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

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ABSTRACT

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. 79 of 81 remaining had aortic valve phenotype described in operative reports, including tri-leaflet, bicuspid, and difficult-to-classify valves with small degrees of non-calcific fusion (raphe) 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 tomography, 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 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. This entity warrants further study in a prospective multi-center registry.

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 IIa) based on a risk ratio of relative aortic size (cross sectional area to height ratio ≥10 cm^2/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

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extensive fusion (raphe) 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's 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 (raphe) 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-raphe) 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 (raphe) 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 using atraumatic 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 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 least often at the left/non commissure 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 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.

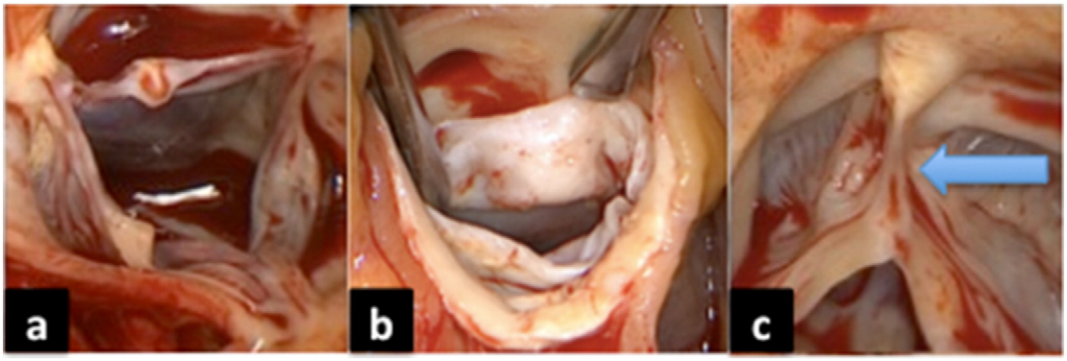

Fig. 1. Commonly recognized aortic valve phenotypes. (a): Normal tri-leaflet valve; (b): 'naturally bicuspid' 2 leaflet BAV; (c): 'functional' BAV with three leaflets and fusion (arrow) beginning at a commissure, close-up view.