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Review article

Bicuspid aortic valve: The most frequent and not so benign congenital heart disease ☆

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ABSTRACT

Bicuspid aortic valve (BAV) is the most frequent congenital heart disease, with an incidence of approximately 1%. It can be silent and associated with normal valve function. However, a series of complications, even catastrophic, may occur with time: valve incompetence, valve stenosis by dystrophic calcification, infective endocarditis, progressive dilatation of the ascending aorta, aortic dissection, sudden death.

The problem of BAV is not just about the number of semilunar cusps, but also the aortic wall. Severe noninflammatory degenerative changes (elastic fiber fragmentation, smooth muscle cells death, mucoid extracellular matrix accumulation=MEMA) are observed in the aortic wall of BAV patients, with intrinsic weakness accounting for progressive aneurysmal dilatation of the ascending aorta, valve incompetence, and wall dissection. The link between valve and aortic wall pathology finds most probably an explanation in the embryology of the arterial pole since neurocrestal cells play a role in the development of both the ascending aorta, aortic arch, and semilunar valves. The frequent association of adult aortic coarctation and BAV provides evidence for this hypothesis. BAV has a significant genetic component as to require screening of first-degree relatives, as outlined by AHA/ACC 2022 guidelines.

1. Incidence of bicuspid aortic valve

In 1886, Osler observed bicuspid aortic valve (BAV) in 1.20% among 800 consecutive autopsies [1], Whaucope, in 1928, reported a rate of 0.50% among 9.966 [2] and Gross 0.56% among 5.000 autopsies [3] in 1937 (Fig. 1).

An in vivo prevalence, by echocardiography, of 0,5% (4 out 817) was reported in primary school children by Basso et al. [4] and of 0.8% (167 out 20.946) in young male conscripts by Nistri et al. [5] (Fig. 2).

Overall BAV doubles the incidence of congenital heart disease. It is present since birth and at first is compatible with normal function. Leonardo Da Vinci postulated that tricuspid shaped aortic valve works much better than the bicuspid or quadricuspid (Fig. 3) [6]. It becomes symptomatic later, at the time of complications.

The biggest puzzle is that BAV is not only a congenital valve defect, it can be also a genetically determined disease of the ascending thoracic aorta (Fig. 4A), because of degenerative changes of the aortic wall (Fig. 4B), at a risk of dissection and rupture. The mechanism is ascribed to fibrillin deficiency with the release of lytic enzymes (metalloproteinases) and damage of lamellar units of tunica media (Fig. 4C and D) [7,8].

2. Anatomy and embryology of the aortic valve

Normal tricuspid aortic valve (TAV) consists of three semilunar, swallow nest cusps, 3 commissures (the highest part of attachment of the cusps at the aortic sino-tubular junction), and 3 interleaflet triangles (Fig. 5).

The histology of the normal ascending aortic wall shows a thin intima, thick elastic media, and a thin adventitia (Fig. 6A). The tunica media consists of about 80 lamellar units with parallel elastic lamellae sandwiching smooth muscle cells and extracellular matrix (Fig. 6B-D). Aorta is like an organ and the smooth muscle cells

Abbreviations: AV, atrioventricular; BAV, bicuspid aortic valve; CHD, congenital heart disease; SD, sudden death; TAV, tricuspid aortic valve; TAVI, transcatheter aortic valve implantation.

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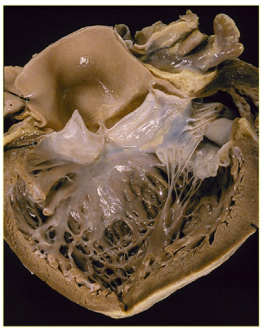

Prevalence of BAV in Autopsy Studies

Author, Year	N.	%
Osler, 1886 [1]	800	1.20
Whaucope, 1928 [2]	9966	0.50
Gross, 1937 [3]	5000	0.56

Fig. 1. Prevalence of bicuspid aortic valve (BAV) in autopsy series. On the left a cardiac specimen with BAV and without raphe.

Prevalence of BAV in children and young people at echocardiography

a

Author, Year	N.	BAV	Prevalence %
Basso et al., 2004 [5]	817	4	0.5
Nistri et al., 2005 [6]	20.946	167	0.8

b

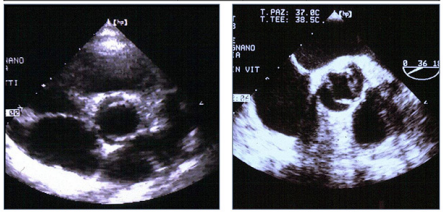

Fig. 2. (a) Prevalence of BAV at echocardiography in children and conscripts. (b) Bicuspid aortic valve detected in an 8 years-old child by screening at Grammar School.

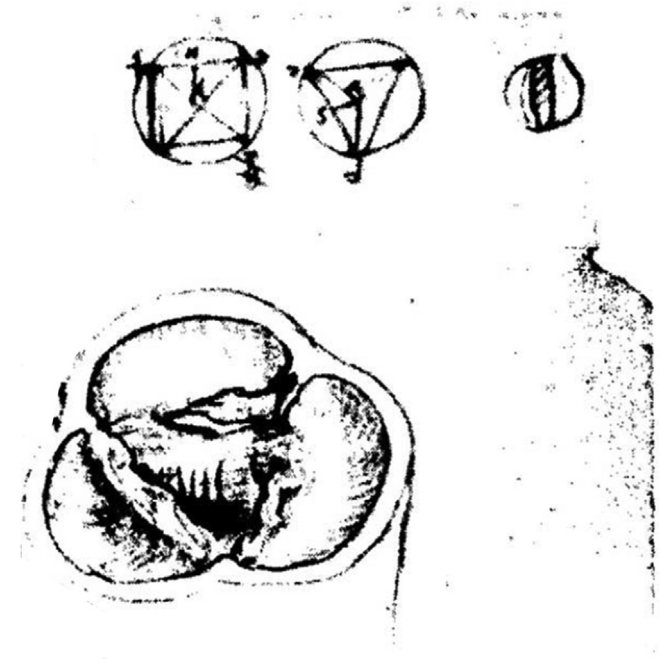

Fig. 3. Leonardo da Vinci drawing of quadricuspid, tricuspid and bicuspid aortic valves. Leonardo claims that tricuspid shape is functionally superior.

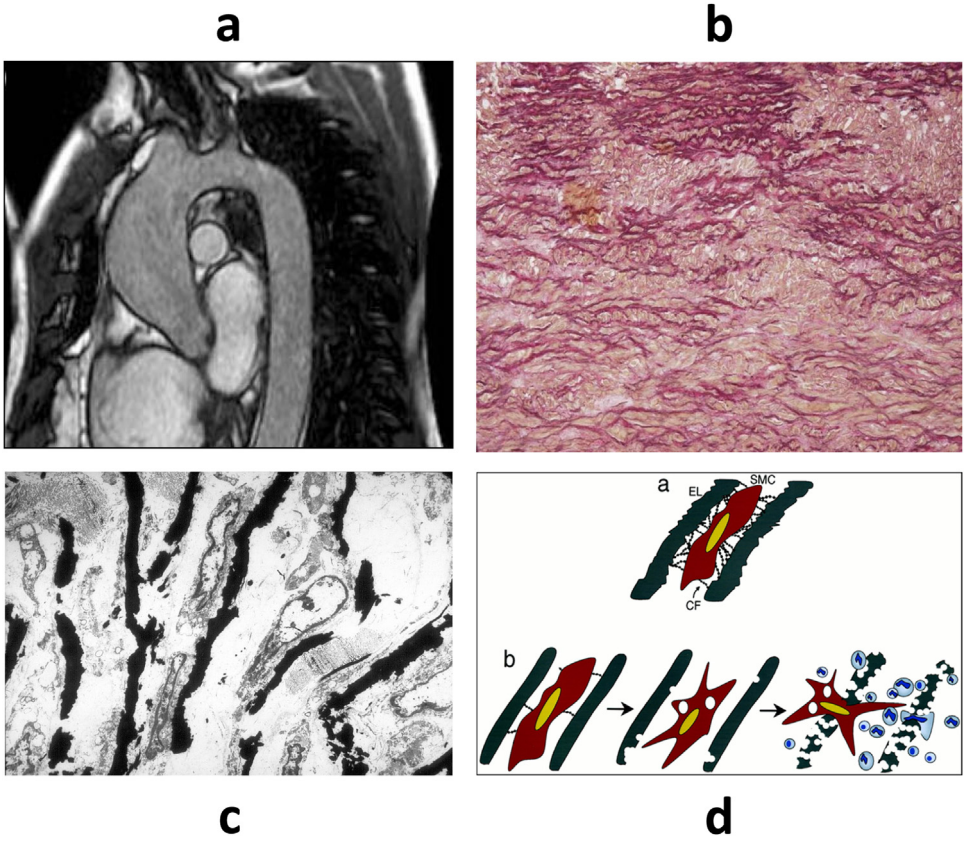

Fig. 4. Dilated ascending aorta in BAV. (a) Angio-TAC. (b) Degenerative changes of the tunica media at histology (Weigert-Van Gieson stain). (c) Fragmented elastic lamellae at transmission electron microscopy. (d) Release of metalloproteinases disrupts elastic fibres.

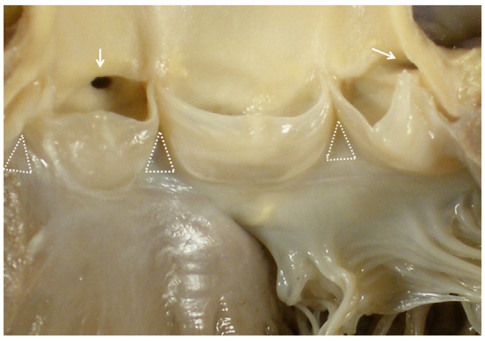

Fig. 5. Normal tricuspid aortic valve. Note the 3 swallow nest cusps, the interleaflet triangles (white triangles) and coronary ostia (white arrows).

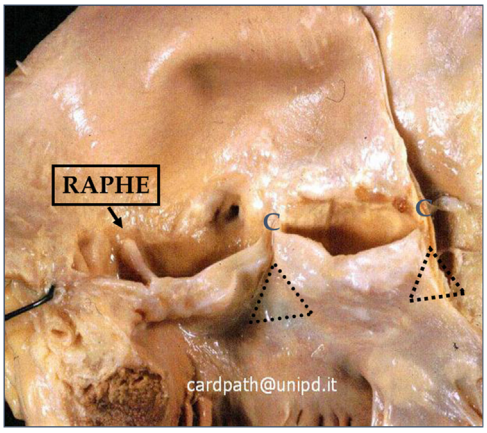

Fig. 7. BAV with a ventral raphe and no interleaflet triangle underneath in a 57 years-old male patient.

are the parenchyma (specific tissue cells) and not the mesenchyme (interstitial cells).

Conversely, BAV consists of two cusps and two interleaflet triangles. One cusp appears divided in two parts by a raphe, underneath which there is no interleaflet triangle (Fig. 7).

The raphe is an "aborted" commissure during embryonic development. Experimental studies, carried out by Sans-Coma et al. [9] on Syrian hamsters affected by inherited BAV, demonstrated that fusion of aortic embryonic valve cushions is the key factor in the formation of congenital BAV (Fig. 8). In other words, the raphe is an aborted commissure occurring during embryogenesis. BAV without raphe does exist as well (Fig. 1).

As far as the specialized AV conduction axis, the His bundle normally runs underneath the membranous interventricular sep-

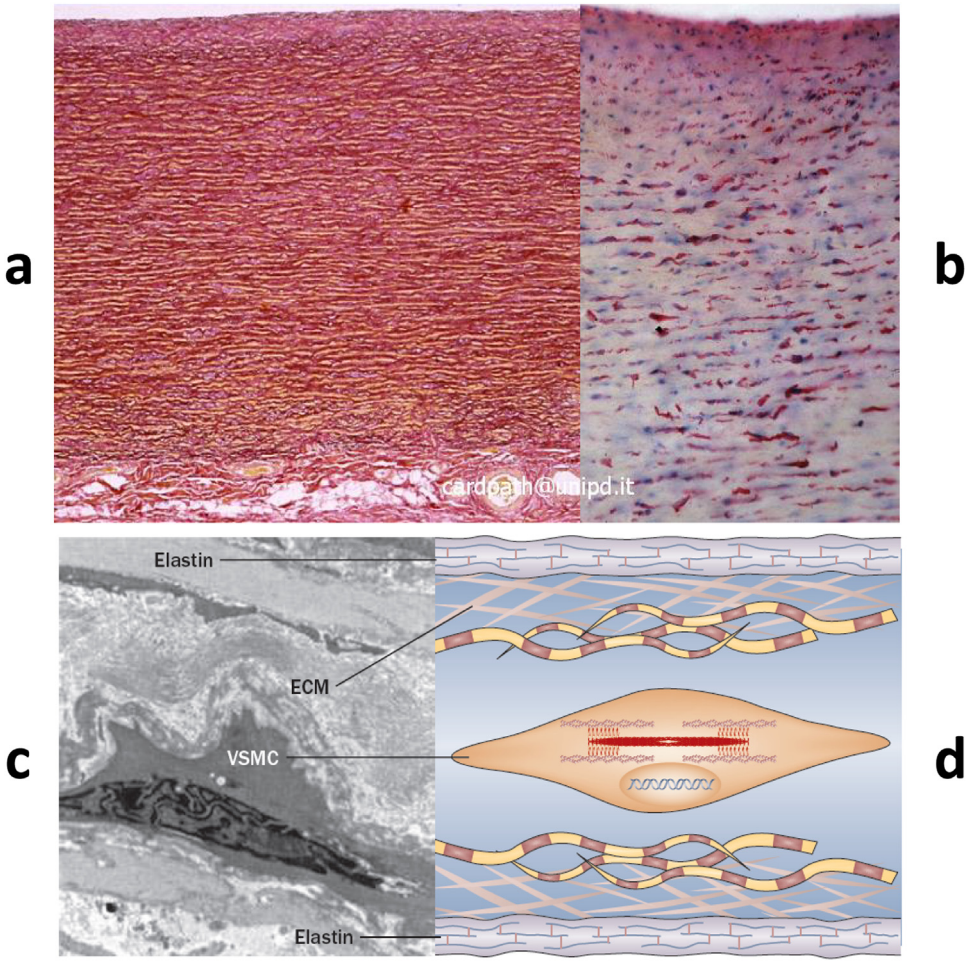

Fig. 6. (a) Histology of lamellar units of the aortic tunica media (Weigert-Van Gieson stain). (b) Immunohistochemistry for smooth muscle cells. (c) Smooth muscle cell at transmission electron microscopy. (d) Drawing of a lamellar unit.

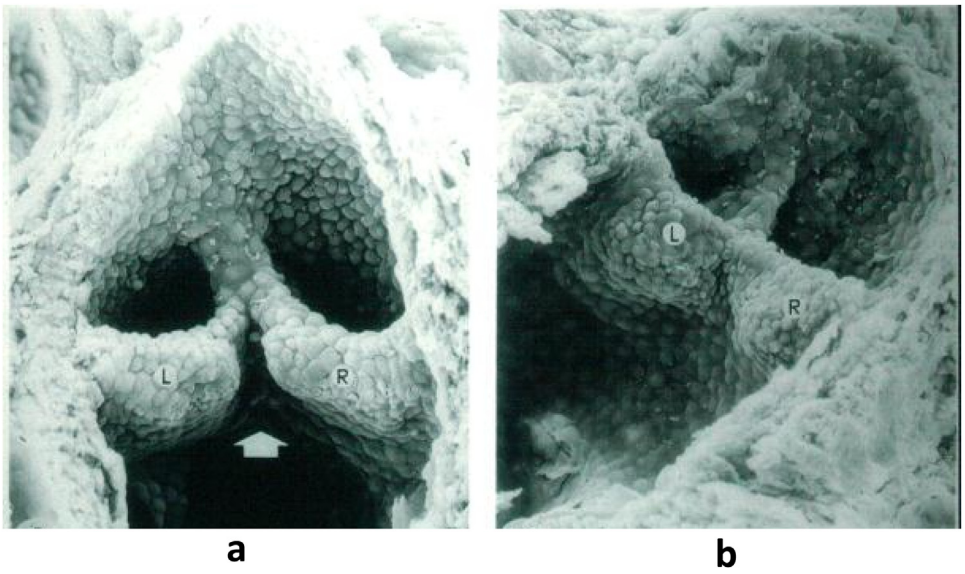

Fig. 8. Normal aortic valve development (a) vs BAV (b) in Syrian hamster embryos. Note that the raphe results from fusion of two cusps.

tum, in correspondence with the interleaflet triangle between the posterior and right anterior semilunar cusps (Fig. 9A). If during development of BAV the posterior and right anterior cusps merge, the membranous septum is located under the raphe over the His bundle course (Fig. 9B).

The heart is of mesoderm origin, however components of the cardiac outflow tracts derives from the neural crest, an ectoderm derivative. The neural crest participates both in the septation of cardiac outflow tracts and the genesis of smooth muscle cells of the ascending aortic wall [10]. Neural crest was postulated as a possible pathogenetic factor of both coarctation of the aorta and BAV, so frequently associated [11].

Among the several types of BAV from commissural fusion, there are two main ones [12,13]. Type 1 (about 70%) derives from merging of the right and left anterior cusps (so called ventro-dorsal arrangement) with both coronary arteries originating from the anterior sinus (Fig. 10A). Type 2 (about 30%) comes from the merging of anterior right and posterior cusps (so called side-by-side arrangement) with the two coronary arteries originating from the opposite sinuses (Fig. 10B).

3. Is BAV a genetically determined malformation?

Familiarity occurs in approximately 9% of BAV and inheritance is consistent with an autosomal dominant pattern with reduced penetrance [14]. Among a total of 309 probands and first relatives, BAV was identified in 74 subjects (24%) [15]. Genome Wide Scan demonstrated that BAV exhibited linkage to chromosomes 18q, 5q, and 13q [16]. These chromosomal regions likely contain genes whose mutation results in BAV.

By the way, Turner's syndrome may be associated to BAV and aortic arch coarctation.

BAV has a significant genetic component and meets the established criteria for disease screening of first degree relatives, according to AHA/ACC 2022 guidelines [17].

Mice lacking endothelial nitric oxide synthase (eNOS) showed a strong association with the presence of a BAV [18]. Moreover, mutations in NOTCH1 were found to cause aortic valve disease, BAV included [19].

Recent genome-wide study (GWAS) in 2.236 BAV subjects and 11.604 controls identified a new risk locus is chromosome 3q29 [20]. The locus encloses a deleterious missense variant in MUC4 (p.Ala4821Ser), a gene that is involved in epithelial-to-mesenchymal transformation.

4. Association with other congenital heart diseases

BAV may be associated with other congenital heart diseases (CHD). Among specimens with cardiac malformations from the Congenital CardioVascular Registry at the University of Padua, BAV was found in 51% of ventricular septal defect (VSD) with aortic arch obstruction, in 37% of adult aortic arch coarctation (Fig. 11), in 20.5% of isolated VSD, in 7.5% of AV canal, in 2% of Tetralogy of Fallot and only 1% of complete TGA. The latter would suggest that it is incidental occurrence like in normal population. All together BAV was observed in 67 of 474, CHD (14%) [21].

5. Natural history and complications

BAV is a structural defect present at birth (=CHD), but it becomes symptomatic with time in youth and adulthood, even with fatal complications.

a) BAV stenosis by dystrophic calcification

In surgical pathology series of calcific aortic stenosis (Fig. 12) BAV accounted from 31% to 46%. Our last surgical pathology investigation of 181 consecutive stenotic aortic valves removed at surgery, senile tricuspid aortic (TAV) stenosis accounted for 63%, BAV for 22% and rheumatic for 15% [22]. BAV calcific aortic stenosis (Fig. 13) manifests itself about 10 years earlier than TAV senile aortic stenosis [23].

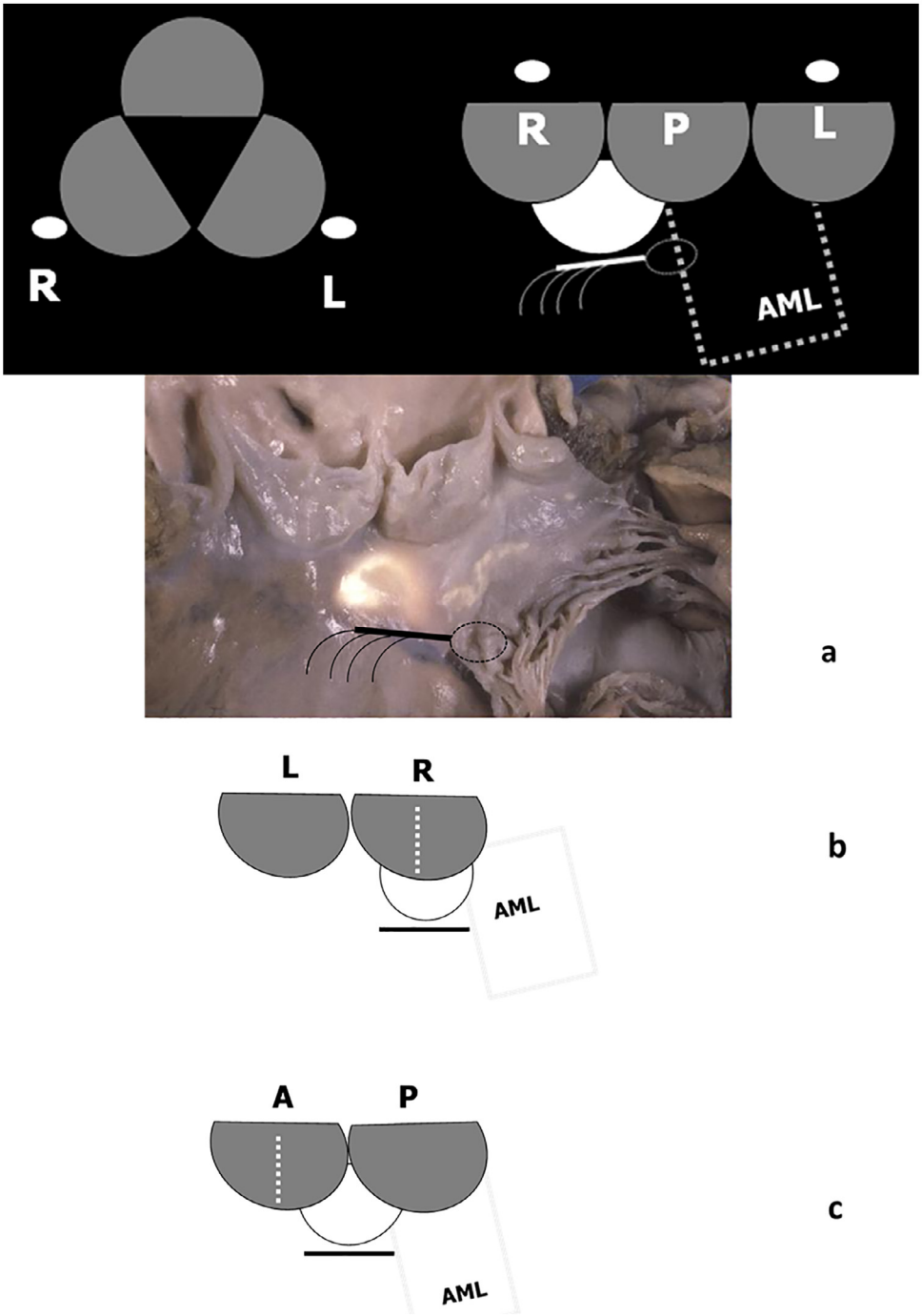

Fig. 9. Course of the His bundle (straight horizontal line) in the normal heart (a) and in BAV (b and c). (a) The course of His bundle is underneath the membranous septum. R=right anterior cusp and right coronary artery P=posterior non coronary cusp. L=left anterior coronary cusp and left coronary artery. AML=anterior mitral leaflet (b) BAV by fusion of the posterior and right anterior cusps. The raphe is just over the membranous septum and the His bundle. L=left cusp in bicuspid valve. R=right cusp in bicuspid valve. (c) BAV by fusion of the anterior right and left cusps. The membranous septum and His bundle is far from the raphe. A=anterior cusp in bicuspid valve. P=posterior cusp in bicuspid valve.

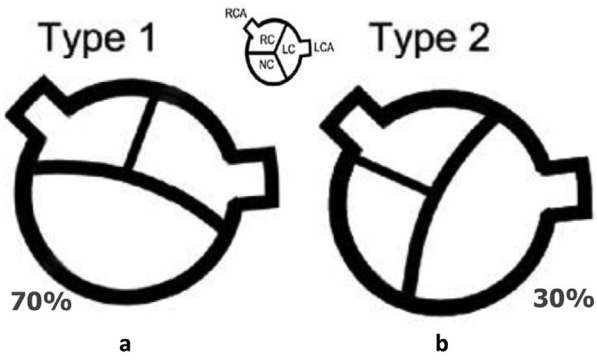

Fig. 10. The most frequent shapes of BAV. (a) Type 1 (ventro-dorsal cusps). (b) Type 2 (side by side cusps).

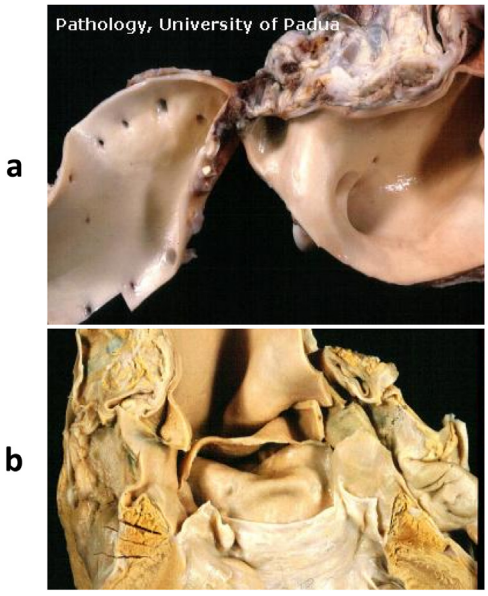

Fig. 11. (a) Aortic arch coarctation. (b) Cardiac specimen with BAV, intimal tear, dilated and dissected ascending aorta.

Etiology of aortic valve stenosis
Surgical pathology studies

Author, Year	Country	N.	Senile	BAV	RVD	Others
Subramanian et al., 1984	USA	374	10	**46**	35	10
Cormier et al., 1988	France	675	45	**31**	16	8
Passik et al., 1987	USA	646	33	**38**	24	5
Turri et al., 1990	Italy	140	34	**34**	38	5

BAV= bicuspid aortic valve; RVD= rheumatic valve disease

Fig. 12. Surgical pathology series of aortic stenosis by senile tricuspid, BAV and RVD (rheumatic valve disease). BAV rate varies from 31% to 46%.

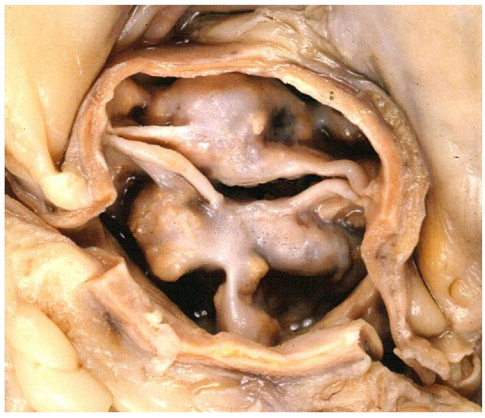

Fig. 13. Type 1 autopsy specimen with BAV stenosis by dystrophic calcification in a 65 years-old patient. Note the raphe and the origin of both coronary arteries from the anterior Valsalva sinus.

b) Infective endocarditis

Nowadays BAV represents the most frequent predisposing factor of infective endocarditis. In a recent surgical pathology experience from the Mayo Clinic, BAV was the underlying predisposing cardiac pathological substrate (25% of cases) [24]. BAV can be the target of infection in drug addicts (Fig. 14).

BAV cusp tears or perforation by infective endocarditis may account for acute or chronic aortic valve incompetence (Fig. 15).

Infective extension to the Valsalva sinuses may account for aneurysms, fistulae into the atria and involvement of the conduction system with av block [25].

BAV belongs to non-cyanotic congenital heart disease (CHD). According to the guidelines of European Society of Cardiology on prevention, diagnosis and treatment of endocarditis, antimicrobial prophylaxis is recommended for people with BAV at the time of dental procedures or other risk maneuvers or bacteremia [26].

c) BAV incompetence

In surgical pathology series of aortic valve incompetence (Fig. 16) BAV accounted from 5% to 20%.

Acute aortic regurgitation may occur in BAV patients also due to rupture of a cord attaching the raphe to the aortic wall at the sinotubular junction [27].

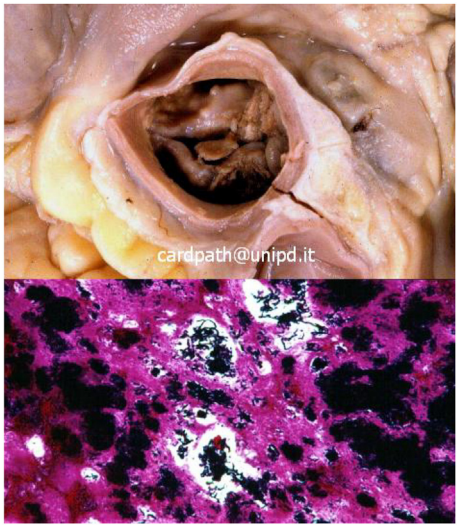

Fig. 14. Infective endocarditis by staphylococcus aureus an 18 years-old drug addict. (a) cardiac specimen with BAV and vegetations. (b) Cocci colonies, Gram positive.

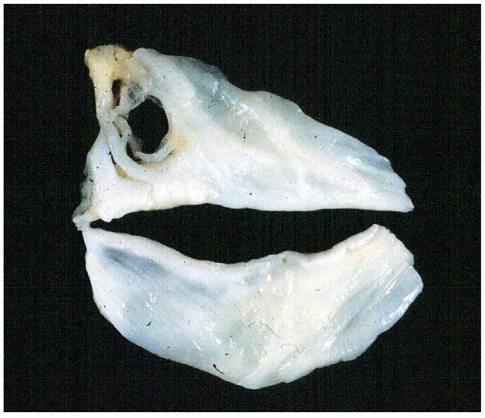

Fig. 15. Large perforation of a BAV leaflet by previous infective endocarditis, resulting into chronic valve regurgitation. Female, 42 years-old.

Etiology of Aortic Regurgitation
Surgical Pathology Studies

Author, Year	Country	N.	RHD %	TAV %	I.E. %	BAV %	Others %
Olsen et al., 1984	USA	225	46	21	9	20	4
Guiney et al., 1987	UK	72	26	34	21	9	10
Turri et al., 1990	Italy	254	20	59	11	7	3
Michel et al., 1991	France	313	38	35	11	5	11

BAV=bicuspid aortic valve; RVD=rheumatic valve disease; TAV=tricuspid aortic valve

Fig. 16. Surgical pathology series of aortic valve regurgitation. BAV aetiology accounts from 5% to 20%.

Anulo-aortic ectasia is one of the main cause of aortic regurgitation. However, incompetence may be also due to isolated malformation of the cusps (Fig. 17).

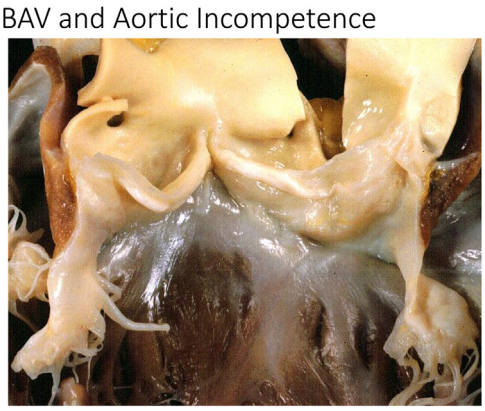

Fig. 17. Autopsy specimen with BAV incompetence due to malformed cusps. Note thickneed free margin of the cusps, probably due also to longstanding wear and tear. Male, 52 years-old.

d) BAV aortopathy

Association of congenital BAV with "Erdheim's idiopathic cystic medial necrosis" [28] of the aortic wall was first proven by McKusick in 1972 [29].

In the seminal work of Maude Abott, BAV was found to be associated with ascending aorta rupture [30]. She argued "for a weakness of the aortic wall." She also reported aortic coarctation to be particularly frequent in BAV with aortic dissection (Fig. 11).

A significant number of people affected by BAV undergo progressive dilatation of both sinusal and tubular part of the ascending aorta, due to degenerative changes of the tunica media (medionecrosis, elastic disruption, mucoid extracellular matrix accumulation) [31] with lamellar units disappearance and loss of elastic properties of the aorta (Fig. 18).

Deficient fibrillin I content, not genetically determined as in Marfan syndrome, was advanced as a trigger of lytic metalloproteinases release with disruption of lamellar units [8] (Fig. 4).

The phenomenon starts early in the youth. Half of 20 years old conscripts with BAV showed at echocardiography screening a

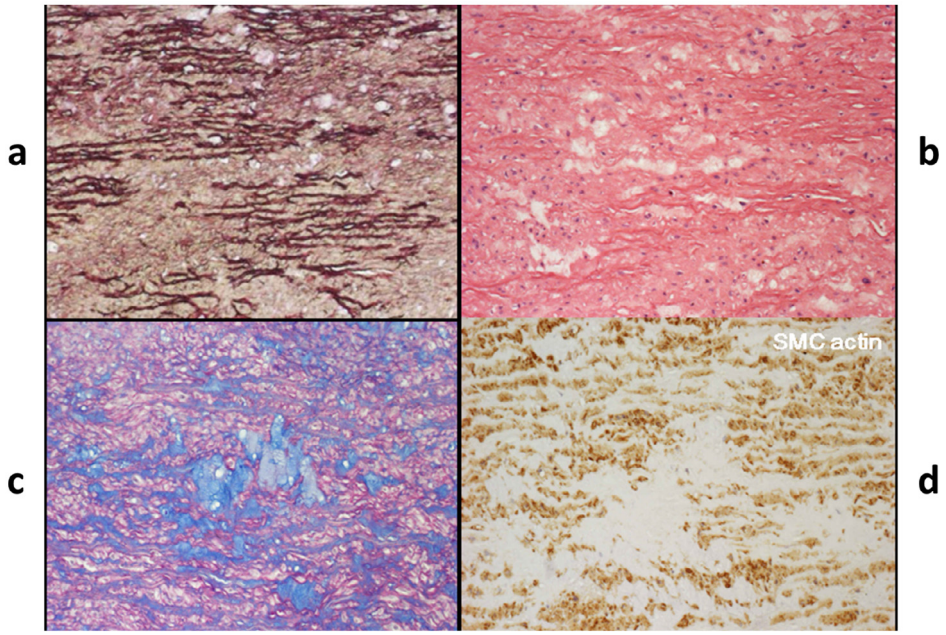

Fig. 18. Degenerative changes of the aortic tunica media in BAV aortopathy. Weigert-Van Gieson stain (a) and H&E (b), Alcian-Pas stain (c) and smooth muscle cells immunohistochemistry (d).

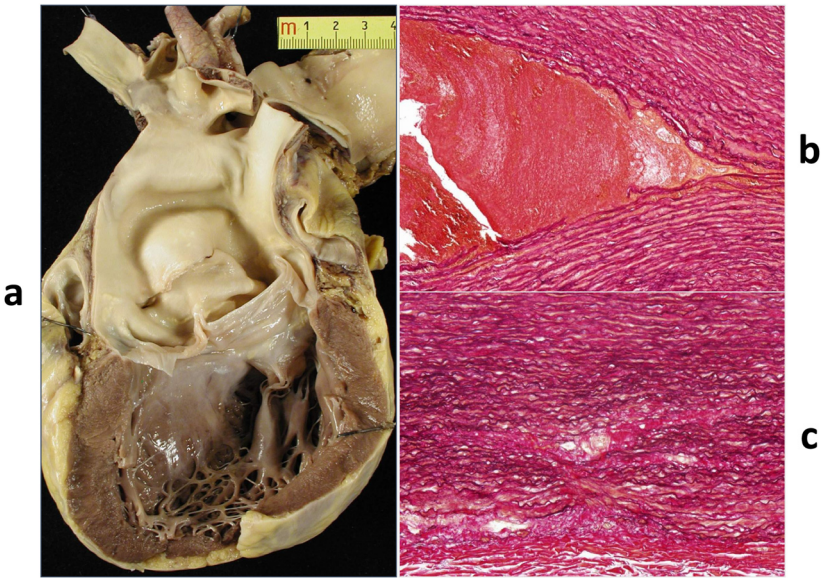

Fig. 19. Aortic dissection in a 38 years-old BAV male: (a) Remarkable dilatation (7 cm diameter) of ascending tubular aorta with intimal tear. (b) Dissection of the tunica media. Weigert-Van Gieson stain. (c) Patchy mucoid extracellular matrix accumulation (MEMA) in the tunica media. Alcian Pas stain.

Frequency of BAV In Aortic Dissection

Author, Year	N.	BAV (%)
Gore, 1952	85	13
Edwards, 1978	119	9
Larson, 1984	161	11
Giusti, 1990	87	12

Fig. 20. BAV from autopsy series of aortic dissection. The rate of BAV varies from 9% to 13%.

large ascending aorta at sinusal, sino-tubular and/or tubular portions [32].

An epidemiological study of BAV subjects with normal function in Olmsted County demonstrated that 23% had developed aortic aneurysm within 25 years follow-up and that aortic dissection occurrence was significantly higher than in general population [33].

According to Nistri et al. [34] BAV is more prevalent in Marfan patients (4.7%) than in general proband (0.5%). The association of the two disorders seems to cause a more severe involvement of the aorta.

Knowledge of normal values of aortic root diameter is mandatory to establish aortic dilatation, to follow up the patients overtime and to plan appropriate therapeutic inventions [35,36].

e) BAV, aortic dissection and sudden death

Aortopathy in BAV patients is at risk of dissection and sudden death. Accelerated structural degeneration of the tunica media with progressive dilatation of the aorta can account for intimal tear, dissection and external rupture, probably precipitate by hypertensive attack (Fig. 19).

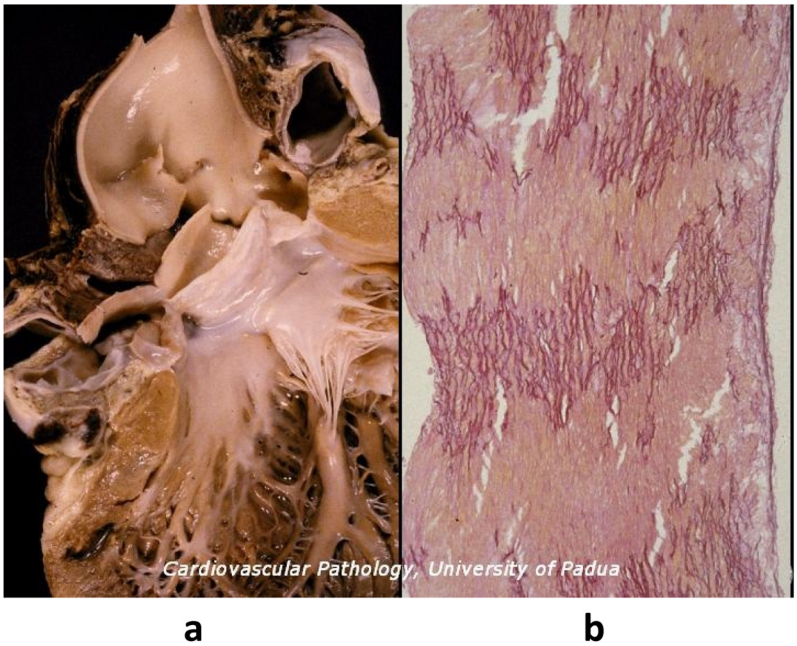

Fig. 21. Aortic dissection in a 35 years-old male affected by BAV: (a) Gross view of the "explosion" of the aorta with intimal tear and wall dissection. The diameter of ascending tubular aorta was 3.8 cm. (b) Extensive loss of elastic fibres in the tunica media. Weigert-Van Gieson stain.

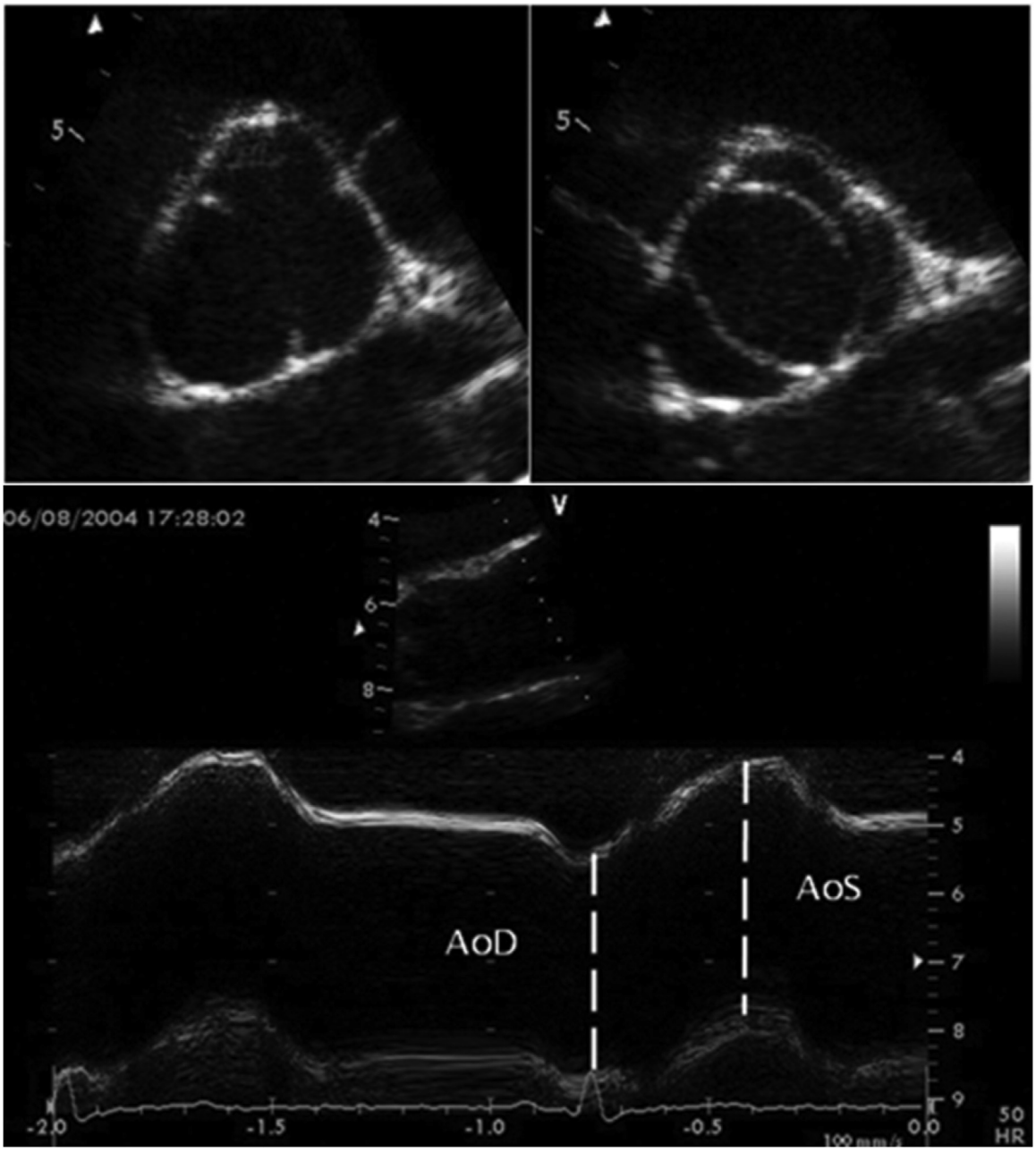

Fig. 22. The impaired systo-diastolic excursion of the aortic wall at 2D echocardiography in 28 years old BAV patient with stiffness (degenerative changes of the tunica media?).

Autopsy experience on prevalence of BAV in subjects with aortic dissection varied from 9 to 13% (Fig. 20), ten times then the rate of BAV in normal population. These data strongly are in favor of a causative link between BAV and aortic dissection.

BAV may remain asymptomatic after birth for decades. Screening by 2D eco with Doppler should be carried out in any children for identification of affected subjects. When BAV is identified, individuals should be followed up to define the optimal timing of intervention, before complications occur.

6. Treatment

Surgical replacement of both aortic valve or ascending aorta (Bentall procedure) is due when the diameter exceeds the threshold of 4.5 cm [36]. In patients with BAV, the Bentall procedure has an operative mortality no worse than isolated aortic valve replacement [37].

A policy of prophylactic replacement of even normal or mildly enlarged ascending aorta at the time of aortic valve replacement (or for any other cardiac surgical procedure) is going to be taken into consideration in patients with BAV [38].

In our long standing experience of pathology of sudden death (SD) in subjects aged less than 35 years-old, aortic dissection accounted for SD in 3.5%, half of them due to BAV with aortopathy [39]. In two cases, aortic rupture occurred with the maximal diameter of the ascending aorta of 3.8 cm (Fig. 21) and 4.2 cm, respectively, thus casting doubts on the threshold of 4.5 cm for surgical intervention. The speed of diameter increase is much more reliable than the diameter "per sé," suggesting the need of frequent periodical 2D echocardiography check.

The diameter of the aorta is the current landmark to clinically assess the severity of tunica media structural deterioration in BAV aortopathy. However, simple measure of aortic diameter may fail to early identify the severity of the aortic wall degeneration in BAV subjects. Even in the absence of severe dilatation, stiffness of the aortic wall with loss of aortic elasticity may be assessed by echocardiography of the aorta, with the evaluation of systo-diastolic range [40] (Fig. 22).

As far as Bentall procedure (concomitant replacement of both aortic valve and dilated ascending aorta) [41], a decellularized homograft has been tested in juvenile sheep as a scaffold for seeding self-smooth cells in the media with biological compatibility, preventing immune reaction and dystrophic calcification [42]. The homograft undergoes transformation into an autograft [43]. Whether this autograft may be effective at distance in BAV pts, without the risk of disease recurrence, remains to be proven.

Repopulation of the tunica media by smooth muscle cells might represent a mechanisms of biological repair, preventing prosthetic replacement of the ascending aorta [42,43]. There are promising data from experiments in sheep, to be confirmed in clinical practice.

Moreover, it is controversial whether also the tunica media of the pulmonary artery is also affected in BAV patients and consequently unsuitable as autograft in Ross operation [44,45].

Aortic stenosis by BAV had been considered contraindicated to transcatheter aortic valve implantation (TAVI) because of asymmetric, oval shaped annulus, leading to prosthesis deformation and causing paravalvular leak [46]. This contraindication has been disproved at least in selected high risk patients [47].

Roberts recommended a policy of prophylactic replacement of the ascending aorta in cases of BAV, even in the presence of normal or mild enlargement of the aorta [48]. Bentall procedure has a superior long term survival and lower rate of aortic re-operations [36]. Wrapping of the ascending aorta with Dacron mesh may be an alternative for treatment of aneurysmal dilatation [49].

7. BAV and hemodynamic impact on the aorta

The hemodynamic factors and mechanism of early failure of congenital BAV have been experimentally investigated in 2004 by Robicsek at al. with computerized digital modelling on cryopreserved, non-diseased BAVs [50]. Unlike normal tricuspid valve, the function was characterized by excessive folding and creasing, extended area of cusps contact, significant stenosis with asymmetrical flow patterns and turbulence. In the mind of the authors, these abnormal flows might cause higher and uneven stress distribution in the ascending aorta, with dilatation and risk of dissection.

In 2005 Guntheroth and Spiers [51] wondered “Does aortic root dilatation with BAV occur as a primary tissue abnormality or as a relatively benign poststenotic phenomenon?.” Their answer was: “The most important issue is whether we should unnecessarily frighten 1% to 2% of the general population who have BAVs with the specter of aortic dissection.”

The wonder deserves a clarification. Our paper tried to do.

P.S. All the gross and histologic pictures belong to the Cardiovascular Pathology Registry, University of Padua, Italy.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Gaetano Thiene: Conceptualization, Data curation, Investigation, Methodology, Resources, Supervision, Writing – original draft, Writing – review & editing. **Stefania Rizzo:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Resources, Supervision. **Cristina Basso:** Conceptualization, Data curation, Investigation, Methodology, Resources, Supervision, Validation, Visualization.

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