Chapter 15
Bicuspid Aortic Valve

Yskert von Kodolitsch and Harald Kaemmerer

Abstract Bicuspid aortic valve (BAV) has a prevalence of 0.5–1.39% in the general population. The prevalence of BAV in aortic dissection is 3.5–11.8%. Unfortunately, the incidence of aortic dissection in BAV remains unknown. The etiology of BAV is polygenetic, where environmental factors and unknown genetic factors seem to interact to cause BAV. In some instances, chromosomal aberrations or defined gene defects cause BAV.

Congenital BAV must be distinguished from acquired BAV. Congenital aortic valve malformations differ by number of cusps, ranging from one to five. BAV cusps can be subclassified according to patterns of calcification, severity of calcification, presence of a raphe, and fusion of cusps. We tend to perceive BAV as an isolated congenital heart defect. However, we identified 20 well-defined syndromic, complex, or isolated congenital heart defects that are associated with BAV disease, some of which are apparently quite frequent.

BAV aortopathy can be classified according to presence and type of aortic valve dysfunction, shape of the proximal aorta, aortic arch involvement, and coexistence with coarctation of the aorta.

Factors that may increase the risk for aneurysmal formation, aortic rupture, or dissection in BAV comprise aortic valve characteristics, comorbidities of BAV, and behavioral factors. Candidates for biomarkers of BAV aortopathy comprise a family history with early dissection or death, increased aortic growth rates, proximal aortic shape, aortic stiffness and aortic elasticity markers, aortic wall shear stress, endothelial dysfunction, and serological biomarkers.

Keywords Bicuspid aortic valve • Aortic dilatation • Aortic regurgitation • Aortic stenosis • Aortopathy • Genetics

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K. Niwa, H. Kaemmerer (eds.), *Aortopathy*, DOI 10.1007/978-4-431-56071-5_15

List of Abbreviations

AOA	Aortic arch
ASC	Ascending aorta
AVA	Aortic valve annulus (anatomical ventriculo-arterial junction)
AVR	Aortic valve replacement
BAV	Bicuspid aortic valve
BAV-COA	Coexistence of bicuspid aortic valve and coarctation of the aorta
BAV-I	BAV with predominant insufficiency
BAV-LN	BAV with fusion of the left and noncoronary cusp
BAV-MO	BAV morphotype
BAV-RI	BAV with balanced stenosis and insufficiency
BAV-RL	BAV with fusion of the right and left coronary cusp
BAV-RN	BAV with fusion of the right and noncoronary cusp
BAV-S	BAV with predominant stenosis
CHD	Congenital heart defect
COA	Coarctation of the aorta
DESC	Descending thoracic aorta
HTN	Arterial hypertension
SOV	Sinus of valsalva
STJ	Sinotubular junction
TAV	Tricuspid aortic valve

15.1 Introduction

Bicuspid aortic valve (BAV) may simply be viewed as "an aortic valve that has two cusps instead of three," and BAV aortopathy may simply be considered as "post-stenotic dilatation of the ascending aorta."

More than 500 years ago, Leonardo da Vinci explained and depicted BAV for the first time. Paget recalled in 1844 the tendency of the BAV to develop disease, Peacock mentioned the tendency of these valves to develop obstructions or regurgitation early, Osler described the predilection of these valves to infective endocarditis, and Victor Babes (1891), in Germany, and 3 decades later Maude Abbott, in North America (1927), commented on an association between congenital BAV and aortic aneurysm, dissection, and rupture, and since Abbott described aortopathy in BAV [1]. Since then, the literature on BAV disease has grown into complex field on detailed and conflicting knowledge.

15.2 Frequency of BAV and BAV Aortopathy

Besides mitral valve prolapse, BAV is the most frequent congenital heart defect in the general population. Autopsy studies and echocardiographic screening studies yield strikingly similar results on the frequency of BAV in the general population. The prevalence ranges from 0.5 to 1.39% at autopsy and between 0.5 and 0.9% on echocardiographic screening. Autopsy studies and a clinical register of aortic dissection assess the prevalence of BAV in individuals with aortic dissection. Both types of studies report BAV in 7.5–11.2% and 3.5–11.8% of aortic dissections. Nistri et al. found aortic dilatation, which they defined with diameters >2 standard deviation above normal, in 68.9% of young Italian conscripts with BAV at echocardiographic screening [2]. The widely cited 2% prevalence of BAV appears to stem from a single autopsy study published in 1923 [3]. Cohort studies that register aortic events in BAV report on 0.5–0.8% incidence of aortic dissection with various difference of intervals of follow-up, treatment standards, reasons for inclusion, and ages at inclusion into the cohort. Hence, the accurate prevalence and natural history of BAV aortopathy are difficult to interpret in these studies (Table 15.1).

15.3 Classification of BAV: Etiology

BAV is a congenital heart anomaly, and to the best of our knowledge, the literature reports exclusively genetic causes of BAV. However, other causes of BAV such as intrauterine infection or intoxication appear to be a possible cause. Moreover, the

Table 15.1 Frequency of BAV and BAV aortopathy

Type of study	Frequency of BAV in the general population	Frequency of aortopathy in BAV
Autopsy	0.5–1.39% (meta-analysis of necropsy studies) [4]	7.5–11.2% of fatal aortic dissections have BAV [5–7]
	Roberts mentioned in one study where BAV was diagnosed in 18/800 autopsies (2) [3]	
Population screening with transthoracic echocardiography	0.5–0.9% (screening of neonates, primary school students, military) [2, 4, 8–10]	68.9% of BAV exhibits dilatation of proximal aorta [2]
Registry of aortic dissection		3.5–11.8% of aortic dissections have BAV [11, 12]
Cohort studies [13–17]		0.5–0.8% incidence of aortic dissection during follow-up in BAV [13, 15, 18]. The frequency of aortic dissection was 0.1% per patient-year of follow-up [15] and 3.1 cases per 10,000 patient-years, respectively [18]

BAV phenotype is highly variable, and epigenetic modifiers and environmental factors are likely to play an important role in BAV disease event when a distinct causative genetic defect can be identified [19].

We classify the genetic causes of BAV according to frequency and mechanisms (Table 15.2). First, male predominance and familial occurrence of BAV are found in BAV, which argue for a genetic mechanism in a majority of individuals with BAV. Second, only a small fraction of individuals with BAV have chromosomal disorders. However, some chromosomal disorders, such as Turner syndrome, have BAV in up to 30%. Third, BAV may be a monogenetic disease, where autosomal dominant traits are most frequent, but where other traits, such as autosomal recessive or X-linked traits, may occur. Monogenetic BAV can occur sporadically [20].

NOTCH1, *TGFBR1*, and *FBN1* are examples for genes, where series of patients suggest a causative relationship between gene defect and BAV phenotype. Conversely, *ACTA2* and *SMAD6* are examples for genes, where studies of individual patients or studies of relatives suggest such a causative relationship. In most of these genes, the pathogenic mechanism is unclear, and the association of mutation with phenotype is not firmly established. The *NOTCH1*, however, is a good example for a gene, where the association with BAV is well established, whereas the *FBN1* gene or the *DMD* gene is an example, where this relationship has been questioned. In all putatively causative genes however, the BAV phenotype and the associated cardiovascular and systemic phenotype are variable.

The etiology of BAV is polygenetic, where environmental factors and unknown genetic factors seem to interact. In some instances, chromosomal aberrations or defined gene defects cause BAV.

15.4 Classification of BAV: Valve Anatomy

An aortic valve may be considered "bicuspid" when we identify two cusps instead of three. However, numerous classification systems are available to further differentiate or classify BAV on the basis of anatomical criteria (Table 15.3).

First, anatomical classifications distinguish BAV from other anatomical variants of the aortic valve. These classifications include differentiation of congenital from acquired BAV and differentiation of BAV from unicuspid (UAV), quadricuspid (QAV), or pentacuspid (PAV) aortic valves according to the number of aortic valve cusps.

Second, anatomical classifications subclassify congenital BAV according to anatomical features of the aortic valve. Such classifications distinguish BAV according to patterns of valve calcification and the grade of valve calcification. However, most anatomical classifications focus on characterizing BAV according to which cusps are fused to one cusp and whether a raphe is present or absent. Unfortunately, there are many variants of such anatomical classifications, where some use the same expression to characterize different types of valves. We believe

Table 15.2 Classification of BAV according to etiology

Etiology (syndrome)	Percent of BAV per etiology (number of individuals with BAV per number of individuals with etiology)
Familial occurrence of BAV	
Familial BAV	10.1% (21/207) of siblings of 181 children have BAV [21]
	4.6% (16/348) [22], 8% (4/52) [23], and 9.1% (17/186) [24] of first-degree relatives have BAV
Chromosomal disorders	
Monosomy X (Turner) [25, 26]	11.5% (28/244) [27], 12.5% (74/594) [28], 12.8% (15/117) [29], 14% (25/179) [30], 17.5% (7/40) [31], 29.6% (74/250) [32], and 22.6% (47/208) [33]
22q11.2 deletion (DiGeorge, velocardiofacial, VCF)	3.2% (3/93) [33] and 16.7% (1/6) [34]
7q11.23 deletion (Williams) [35, 36]	3% (1/32) [36]
1q21.1 microdeletion [20]	4.8% (1/21) individuals with 1q21.1 microdeletion [37]
17q21.31 deletion (Koolen-De Vries)	18.2% (2/11) [38]
9q subtelomeric deletion (Kleefstra)	6.7% (1/15) [39]
Trisomy 21 (Down) [35]	4% (2/55), but unclear whether BAV or pulmonary bicuspid valve [40]
Monogenetic disorders: gene symbol (syndrome)	
1. Disorders with evidence from case series	
NOTCH1 (aortic valve disease 1, AOVD1)	4.2% (2/48) with sporadic BAV [41]
	10.4% (4/48) with BAV and aortic aneurysm [42]
	18.2% (2/11) of BAV had NOTCH1 mutation [43]
KMT2D, KDM6A (Kabuki) [44]	20% (4/20) [44]
	15.4% (2/13) [45]
GATA5 (non-syndromal BAV) [46]	4% (4/100) with non-synonymous GATA5 variants in 100 BAV cases [46]
FLN1 (periventricular nodular heterotopia)	9% (1/11) [47]
PTPN11, SOS1, KRAS, RAF1 (Noonan) [48]	0.8% (1/118) [49]
CREBBP (Rubinstein-Taybi)	2% (3/138) [50]
TGFBR1, TGFBR2 (Loeys-Dietz) [51, 52]	50% (2/4) families with TGFBR1 mutation [52]
	One report of an individual with BAV with a TGFBR2 mutation [51]
FBN1	4.7% (12/257) individuals with clinical diagnosis of Marfan syndrome (an FBN1 mutation is some); a BAV was present [53]
KCNJ2 (Anderson; long QT syndrome 7)	7.1% (3/42) of one kindred with autosomal dominant segregation of ventricular arrhythmias [54]
2. Disorders with evidence from case reports	
ACTA2 (familial thoracic aortic aneurysm) [55]	BAV in four families with ACTA2 mutation [55, 56]

(continued)

Table 15.2 (continued)

Etiology (syndrome)	Percent of BAV per etiology (number of individuals with BAV per number of individuals with etiology)
FLNB (Larsen)	One report of an individual with BAV with Larsen syndrome [57]
SMAD6 (aortic valve disease 2, AOVD2)	One report of an individual with BAV, aortic valve stenosis, and coarctation with calcification of the aorta [58]
GATA6	One report of carrier of the mutation with BAV in a family with GATA6 mutation [59]
Autosomal dominant heart-hand syndrome	One report of an individual with BAV, patent ductus arteriosus, and hand anomalies [60]
DMD (Becker's muscular dystrophy) [61]	One report of an individual with BAV with Becker's muscular dystrophy [61]

that a uniform classification system should be used. Buchner et al. distinguished BAV with raphe, where they classify BAV-RL, BAV-RN, and BAV-LN, depending on which aortic cusps, the right (R), left (L), or noncoronary (N), are fused, from BAV without raphe, where BAV-LA designated BAV with lateral orientation of the free edge of cusps and BAV-AP with anterior-posterior orientation. This classification covers all other classification systems and it is simple.

Third, we tabulate classification systems that combine the above described anatomical classification of BAV with other features of BAV disease, such as valvular function or aortic shape. However, such classifications may yield >20 subtypes, which are complicated to use without offering the reward of improving clinical management. Moreover, these combi-classifications are only in use to describe all possible combination of BAV anatomy with additional BAV disease features rather than that they establish new disease entities (such as a typical aortopathy in LR-BAV), and hence they do not provide additional insight into BAV disease.

Congenital BAV must be distinguished from acquired BAV. Congenital aortic valve malformations differ by number of cusps, ranging from one to five. BAV cusps can be subclassified according to patterns of calcification, severity of calcification, presence of a raphe, and fusion of cusps. Combi-classifications, where anatomical subtypes of BAV are combined with additional features of BAV disease, may be too complex for routine clinical use.

15.5 Classification of BAV: Associated Congenital Heart Defect (CHD)

We classify BAV into four categories according to the presence of associated congenital heart defects (CHDs):

Table 15.3 Classification systems of BAV valve anatomy

Classification	Frequency
Classifying BAV as congenital versus acquired	
Angelini distinguished congenital from acquired BAV by anatomic characteristics as follows	
1. Congenital BAV has two cusps, two sinuses, and two interleaflet triangles	Congenital BAV: 10.9%
2. Acquired BAV has two cusps, three sinuses, and three interleaflet triangles [62]	Acquired BAV: 89.1% [62]
Classifying congenital aortic valve malformation by number of cusps	
Unicuspid aortic valve (UAV). Mookadam classified UAV according to anatomy as follows [63, 64]	0.02% of patients referred to echocardiography [65]
1. Uni-commissural type with slit-shaped UAV	Male/female ratio: 4:1 [63]
2. A-commissural type with pinhole-shaped UAV	Uni-commissural type seems more frequent than the a-commissural type [63]
	In 96 patients with aortic valve replacement, 100% and 0% of UAV, 77% and 12% of BAV, and 64% and 36% of TAV had aortic stenosis and pure valve regurgitation, respectively [66]
Quadricuspid aortic valve (QAV) [67]. Hurwitz and Roberts classified UAV according to seven anatomical types A–G [68], where A is QAV with four equal cusps; B, three equal and one smaller cusp; C, two equal larger and two equal smaller; and G, four unequal cusps	0.008–0.033% of autopsies and 0.043% of echocardiographies [67]
	Male/female ratio: 1.6:1.
	Type A: 12%
	Type B: 60%
	Type C: 15% [68]
Pentacuspid aortic valve (PAV) [69]	Six patients with PAV reported in the literature [70]
Classifying BAV by cusp calcification	
Thubrikar et al. classified aortic cusps by pattern of calcific deposits [66]:	Occurrence of calcification patterns per cusp in BAV
1. Any calcification deposits without pattern	11.4% without pattern
2. Coaptation pattern with deposits along the line of cusp coaptation	88.6% with pattern
3. Radial pattern with deposits as spokes spread inward from the cusp attachment to the center of the cusp	Raphe was always calcified
Beppu et al. assessed the sclerotic index in BAV on TTE by dividing each aortic cusp into three segments along the coaptation line (six segments in all), where they also scored the raphe, if present. They scored each segment and raphe as 4 with calcium >3 mm, 2 with presence of calcium, 1 with echo density less than calcium, and 0 with no increased echo density [71]. Warren et al. suggested an alternative grading of cusp calcification [72]	Sclerotic index ranged from 0 to 13 with good linear correlation with the patient's age [71]

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Table 15.3 (continued)

Classification	Frequency
Classifying BAV by cusp morphology	
Brandenburg et al. classify BAV according to cusp fusion and raphe [73]:	
Type 1 with fusion of right and left cusp (R-L),	Type 1 (R-L): 70–79.6%
Type 2 with fusion of right and noncoronary cusp (R-N)	Type 2 (R-N): 1 24.4%
Type 3 with fusion of left and noncoronary cusp (L-N)	Type 3 (L-N): 0.5% [74]
Beppu et al. assessed the eccentricity index of BAV as the ratio of the widths of each cusp measured as distance from edge of cusp to aortic wall. They classified BAV according to this index [71]:	
Eccentric valve: index $\geq$1.2	Eccentric aortic valve: 57.3%
Symmetric valve: index $<$1.2	Symmetric aortic valve: 42.7%
Sadee et al. classify three BAV groups [75]:	
Group 1: purely bicuspid BAV	Group 1: 23%
Group 2: BAV with a conjoined cusps containing a raphe	Group 2: 34%
Group 3: BAV with a conjoined cusps and central indentation of free cusp edge [75]	Group 3: 43% [75]
Tokunaga classify four types of BAV [76]:	
Type 1: two cusps are situated right and left; a coronary artery arises from each related sinus of Valsalva	Type 1 (44.7%)
Type 2: type 1 plus raphe in the right cusp	Type 2 (22.4%)
Type 3: one cusp is located anteriorly, the other is posteriorly, and both coronary arteries arise from anterior cusp	Type 3 (3.5%)
Type 4: type 3 + raphe in the anterior cusp	Type IV (29.4%)
Buchner classified five types of BAV according to presence and location of raphe [77]:	
BAV with raphe	
BAV-RL, fusion of the right and left coronary cusps	BAV-RL: 72.4%
BAV-RN, fusion of the right and noncoronary cusps	BAV-RN: 13.3%
BAV-LN, fusion of the left and noncoronary cups	BAV-LN: 0%
BAV without raphe	
BAV-LA, lateral orientation of the free edge of cusps	BAV-LA: 10.5%
BAV-AP, anterior-posterior orientation	BAV-AP: 3.8%

(continued)

Table 15.3 (continued)

Classification	Frequency
Sonoda et al. classified the BAV based on the cusp location in the short axis view of the valve on the transesophageal echocardiogram [78]	
A-P-BAV: BAV with leaflets arranged anteroposteriorly and commissures to the right and to the left	A-P-BAV: 66.7%
R-L-BAV: BAV with leaflets orientated laterally and commissures positioned anteriorly and posteriorly	R-L-BAV: 33.3%
Classifying BAV by cusp morphology plus other features (combi-classifications of BAV)	
Sievers classification combines three "blocks"—type, spatial position of the free edge of cusps, and valvular function:	
Type 0, no raphe; spatial subtype, orientation of the free edge of the cusps anteroposterior (ap) or lateral (lat)	Type 0, lat, I: 2%; type 0, lat, S: 2%; type 0, ap, I: 0.3%; type 0, ap, S: 2%; type 0, ap, B: 0.3%
Type 1, one raphe; spatial subtypes, L-R, R-N, N-L (see Brandenburg classification)	Type 1, L-R, I: 26%, type 1, L-R, S: 39%, type 1, L-R, B: 5%; type 1, R-N, I: 7%; type 1, R-N, S: 5%; type 1, R-N, B: 2%; type 1, R-N, No: 0.3%; type 1, N-L, I: 1%; type 1, N-L, S: 1%; type 1, N-L, B: 1%
Type 2, two raphes; spatial subtypes, L-R/R-N	Type 2, L-R/R-N, I: 2%; type 2, L-R/R-N, S: 2%; type 2, L-R/R-N, B: 1%
Subclassification according to functional status of the valve: predominant insufficiency (I), predominant stenosis (S), balanced insufficiency and stenosis (B), or no insufficiency and stenosis (No) [79]	
Schaefer et al. combine cusp morphology and aortic shape to classify BAV [80]:	
BAV classification:	
Type 1, fusion of right and left coronary cusp	BAV 1N: 60%
Type 2, right and noncoronary fusion	BAV 1A: 50%
Type 3, left and noncoronary fusion	BAV 1E: 5%
Aortic shape classification:	
Type N, normal shape	BAV 2N: 32%
Type E, sinus effacement	BAV 2A: 54%
Type A, with ascending dilatation	BAV 2E: 14%

1. Smaller series report on the presence of BAV in syndromic or complex CHD, such as Ebstein's anomaly, Shone's complex, hypoplastic left heart syndrome, double-outlet right ventricle, tetralogy of Fallot, or complete transposition of the great arteries.

Table 15.4 Classification of BAV according to associated congenital heart defect (CHD)

Associated CHD	Frequency of BAV
1. BAV in syndromic or complex CHD (≥ 2 additional cardiovascular malformations)	
Ebstein's anomaly [81]	0.8% (2/250) [81], 7.6% (8/106) [82], and 4.8% (5/104) of Ebstein patients [83]
Shone's complex [84, 85]	84.2% (16/19) [86] and 88.9% (24/27) in patients with operation for Shone's complex [87]
Hypoplastic left heart syndrome (HLHS) [81, 88–91]	11.2% (64/570) of HLHS or interrupted aortic arch (IAA) [81]
	12.1% (4/33) of relatives of a subset of infants with isolated HLHS [88]
Double-outlet right ventricle (DORV) [81]	0.7% (5/773) of DORV [81]
Tetralogy of Fallot (TOF) [81]	0.6 (7/1213) of TOF [81]
	1.7% (1/59) of TOF [92]
Complete transposition of the great arteries (TGA) [92]	0.1% (1/1567) of TGA [81]
	1.0% (1/103) of TGA [92]
BAV in combination with the other CHDs	
2. Association with evidence from larger series	
Coarctation of the aorta (COA) [92] [81, 93]	55.0% (459/835) of isolated COA [81]
	17.6% (111/629) of complex COA [81]
	31.4% (49/156) of BAV has a history of prior COA repair [94]
	25–85% of BAV has COA [95]
	59.6% (268/449) of COA has BAV [96]
Patent ductus arteriosus (PDA) [97, 98]	20.9% (53/253) of PDA [99]
	8.3% (1/12) of PDA [92]
Ventricular septal defect (VSD) [97] [92, 98]	20.5% (17/83) of isolated VSD [92]
	51.1% (24/47) of VSD and aortic arch obstruction [92]
Atrial septal defect (ASD) [100]	1% of 294 adults with ASD [101]
Complete atrioventricular septal defect (CAVC) [81]	1.0% (11/1074) of CAVC [81]
Total anomalous pulmonary venous return (TAPVR) [81]	0.8% (2/247) of TAPVR [81]
Partial anomalous pulmonary venous return (PAPVR)	0.9% (2/233) of PAPVR [81]
3. Rare association of BAV with CHD	
Coronary arterial anomaly [102]	Casuistic reports on BAV with anomalous origin of the:
	Right coronary artery between the left and right coronary sinus of Valsalva [22], from the left sinus of Valsalva [103–105], from the ascending aorta high above the left posterior sinus of Valsalva[106], from the left ventricle [107], or from the pulmonary artery (ARCAPA) [108]
	Left coronary artery arising from the right sinus of Valsalva [109, 110]
	Single coronary artery [111–114]
	26% of 59 BAVs have left coronary artery dominance and 44% of left coronary ostia origin at or above aortic sinotubular junction [102]

(continued)

Table 15.4 (continued)

Associated CHD	Frequency of BAV
Bicuspid pulmonary valve (BPV) [115]	0.75% (24/3216) of cases with congenital heart disease had bilaterally BPV [116]
	Main pulmonary artery (MPA) diameters are larger in 194 individuals with BAV but without BPV than in 178 controls [117]
Mitral valve anomalies	3.1% (8/257) of black patients with MVP have BAV [118]
	4.7% (9/192) of adults with BAV have a myxomatous mitral valve [80]
	Elongation of the AML in BAV [119]
	8.9% (16/180) of patients with combined aortic and mitral valve replacement had BAV [120]
Mitral valve atresia	11.5% (3/26) of mitral atresia [92]
4. Rare associations of BAV and CHD (casuistic reports)	
Myocardial abnormalities	Left ventricular noncompaction [121], outflow tract diverticula adjacent to the commissures of a BAV [122], septal diverticulum [123], subannular aneurysm [124], hypertrophic cardiomyopathy [125]
Familial aorto-cervicocephalic arterial dissections [126]	Three families with BAV and cervicocephalic arterial dissections [126]
Intracranial aneurysms (IA) [127]	10% (6/61) of IA [127]
	1.8% (1/56) with subarachnoid hemorrhage related to IA [128]
	0.6% (2/317) of IA [129]
Miscellaneous vascular anomalies	Circumaortic innominate vein [130], isolated spontaneous dissection of the celiac trunk [131], aortic diverticulum [132], lusory artery [133], aberrant right subclavian artery aneurysm [134], persistent left and absent right superior vena cava [135]

2. BAV frequently associates with one typical additional CHD, where coarctation of the aorta (COA), patent ductus arteriosus (PDA), ventricular septal defect (VSD), and atrial septal defect (ASD) are the most common associates of BAV.
3. Coronary arterial anomaly, bicuspid pulmonary valve (BPV), and mitral valve anomalies are rare in BAV, but their association with BAV is well established.
4. There are only sparse or conflicting data on the potential association of BAV with CHD or vascular malformation such as myocardial abnormalities, familial aorto-cervicocephalic arterial dissections, intracranial aneurysms, and various arterial or venous vascular anomalies (Table 15.4).

We tend to perceive BAV as an isolated CHD. However, we identified 20 well-defined syndromic, complex, or isolated congenital heart defects that are associated with BAV disease; some of them are apparently quite frequent.

15.6 Classification of BAV: Aortopathy

BAV may be associated with aortic dilatation or aneurysm of the proximal aorta, the aortic arch, the descending aorta, or the abdominal aorta. Some studies classified BAV into four groups by type of aortopathy. BAV aortopathy was classified:

1. Type and presence of aortic valve dysfunction
2. Geometrical configuration of the proximal part of the aorta
3. Involvement of the aortic arch
4. According to presence of coarctation of the aorta (COA)

None of these classifications have been applied prospectively in large cohorts of unselected individuals with BAV, and hence their overlap and comprehensiveness cannot be estimated properly. However, all classifications provide useful means to describe subtypes of BAV aortopathy for future assessment of prognosis (Table 15.5).

15.7 Classification of BAV Aortopathy: Risk Factors

Patients with BAV may exhibit additional factors that may increase diameter of the aorta and increase the risk of aortic aneurysm formation, aortic dissection, and rupture. We distinguish risk that may arise from three types of risk factors:

1. From aortic valve characteristics, such as BAV morphotype, BAV stenosis, and BAV regurgitation
2. From comorbidities of BAV, such as arterial hypertension (HTN), atherosclerosis, and coarctation of the aorta (BAV-COA), or from sleep apnea, comprising obstructive (OSA) and central sleep apnea (CSA)
3. From behavioral factors including pregnancy, sports, high-performance aviation with G-force exposure, and drug abuse comprising cocaine, methamphetamine, and sildenafil

The evidence for increased risk for aortic complications is not equally strong for all factors in BAV (Table 15.6).

15.8 Classification of BAV Aortopathy: Candidate Biomarkers

Biomarkers should provide information of the development and evolution of BAV aortopathy. Aortic diameters clearly provide the single most important information on presence and risk of BAV aortopathy. Therefore, guidelines base their recommendations of timing for elective surgery of the aortic root predominantly on

Table 15.5 Classifications of BAV according to aortopathy

Classification	Frequencies
1. According to BAV dysfunction	
Aydin et al. classified ascending aortic aneurysm (AAA) in relation to bicuspid aortic valve (BAV) dysfunction similar to Hahn et al. as follows [136, 137]:	
ACA with BAV severe stenosis	ACA with BAV stenosis: 50%
ACA with BAV severe regurgitation	ACA with BAV regurgitation: 26.9%
ACA without BAV dysfunction	ACA without BAV dysfunction: 23.1% [136]
2. According to shape of the proximal aorta	
Bauer et al. classified the configuration of proximal aortopathy according to diameter enlargement at level 1 (aortic annulus), level 2 (aortic sinus), level 3 (sinotubular junction), and level 4 (ascending aorta) as follows [138]:	
Normal: levels 1–4 normal	
Marfanoid: 1–3 enlarged, 4 normal	
Symmetric dilatation: 1–2 normal, 3–4 enlarged	
Asymmetric dilatation: 1–3 normal, 4 enlarged	
3. According to involvement of the aortic arch	
Fazel et al. classified the extent of BAV aortopathy based on cluster analysis as follows [139]:	
Cluster I, aortic root alone	Cluster I: 13%
Cluster II, tubular ascending aorta alone	Cluster II: 14%
Cluster III, tubular portion and transverse arch	Cluster III: 28%
Cluster IV, aortic root and tubular portion with tapering across the transverse arch	Cluster IV: 45%
4. According to coexistence with coarctation of the aorta (Co-COA)	
BAV aortopathy according to location and presence of COA (irrespective of previous COA repair) [140–142]:	
Type A: aneurysm of ascending aorta without COA	
Type A-COA: aneurysm of ascending aorta with COA	
Type B-COA: aneurysm of thoracic aorta in other locations than the ascending aorta	
Type C-COA: aneurysmal formation at the site of COA or previous COA repair	

diameters [176–178]. Nonetheless, aortic size has to be judged differently depending on sex, body size, body surface, and the individual tissue stability of the aortic wall [179]. Additional biomarkers may be helpful to further stratify the risk of acute aortic events in BAV aortopathy.

Candidates for biomarkers of BAV aortopathy comprise a family history with dissection or death at younger age, increased aortic growth rates, proximal aortic shape, biomarkers of aortic stiffness and aortic elasticity markers, biomarkers of

Table 15.6 Risk factors and predictors of BAV aortopathy

1. Aortic valve characteristics
Bicuspid aortic valve morphotype (BAV-MO)
BAV-RL was associated with enlarged SOV diameters [143–145], rapid growth of SOV diameters [94], and lower age at aortic operation [145]
BAV-RN was associated with enlarged diameters of ASC [143] and with rapid growth of ASC diameters [146]
Progression of cusp sclerosis was faster in BAV-RL than BAV-RN, and it was faster in eccentric cusps than symmetric cusps
Aortic valve pressure gradient increased approximately 18 mmHg by each decade, but in eccentric BAV and BAV-RL, aortic valve pressure gradient increased 27 mmHg per decade [71]
Bicuspid aortic valve stenosis (BAV-S)
BAV-S was a protective factor for SOV dilatation [147, 148]
BAV-S severity related to enlarged diameters of ASC [143, 149]
BAV-S gradient predicted growth of ASC diameters in children [146]
BAV-S had a higher risk of rupture, dissection, or death before operative repair than did those with normally functioning valves [16]
Bicuspid aortic valve regurgitation (BAV-I)
Absence of BAV-I or mild BAV-I/BAV-S lead to aortic surgery in only 5 ± 2%, without any aortic dissection during 20 years of follow-up [13]
BAV-I severity related to enlarged SOV diameters [149]
Moderate or severe BAV-I was not associated with rapid aortic dilatation in one study [94], but it was an independent determinant of SOV diameter in another study [143]
BAV-I was associated with extension of dilatation from ASC past the innominate artery into AOA and DESC [150]
BAV-I at AVR was associated with a tenfold higher risk of post-AVR aortic dissection compared with BAV-S [151]
2. Comorbidities
Arterial hypertension (HTN)
In the general population, 4–17% with HTN had dilatation of SOV [152]
In BAV, SOV diameter was significantly larger than individuals in the general population with HTN [143]
HTN (>140/90 mmHg) was associated univariately with rapid aortic dilatation [94]
Atherosclerosis
In the general population, distal aortic dilatation showed only weak association with risk factors for atherosclerosis and aortic atherosclerotic plaques [153]
BAV with coarctation of the aorta (BAV-COA)
BAV-COA after repair or with mild pressure gradients was the only predictor of ASC aneurysm [154]
Aortic dissection or rupture occurred exclusively in BAV-COA [154]
BAV-COA were younger at AVR and ASC surgery than isolated BAV [155]
In children with BAV-COA, SOV, and ASC, diameters were larger than isolated BAV [156]
Maximal velocity, secondary flow, pressure loss, time-averaged wall shear stress, and oscillatory shear index downstream of the COA in those with BAV-COA were higher [157] than isolated BAV
One study found that prior COA repair was protective against rapid aortic dilatation in BAV-COA [94]

(continued)

Table 15.6 (continued)

Sleep apnea
Obstructive (OSA) and central sleep apnea (CSA) are frequent in patients with aortic dissection and Marfan syndrome
Aortic diameters and stiffness are increased in sleep apnea [158–163]
Therefore, OSA and CSA are likely to increase the risk for aortic aneurysm and dissection in BAV
3. Behavioral factors
Pregnancy
One review of the literature identified that BAV was observed in 10% (4/40) of women with prepartum type A aortic dissection [164] and in 4.9% (6/122) of parturients with aortic dissection [165]
In a cohort of 88 women with BAV, there was no aortic dissection in 216 pregnancies and 186 deliveries [14]
Sports
2.5% (4/158) of trained athletes with sudden death had BAV with valve stenosis but no aortic dissection or rupture [166]
88 consecutive athletes with BAV had a significantly higher increase of aortic diameters than in 56 athletes with a normal tricuspid valve during 5 years of follow-up, but diameters remained within normal ranges [167]
High-performance aviation with G-force exposure
Exposure to G-force and anti-G maneuvers did not worsen cardiac and valve function in eight aviators with BAV [168]
Drug abuse
Cocaine
37% (14/38) of hospitalized patients with aortic dissection used cocaine in the minutes or hours preceding their presentation [169]
IRAD identified cocaine use in 0.5% (5/921) of individuals with aortic dissection (one type A, four type B) [170]
A literature analysis identified 15 patients with type A aortic dissection and 6 with type B dissection associated with a recent cocaine use [171] 69.2% (9/10) of aortic dissections in cocaine users had type B dissection, but none of them had BAV [172]
Methamphetamine
In 5.5% (6/109) of individuals with aortic dissection and 20% (6/30) of patients under the age of 50 with aortic dissection, acute aortic dissection was secondary to hypertensive crises from methamphetamine use [173]
In a population-based case-control study of 30,922,098 hospital discharges of persons, aged 18–49 years, significant association of amphetamine abuse/dependence and thoracic and thoracoabdominal aortic dissections was identified in 3116 individuals [174]
Sildenafil
There are casuistic reports on post-sildenafil aortic dissections, in one individual with BAV and post-sildenafil type A dissection [175]

Table 15.7 Candidate biomarkers of BAV aortopathy

1. Family history with dissection or death in the young
The ESC guideline considers a family history of dissection as a risk factor in BAV that justifies earlier surgical intervention for aortopathy [177]
Aortopathy was prevalent in relatives of BAV patients [180, 181]
32% of 48 first-degree relatives of individuals with BAV who had morphologically normal TAV exhibited functionally abnormal and dilated aortic roots [180]
First-degree relatives had a higher prevalence of thoracic aortic aneurysms and sudden death with a relative risks of thoracic aortic aneurysm development of 10.9 in brothers and 1.8 in fathers and sisters of index patients with BAV [182]
2. Increased aortic growth rates
Cohort studies of adults with BAV estimate mean annual rates of progression of diameters (mm/year) as 0.18 at AVA, 0.17 at SOV, 0.18 at STJ, and 0.37 at ASC [94] and as 0.5 at SOV, 0.5 at STJ, and 0.9 at proximal ASC [183] and as 0.2 at ASC [184]
Cohort studies with comparison of adults with BAV versus adults with TAV estimate mean annual rates of progression of diameters (mm/year) at ASC as 0.77 vs. 0.16 [185], 0.86 vs. 0.82 (n.s.) at SOV, 1.06 vs. 0.63 (n.s.) at STJ, and 0.81 vs. 0.75 at proximal ASC (n.s.) [17]. One study estimated annual aortic growth rates as 0.19 cm/year vs. 0.13 cm/year [16]
A cohort study of children aged <19 years (mean 8.5 ± 5.3) with isolated BAV and normal z-scores on initial examination estimated the rate of ASC diameter growth as 0.18 ± 0.30 z-score per year [146]. In a cohort study of 28 children with functionally normal BAVs and of 25 controls (mean age 9.0 ± 4.8 vs. 8.7 ± 6.1 years), aortic growth rates were 1.2 ± 0.08 vs. 0.6 ± 0.08 mm/year ($P < 0.0001$) [186]
3. Proximal aortic shape
Proximal aortic shape with extension of dilatation from SOV beyond STJ into ASC indicated increased risk for rupture and dissection in Marfan syndrome [187]
BAV-S with asymmetrical tubular dilatation was called "BAD-MATE syndrome," which may have a prognostic meaning [188]
An ellipsoidal or spherical shape of the proximal aorta may be the origin of a transverse tearing of the aortic intima as initiating event for acute dissection [189]
BAV-RL was associated with normal aortic shape but larger diameters of SOV (type N) and BAV-RN with larger distal ASC and AOA dimensions (type A) [80]
4. Aortic stiffness/aortic elasticity
Nine studies with comparison of adults with BAV and healthy adults with TAV who were matched for age and gender all identified increased aortic stiffness parameters in the following BAV groups (mean age in years ± standard deviation):
10 BAV individuals (47 ± 4) [190]
16 men (median age 31 years) with nonstenotic BAV and proximal ascending aortic diameters ≥40 mm [191]
20 individuals (27 ± 11 years) with nonstenotic BAVs with larger SOV diameters [192]
29 individuals with BAV-RL (mean age 41.5 years) and larger SOV diameters [144]
40 BAV individuals (44 ± 16 years) with larger SOV diameters [193]
49 males with BAV (19.4 ± 1.4 years) and larger SOV diameters [194]
50 individuals with BAVs (52 ± 14 years) without significant valve dysfunction but larger ascending aortic diameters [195]
50 individuals with BAV (median age 30; 16–56 years) with aortic diameter ≤4 cm [196]
127 BAV outpatients (23 ± 10 years) with no or mild valvular impairment but larger aortic diameters [197]

(continued)

Table 15.7 (continued)

Two studies with comparison of children with BAV and healthy children with TAV who were matched for age and gender both identified increased aortic stiffness parameters in BAV:
48 pediatric individuals (mean age 11.9 ± 4.8 years) with an isolated BAV and larger aortic root diameters [198]
53 consecutive pediatric individuals with BAV (mean age 16 ± 4 years) with mild aortic valve disease maximum rates [199]
Three studies showed that increased stiffness parameters were statistically independent of aortic dilatation [198–200]
In one study BAV-RL showed significantly stiffer and less distensible elasticity parameters than BAV-RN [198]
5. Aortic wall shear stress (AWASS) [201]
Four-dimensional flow MR imaging revealed nested helical flow at peak systole in ASC in 15 of 20 individuals with BAV but not in 25 patients with a TAV and not in 8 healthy volunteers. Helical flow was eccentric in all cases, it was present irrespective of aortic dilatation and BAV-S, and it was right-handed in 11 BAV-RL and left-handed in 4 BAV-RN [202]
Systolic flow displacement calculated from conventional 2D PC-MRI in the ASC related to future aortic growth in 17 adults with BAV-RL [203]
19 patients with BAV and eccentric systolic blood flow in ASC had significantly and asymmetrically elevated wall shear stress as compared to both 7 patients with BAV and normal flow and to 20 patients with TAV and no valvular disease [204]
Among 13 patients with BAV, 10 with abnormal flow patterns demonstrated significantly higher growth rates than those without, and 7 BAV with markedly eccentric flow exhibited more rapid growth than those without [205]
Patients with BAV had increased 99th percentile wall stress in ASC [206]
6. Endothelial dysfunction
16 men with nonstenotic BAV but dilated aortas had decreased brachial flow-mediated vasodilation to hyperemia as marker of endothelial dysfunction than both 16 men with BAV and nondilated aorta and 16 normal controls [191]
Flow-mediated dilatation (FMD) as marker of endothelial dysfunction was decreased in 43 individuals with BAV, but its decreases were unrelated to aortopathy [207]
7. Serological biomarkers reported in BAV (alphabetical order)
ACE insertion/deletion polymorphism [208]
ADMA (asymmetric dimethylarginine) [207]
α1AT (soluble alpha-1 antitrypsin) [209]
MicroRNA: miR-1 [210], miR-21 [210], miR-29b [211]
MMP-2, MMP-8, and MMP-9 [191, 209, 210, 212–214]
MPO (myeloperoxidase) [207]
OPG (osteoprotegerin) [215]
sRAGE (soluble receptor for advanced glycation end product) [216]
RANKL [215]
TGFb1 (transforming growth factor-beta1) [217]
TIMP [210, 214]
Transcript biomarkers FHL1, collagens α1(XI), α2(V), α1(III), and α1(I) [218]

aortic wall shear stress (AWASS), biomarkers of endothelial dysfunction, and serological biomarkers (Table 15.7).

No single candidate biomarker of BAV aortopathy has currently accumulated evidence enough for introduction into clinical routine. However, many of the candidate biomarkers exhibit promising data. Some of these markers are likely to improve future management of BAV disease.

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