial or cursory visualization of these valves is misleading because they appear much more like tri-leaflet than classical bicuspid valves. Because of the subtle nature of this anatomic finding, it is likely that BAVs with very small raphes have also not been recognized both during aortic surgery as well as during autopsies of patients who suffered death from aortic dissection or rupture.

The sometimes-poor acoustic windows and lower spatial resolution of TTE limit its ability to diagnose BAV in general, and probably even more so in the case of forme fruste BAVs because they lack the classical TTE findings associated with BAV. After positive identification and documentation of forme fruste BAVs during aortic surgery, we have demonstrated retrospective that TEE, CT and MRI can sometimes show these limited degrees of leaflet fusion, by specific careful attention to the appearance of the commissures in the short-axis view of the aortic valve during "open systole" (Fig. 5). While raphes calcification sometimes enhances the ability to diagnose BAV using CT techniques [11,12], in our modest experience, forme fruste BAV has not been consistently associated with calcification along the limited lines of leaflet fusion. Lee et al. published data showing better accuracy of both coronary CTA (using retrospective gating) and MRI compared with TEE in diagnosing BAV, using both the diastolic and systolic appearance of the valve, in a series with very little valve calcification [14]. Importantly, they cited challenges in making this diagnosis when the valve shape was not a "fish-mouth" (rounded) in systole, leading to classification of valves

Fig. 3. Examples of forme fruste BAVs with very small raphes. (a, b): triple (a) and double (b) arrows show a striking difference in appearance between two commissures in the same patient. (c) Distinct and (d) close-up views of the aortic valve in separate patients with forme fruste BAVs; arrows point to very small raphes in both.
in at least 10% with either CT or MRI. They also commented on whether or not the surgeons' intra-operative diagnosis of BAV was reliable, alluding to the need for more attention to realizing BAVs with limited leaflet fusion in the OR. Malaise et al. reported superb accuracy of MRI compared with TTE to diagnose BAV in patients who had indications for valve surgery (with or without aneurysm) [10]. With their technique predicated on triangular vs. oval shaped valve opening, one wonders whether or not the BAV was present but not noticed during surgery in their series as well. With any imaging modality that can visualize the aortic valve in the short axis during systole, specific attention to asymmetry among the commissures seems to be necessary to identify very small raphes, rather than the shape of the valve orifice. Unfortunately, all three imaging modalities have certain limitations. Both CT and MRI have an appeal over TEE from the patient's perspective, due to the invasive nature of TEE. True co-axial imaging of the aortic root is necessary to better identify these limited raphes, which may be more difficult to achieve with TEE. While the spatial resolution of CT can be significantly better than MRI and workstation capabilities allows for more reliable 3-D reconstruction, the need for ionized contrast and radiation exposure render it imperfect as a standard test.

Huntington et al. and others have demonstrated that BAV is heritable, with over 1 in 3 first-degree relatives diagnosed with either BAV or aneurysm utilizing TTE [15]. Our study then implies that using TTE to detect BAV in FDRs may have under-estimated the true degree of heritability. The entity of forme fruste BAV could also explain why certain FDRs of BAV patients seem to inherit 'aortopathy' without seeming to inherit the BAV (i.e. TTE cannot detect forme fruste BAV). Since FDRs of index patients can potentially harbor a significant aneurysm burden or functional valve pathology, early detection of disease in these individuals could have an important effect on the prevention of future aortic complications. The soft finding (not for statistical comparison) that obvious BAV patients were around 9 years younger than trileaflet or forme fruste BAV patients at the time of surgery could be informative as to the natural history of the entity or point to an opportunity to diagnose an at-risk population sooner.

This study is limited by the relatively small number of patients and by observation at a single center. We have documented multiple cases of incomplete BAV with videos, photographs and multiple imaging modalities that corroborated intra-operative observations in some, but not all cases. While it is possible that limited leaflet fusion represents a different clinical entity than BAV, the great majority of forme fruste BAVs we observed in this series had involvement of the right/left commissure (56.7%), with decreasing incidence of the right/non and left/non commissures, which is strikingly consistent with the phenotypic distribution of BAV described in the scientific literature [8]. In embryonic cardiac development, the endocardium, secondary heart field and neural crest contribute progenitor cells that give rise to septal tissues or valve leaflets and mediate cardiac septation and valve development. While the genetic etiology of BAV syndrome is yet to be elucidated, one may speculate as to whether or not the predilection for incomplete valve leaflet separation to occur most frequently at the right/left commissure is related to the embryologic process and local biochemical milieu at the site of aorto-pulmonary truncal septation [16]. Since the process of conotruncal septation and semilunar valve development occurs early in gestation, the author presumes that the final valve morphology is probably determined at an early stage in utero. With

![Fig. 4. Separation of valve leaflets to distinguish small raphes. Using atraumatic forceps, leaflets are gently separated to reveal very small raphes (arrows) in two different patients (a) and (b).](image)

![Fig. 5. Imaging examples of forme fruste BAV. Short axis views of the aortic valve in systole. All have triangular shaped valve orifices. Arrows point to very small raphes on (a) TEE, (b) 4DCT, and (c) MRI.](image)
our observation of dilated ascending aorta and aneurysm in patients with very small rakes, it will ultimately be interesting to determine if these truly are forme fruste BAVs, or if the findings instead represent a valve/aneurysm syndrome that is genetically distinct from BAV.

Forme fruste BAVs with very small rakes are probably difficult to detect with echocardiography, and their subtlety has likely made their identification both in the OR and at autopsy elusive. Better recognition by practitioners across multiple disciplines is necessary to understand the significance of this BAV phenotype, and by extension, the impact of BAV in general. A multi-center registry to track imaging, surgical and autopsy data could be useful in defining the relationship of forme fruste BAV with dilated aorta/aneurysm, aortic dissection/rupture and with valve function over time. Identification and awareness of BAVs with less well-developed rakes may help understand the range of severity of aortopathy and the fate of the ascending aorta and valve durability across a broader range of BAV phenotypes. Such data could provide practitioners with more accurate guidance regarding valvular and aortic implications of BAV.

Grant support
None.

Funding sources
None.

Conflict of interest
The authors report no relationships that could be construed as a conflict of interest.

Acknowledgments
The authors wish to acknowledge Justin Schick, who participated in image analysis and creation of valve models as the concept was being developed.

References