New insights into the left ventricular morphological and functional changes in patients with bicuspid aortic valve disease

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eingereicht von: Kushtrim Disha

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                      Zentralklinik Bad Berka GmbH

Betreuer: Prof. Michael A. Borger, MD, PhD

                      Prof. Dr. med. Evaldas Girdauskas

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1.1 Bicuspid aortic valve (BAV) disease

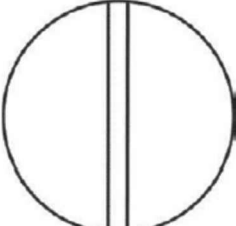### 1.1.1 Epidemiology, definition and classification

The bicuspid aortic valve (BAV) represents the most frequent cardiac malformation of the human heart, with an estimated prevalence between 0.5% and 2% (1-5), and a male predominance of nearly 3:1. It may be sporadic or familial, and may be sporadically transmitted through families by an autosomal dominant pattern (6). Certain groups of patients present with higher prevalence of BAV, such as patients with coarctation of the aorta, females with Turner syndrome, patients with patent ductus arteriosus, supravalvular aortic stenosis, ventricular septal defect and Shone's syndrome (7-12). The first documented description of the bicuspid aortic valve was made by Leonardo da Vinci, who more than 400 years ago sketched the bicuspid variant of the aortic valve. Da Vinci is also known to have described the optimal geometric properties of the tricuspid aortic valve as compared to the quadricuspid valve. Later on, in 1844 Paget described the susceptibility of the BAV to develop a disease and in 1858 Peacock depicted the propensity of the bicuspid variant of the aortic valve to develop obstructive as well as regurgitant lesions (2). Furthermore, in 1886 Osler described the predisposition of BAV to develop infective endocarditis (13). Later on, by means of the autopsy studies, Wauchope determined that BAV is the most frequent congenital anomaly of the human heart (13, 14). The first description of the association of BAV with aortic dissection was reported by Abbott (15), whereas Larson and Edwards contributed to emphasizing the BAV as a notable (with at least ninefold greater) risk factor of aortic dissection (4). The significance of BAV in the population as well as its incidence has begun to be clarified in the 20th century with the development of cardiac imaging (i.e. echocardiography, magnetic resonance imaging, computed cardiac tomography etc.). Moreover, due to the significant burden of BAV in the

surgical setting, in the recent years there are a plentiful of scientific contributions that have shed light on the etiology, histology, embryology and genetics of BAV. Although much of the research focus has been directed towards the abnormal bileaflet valve and the possibly associated aortopathy, BAV is a significantly more complex disease. Furthermore, it is not only a valvulopathy due to a disorder of valvulogenesis, but it comprises aspects of genetic disorder of aorta and/or cardiac development (16).

The bicuspid aortic valve consists usually of two cusps of unequal size. Due to the fusion of two cusps, there is one larger cusp and a smaller one. The larger cusp usually includes a central raphe or a ridge that results from fusion of the commissures, thereby producing a pseudo-commissure which is due to obliteration of the commissural area. Moreover, there are also two normally formed commissures present. The raphe or fibrous ridge is formed due to congenital fusion of the two parts of the conjoined cusps and can be identified in the majority of BAV patients (17). However, the pathologic examination has shown that raphe does not contain valve tissue (18), and it can be developed partially and totally. Bicuspid valvulopathy comprises a continuous spectrum, from absence of one commissure (resulting in two cusps, sinuses and commissures only) to an underdevelopment of one or two commissures and adjacent cusps (resulting in presence of one or two raphes) (19). Nowadays, the most widely used classification system for BAV is the one proposed by Sievers in 2007 (19) (*Figure 1*), based on 304 surgical specimens. It is based on three characteristics, such as the number of raphes, the spatial position of cusps or raphes, and the functional status of the valve. The number of raphes is the main category and is termed "type", resulting in "type 0" (valve with no raphe), "type 1" (valve with one raphe) and "type 2" (valve with two raphes). Furthermore, the first subcategory deals with the spatial arrangement of the free edge of the cusps. Every valve "type" has its own spatial arrangement. For type 0 there is an antero-posterior or lateral orientation of the free edge of the cusps. For types 1 and 2, this subcategory is defined by the orientation of

the raphes in relation to the sinuses. Therefore, type 1 comprises three modalities of the first subcategory: L/R (the raphe exists between the left and the right coronary sinuses), R/N (the raphe exists between the right and the noncoronary sinuses) and N/L (the raphes exists between the noncoronary and the left coronary sinuses). Type 2 comprises one modality of the first subcategory, namely L-R/R-N. The second subcategory relates to the functional status of the valve: predominant stenosis (S) or insufficiency (I), balanced insufficiency and stenosis (B), or no valve dysfunction (No). Of the 304 surgical specimens, 88% were classified as type 1, 7% as type 0 and 5% as type 2. In type 1, 71% had a L/R raphe, 15% R/N raphe and only 3% a N/L raphe.

Figure 1. Schematic presentation of the Sievers' classification of bicuspid aortic valve as viewed by the surgeon's position (19)

main category: number of raphes	0 raphe - **Type 0**		1 raphe - **Type 1**			2 raphes - **Type 2**
	21 (7)		269 (88)			14 (5)
1. subcategory: spatial position of cusps in Type 0 and raphes in Types 1 and 2	lat 13 (4)	ap 7 (2)	L – R 216 (71)	R – N 45 (15)	N – L 8 (3)	L – R / R – N 14 (5)
2. subcategory:						
I	6 (2)	1 (0.3)	79 (26)	22 (7)	3 (1)	6 (2)
S	7 (2)	5 (2)	119 (39)	15 (5)	3 (1)	6 (2)
B (I + S)		1 (0.3)	15 (5)	7 (2)	2 (1)	2 (1)
No			3 (1)	1 (0.3)		

1.1.2 Diagnosis

Although most of BAV patients are asymptomatic, often the diagnosis is suspected during a routine physical exam and auscultation, in which an ejection sound is noted, that is best heard at the apex. A functionally normal BAV may exhibit an ejection sound followed by an early peaking systolic flow murmur. This ejection sound is produced by the sudden cranial movement of the dome shaped bicuspid valve in systole and commonly corresponds with the valve cusp mobility (20). However, as the valve cusps become more immobile, the ejection sound may diminish (21). Associated murmur of aortic stenosis, regurgitation or coarctation can be heard if these conditions are present. In the present era, the diagnosis is often confirmed by means of transthoracic echocardiography. For the diagnosis of BAV by means of transthoracic 2D echocardiography, a sensitivity of 78%, a specificity of 96% and a predictive accuracy of 93% has been reported (22). However, a recent retrospective study found a rather low sensitivity of 59% even after expert re-evaluation (23). In patients with heavily calcified valves, the echocardiographic diagnosis can be demanding (24). In these cases, the diagnosis can be established by visualizing the valve in systole in the short-axis view. To diagnose a BAV, a transesophageal echocardiography (TEE) may be useful in some cases, given its high sensitivity and specificity of 87% and 91%, respectively (25). Moreover, TEE can be useful in the assessment of BAV endocarditis with potential involvement of aortic root, as well as aortic dissection. In some cases, cardiovascular magnetic resonance imaging (MRI) or computed tomography can be alternatively used for the diagnosis and assessment of BAV. MRI enables to obtain views of the valves without interference from calcification, thus yielding a rather high sensitivity and specificity (98%) in identifying BAV (26). Besides, MRI is more commonly used to visualize the thoracic aorta and the left ventricle, and it provides crucial information about the associated cardiovascular lesions which cannot be effectively assessed by standard transthoracic echocardiography (such as aortic coarctation and ascending aortic aneurysm) (21).

1.1.3 Clinical presentation

Symptoms of BAV usually develop in the adulthood, although its clinical presentation can vary from critical aortic valve disease in the infancy to the completely asymptomatic aortic valve or thoracic aorta disease in the advanced age. The clinical presentation of BAV encompasses aortic valve dysfunction (stenosis or insufficiency), aortopathy and acute aortic syndrome (i.e., aortic dissection and rupture), as well as acquired valve complication such as endocarditis.

BAV disease is commonly asymptomatic in the childhood, whereas only 1 in 50 children develop clinically relevant aortic valve disease in the adolescence (27). Both aortic stenosis due to the small valve orifice size as well as pure aortic insufficiency secondary to the prolapsed valve cusp may develop in the childhood. However, little is known about the natural clinical course in children with "clinically normal" BAV (16). In two large series, clinical course of the non-surgically treated BAV patients correlated well with the age and the presence of moderate or severe valve dysfunction (stenosis or insufficiency), even though fatal events were rare (28, 29).

Angina pectoris, exertional dyspnea, syncope and congestive heart failure represent the classical symptoms of aortic stenosis. Congestive heart failure presents the most common complication of aortic stenosis, leading to progressive exertional dyspnea because of combined diastolic and systolic LV dysfunction (28). Angina pectoris occurs due to the increased oxygen consumption in patients with compensatory left ventricular hypertrophy. Syncope occurs because of cerebral hypoperfusion due to the inability to increase stroke volume during physical activity.

The clinical presentation of patients with BAV and associated cardiac malformations depends on the structural complexity of the congenital heart disease. In patients with ventricular

septal defect (VSD), clinical course depends on the ventricular septal defect size and the degree of aortic stenosis. In patients with coarctation of aorta, the presence and the degree of hypertension increases the risk of aortic dissection.

1.1.4 Aortic stenosis

Aortic stenosis (AS) is the most common complication of BAV disease. Although early surgical pathology reports attributed the majority of fibrocalcific aortic stenosis to a rheumatic origin (30), later reports revealed that half of adults with severe aortic stenosis have a BAV (3, 31). Although the natural course of BAV is progressive calcific degeneration, the process that leads to fibrosis, calcification and stenosis is still not completely understood. However, it is widely accepted that patients with BAV develop aortic stenosis earlier than those with tricuspid aortic valves (TAV) which is most likely due to the abnormal shear stress on the cusps which in turn leads to early thickening, calcification and stenosis (32). The development of aortic stenosis is triggered by endothelial dysfunction which involves inflammation, deposition of lipoprotein, calcification and ossification of the aortic side of the cusps (33). An in-vitro study revealed three characteristic features of the clinically "normal" BAV: (a) excessive folding and creasing that persist throughout the cardiac cycle; (b) broad areas of cusp contact; (c) significant morphologic stenosis; and (d) asymmetrical flow patterns and turbulence (32). Nevertheless, stenosis development is faster if aortic cusps are asymmetrical and have an antero-posterior orientation (3), and calcification seems to occur at younger age in men than in women (30). Moreover, the prevalence of BAV is reported in half of the patients undergoing surgical aortic valve replacement for AS and in two-thirds of these patients between 50 and 70 years old (31).

In children with significant aortic stenosis, myocardial fibrosis may develop, which is partially reversible after relief of the obstruction (34). Nevertheless, more severe disease and poor outcomes have been reported in children who present with aortic stenosis in the infancy

(35). Those with baseline peak left ventricular to aortic gradients >50 mmHg present with a risk of adverse cardiac events of 1.2% per year (36).

1.1.5 Aortic regurgitation

Aortic regurgitation (AR) may present concurrently with AS in the BAV setting or may occur as a pure AR without signs of calcification. In the first case, AR is usually of a mild to moderate degree, as it develops secondarily to the severely calcified and partially immobile valve cusps. Pure AR in BAV can occur due to redundant (myxoid degeneration) or prolapsing cusps, infective endocarditis, or secondarily to balloon valvuloplasty in children (37, 38). In an autopsy series, the most common indications for AVR due to pure AR were post-inflammatory cusp changes (46%), aortic root dilatation (21%), valve prolapse due to incomplete closure of BAV (20%) and endocarditis (9%) (39). Moreover, as the patients age, aortic root dilatation is apparently the most prevalent cause of pure AR. In patients with generalized aortic root dilatation, marked ventricular dilatation, hypertrophy, and dysfunction is more prevalent than in patients with localized or no dilatation (37). The actual prevalence of pure AR in BAV population has been reported to range from rare to common (3, 21, 40). One large surgical series reported that pure AR was seen in 13% of surgically excised valves during aortic valve replacement (17). In the presence of more-than-mild pure AR at baseline, follow-up studies have shown that interventions due to pure AR were relatively uncommon occurring in 3% and 6% of each of the study population (28, 29). Nevertheless, about 15 to 20% of BAV have insufficient valve closure and present at age 20 to 40 with an asymptomatic diastolic murmur, cardiomegaly, or symptoms due to AR (41). Despite variations in the reported prevalence, moderate-to-severe AR is of clear clinical relevance, as it is an independent predictor of late adverse cardiac events. In the presence of significant AR, the natural course is determined by the left ventricular response to chronic volume overload. These patients will eventually require

surgery due to progressive left ventricular dilatation (3% to 4% per year) and onset of symptoms (at a rate of ≈6% per year) (42, 43).

1.1.6 Surgical aortic valve replacement: indication and timing of treatment

Indications for surgical treatment of BAV disease (AS, AR or combined) are well established and are similar to those with TAV disease or degenerative aortic valve disease (44, 45). According to the ACC/AHA and 2017 ESC/EACTS guidelines, aortic valve replacement (AVR) is recommended for symptomatic patients with severe high-gradient AS (Class IB), and for asymptomatic patients with AS and left ventricular (LV) dysfunction (LVEF <50%) (ACC/AHA: Class IB; ESC/EACTS: Class IC). Severe AS in patients with normal LV systolic function is defined by a peak velocity (V_{max}) ≥4.0 m/s and/or mean gradient (ΔP) >40 mmHg in echocardiography. It usually corresponds to an aortic valve area (AVA) of ≤1.0 mm^2. In patients with low forward flow, severe AS may be diagnosed even with lower aortic valve velocities and lower aortic valve gradients. In these patients, aortic valve area should be calculated. Moreover, AVR is reasonable in asymptomatic patients with a very severe AS (V_{max} ≥5.0 m/s) and low surgical risk (ACC/AHA: Class IIaB; ESC/EACTS: Class IIaC).

In patients with pure aortic regurgitation (AR), AVR is indicated for symptomatic patients with severe AR regardless of LV systolic function (ACC/AHA & ESC/EACTS: Class IB). Echocardiographic criteria for the definition of severe AR include several indices such as: qualitative, semiquantitative and quantitative. Qualitative indices include valve morphology (abnormal/flail/large coaptation defect), color flow regurgitant jet (large in central jets, variable in eccentric jets), continuous wave signal of regurgitant jet (dense) and other (holodiastolic flow reversal in descending aorta, EDV >20 cm/s). Semiquantitative indices include: vena contracta width (>6 mm), and pressure half time (PHT <200 ms). Quantitative indices include: effective regurgitant orifice area (EROA ≥30 mm^2), regurgitant volume (R Vol ≥60 ml/beat), and the presence of enlargement of cardiac chambers (LV). Additionally, diagnosis of chronic severe

AR requires evidence of LV dilatation. In asymptomatic patients, surgery should be considered if resting LVEF ≤50% (ACC/AHA & ESC/EACTS: Class IB), or if resting LVEF >50% with severe LV dilatation (LVEDD >70 mm or LVESD >50 mm) (ACC/AHA & ESC/EACTS: Class IIaB).

Isolated surgical AVR is nowadays performed through minimally-invasive approaches using a partial upper mini-sternotomy or a right-lateral mini-thoracotomy. Moreover, standard cardiopulmonary bypass should be employed with or without moderate systemic hypothermia. Nowadays, the choice of valve prosthesis is a matter of intense scientific discussion and tissue valve prostheses have been increasingly used. BAV patients require aortic valve surgery at a younger age compared to those with TAV. Hence, it is of utmost importance to choose the best available valve prosthesis which has: (a) a long-term durability and freedom from reoperation, (b) superb hemodynamic profile, and (c) low risk of thromboembolic complications and anticoagulation-related hemorrhage. However, there is no perfect valve substitute, hence as formulated by the contemporary guidelines, "the choice of valve intervention (repair or replacement) as well as type of prosthetic heart valve, should be a shared decision-making process that accounts for the patients' values and preferences, with full disclosure of indications for and risks of anticoagulant therapy and the potential need for and risk of reoperation" (ACC/AHA: Class IC) (44). Valve prostheses are divided into: mechanical or biological. The latter include homografts, pulmonary autografts and xenografts (porcine, bovine or equine). Whereas all mechanical prostheses require lifelong anticoagulation, in biological prostheses there is no need of long-term anticoagulation, unless atrial fibrillation or other indications are present. However, biological prostheses are subject to structural valve deterioration (SVD) over time, especially in younger patient population. Therefore, in patients at risk of accelerated structural valve deterioration (especially in patients ≤40 years old or those with hyperparathyreoidism), a mechanical valve prosthesis is recommended (ESC/EACTS: IC).

1.2 Non-valvular manifestations of BAV disease

1.2.1 Bicuspid aortopathy and acute aortic syndrome

Bicuspid aortopathy is the most frequent nonvalvular manifestation of the BAV disease. Nearly half of all BAV subjects present with ascending aortic dilatation and/or enlargement of aortic root (46, 47). Some studies have documented the presence of aortic root dilatation in the childhood, implying that this process begins early in life (48-50). Serial follow-up data have documented larger aortic dimensions in children with BAV as compared to those with TAV (48). Due to histological aortic wall changes that were identified in patients with BAV, some researchers have suggested the presence of a common underlying developmental defect of the aortic valve and aortic wall (51, 52). In adult patients with BAV disease, the diameter of aortic annulus, sinus, and proximal ascending aorta are larger than in adults with TAV (46, 53, 54). However, in patients with larger aortas at baseline, progressive aortic dilatation is more common at follow-up (55-57). It is of immense importance to serially follow the size and shape of the ascending aorta in these patients.

Patients with BAV stenosis vs regurgitation show different types of aortopathies, in terms of configuration, histopathology, progression, and risk of aortic dissection. Asymmetrical dilatation of the mid-ascending aorta with a nearly normal aortic root is typically associated in patients with BAV stenosis (58). On the other hand, there is often a concomitant aortic root dilatation in patients with BAV regurgitation ("root dilatation phenotype") (59). This relatively rare subset (10-15%) consists of mainly young males which present with predominantly aortic root dilatation at the level of the aortic annulus and sinuses of Valsalva. Root dilatation phenotype has been proposed to constitute a predominantly genetic form of BAV disease (60), as opposed to the different disease of BAV stenosis and mid-ascending aortic dilatation. Different risk factors are found to be associated with dilatation of the ascending aorta, such as

increased systolic blood pressure, male sex, significant valve disease, and age as the most important variable (29, 46, 59, 61).

The most devastating complication of BAV disease is the aortic dissection. The actual incidence of aortic dissection in BAV population is a subject of intense discussion. Although the risk of aortic dissection in patients in BAV is 5 to 9 times higher than in the general population, the prevalence of dissection has been found to be 0.1% per patient-year of follow-up (29). Contradictory data on the risk of late aortic events after AVR for BAV disease have also been reported. While some researchers report low risk of long-term post-AVR aortic events (62-65), others have reported an excessive risk (66). Nevertheless, a substantial risk of late aortic events after AVR have been reported in the subset of patients with pure BAV regurgitation as compared to those with BAV stenosis (67), which may reinforce the tendency towards a custom-tailored approach regarding the concomitant aortic replacement in the setting of mild-to-moderate aortic dilatation during AVR.

1.2.2 Non-valvular manifestations proximal to the BAV disease

There is a paucity of data on the manifestations of BAV disease below the aortic valve (i.e. left ventricle and mitral valve). In recent years, several studies addressed the manifestations of BAV disease proximal to the aortic valve, with the focus on the left ventricular changes and the morphology and dysfunction of the mitral valve. However, the whole spectrum of cardiovascular abnormalities related to BAV are to date still underreported.

Left ventricular dysfunction in BAV disease

Subclinical left ventricular (LV) systolic and diastolic dysfunction has been previously reported even in BAV subjects without significant valvular dysfunction as compared to control subjects (68, 69). Subclinical myocardial dysfunction in BAV subjects without valvular dysfunction was also observed independently of age, peak aortic jet velocity and ascending

aortic diameter, which may furthermore indicate the presence of intrinsic myocardial disease (69). In a prospective study, the LV strain values of BAV patients without significant valvular dysfunction were also found to be lower as compared with the control group (70). Moreover, athletes with BAVs presented with a significant progressive increase in LV dimensions (71). Although young and trained athletes with BAVs were found to have normal LV performance, they still tend to have lower strain than healthy subjects in the LV basal segments (72). Furthermore, the subjects with BAV presented with larger LV mass index as compared to the control group (69, 73, 74). This interesting observation has been found even in BAV subjects without valvular dysfunction (i.e. non-stenotic BAVs), raising further questions regarding the possible trigger and pathway of LV dysfunction in this study subset. This may indicate an altered remodeling process of LV in BAV subjects, showing a variety of deformation properties of LV, in particular the significant reduction of the rotation of the LV at the mitral valve level (70). Nevertheless, an increased body of evidence has emerged regarding the LV diastolic dysfunction in subjects with normally functioning BAVs, and its possible relationship with the reduced aortic elasticity and bicuspid aortopathy (69, 73, 75).

The elongated anterior mitral leaflet (AML)

Perhaps the least researched manifestation of BAV disease is the disproportionally elongated anterior mitral leaflet (AML). In patients with BAV, degenerative changes of the mitral valve have been previously documented (39, 76), yet the pathology and pathophysiology of concomitant congenital BAV and mitral valve (MV) disease is still unknown. Echocardiographic study found an overall prevalence of degenerative myxomatous MV disease in 4.7% BAV patients, although the severity of mitral regurgitation in patients with myxomatous MV has not been reported (76). Despite obvious association between both diseases (i.e. BAV and degenerative MV), it is still uncommon to find patients with clinically significant combination of both disorders (77). There is an evidence of elongated AML in

patients with BAV compared with TAV patients or control groups (78). The combination of significant BAV disease and MV requiring surgical intervention was classified as one extreme of the continuous spectrum of BAV related entities, namely the Weak Aorto-Mitral Bicuspid Relation (WAMBIRE) consisting of: 1) BAV type 1, L-R, 2) aortic regurgitation, 3) anterolateral ascending aorta dilatation, 4) isolated noncoronary sinus dilatation with normal sized left and right coronary sinuses, 5) malalignment of noncoronary sinus in the left ventricular outflow tract, 6) dilatation of aortic annulus, 7) dilatation of the interleaflet triangles adjacent to the noncoronary sinus, 8) dilatation of anterior mitral annulus, an 9) enlargement of AML with or without prolapse or regurgitation (79).

1.2.3 Cardiovascular magnetic resonance imaging for bicuspid aortic valve syndrome

Although echocardiography is an established diagnostic modality in aortic valve diseases, cardiovascular magnetic resonance imaging (CMR) has emerged as a novel and complementary tool for these patients. Moreover, CMR is nowadays established as a follow-up modality for patients with bicuspid aortopathy, due to the accurate assessment of the aortic diameter as well as the vascular anatomy such as proximal aortic phenotype, the length of the proximal aorta and the various cross-sectional diameters. Furthermore, CMR allows to quantify the systolic transvalvular flow and functional parameters of the aortic root. On the other hand, CMR is a valuable tool for precise assessment of the valvular anatomy (i.e. BAV disease) and the ventricular morphological and functional changes. Various BAV morphologies can be non-invasively differentiated by means of CMR with low inter-observer variability (80). Assessment of the left ventricle can be obtained using the ECG gated, breath hold steady state free precision (SSFP) cine images in the left ventricular inflow-outflow tract view at end-diastole and end-systole, using bright-blood imaging.

2. Publications

Article 1:

Disha K, Espinoza A, Rouman M, Secknus MA, Kuntze T, Girdauskas E. Long-Term Recovery of Reduced Left Ventricular Ejection Fraction after Aortic Valve Replacement in Patients with Bicuspid Aortic Valve Disease. Thorac Cardiovasc Surg. 2016 Aug;64(5):418-26.

Article 2:

Girdauskas E, Disha K, Espinoza A, Misfeld M, Reichenspurner H, Borger MA, Kuntze T. Mitral regurgitation after previous aortic valve surgery for bicuspid aortic valve insufficiency. J Cardiovasc Surg (Torino). 2017 Jun;58(3):473-480.

Article 3:

Disha K, Dubslaff G, Rouman M, Fey B, Borger MA, Barker AJ, Kuntze T, Girdauskas E. Evidence of subannular and left ventricular morphological differences in patients with bicuspid versus tricuspid aortic valve stenosis: magnetic resonance imaging-based analysis. Interact Cardiovasc Thorac Surg. 2017 Mar 1;24(3):369-376.

Long-Term Recovery of Reduced Left Ventricular Ejection Fraction after Aortic Valve Replacement in Patients with Bicuspid Aortic Valve Disease

Kushtrim Disha[1]   Andres Espinoza[1]   Mina Rouman[1]   Maria-Anna Secknus[2]   Thomas Kuntze[1]
Evaldas Girdauskas[1]

[1] Department of Cardiac Surgery, Central Hospital Bad Berka, Bad Berka, Germany
[2] Department of Cardiology, Central Hospital Bad Berka, Bad Berka, Germany

Address for correspondence Kushtrim Disha, MD, MPH, Department of Cardiac Surgery, Zentralklinik Bad Berka, Robert-Koch-Allee 9 Bad Berka 99437, Germany (e-mail: k_disha@hotmail.com).

Abstract

Background   Long-term prognosis of patients with bicuspid aortic valve (BAV) disease and poor left ventricular ejection fraction (LVEF) who underwent aortic valve replacement (AVR) is unknown. We aimed to analyze the recovery of LVEF and incidence of adverse events after AVR in patients with BAV and poor LVEF.

Materials and Methods   A total of 90 consecutive BAV patients (mean age 57 ± 10 years, 89% male) with baseline LVEF $\leq40\%$ underwent an isolated AVR between January 1, 1995, and June 30, 2008, and served as our study population. Follow-up data (800 patient-years) were obtained for all 90 hospital survivors. A subgroup of patients who underwent AVR for BAV stenosis (Group aortic stenosis [AS], $n = 70$) was compared with those who underwent AVR for BAV regurgitation (Group aortic regurgitation [AR], $n = 20$). Primary end point was the recovery of LVEF in AS Group versus AR Group. Secondary end points were survival and freedom from adverse cardiac events (i.e., cardiac-related death and need for reinterventions due to persisting heart failure).

Results   There was a significant increase in LVEF (mean follow-up 9.0 ± 5 years) in AS versus AR Group (i.e., $32 \pm 7\%$ [baseline] and $53 \pm 9\%$ [follow-up], $p < 0.001$ in AS Group vs. $33 \pm 7\%$ [baseline] and $38 \pm 13\%$ [follow-up], $p = 0.07$ in AR Group). Recovery rate of LVEF was significantly higher in AS Group versus AR Group (i.e., 2.8 percentage points (pp)/year vs. 0.7 pp/year, respectively). In Group AS, 86% of patients were responders, whereas in Group AR, only 30% ($p < 0.001$). The subjects in Group AR did not show a difference between baseline and follow-up left ventricular end-diastolic diameter (LVEDD) (baseline 61 ± 12 vs. follow-up 58 ± 8, $p = 0.813$), whereas in Group AS, there was a significant difference of LVEDD (baseline 56 ± 7 vs. follow-up 54 ± 6 mm, $p = 0.019$). Ten-year survival was $76 \pm 6.5\%$ in AS Group versus $78 \pm 11\%$ in AR Group ($p = 0.3$). Prevalence of late adverse cardiac events was 7% in AS Group versus 40% in AR Group ($p = 0.03$).

Conclusion   The recovery of reduced LVEF after AVR surgery is significantly impaired in patients with BAV regurgitation as compared with BAV stenosis.

Keywords
► ejection fraction
► AVR
► bicuspid aortic valve

Introduction

While representing the most common congenital cardiac anomaly,[1,2] bicuspid aortic valve (BAV) disease conveys a substantial surgical burden. Almost one half of the patients who are operated on or die from the aortic valve disease possess this anomaly.[3] BAV is recognized as a prevalent cause of aortic valve stenosis and regurgitation,[1,3] and as such it may impact the anatomical structures proximal and distal to the dysfunctional valve. Moreover, BAV patients may experience life-threatening aortic complications due to abnormal aortic distensibility and stiffness (i.e., bicuspid aortopathy).[4,5] As opposed to the patients with a regular tricuspid aortic valve, subjects with BAV experience valvular lesions earlier in life. This difference might be explained by an abnormal stress distribution on the cusps of BAV.[6]

Aortic valve replacement (AVR) is a well established and evidence-based therapy to treat patients with symptomatic aortic valve disease. Over the course of last decades, there has been a controversy regarding treatment of patients with severe aortic valve disease in combination with an advanced systolic left ventricular dysfunction.[7] It has been demonstrated that patients presenting with significant aortic valve stenosis and systolic left ventricular dysfunction improved their left ventricular ejection fraction (LVEF) post-AVR surgery.[8–10] On the contrary, AVR surgery in patients with aortic valve regurgitation and reduced LVEF was associated with a considerable perioperative mortality and high prevalence of persisting congestive heart failure.[11–13] Furthermore, the long-term recovery of low LVEF post-AVR surgery in subjects with aortic valve stenosis versus regurgitation has been proposed to follow distinct pathogenetic pathways.[7]

Until now, there is a lack of clinical data on the recovery of impaired LVEF in BAV patients who underwent AVR surgery. Moreover, the risk of late adverse cardiac events in this specific patient cohort as well as potential differences between stenosis versus regurgitation subgroups have not been systematically evaluated. In the present study, we aimed to analyze the differences in the recovery of impaired LVEF after AVR surgery in patients with BAV stenosis versus those with BAV regurgitation.

Materials and Methods

Inclusion Criteria

A review of our institutional AVR surgery database was conducted, to identify all BAV patients who underwent an isolated AVR for aortic valve stenosis or regurgitation between January 1, 1995, and June 30, 2008. Approval of the local Ethics Committee was obtained and individual patient consent was waived. We implemented strict inclusion criteria to precisely define our study population. The inclusion criteria were as follows: (1) an intraoperatively confirmed congenitally BAV, (2) a baseline impaired LVEF $\leq 40\%$ as identified by a preoperative echocardiography, and (3) an isolated AVR surgery due to a severely stenotic or regurgitant aortic valve. Moreover, patients were not included if they underwent an emergency surgery (AVR), or required a combined surgical procedure (i.e., coronary artery bypass grafting [CABG], mitral valve surgery). We excluded all patients with a history of known coronary artery disease (CAD) and/or prior interventions due to CAD (i.e., percutaneous coronary intervention [PCI] or CABG). Only hospital survivors with a postoperative follow-up of at least 5 years post-AVR were considered.

Definitions and Measurements

The bicuspidality of aortic valve was confirmed through the intraoperative valve description by the surgeon. The valve was determined as bicuspid if there were only two cusps. If a median raphe existed in the fused cusp, care was taken to distinguish it from a postinflammatory fusion. We assumed that, in a true bicuspid valve, the median raphe did not extend to the height of valve commissures on the aortic wall. All patients underwent routine two-dimensional transthoracic echocardiography preoperatively. LVEF was calculated using the Simpson formula (i.e., volumetric method) by measuring the end-diastolic and end-systolic volumes in the apical four-chamber views.[14] The preoperative LVEF was also determined by LV angiography in all patients. There was no relevant discrepancy between echocardiographic and angiographic measurements of LVEF in our study, which is in accordance with the published data.[15] Postoperative recovery of LVEF was determined by follow-up transthoracic echocardiography only. All preoperative and postoperative echocardiographies as well as Doppler quantifications were performed using the most current guidelines valid at the time of examination.

Aortic valve dysfunction was established using validated echocardiographic assessment guidelines.[16,17] In the presence of low transvalvular gradients (i.e., low-flow, low-gradient aortic stenosis [AS]), a dobutamine stress echocardiography was performed in all patients to differentiate between truly and pseudo-severe AS.

Study Population

A total of 510 BAV patients who underwent isolated AVR surgery were identified from our institutional AVR surgery database ($n = 1,950$), and 90 (18%) of them met the study inclusion criteria. A total of 70 patients were assigned to the stenosis group (Group AS) and the remaining 20 patients had pure/predominant aortic valve insufficiency (Group AR). All patients with AR had an isolated regurgitation (i.e., mean transvalvular gradient ≤ 20 mm Hg). BAV patients with mixed aortic valve disease (i.e., AS/AR) were included in Group AS if stenosis was the predominant lesion. A conventional isolated AVR through a median sternotomy (or partial upper ministernotomy) using standard cardiopulmonary bypass with mild systemic hypothermia was conducted in all patients. The standardized surgical and anesthetic protocols which were intraoperatively performed underwent only minor changes over time. Both study subgroups were comparable in terms of pre- and intraoperative variables (►Table 1). In particular, there was no significant difference between the study subgroups in terms of the baseline LVEF and preoperative New York Heart Association (NYHA) functional class. Noteworthy, patients in Group AR presented with

Table 1 Preoperative/intraoperative variables

Variable	Study population		p-Value
	Aortic stenosis (n = 70)	Aortic regurgitation (n = 20)	
Mean age (y)	57.9 ± 10 (39–77)	53.1 ± 10 (24–70)	0.498
Male sex	62 (89)	18 (90)	0.858
BSA (m²)	1.94 ± 0.2 (1.34–2.4)	1.96 ± 0.2 (1.51–2.38)	0.321
Baseline LVEF (%)	32 ± 6 (10–40)	33 ± 6 (22–40)	0.771
Baseline LVEDD (mm)	56 ± 7 (43–79)	61 ± 12 (50–104)	0.021
NYHA class III or IV	50 (71)	11 (55)	0.060
Ascending aorta (mm)	47 ± 4 (40–50)	45 ± 4 (40–50)	0.482
Diabetes mellitus	12 (17)	4 (20)	0.587
Smoking	28 (40)	4 (20)	0.103
Arterial hypertension	31 (44)	6 (30)	0.308
β-Blocker therapy	19 (27)	4 (20)	0.396
Peripheral arterial disease	2 (3)	1 (5)	0.703
COPD	4 (6)	1 (5)	0.862
Endocarditis	3 (5)	3 (15)	0.118
Urgent surgery	28 (40)	6 (30)	0.274
CPB time (min)	68 ± 16 (39–110)	75 ± 30 (46–190)	0.187
Cross-clamp time (min)	35 ± 10 (20–66)	36 ± 8 (24–53)	0.373
Mechanical valve prosthesis	56 (80)	17 (85)	0.720
Mean prosthesis size (mm)	26 ± 1.8 (21–29)	27 ± 2.0 (21–29)	0.734

Abbreviations: BSA, body surface area; COPD, chronic obstructive pulmonary disease; CPB, cardiopulmonary bypass; LVEDD, left ventricular end-diastolic diameter; NYHA, New York Heart Association.
Note: Data presented as numbers (%) or as mean ± SD (range).

a significantly greater baseline left ventricular end-diastolic diameter (LVEDD) as compared with patients in Group AS. Arterial hypertension was the most common comorbidity (41%) and one-third of all patients were smokers. Aortic valve was replaced with a mechanical prosthesis in 80% of patients in the Group AS and in 85% of patients in the Group AR. Although the ascending aortic diameter by the time of the operation was 47 ± 4 mm, at that time there was an institu-

tional strategy not to replace the ascending aorta with a diameter of ≤ 50 mm. The most important postoperative inhospital outcomes are listed in ►**Table 2**.

Primary end point of our study was the long-term recovery of LVEF in percentage points (pp) in both study subgroups (i.e., Group AS vs. Group AR), as determined by the most recent follow-up echocardiography. We defined our study patients as "responders" if their LVEF improved at least 10 pp from the

Table 2 Inhospital outcomes

Variable	Aortic stenosis (n = 70)	Aortic regurgitation (n = 20)	p-Value
Low cardiac output	6 (9)	4 (20)	0.210
Intra-aortic balloon pump	0 (0)	0 (0)	
Reoperation for bleeding	5 (7)	0 (0)	0.194
Stroke	0 (0)	1 (5)	0.067
Dialysis-dependent renal failure	1 (1)	0 (0)	0.581
Tracheostomy	1 (1)	0 (0)	0.763
ICU stay (d)	3.6 ± 8 (1–65)	3.1 ± 2 (1–12)	0.515
Hospital stay (d)	17 ± 11 (6–68)	19 ± 8 (9–36)	0.749

Abbreviation: ICU, intensive care unit.
Note: Data presented as numbers (%) or as mean ± SD with range.

baseline during post-AVR course. Secondary end points were overall survival and long-term freedom from adverse cardiac events. Adverse cardiac events were defined as cardiac-related death (congestive heart failure, valve-related complications, and sudden cardiac death) or the need for late reintervention due to progressive congestive heart failure (need for cardiac resynchronization therapy [CRT]/implantable cardioverter defibrillator therapy, left ventricular assist device [LVAD] implantation, or heart transplantation).

Follow-up

All hospital survivors were followed up using standardized follow-up protocol. The follow-up protocol consisted of a telephone interview with the patients, their family members, and/or patients' family physician. In addition, we obtained the most recent echocardiography reports from the patients' cardiologist or family physician. For all patients who died during the follow-up, the cause of death was obtained from the patients' hospital charts (i.e., requested from an external hospital or family physician). As already stated in our previous publication,[18] all available contact persons (i.e., family members, family physicians, and patient's cardiologists) were contacted in all cases of out-of-hospital death, to confirm or exclude the sudden cardiac death.

Statistical Analysis

Data were tested for normal distribution using the Kolmogorov–Smirnov test. Data are expressed as mean value ± standard deviation for continuous variables, as numbers with percentage for categorical variables. Unpaired two-sided t-test was used to compare continuous variables between the study subgroups. In-group comparisons of the baseline versus the most recent follow-up LVEF were performed using the paired t-test. Categorical variables were analyzed by χ^2 test or Fisher exact test as appropriate. Survival analysis and freedom from adverse cardiac events estimates were calculated using the Kaplan–Meier method. Multivariate analysis of risk factors for nonimprovement of LVEF post-AVR was performed using Cox regression model. All variables which were found $p < 0.1$ at univariate analyses as well as variables of known clinical relevance: arterial hypertension, diabetes, preoperative NYHA class, presence of atrial fibrillation, and preoperative LVEDD ≥ 65 mm were included in the multivariate model. As previously noticed (see inclusion criteria), CAD was an exclusion criterion of the study, and as such was not included in the multivariate model. The p-values of 0.05 or less were considered statistically significant. All statistical analyses were performed with IBM SPSS 19.0 software (IBM Corp., New York, United States).

Results

The follow-up data (a total of 810 patient-years) were obtained for all 90 hospital survivors (100%). The mean length of follow-up was 9.0 ± 4.5 years and was comparable in Group AS versus Group AR (Group AS 8.6 ± 4.4 vs. 10.4 ± 5.0 years in Group AR, $p = 0.1$).

Long-Term Survival

A total of 15 (17%) patients died during the follow-up, and 7 of them suffered cardiac-related death. The causes of late deaths are summarized in ►**Table 3**. The causes of cardiac-related death were end-stage congestive heart failure in two patients and sudden cardiac death in another three patients. Two remaining patients died of Coumadin anticoagulation induced severe cerebral hemorrhage. The overall survival was 81 ± 5% at 10 years and 72 ± 6% at 15 years postoperatively (►**Fig. 1**). Survival rate was comparable in both study groups at 10 years post-AVR (i.e., 76 ± 6.5% in Group AS vs. 78 ± 11% in Group AR, $p_{(log\ rank)} = 0.3$) (►**Fig. 2**).

Recovery of Left Ventricular Ejection Fraction

Mean echocardiographic follow-up was 8.0 ± 5.0 years. At follow-up, there was no significant difference in mean transvalvular gradient across the aortic valve prosthesis between the

Table 3 Causes of late deaths

Cause of death	Aortic stenosis N	Aortic regurgitation N
Cardiac death	5 (42%)	2 (67%)
Congestive heart failure	2	
Valve related		
Hemorrhage	2	
Sudden death	1	2
Aortic-related death		1 (33%)
Type-A acute aortic dissection		1
Noncardiac death	7 (58%)	
Malignancy	4	
Chronic end-stage disease	2	
Infection	1	
Total deaths	12	3
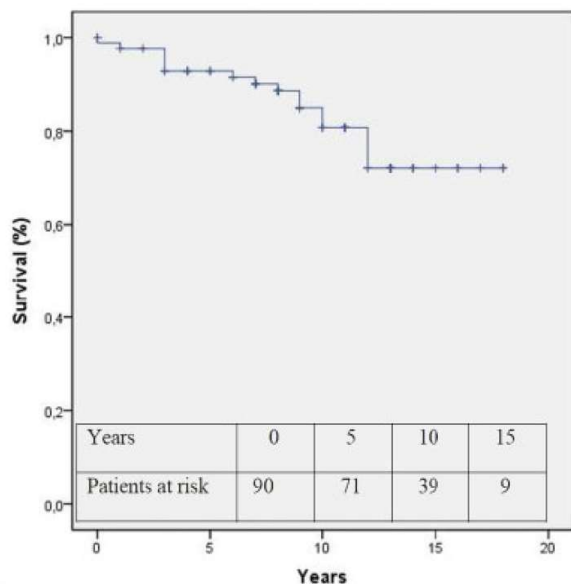
Fig. 1 Overall survival (Kaplan–Meier) of all BAV patients. BAV, bicuspid aortic valve.

Fig. 3 Correlation between prosthetic valve size and body size area (BSA) in both study subgroups (AS, aortic stenosis group; AR, aortic regurgitation group).

two study subgroups (12 ± 5 mm Hg for Group AS vs. 12 ± 3 mm Hg for Group AR) ($p = 0.877$). To exclude the influence of a patient-prosthesis mismatch in LVEF recovery, we performed a statistical distribution of each valve size used in relation to the corresponding patient's body surface area (BSA). We found no differences in correlation pattern between the patient's BSA and the corresponding valve size for both study subgroups (►**Fig. 3**). A total of 54 (60%) study patients were revealed as echocardiographic responders (i.e., LVEF improvement of at least 10 pp from the baseline). In Group AS, 86% of
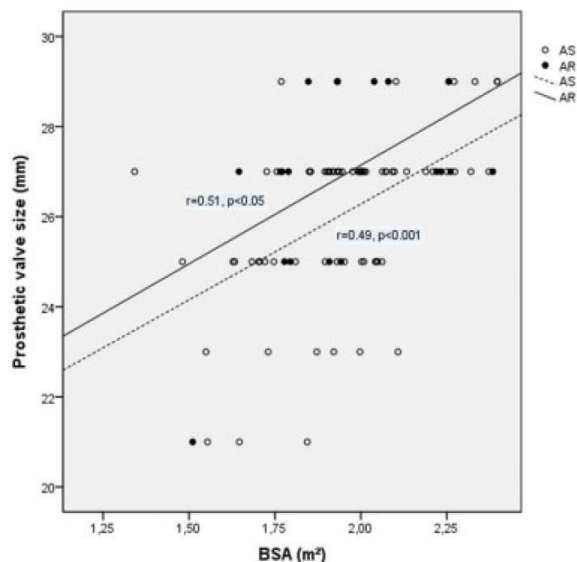
patients were responders, whereas in Group AR, only 30% ($p < 0.001$). The mean change between baseline LVEF and last follow-up LVEF was 21 ± 10 pp in Group AS versus 7 ± 14 pp in Group AR ($p < 0.001$) (►**Fig. 4**). Mean LVEF improved significantly after AVR surgery as compared with baseline in Group AS ($p < 0.001$), whereas there was a trend toward improvement of LVEF in Group AR ($p = 0.073$). The mean annual recovery rate of LVEF was 2.16 pp/year for the whole study population and was significantly higher in Group AS (i.e., 2.76 pp/year in Group AS vs. 0.7 pp/year in Group AR, $p < 0.05$).
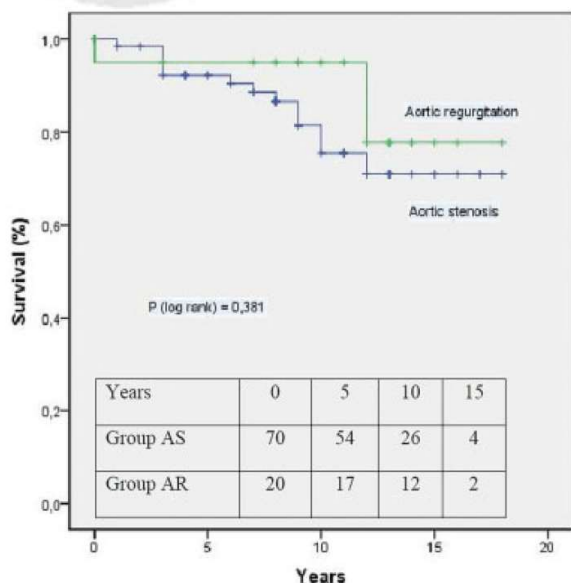
Fig. 2 Overall survival according to groups (AS vs. AR). AR, aortic regurgitation; AS, aortic stenosis.
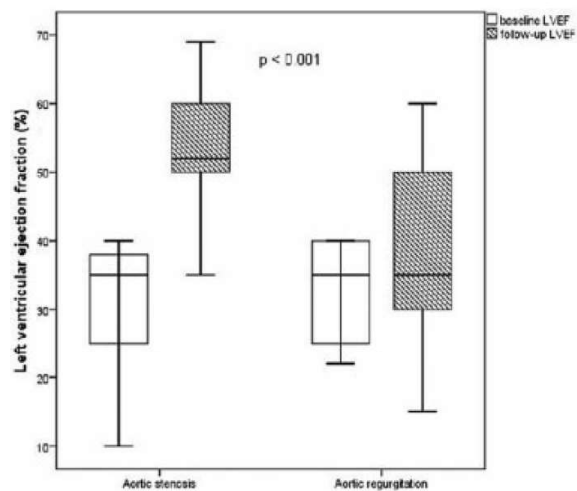

Fig. 4 Comparison of LVEF at baseline and follow-up post-AVR in Group AS versus Group AR. Solid horizontal line, mean EF; crosshatched box, 1SD; vertical line, highest and lowest mean values. AR, aortic regurgitation; AS, aortic stenosis; AVR, aortic valve replacement; EF, ejection fraction; LVEF, left ventricular ejection fraction.

Table 4 Predictors of nonimprovement of LVEF post-AVR (as determined by the Cox regression analysis)

Variables	Hazard ratio	p-Value	95% CI	
AV regurgitation	3.615	0.012	1.325	9.865
Gender	0.742	0.806	0.068	8.057
Age > 65 y	0.937	0.907	0.317	2.774
Prosthetic valve ≤ 25 mm	0.726	0.370	0.360	1.464
Baseline LVEF ≤ 25%	1.204	0.506	0.696	2.083
Baseline LVEDD ≥ 60 mm	3.094	0.021	1.183	8.095
Urgency of surgery	1.359	0.527	0.525	3.516

Abbreviations: AVR, aortic valve replacement; CI, confidence interval; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction.

We noted a significantly greater baseline left ventricular end-diastolic diameter (LVEDD) in Group AR (61 ± 12 mm) versus Group AS (56 ± 7 mm) (p = 0.021). However, on follow-up, there was no significant difference in LVEDD between the two groups (Group AR 58 ± 8 vs. Group AS 54 ± 6 mm, p = 0.072). Of note, the subjects in Group AR did not show a difference between baseline and follow-up LVEDD (baseline 61 ± 12 vs. follow-up 58 ± 8, p = 0.813), whereas in Group AS, there was a significant difference of LVEDD (baseline 56 ± 7 vs. follow-up 54 ± 6 mm, p = 0.019).

We conducted a risk factor analysis to identify potential predictors of nonimprovement of LVEF post-AVR surgery. Univariate analyses were performed at the first step and included all baseline variables that might have an influence on postoperative LVEF recovery. Variables with p < 0.1 at univariate analyses were entered into a Cox regression model using a forward stepwise condition. BAV regurgitation (hazard ratio [HR] 3.615, p = 0.012) as well as baseline LVEDD ≥ 60 mm (HR 3.094, p = 0.021) were identified as independent predictors of nonimprovement of LVEF post AVR surgery (►**Table 4**). Of note, severely reduced systolic LVEF (i.e., baseline LVEF ≤ 25%) was not predictive of LVEF recovery in the Cox regression analysis (►**Table 4**).

Adverse Cardiac Events

The risk of cardiac-related events was significantly higher in Group AR as compared with Group AS at 15 years post-AVR (i.e., 7% in Group AS vs. 40% in Group AR, p = 0.001). Freedom from cardiac-related events at 15 years post-AVR was 84 ± 7% in Group AS versus 34 ± 17% in Group AR ($p_{(\text{log rank})}$ = 0.028) (►**Fig. 5**).

None of our study patients underwent a heart transplant and/or LVAD implantation during the follow-up. One patient in Group AR died of sepsis-induced multiorgan failure, while waiting on the heart transplant list. A total of four patients required ICD/CRT therapy, at mean time interval of 8.2 years post-AVR. All four patients were echocardiographic nonresponders (i.e., LVEF improvement less than 10 pp post-AVR) and three of them (75%) belonged to the Group AR.

Redo-Cardiac Interventions

A total of five patients underwent redo-cardiac surgery. One patient required re-replacement of his aortic valve prosthesis due to prosthetic valve endocarditis. The second patient had a new-onset three-vessel CAD combined with ischemic mitral valve regurgitation. He underwent triple CABG and simultaneous mitral valve repair at 15 years post-AVR. The third patient in Group AR presented with a progressive aortic root aneurysm at 5 years post-AVR and underwent a composite graft replacement of aortic root. The fourth patient required a combined mitral and tricuspid valve surgery at 11 years postoperatively. The last patient had to be reoperated 3 months post-AVR due to ventricular septum defect after septum myectomy.
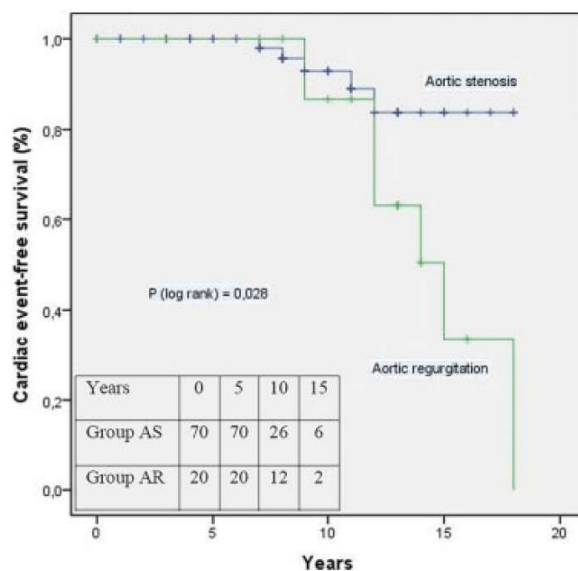

Fig. 5 Freedom from cardiac-related events according to groups (AS versus AR). AR, aortic regurgitation; AS, aortic stenosis.

Discussion

Impaired LVEF is a major prognostic indicator of postoperative outcome in patients undergoing AVR for aortic valve stenosis and regurgitation.[9,13,19–22] To the best of our knowledge, the present study is the first to report long-term recovery of impaired systolic LVEF after AVR in patients with the BAV disease. What is the rationale behind the analysis of LVEF recovery in this specific cohort of patients? First of all, BAV patients tend to be younger and present with less comorbidities at the time of AVR surgery. Therefore, BAV patients are "exposed" to longer post-AVR survival times and higher likelihood of cardiac-related events. Second, BAV disease is the most common congenital anomaly of human heart with 1 to 2% prevalence in the general population. Therefore, it might be important to elucidate the long-term prognosis of BAV patients with a reduced systolic LVEF undergoing AVR surgery. Third, BAV patients develop hemodynamically relevant valvular lesions earlier in life.[6] Long-standing valvular dysfunction, if remains undetected, paves the way for a possibly earlier impairment of LVEF. In accordance to this statement, Donal et al[23] demonstrated that the functional severity of echocardiographically comparable aortic valve disease tends to be greater in bicuspid versus tricuspid AS, thus causing more severe "afterload mismatch" in BAV patients. Moreover, Kurt et al demonstrated convincingly that even healthy subjects with BAV disease are prone to occult left ventricular dysfunction as compared with subjects with tricuspid aortic valve (i.e., subclinical impairment of left ventricular mechanics in BAV).[24] Similarly, a recent echocardiographic study by Demir[25] demonstrated an impaired LV systolic and diastolic function in the subjects with BAV versus the subjects with tricuspid aortic valve. Based on the results of these studies, it might be hypothesized that BAV is not only a valvular dysfunction but possibly a ventricular disease as well.[24,25] Therefore, in our current study, we aimed to address the recovery of impaired LVEF after AVR surgery in patients with BAV disease and to compare this recovery in Group AS versus Group AR.

Aortic Stenosis

As a consequence of increased afterload on the left ventricle in AS, physiologic adaptation through sarcomere replication occurs and leads to concentric left ventricular hypertrophy subsequently.[26] This compensatory mechanism attempts to normalize wall stress, thus preserving systolic LV function. Over the time course, left ventricle becomes unable to maintain a normal stroke volume against the increasing systolic load, and an overload state defined as "afterload mismatch" occurs.[27,28] If this process is causative of systolic LV dysfunction, AVR surgery should lead to LVEF recovery and survival benefit.[8,9,22,29,30] However, some AS patients demonstrate no LVEF recovery post-AVR and are supposed to have a fixed myocardial damage.[9] Our results revealed significant LVEF improvement in Group AS post-AVR, with 86% BAV stenosis patients being echocardiographic responders. These favorable results are in accordance with previous publications.[9,29,30] Connolly et al[9] focused on the correlation analysis between LVEF improvement and the extent of CAD. We did intentionally not include patients with a history of CAD in our study, whereby minimizing the potential impact of this confounding factor. In summary, our results demonstrate echocardiographic recovery of systolic LVEF post-AVR surgery in patients with BAV stenosis and impaired systolic LVEF.

Aortic Regurgitation

Patients with AR differ pathogenically from those with AS in that both pressure and volume overload are combined, which results in an increased LV preload and afterload.[7] As a consequence of the increased left ventricular end-diastolic wall stress eccentric hypertrophy occurs[7] and a compensatory mechanism, so-called "afterload mismatch, preload reserve" is triggered.[31] Left ventricle employs Frank–Starling mechanism, characterized by the increase in afterload which is matched to the increase in preload (i.e., "preload reserve"). In case of persisting AR, left ventricle dilates further and the preload reserve ultimately fails, which leads to progressive systolic LV dysfunction.[7]

Although patients with AR account only for a small cohort of patients requiring AVR surgery, they represent a high-risk subgroup for perioperative morbidity and mortality.[32] Similarly to our findings, Kennedy et al observed significantly reduced LVEF recovery in a small group of AR patients, who were not stratified according to the underlying aortic valve morphology, after AVR surgery as compared with AS patients.[30] These authors concluded that AR patients should undergo expeditious AVR surgery before any considerable decline of systolic LVEF.[30] Moreover, Bonow et al analyzed a cohort of 50 patients with AR and found that an impaired systolic LVEF (i.e., LVEF < 45%) and/or prolonged duration of LV dysfunction was associated with a persistent congestive heart failure after AVR surgery.[21] Of note, we found a considerably higher rate of cardiac-related events in Group AR versus Group AS in our follow-up study (►Fig. 5). Only 34% patients in Group AR were free of cardiac-related event as compared with 84% patients in Group AS at 15 years post-AVR. These data are in support of different pathophysiologic mechanisms in patients with AR as compared with those with AS.

Nonetheless, a specific "valvular cardiomyopathy" has been reported in the presence of valvular dysfunction.[33] Herpel et al reported on severe loss of cardiomyocytes and increased interstitial fibrosis in a histological analysis of explanted human hearts with an end-stage valvular cardiomyopathy.[34] Although the authors did not correlate distinct types of valvular dysfunction (i.e., AS vs. AR) with the specific biomolecular and histological changes in the muscle matrix, the concept of specific "valvular cardiomyopathy" may still be relevant. Based on our data and those from others, we may hypothesize that "fixed myocardial damage" occurs in the presence of long-standing BAV regurgitation, which may impede LVEF recovery after AVR surgery. Connolly et al used the term of "fixed myocardial damage" to explain the nonimprovement of LVEF after AVR surgery for severe aortic valve stenosis.[9]

To maintain a sufficient cardiac output, while faced with an increased preload and afterload in significant aortic valve

regurgitation, the Frank–Starling mechanism might be employed. If severe aortic valvular regurgitation persists over long term, this compensation mechanism fails and leads ultimately to a reduction of LV stroke volume (i.e., vicious circle of heart failure). Possible explanation of "fixed myocardial damage" in patients with AR might be the earlier activation of Frank–Starling mechanism as compared with patients with aortic valve stenosis. By engaging this mechanism, the cardiac muscle experiences an extensive stretch which leads to an increased ventricular wall tension and subsequently to an increased myocardial oxygen consumption. In addition, in the presence of a BAV which is accompanied with the risk of earlier aortic valve dysfunction[6] and subclinical impairment of LV mechanics,[24] these pathophysiologic pathways might be further accelerated.

Although AVR surgery is still feasible and safe in the setting of significantly impaired systolic LVEF in patients with AR, the risk of post-AVR cardiac events remains significantly increased in this cohort of BAV patients (i.e., as compared with BAV stenosis patients). Current ESC/EACTS Guidelines on the management of valvular heart disease suggest surgery in asymptomatic patients only with severe AR and LVEF $\leq 50\%$. Furthermore, according to the guidelines, surgery should be considered if LVEDD > 70 mm.[35] The rationale behind this statement is the risk of developing irreversible deterioration of myocardial function by a delayed surgery. We found LVEDD ≥ 60 mm as an independent predictor of non-improvement of LVEF post-AVR, which was associated with increased risk of late adverse cardiac events. Based on our data and those from others,[13,29] we would strongly recommend to re-evaluate this strategy and advocate a timely and expeditious surgical intervention in BAV patients with AR, before decline in systolic LVEF and evidence of increasing LVEDD.

Study Limitations

This study is limited by its retrospective nature and the nonrandomized design. Due to the fact that Group AR consisted of a smaller number of patients comparing to Group AS, we acknowledge it might explain the absence of statistically significant differences between groups. Several studies have proved LVEF to serve as a reproducible and readily accessible functional parameter of left ventricular hemodynamics.[36] Follow-up echocardiography examinations have been performed by different practicing out-of-hospital cardiologists and thus may be the subject of interobserver variability. Similarly, we are unable to ensure that the duration of AS and regurgitation before AVR surgery was comparable between the study subgroups. Furthermore, our study is limited by lack of a real (i.e., medically treated) control group, which remains practically impossible due to ethical issues.

Note

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ORIGINAL ARTICLE

CARDIAC SURGERY

Mitral regurgitation after previous aortic valve surgery for bicuspid aortic valve insufficiency

Evaldas GIRDAUSKAS [1] *, Kushtrim DISHA [2], Andres ESPINOZA [2], Martin MISFELD [3], Hermann REICHENSPURNER [1], Michael A. BORGER [4], Thomas KUNTZE [2]

[1]Department of Cardiovascular Surgery, University Heart Center Hamburg, Hamburg, Germany; [2]Department of Cardiac Surgery, Heart Center, Central Hospital of Bad Berka, Bad Berka, Germany; [3]Department of Cardiac Surgery, Heart Center Leipzig, Leipzig, Germany; [4]Division of Cardiac, Vascular and Thoracic Surgery, Columbia University Medical Center, New York, NY, USA

*Corresponding author: Evaldas Girdauskas, Department of Cardiovascular Surgery, University Heart Center Hamburg, Martinistrasse 52, 20246 Hamburg, Germany. E-mail: e.girdauskas@uke.de

ABSTRACT

BACKGROUND: Regurgitant bicuspid aortic valves (BAV) are reported to be associated with myxomatous degeneration of the anterior mitral leaflet. We examined the risk of late new-onset mitral regurgitation (MR) in patients who underwent aortic valve/aortic root surgery for BAV regurgitation and concomitant root dilatation.
METHODS: A total of 97 consecutive patients (47±11 years, 94% men) were identified from our institutional BAV database (N.=640) based on the following criteria: 1) BAV regurgitation; 2) aortic root diameter >40 mm; 3) no relevant mitral valve disease (*i.e.*, MR<2+) and no simultaneous mitral intervention at the time of BAV surgery. All patients underwent isolated aortic valve replacement (AVR subgroup, N.=59) or aortic root replacement with a composite graft (*i.e.*, for root aneurysm >50 mm) (ARR subgroup, N.=38) from 1995 through 2008. Echocardiographic follow-up (1009 patient-years) was obtained for all 96 (100%) hospital survivors. The primary endpoint was freedom from new-onset MR>2+ and redo mitral valve surgery.
RESULTS: Nine patients (9.4%) showed new-onset MR>2+ after mean echocardiographic follow-up of 10.4±4.0 years postoperatively. Myxomatous degeneration and prolapse of the anterior mitral leaflet was found in all 9 patients, and the posterior leaflet was involved in 3 of them. Two patients (2%) in AVR subgroup underwent re-do mitral surgery. No MR>2+ occurred in ARR subgroup. Freedom from MR>2+ or mitral surgery at 15 years was significantly lower in AVR subgroup *vs.* ARR subgroup (*i.e.*, 38% *vs.* 100%, P=0.01).
CONCLUSIONS: The risk of new-onset MR is significantly increased in patients with BAV regurgitation and aortic root dilatation who undergo isolated AVR rather than root replacement. The mechanism by which aortic root replacement may prevent the occurrence of late MR in BAV root phenotype patients is to be determined.

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Key words: Mitral valve insufficiency - Bicuspid aortic valve - Transcatheter aortic valve replacement.

The bicuspid aortic valve (BAV) is the most common congenital abnormality of the human heart, affecting approximately 1-2% of the general population.[1] BAV disease has been shown to be a very heterogeneous disorder with different forms (*i.e.*, BAV phenotypes) being potentially caused by unique pathogenetic mechanisms with different natural histories and prognoses.[2] A large number of recently published studies have identified several different clinical/morphological BAV phenotypes. These phenotypes are based on BAV morphology and/or expression of proximal aortic disease (*i.e.*, BAV-associated aortopathy) as determined by novel cardiovascular imaging methods,[3] longitudinal echocardiography data[4] and large-scale surgical reports.[5] One of the most common phenotype classification systems involves dividing patients into those

with pure aortic valve insufficiency and root dilatation (*i.e.* BAV root phenotype) and those with aortic stenosis (with or without aortic insufficiency) and dilation of the tubular (supracoronary) ascending aorta (*i.e.* BAV stenosis phenotype).[2] Other BAV-associated cardiovascular abnormalities (*e.g.*, mitral valve disease) are less known and have not been examined within these BAV phenotype classification systems.

Degenerative mitral valve disease in patients with BAV has also been reported.[6, 7] Myxomatous degeneration of the anterior leaflet of the mitral valve has been described as the most common mitral pathology in patients with BAV disease.6 Moreover, the anterior mitral leaflet in BAV disease have been found to be significantly elongated and "hypermobile" as compare to patients with tricuspid aortic valves.[7] These changes were predominantly found in BAV patients with aortic valve insufficiency.[6, 7]

The prevalence of clinically important BAV disease in patients referred for surgical treatment of mitral regurgitation (MR) was relatively low (*i.e.* 1.6%) in a previously published study.[6] However, late progression of mitral valve disease after aortic valve surgery for BAV disease, especially for BAV insufficiency, has not been investigated. Therefore, the aim of this study was to assess the risk of late new-onset MR in BAV patients who underwent previous aortic valve/aortic root surgery for BAV regurgitation and concomitant aortic root dilatation (*i.e.*, BAV root phenotype). Because BAV root phenotype is thought to be a genetic disease with characteristics that are more similar to connective tissue disorders, we therefore opted to focus on BAV root phenotype patients only.[8, 9]

Materials and methods

We reviewed our institutional BAV database (N.=640) to identify all BAV patients who underwent isolated aortic valve replacement (AVR)/aortic root surgery for BAV insufficiency in the presence of concomitant aortic root dilation >40 mm between January 1995 and April 2008 at the Central Hospital Bad Berka, Germany. Study approval was obtained from our local ethics committee. Individual patient consent was waived.

Only patients with isolated/predominant BAV insufficiency were included. Consequently, all BAV patients with a mean transvalvular pressure gradient >20 mmHg

were excluded. Moreover, all study patients had aortic root diameter >40 mm. Maximal aortic diameter was diagnosed at the level of aortic root (*i.e.*, aortic phenotype type I according to Fazel *et al.*[3]) in all patients. Further inclusion criterion was the absence of clinically significant MR (*i.e.*, MR <2+) at the time of AVR surgery. Consequently, all cases of simultaneous mitral valve intervention were excluded. Patients with Marfan syndrome were also excluded. Based on these inclusion criteria, a total of 97 consecutive BAV patients (15% of total BAV cohort, mean age 47±11 years, 94% men) were identified and served as a focus of the current study.

All included patients underwent isolated AVR (AVR subgroup, N.=59) or aortic root replacement with a composite graft (ARR subgroup, N.=38) from 1995 through 2008. Patients underwent isolated AVR if the maximal aortic root diameter was less than 50 mm, and aortic root replacement if the aortic root diameter was 50 mm or greater.

The primary endpoint of our study was late new-onset MR >2+ and/or redo mitral valve surgery after isolated AVR/aortic root replacement surgery.

Definitions and measurements

The morphology and function of the aortic and mitral valve was assessed by preoperative echocardiography in all patients. BAV was suspected if two-dimensional short-axis imaging of the aortic valve demonstrated the existence of only two commissures delimiting two aortic valve cusps. The final decision regarding the bicuspidality of the aortic valve was made intraoperatively. Aortic and mitral valve insufficiency were quantified as described previously.[10] Only BAV patients who had no/trivial or mild MR at preoperative echocardiography were eligible.

Aortic root dimensions were assessed preoperatively by means of transthoracic 2-dimensional echocardiography, using the leading edge convention in a parasternal long-axis view.[11] Preoperative computed tomography (CT) or magnetic resonance angiography (MRA) of the thoracic aorta was also used to assess aortic root diameters. If discrepancies existed between echocardiographic and CT/MRA-derived aortic dimensions, then CT/MRA measurements were used. If aortic root diameter >50 mm was observed by CT/MRA, aortic root replacement surgery (ARR subgroup, N.=38) was

performed. In all remaining patients with aortic root diameter of 40-50 mm, isolated AVR surgery (AVR subgroup, N.=59) was performed.

Study population

Pre- and intraoperative variables were comparable between study subgroups (Table I). Of note, there were no significant differences in the clinical presentation and prevalence of common risk factors. Particularly, the degree of preoperative MR was not different between both subgroups (Table I). The only significant difference was larger aortic root dimensions in ARR vs. AVR subgroups (i.e., 59 vs. 45 mm, respectively, P=0.001).

All 97 patients underwent conventional isolated AVR (AVR subgroup) or aortic root replacement (ARR subgroup) surgery, as described previously.10 Aortic root replacement surgery was associated with longer cardiopulmonary bypass and aortic cross-clamp times as compared to isolated AVR surgery. The regurgitant BAV was replaced with mechanical valve prosthesis in the majority of patients (96% in AVR subgroup vs. 100% in ARR subgroup). The mean labeled valve prosthesis size was comparable between study subgroups.

TABLE I.—Demographics and intraoperative variables.

Variable	AVR subgroup (N.=59)	ARR subgroup (N.=38)	P value
Mean age (years)	47±11 (19-71)	47±12 (17-67)	0.9
Gender, male	56 (95%)	34 (90%)	0.3
BSA (m²)	1.98±0.2	2.04±0.2	0.1
NYHA class III/IV	25 (42%)	9 (24%)	0.08
Maximum root diameter (mm)	45±4 (40-51)	59±10 (48-85)	0.001
LVEF (%)	55±13 (22-85)	54±10 (30-86)	0.3
Mean MR (degree)	0.3±0.5	0.5±0.6	0.1
No/trivial MR	42 (71%)	23 (61%)	0.3
Mild MR	17 (29%)	15 (39%)	0.4
Arterial hypertension	37 (62%)	20 (53%)	0.4
Diabetes	4 (7%)	0	0.3
History of smoking	19 (32%)	10 (26%)	0.5
Peripheral arterial disease	0	1 (3%)	0.8
COLD	3 (5%)	1 (3%)	0.9
Urgent/emergent surgery	3 (5%)	4 (11%)	0.5
CPB time (min)	69±16 (40-139)	103±20 (73-156)	0.001
Cross-clamp time (min)	35±8 (21-53)	56±11 (42-84)	0.001
Mean prosthesis size (mm)	27.7±1.4 (25-31)	27.0±2.0 (23-29)	0.1
Mechanical prosthesis	54 (96%)	38 (100%)	0.7

BSA: body surface area; COLD: chronic obstructive lung disease; CPB: cardiopulmonary bypass; LVEF: left ventricular ejection fraction; MR: mitral regurgitation.

Follow-up

Follow-up consisted of a clinical interview (i.e., patients, their family members and/or the patients' family physicians) and echocardiographic examination. Follow-up echocardiography protocols and cine-sequences were obtained from patients' cardiologists or family physicians. Moreover, follow-up echocardiography was performed at our hospital in 34 patients (35%). All medical records of patients who died during follow-up were requested and surgical reoperation reports were analyzed. A total of 42 (44%) patients were treated in our institution during postoperative course and their records were also examined.

Statistical analysis

All statistical analyses were performed with the SPSS v.19.0 software (IBM Corp, Armonk, NY, USA). Categorical variables are expressed as percentages and continuous variables are expressed as mean±SD with range throughout the manuscript. Two-tailed Student's t-test for continuous variables and χ^2 test for categorical variables were used for univariate comparisons between groups. Kaplan-Meier method was used for survival analyses (i.e., overall survival and freedom from late new-onset MR >2+). Statistical differences between preoperative and follow-up MR degree were analyzed using paired t-test. All P values of <0.05 were considered statistically significant.

Results

Survival

In-hospital mortality was 1/97 (1.0%). One patient in the AVR subgroup died suddenly a day before hospital discharge and an autopsy revealed acute ruptured type A aortic dissection.

Clinical follow-up data (a total of 1026 patient-years) were obtained for all surviving patients (N.=96, 100%). The mean length of follow-up was comparable between both study subgroups (i.e., 11.0±3.6 years in AVR subgroup vs. 12.0±3.8 years in ARR subgroup, P=0.2). A total of 8 patients (14%) died in AVR subgroup vs. 4 patients (11%) in ARR subgroup during follow-up. The majority of late deaths were cardiac related (i.e., 75% of deaths in both subgroups) and are summarized in Table

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TABLE II.—*Causes of late death in both study subgroups.*

Cause of death	AVR subgroup (N.=8)	ARR subgroup (N.=4)
Cardiac-related death	6 (75%)	3 (75%)
Aortic dissection	1	0
Valve related		
Stroke	1	0
Hemorrhage	1	0
Endocarditis	0	2
Sudden death	3	1
Non-cardiac-related death	2 (25%)	1
Malignancy	2	0
Trauma	0	1

II. Overall 10- and 15-year survival was comparable between study subgroups (*i.e.*, 90±4% and 78±8% in AVR subgroup *vs.* 90±6% and 85±7% in ARR subgroup, $P_{log-rank}$=0.6) (Figure 1).

New-onset mitral regurgitation

Echocardiographic follow-up (*i.e.*, a total of 1009 echocardiography-years) was obtained for all hospital survivors. The mean length of echocardiographic follow-up was comparable in both study subgroups (*i.e.*, 10.0±3.7 years in AVR subgroup *vs.* 11.4±4.1 years in ARR subgroup, P=0.1). Postoperative echocardiographic follow-up revealed MR>2+ in 9 (15%) patients in AVR subgroup (moderate MR in 5 patients and severe MR in 4 patients). None of the ARR patients developed MR>2+ during follow-up. Myxomatous degeneration and prolapse of the anterior mitral leaflet (AML) was present in all 9 patients with MR>2+, while the posterior mitral leaflet (PML) was involved in 3 of them. Moreover, AML prolapse was associated with severe tethering of the PML in 2 patients with progressive left ventricular (LV) remodeling and severe systolic LV dysfunction (*i.e.*, combined type II and III b MR). Both patients had severely reduced systolic LV function (*i.e.*, LVEF<35%) before AVR surgery and showed no evidence of reverse remodeling during the postoperative follow-up. Mitral insufficiency progressed in both patients from mild MR preoperatively to severe MR at 8 and 12 years post-AVR surgery.

The mean MR severity increased significantly in AVR subgroup from 0.3±0.5 grade preoperatively to 0.9±0.8 grade at the latest follow-up (P=0.001). In contrast, there was no significant difference in the mean
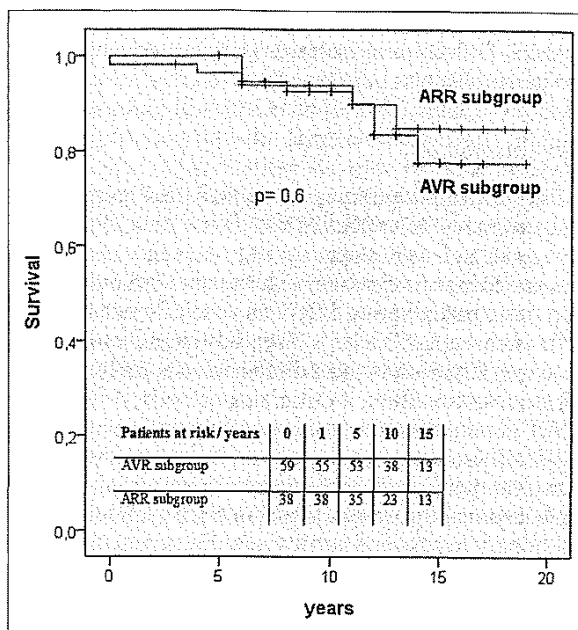

Figure 1.—Overall survival (Kaplan-Meier curve) in both study subgroups. AVR: isolated aortic valve replacement subgroup; ARR: aortic root replacement subgroup.

echocardiographic MR severity between preoperative and follow-up examinations in ARR subgroup (*i.e.*, 0.5±0.6 grade preoperatively *vs.* 0.6±0.5 grade during follow-up, P=0.3). Similar to preoperative findings (Table I), follow-up echocardiography revealed no difference in postoperative systolic LVEF between both study subgroups (*i.e.*, 54±13% in AVR subgroup *vs.* 55±12% in ARR subgroup, P=0.8). Distribution of echocardiographic MR severity before AVR surgery and at the latest post-AVR follow-up in both study subgroups is presented in Figure 2.

Freedom from new-onset MR>2+ at 15 years postoperatively was significantly lower in AVR subgroup *vs.* ARR subgroup (*i.e.*, 38% *vs.* 100%, $P_{log-rank}$=0.01) (Figure 3).

Redo mitral valve surgery

Two patients (2%) in AVR subgroup underwent elective re-do mitral valve surgery due to severe symptomatic MR at 5 and 8 years post-AVR. Intraoperatively,
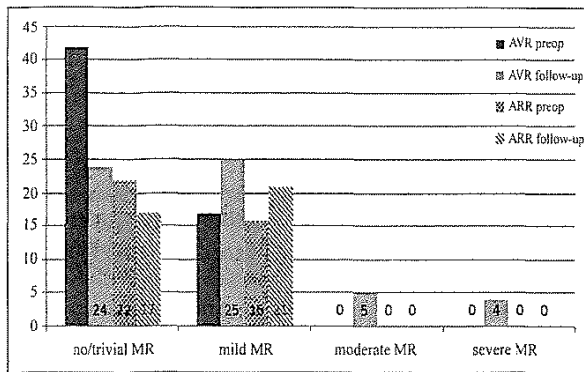
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Figure 2.—Distribution of echocardiographic MR severity in both study subgroups. AVR preop: isolated aortic valve replacement subgroup, preoperatively; AVR follow: isolated aortic valve replacement subgroup, at the latest echocardiographic follow-up; ARR preop: aortic root replacement subgroup, preoperatively; ARR follow: aortic root replacement subgroup, preoperatively, at the latest echocardiographic follow-up.
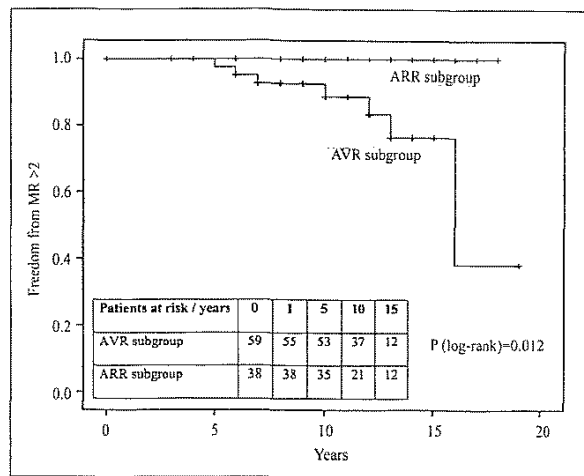

Figure 3.—Freedom from MR>2 (Kaplan-Meier curve) in both study subgroups. AVR: isolated aortic valve replacement subgroup; ARR: aortic root replacement subgroup.

a markedly elongated AML (i.e., 37 mm and 39 mm, as measured at A2 segment in parasternal long axis view) with typical findings of myxomatous degeneration could be confirmed. Successful mitral valve repair using Goretex neo-chordae for correction of AML prolapse and 38 mm semi-rigid complete annuloplasty ring was performed in the first patient. The second patient presented with severe LV remodeling (i.e., LVEF 20%) and multi-factorial MR (i.e., myxomatous degeneration of AML in combination with a severe symmetric leaflet tethering). Due to the tenting height of 17 mm and posterior leaflet angle of 60 degrees as well as left ventricular end-diastolic diameter of 80 mm, mitral valve replacement using bio-prosthesis was performed. Both patients survived the redo surgery uneventfully. One patient with severe MR declined re-do mitral surgery. The fourth patient with severe MR and end-stage heart failure (i.e., LVEF 10-15%) was evaluated for heart transplant at 12 years after AVR-surgery and died of septic multi-organ failure 1 year after being listed for heart transplantation.

The 5 patients with new-onset moderate MR are currently undergoing regular echocardiographic surveillance at 6 months intervals. Elective re-do mitral valve repair surgery has been scheduled in one of these patients due to marked symptomatic deterioration (NYHA III) during the last year of follow-up.

Discussion

Despite clinically obvious heterogeneity of BAV disease, the long-term outcomes of individual BAV phenotypes have not been systematically analyzed. In particular, the relatively uncommon cohort of young, male BAV patients with predominant aortic root involvement and aortic insufficiency (so-called BAV root phenotype) remains to be more thoroughly defined.[12, 13] Recent data suggest that BAV root phenotype may represent the genetically-triggered BAV entity, and candidate gene mutations have been demonstrated in such BAV families.[8, 9] In accordance with the congenital hypothesis, an increased prevalence of aortic root involvement was revealed in first degree relatives of BAV patients presenting with a root phenotype.[14] This form of BAV aortopathy appears to behave completely differently from the hemodynamically-triggered aortopathy observed in patients with BAV stenosis and concomitant asymmetric dilatation of the tubular ascending aorta.[15]

The wide spectrum of cardiovascular abnormalities involving embryologically related structures of the fibrous skeleton of heart that are associated with a BAV root phenotype has been described as WAMBIRE (i.e., weak aorto-mitral bicuspid relation) complex.[16] This entity represents the most extensive form of BAV disease and combines dilatation of aortic root with degenerative

changes of intervalvular fibrous body and anterior leaflet of the mitral valve (*i.e.*, anatomic structures which are embryologically related with the fibrous portion of the left ventricular outflow tract [LVOT]).[6, 16] Degenerative changes of the mitral valve present mostly as myxomatous involvement of the AML,[6] and are associated with disproportionate elongation and hypermobility of this structure.[7] Although the exact prevalence of WAMBIRE complex is unknown, the coexistence of clinically important BAV disease in patients requiring mitral valve surgery for MR was only 1.6% in a previous study.[6] Nonetheless, late progression of concomitant cardiovascular abnormalities after isolated AVR surgery might be anticipated, because of the congenital connective tissue weakness. However, to the best of our knowledge, no comparable follow-up study analyzing late progression of mitral valve disease after AVR surgery in BAV root phenotype patients has yet been reported. In the current study we therefore aimed to define the risk of late new-onset MR in BAV patients who underwent previous AVR/aortic root surgery for BAV regurgitation and concomitant aortic root dilatation (*i.e.*, BAV root phenotype).

The most important finding of our study is that late progressive MR occurs in 10-15% patients with a BAV root phenotype post-AVR surgery and that the risk of MR might be associated with difference in aortic root treatment strategy during the initial procedure. A total of 15% of BAV patients who underwent isolated AVR surgery for BAV insufficiency and aortic root dilatation of 40-50 mm (*i.e.*, AVR subgroup) developed progressive MR>2+ (Figure 4), whereas no new-onset MR occurred in the ARR subgroup. Only 38% of patients in AVR subgroup were free from new-onset MR at 15

years postoperatively (Figure 3). Based on these findings, we hypothesize that stabilization of the fibrous portion of the LVOT (*i.e.*, aorto-ventricular junction / intervalvular fibrous body / anterior mitral valve annulus) by means of aortic root replacement may prevent the progression of coexistent degenerative mitral valve disease in BAV root phenotype patients. Although aortic annular stabilization is similar in AVR and ARR procedures, some technical differences exist between these two subgroups. In case of isolated AVR surgery, aortic valve prosthesis was always implanted in a supra-annular fashion by placing non-everting annular sutures from inside (LV) to outside (aorta). In contrast, everting mattress sutures were routinely used when performing ARR with a composite graft. As a result of such annular suture placement, composite graft is placed in the sub-annular position during the implantation. Sewing ring of the composite graft, tightly positioned and tied in the LVOT, may contribute to a better stabilization of the fibrous portion of the LVOT (*i.e.*, aorto-ventricular junction / intervalvular fibrous body / anterior mitral valve annulus) as compared to the supra-annulary implanted aortic valve prosthesis. Although there are no systematic prospective data to prove this concept, we strongly believe that subannular placement of aortic valve prosthesis might be a technical factor which sufficiently explains the observed difference in MR progression rate between both subgroups in our study.

Mild MR at the time of AVR might be associated with the occurrence of new-onset MR>2+. All 4 patients in the AVR subgroup, who presented with severe MR during follow-up, had mild MR prior to AVR surgery. On the other hand, none of the 16 patients with mild preoperative MR in the ARR subgroup de-
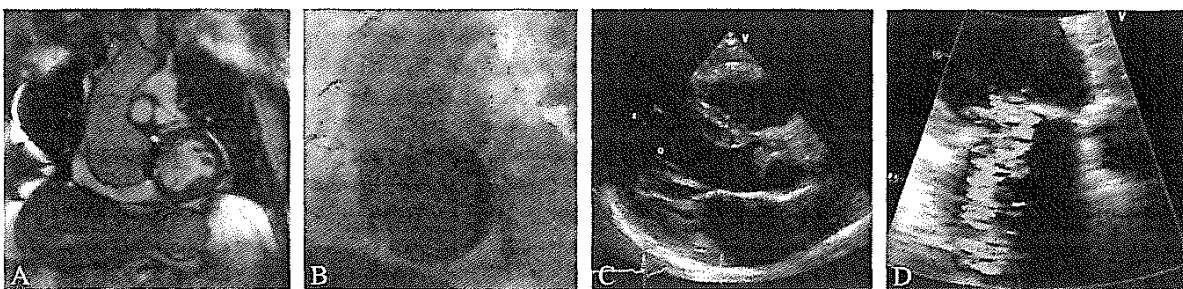

Figure 4. A-D) Progressive aortic root aneurysm and severe MR in a patient who underwent previous isolated AVR surgery for BAV regurgitation and aortic root diameter of 42 mm. Note significantly elongated anterior leaflet of the mitral valve (*i.e.*, AML=39 mm).

veloped new-onset MR>2+ post-ARR surgery. This finding may serve as an additional argument to consider ARR surgery in BAV insufficiency patients presenting with mild preoperative MR. The intriguing question, whether simultaneous mitral valve repair should be performed at the time of AVR surgery in BAV patients with obvious degenerative changes of AML and concomitant mild MR, is outside the scope of this retrospective study.

Our findings further support the hypothesis that BAV insufficiency patients with aortic root dilatation (i.e., BAV root phenotype) may exhibit a genetically-triggered form of connective tissue weakness, which is prone to a wide spectrum of cardiovascular abnormalities. Degenerative changes of adjacent anatomic structures which are embryologically related with the fibrous portion of the LVOT (e.g., AML) may progress over time after isolated AVR surgery and should be monitored by means of regular echocardiographic surveillance.

Limitations of the study

Due to retrospective nature of this study and standardized, diameter-based surgical strategy at our institution during the study period, no direct comparison of ARR vs. AVR treatment was possible in BAV regurgitation patients with a root size of 40 to 50 mm. This is a clear limitation of retrospective study design and therefore our recommendations should be interpreted with caution. Another limitation is the limited sample size, which might be explained by the relative rarity of BAV root phenotype (i.e., 10-15% of all BAV patients). Moreover, given the paucity of published data on BAV root phenotype patients, no external validation with other series was possible.

Moreover, no systematic literature data exist to support our hypothesis, that ARR approach stabilizes anterior mitral annulus better as compared to isolated AVR. Our personal experience in re-do surgery after previous AVR vs. ARR procedures suggests more obvious subannular scarring / pannus tissue formation in the LVOT and brisk fibrotic changes of aorto-mitral continuity / basal AML after prior ARR surgery as compared to isolated supra-annular AVR. However, such a hypothesis has to be systematically addressed in a subsequent prospective study.

Although our study cohort represents a relatively ho-

mogeneous BAV population, a true propensity matching of both subgroups (i.e., AVR and ARR subgroup) was not performed. Therefore, we cannot exclude the possibility that factors other than aortic root treatment strategy might have influenced MR progression in the AVR subgroup. Moreover, a control group of patients with tricuspid aortic valve disease post-AVR surgery was not included.

Conclusions

The risk of new-onset MR is significantly increased in patients with BAV regurgitation and aortic root dilatation who undergo isolated AVR surgery. Aortic root treatment strategy might have an impact on the occurrence of new-onset MR in BAV root phenotype patients, hypothetically via subannular placement of aortic valve prosthesis in ARR subgroup and thereby better stabilization of the fibrous portion of the LVOT.

Although a more complex procedure, ARR surgery should be considered in patients presenting with BAV insufficiency and aortic root dilation (>40 mm) during their initial AVR procedure, particularly if mild MR is present. Nonetheless, the surgical risk of technically more demanding procedure should be balanced against the frequency of late progression of mitral insufficiency.

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Evidence of subannular and left ventricular morphological differences in patients with bicuspid versus tricuspid aortic valve stenosis: magnetic resonance imaging-based analysis

Kushtrim Disha[a,*], Georg Dubslaff[b], Mina Rouman[a], Beatrix Fey[b], Michael A. Borger[c], Alex J. Barker[d], Thomas Kuntze[a] and Evaldas Girdauskas[a,e]

[a] Department of Cardiac Surgery, Central Hospital Bad Berka, Bad Berka, Germany
[b] Department of Radiology, Central Hospital Bad Berka, Bad Berka, Germany
[c] Department of Cardiac Surgery, Columbia University, New York, NY, USA
[d] Department of Radiology, Northwestern University, Chicago, IL, USA
[e] Department of Cardiovascular Surgery, University Heart Center Hamburg, Hamburg, Germany

* Corresponding author. Department of Cardiac Surgery, Central Hospital Bad Berka, Robert-Koch-Allee 9, 99437 Bad Berka, Germany. Tel: +49-36458541134; fax: +49-3645853510; e-mail: k_disha@hotmail.com (K. Disha).

Abstract

OBJECTIVES: Prospective analysis of left ventricular (LV) morphological/functional parameters in patients with bicuspid versus tricuspid aortic valve (TAV) stenosis undergoing aortic valve replacement (AVR) surgery.

METHODS: A total of 190 consecutive patients with BAV ($n = 154$) and TAV stenosis ($n = 36$) (mean age 61 ± 8 years, 65% male) underwent AVR ± concomitant aortic surgery from January 2012 through May 2015. All patients underwent preoperative cardiac magnetic resonance imaging in order to evaluate: (i) left ventricular outflow tract (LVOT) dimensions, (ii) length of anterior mitral leaflet (AML), (iii) end-systolic and end-diastolic LV wall thickness, (iv) LV area, (v) LV end-systolic and end-diastolic diameters (LVESD, LVEDD), (vi) LV end-diastolic and end-systolic volumes (LVEDV, LVESV) and (vii) maximal diameter of aortic root. These parameters were compared between the two study groups.

RESULTS: The LVOT diameter was significantly larger in BAV patients (21.7 ± 3 mm in BAV vs 18.9 ± 3 mm in TAV, $P < 0.001$). Moreover, BAV patients had significantly longer AML (24 ± 3 mm in BAV vs 22 ± 4 mm in TAV, $P = 0.009$). LVEDV and LVESV were significantly larger in BAV patients (LVEDV: 164.9 ± 68.4 ml in BAV groups vs 126.5 ± 53.1 ml in TAV group, $P = 0.037$; LVESV: 82.1 ± 57.9 ml in BAV group vs 52.9 ± 25.7 ml in TAV group, $P = 0.008$). A strong linear correlation was found between LVOT diameter and aortic annulus diameter in BAV patients ($r = 0.7$, $P < 0.001$), whereas significantly weaker correlation was observed in TAV patients ($r = 0.5$, $P = 0.006$, $z = 1.65$, $P = 0.04$). Presence of BAV morphology was independently associated with larger LVOT diameters (OR 9.0, 95% CI 1.0–81.3, $P = 0.04$).

CONCLUSIONS: We found relevant differences in LV morphological/functional parameters between BAV and TAV stenosis patients. Further investigations are warranted in order to determine the cause of these observed differences.

Keywords: Bicuspid aortic valve · Cardiomyopathy · Aortic valve stenosis · Ascending aorta

INTRODUCTION

There is an ever-growing interest in bicuspid aortic valve (BAV) pathology and its association with the anatomical structures distal to the aortic valve (i.e. BAV-associated aortopathy) [1]. BAV accounts for about one-half of isolated aortic stenosis cases requiring surgical aortic valve replacement (AVR) [2]. Asymmetrical flow patterns and turbulence can be observed in the ascending aorta even in patients with an "echocardiographically normal" BAV [3]. Despite an increasing amount of research in this area, the clinical presentation of BAV disease is multifaceted and remains insufficiently defined.

One-half of BAV patients present with non-valvular manifestations of BAV disease [4]. Distal non-valvular manifestations may be summarized under the term "BAV-associated aortopathy" [5–7]. It begins early in life and involves a wide range of manifestations [8] which are a subject of intense clinical and basic research. On the contrary, there is a scarcity of data on proximal non-valvular manifestations of BAV disease. BAV-associated valvular cardiomyopathy is insufficiently explored and might be potentially different as compared with tricuspid aortic valve (TAV) disease. Moreover, to date no prospective study has been conducted in order to analyse and compare the preoperative left

ventricular (LV) functional and anatomical attributes in patients with BAV vs TAV disease.

Cardiovascular magnetic resonance imaging (cMRI) is a non-invasive imaging tool that has the potential to simultaneously assess functional and morphological characteristics of the aortic valve, adjacent distal and proximal anatomical structures [9] as well as functional parameters of the LV, especially in patients with heart failure [10].

The aim of this study was to prospectively assess the morphological and functional LV parameters by means of preoperative cMRI in BAV-stenosis patients, and to compare these metrics with those of TAV stenosis patients. Furthermore, we aimed to search for any significant correlations between valvular and sub-valvular parameters in both study subgroups.

MATERIALS AND METHODS

The data for this study were collected prospectively by enrolling all patients with congenital BAV who were referred for AVR surgery to our institution (Central Hospital, Bad Berka, Germany) with or without concurrent replacement of the proximal thoracic aorta, from January 2012 through May 2015. Approval of our institutional ethics committee was obtained and all patients gave written informed consent. Patients in the study had the following inclusion criteria: (i) presence of BAV as identified by means of preoperative transthoracic and/or transoesophageal echocardiography and cardiac MRI; (ii) indication for conventional AVR surgery due to a severely stenotic aortic valve. The presence of congenital BAV was confirmed intraoperatively by visual inspection by the attending surgeon.

A total of 201 patients with BAV disease underwent elective AVR surgery with or without concurrent replacement of the proximal aorta. We excluded BAV patients who presented with isolated/predominant aortic valve regurgitation ($n = 32$), and those with comparable degree of regurgitation and stenosis (i.e. mixed disease) ($n = 2$). Patients with mixed BAV disease were enrolled only if valve stenosis was the prevailing lesion. Furthermore, in 13 BAV patients no MRI could be performed preoperatively due to contraindications (i.e. presence of implanted cardiac pacemaker/defibrillator or claustrophobia). We excluded all patients who presented with connective tissue disorders (e.g. Marfan syndrome) as well as those who underwent urgent/emergent surgery and/or combined cardiac surgical procedures other than concurrent proximal aortic surgery. Based on the inclusion and exclusion criteria, a total of 154 consecutive BAV patients with predominant stenosis (mean age 61 ± 9 years, 66% male) were identified and served as our study cohort.

During the same study period, a group of patients undergoing AVR for TAV stenosis were entered in our study database in order to enable a between-group comparison. TAV patients over 70 years of age were excluded in order to achieve a similar age profile to BAV patients. Identical inclusion/exclusion criteria were applied in TAV as in BAV patients. A total of 90 TAV patients requiring AVR were screened. Patients with isolated/predominant aortic valve regurgitation ($n = 52$) as well as those with a contraindication for MRI ($n = 2$) were excluded. A total of 36 consecutive TAV-stenosis patients (mean age 64 ± 5 years, 61% male) therefore formed our control group.

The primary purpose of this study was to systematically compare morphological/functional LV parameters between BAV and TAV patients, and to identify correlations between valvular, LV

(i.e. subvalvular) and aortic root parameters. In particular, we aimed to prospectively address whether morphological/functional LV differences exist between BAV and TAV stenosis patients.

Definitions and measurements

Morphology and function of the aortic valve (AV) was determined by means of echocardiography and cardiac MRI in all patients. If only two commissures and two AV cusps were observed, with or without the presence of a raphe and cusp redundancy, a BAV was suspected and all such patients underwent subsequent cardiac MRI. Nevertheless, the intraoperative description of the AV morphology by the attending surgeon was used as the final decision regarding the bicuspidality of the AV. Results of transthoracic echocardiography were in accordance with the intraoperative valve description in 91 (59%) study patients, whereas cardiac MRI demonstrated a rather high sensitivity and specificity in identifying BAV disease (i.e. 98%). TAV stenosis was diagnosed by means of echocardiography and was later confirmed by intraoperative inspection. Severe aortic stenosis for both study groups was determined in accordance with previously published guidelines [11]. Morphological/functional LV parameters were assessed by preoperative cMRI (see below).

Preoperative magnetic resonance imaging examination

All patients with suspected BAV stenosis as well as the TAV patients who met the above-mentioned inclusion criteria underwent a preoperative cardiac phase-contrast cine MRI examination in order to properly visualize the AV and all adjacent proximal and distal structures. MRI examination was conducted according to the previously described standards [12].

The maximal cross-sectional diameters of the proximal aorta were assessed at the level of the aortic annulus, sinuses of Valsalva, sinotubular junction and tubular mid-ascending aorta. As previously recommended [13], aortic diameters were measured as the greatest observed cross-sectional diameter perpendicular to the aortic axis in a mid-vessel slice at end-diastole using inner edge to inner edge approach. The virtual basal ring was found at the level of the basal insertions of the aortic cusps at the left ventricle. The aortic annulus was sized at the same timeframe of the cardiac cycle as LVOT diameter (i.e. early-systole). Furthermore, anatomical structures proximal to the BAV [i.e. LVOT, LV and anterior mitral leaflet (AML)] were visualized using a breath-hold steady-state free precision cine images (tf2D), using the LV inflow–outflow tract view. LVOT diameter (LVOTd) was measured at the early systole, beneath the physiological aorto-ventricular junction, perpendicular to the imaginary mid-aortic to mid-LVOT line (Fig. 1). LV volumes were calculated at the end-diastole (LVEDV) and end-systole (LVESV) in the long-axis views using the biplane ellipsoid model. LV myocardial wall thickness was measured at the anteroseptal and posterolateral walls during end-diastole and end-systole, in the mid-ventricular position. Of note, the short-axis view was used for orientation purposes. LV end-diastolic and end-systolic diameters (LVEDD, LVESD) were assessed in the mid-ventricular portion, perpendicular to the longitudinal LV axis. A virtual longitudinal LV axis line was drawn from the mitral valve level to the LV apex. LVEDD and LVESD were measured using the transversal mid-ventricular line,
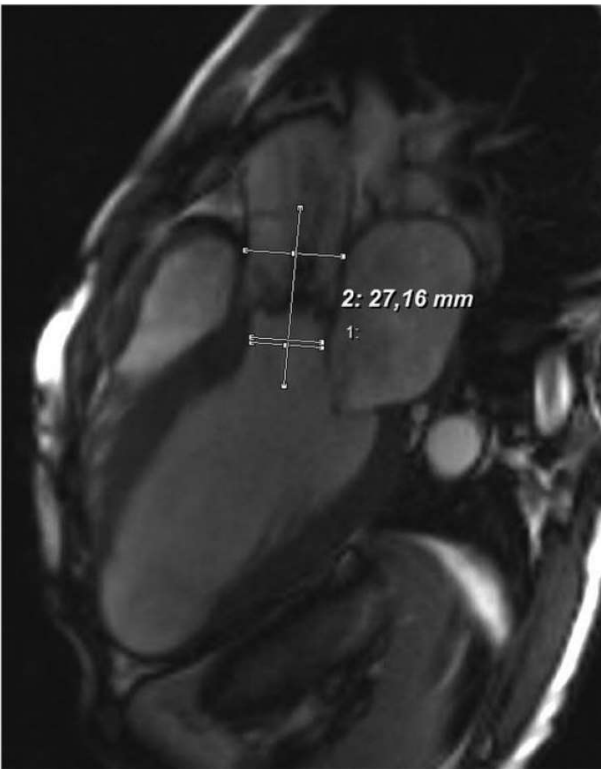
Figure 1: Assessment of the left ventricular outflow tract diameter (LVOTd) in the LV inflow–outflow tract view during early systole, as identified by cardiac MRI. Note the two parallel lines in LVOT. The upper line represents the LVOTd, whereas the lower one represents an orientation line to designate the mid-point of the lower border of LVOT. The transversal line connects the mid-points of LVOT and aortic root and is perpendicular to the line of assessment of LVOTd.

which was drawn perpendicularly to the above mentioned longitudinal LV axis line (Fig. 2A and B). AML length was measured in the mid-A2 segment at end-diastole using the view identical to the echocardiographic parasternal long-axis view, from the hinge point to the tip of the leaflet. Due to the fibrous nature of the leaflet, bright-blood imaging was used in order to distinguish the mitral leaflet from the attached chordae tendinae at the free edge of the leaflet. MRI data were measured by two investigators (K.D. and G.D.). A total of three consecutive measurements were repeated and averaged thereafter for every single variable.

Study population

Demographic and clinical characteristics of the study population are displayed in Table 1. BAV patients were significantly younger and presented with larger proximal aortic diameter as compared with the TAV population. All 190 patients underwent conventional AVR with or without concomitant replacement of ascending aorta. Proximal aortic surgery for co-existent aortic aneurysm was performed in 18 patients (12%), and all of them were in the BAV group. Two further patients (1%) underwent concomitant replacement of the aortic root due to aneurysmal dilatation.

Statistical analysis

Categorical variables are presented as numbers with percentage and continuous variables as mean value ± standard deviation

(range). Continuous variables between the study subgroups were compared using unpaired two-sided *t*-test. Categorical variables were analysed by χ^2 test or Fisher's exact test as appropriate. *P*-values of <0.05 were considered statistically significant. Data were tested for normal distribution using the Kolmogorov–Smirnov test. A Cox-regression analysis was conducted to identify independent predictors of LVOTd >21 mm. A cut-off value of 0.1 at the univariate analysis was set as condition to incorporate variables into the Cox regression model. Correlation analyses were performed using Pearson's correlation. Fisher *r*-to-*z* transformation was implemented to calculate a *z*-value to assess the significance of the difference between correlation coefficients.

Intra-rater reliability of LVOT diameter and AML length measurements was evaluated by duplicate measurements conducted by the same observer. Inter-rater reliability was evaluated for the same measurements conducted by the two study members. Reliability statistics consisted of Lin's concordance correlation coefficient, coefficient of variation and Bland-Altman 95% confidence interval (CI) of agreement (Table 2).

RESULTS

Morphological left ventricular parameters

Baseline MRI measurements in both study groups are displayed in Table 3. BAV patients demonstrated significantly larger LVOTd as compared with their TAV counterparts (21.7 ± 3.0 mm in BAV group and 18.9 ± 2.7 mm in TAV group, *P* < 0.001). Systolic LV area was also found to be significantly larger in BAV subjects (1960 ± 873 mm² in BAV group versus 1699 ± 449 mm² in TAV group, *P* = 0.039). However, there was no statistically significant difference between the groups in terms of diastolic LV area. BAV patients presented with significantly larger LV end-diastolic volume (LVEDV) compared with their TAV counterparts (164.9 ± 68.4 ml in BAV groups versus 126.5 ± 53.1 ml in TAV group, *P* = 0.037). Similarly, the LV end-systolic volume (LVESV) was significantly larger in BAV subjects (82.1 ± 57.9 ml in BAV group versus 52.9 ± 25.7 ml in TAV group, *P* = 0.008). With regard to LV wall thickness, significant differences were observed only for diastolic anterior LV wall thickness (i.e. 15.2 ± 3.0 mm in BAV group and 14.1 ± 1.8 mm in TAV patients, *P* = 0.026). There were no significant between-group differences for LVEDD and LVESD dimensions. The AML was significantly larger in BAV patients (24 ± 3 mm in BAV group versus 22 ± 3 in TAV group, *P* = 0.009). Proximal aortic diameters as assessed by MRI were also found to be significantly larger in BAV vs TAV stenosis patients (42 ± 8 mm in BAV group versus 36 ± 8 mm in TAV group, *P* < 0.001). Of note, echocardiographically defined LV ejection fraction (LVEF) was not significantly different between study groups.

Intra- and inter-rater reliability for assessment of LVOT diameter and AML length are summarized in Table 2. The degree of agreement of both observers was good, with a concordance correlation coefficient above 0.92. Furthermore, there was no evidence of observer-associated bias, as Bland-Altman analysis revealed that all confidence intervals included a zero value.

Correlation analysis between aortic, valvular and ventricular parameters

Correlation analyses were performed between LV parameters (i.e. LVOT diameter, LVEF, LVEDD, LVESD, AML length) and
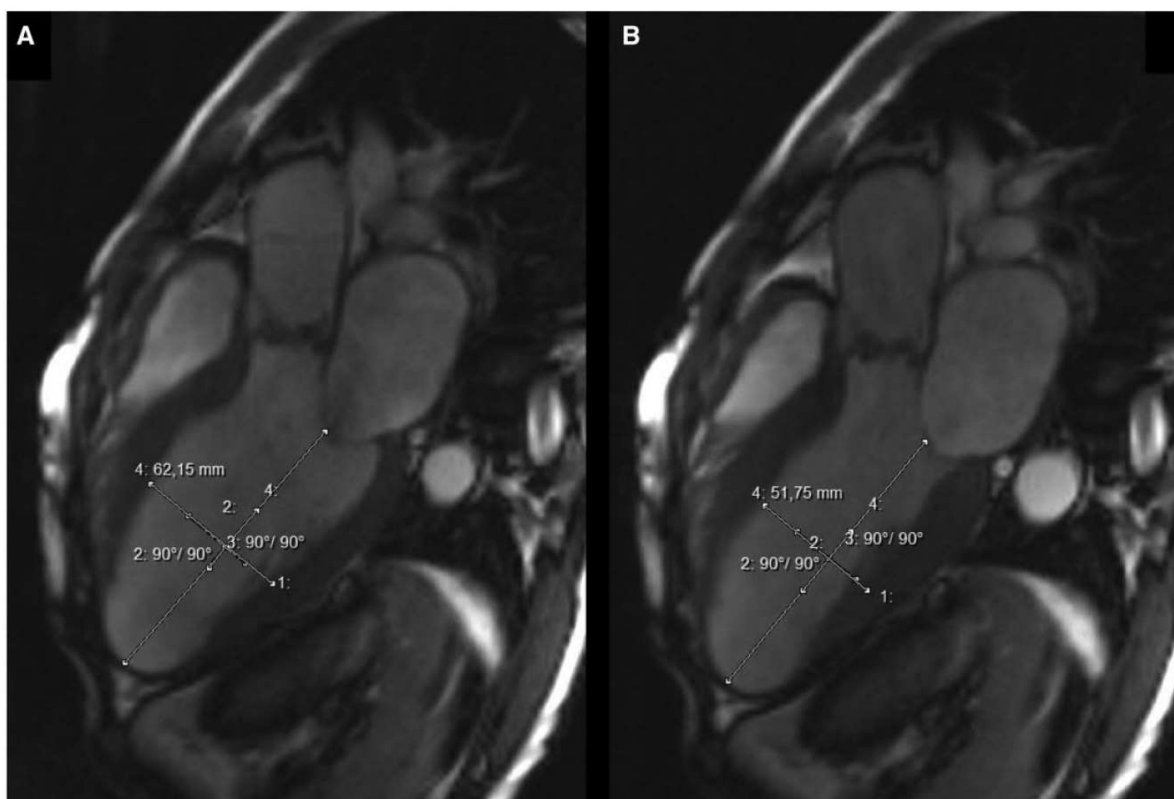
Figure 2: LVOT view of cardiac MRI. (**A**) Assessment of the LVEDD and (**B**) assessment of the LVESD.

valvular/aortic root metrics for both study groups. BAV patients showed a significant correlation between the LVOTd and maximal aortic root diameters at all levels. In particular, LVOTd correlated strongly with the aortic annulus diameter ($r = 0.7$, $P < 0.001$ in BAV group versus $r = 0.5$, $P = 0.006$ in TAV group) (Fig. 3A). Significant correlations were similarly observed with the sinus of Valsalva diameter ($r = 0.56$, $P < 0.001$ in BAV group versus $r = 0.39$, $P = 0.07$ in TAV group) (Fig. 3B) and sinotubular junction diameter ($r = 0.47$, $P < 0.001$ in BAV group versus $r = 0.33$, $P = 0.124$ in TAV group) in BAV group. Only weak correlation was observed between LVOTd and mid-ascending aortic diameter in both study subgroups ($r = 0.26$, $P = 0.006$ in BAV group versus $r = 0.41$, $P = 0.04$ in TAV group). However, a significant difference in correlation coefficients was found only for the correlation between LVOTd and aortic annulus diameter ($z = 1.65$, $P = 0.04$). The remaining correlation patterns of LVOTd and aortic root diameters were comparable between the BAV and TAV groups ($z = 1.15$, $P = 0.12$ for aortic sinus; $z = 0.85$, $P = 0.19$ for aortic sinotubular junction). Furthermore, a significant strong correlation of LVOTd and the LVEDV was found only in the BAV group ($r = 0.55$, $P < 0.001$ in BAV group versus $r = 0.26$, $P = 0.45$ in TAV group; $z = 1.8$, $P = 0.03$). Similarly, LVOTd and LVESV correlated strongly only in BAV patients ($r = 0.55$, $P < 0.001$ in BAV group versus $r = 0.31$, $P = 0.36$ in TAV group; $z = 1.5$, $P = 0.06$).

Predictors of left ventricular outflow tract dilatation

Cox-regression analysis was performed in order to identify independent predictors of LVOT enlargement in the whole study cohort. Based on the median LVOTd value, patients were divided into those having LVOTd ≤ 21 mm vs those with LVOTd > 21 mm. Univariate analysis revealed that 61% of BAV patients versus 21% TAV patients had LVOTd > 21 mm ($P < 0.001$). Ascending aortic diameter (OR 1.2, $P = 0.007$) and the presence of BAV (OR 9.0, $P = 0.04$) were independently associated with LVOTd > 21 mm (Table 4). Of note, body surface area and end-systolic LV diameters were not significantly associated with LVOT diameter > 21 mm.

DISCUSSION

In this study, we aimed to prospectively assess the subvalvular differences observed in BAV and TAV stenosis patients undergoing AVR. Our aim was to test the hypothesis that presence of BAV morphology is associated with a more severe LV remodelling than TAV morphology. To the best of our knowledge, this study is the first to prospectively report MRI-based quantitative assessment of LV parameters in BAV patients undergoing AVR surgery.

What are the possible explanations of our observed LV differences between BAV and TAV stenosis patients? First of all, BAV patients require AVR surgery at a significantly younger age when compared with their TAV counterparts. Younger patients may not develop symptoms until later in their disease process and therefore may have signs of more advanced valvular cardiomyopathy. Second, BAV patients experience relevant aortic valvular lesions earlier in life [3], which in turn, may promote earlier morphological changes of LV architecture. As evidence of this statement, some recent studies detected subclinical impairment of LV systolic and diastolic function even in patients with a "normally"

Table 1: Demographic and clinical characteristics of the study population

Variable	Study population		P-value
	BAV-AS (n = 154)	TAV-AS (n = 36)	
Mean age (years)	60.7 ± 8.8 (34–70)	64.3 ± 5.4 (52–70)	0.002
Male sex	101 (66)	22 (61)	0.613
BSA (m²)	2.00 ± 0.2 (1.50–2.60)	1.95 ± 0.2 (1.53–2.43)	0.224
Baseline LVEF (%)[a]	56 ± 9 (25–70)	57 ± 8 (35–70)	0.553
Peak aortic valve gradient (mmHg)[a]	65 ± 36 (52–119)	56 ± 38 (42–102)	0.021
Mean aortic valve gradient (mmHg)[a]	41 ± 26 (31–72)	35 ± 24 (25–64)	0.037
Concomitant AR[b]	55 (36)	11 (30)	0.769
Mean MR (degree)[a]	0.6 ± 0.5	0.3 ± 0.5	0.165
No/trivial MR	94 (61)	26 (71)	0.255
Mild MR	60 (39)	10 (29)	0.317
NYHA class III or IV	36 (23)	8 (22)	0.375
Ascending aorta (mm)[c]	42 ± 8 (25–65)	36 ± 8 (24–70)	<0.001
Diabetes mellitus	26 (17)	10 (28)	0.133
Smoking	36 (23)	8 (22)	0.882
Arterial hypertension	128 (83)	34 (94)	0.084
β-blocker therapy	51 (33)	20 (56)	0.058
Peripheral arterial disease	4 (3)	0 (0)	0.272
COPD	10 (7)	4 (11)	0.340
Endocarditis	1 (1)	0 (0)	0.588
CPB time (min)	84 ± 24 (51–188)	74 ± 17 (57–114)	0.129
Cross-clamp time (min)	58 ± 15 (36–130)	56 ± 16 (40–85)	0.657
Mechanical valve prosthesis	35 (23)	4 (11)	0.023
Mean biological-prosthesis size (mm)	23.8 ± 2.2 (21–29)	21.8 ± 1.4 (21–25)	<0.001
Mean mechanical-prosthesis size (mm)	24.2 ± 1.7 (21–29)	22.2 ± 1.1 (21–25)	<0.001
Ascending aortic replacement	16 (10)	0 (0)	0.017
Aortic root replacement	2 (1)	0 (0)	0.272
Hemiarch replacement	3 (2)	0 (0)	0.229

Data presented as numbers (%) or as mean ± SD (range).
BSA: body surface area; LVEF: left ventricular ejection fraction; MR: mitral regurgitation; NYHA: New York Heart Association; COPD: chronic obstructive pulmonary disease; CPB: cardiopulmonary bypass.
[a]Measured by preoperative echocardiography.
[b]Nondominant aortic regurgitation in patients with mixed lesions.
[c]Maximal diameter of tubular ascending aorta as measured by magnetic resonance imaging.

Table 2: Intra- and inter-rater reliability of left ventricular outflow tract diameter (LVOTd) and anterior mitral leaflet (AML)

Parameter	Mean value (mm)	SD (mm)	CV (%)	CCC	Bland-Altman 95% CI
Intrarater					
LVOTd	20.3	3.2	1.1	0.99	-0.3 to 0.2
AML length	23.6	3.3	1.3	0.98	-0.6 to 0.5
Inter-rater					
LVOTd	21.1	2.8	5.8	0.92	-2.7 to 1.9
AML length	23.1	3.2	3.3	0.96	-0.9 to 1.7

SD: standard deviation; CV: coefficient of variation; CCC: concordance correlation coefficient.

functioning BAV [14]. Third, BAV patients are known to have marked eccentricity of systolic BAV opening, resulting in a functional severity of given anatomic orifice that is always greater in BAV vs TAV-stenosis [15]. This situation leads to a more severe "afterload mismatch" in BAV patients. Long-standing and potentially underestimated valvular dysfunction in BAV patients may subsequently lead to irreversible myocardial damage and valvular cardiomyopathy. Finally, considering the baseline differences between BAV and TAV patients with regard to LV systolic and diastolic function and LV mechanics [14, 16], we hypothesize that BAV might be associated with a more severe valvular cardiomyopathy. Of interest was the observation of our study that BAV patients presented with significantly larger LVEDV and LVESV compared with TAV patients. Our results prove the profound discrepancy regarding the preload and afterload between the both study groups. Specifically, the long-standing valvular stenosis in BAV patients as compared with TAV patients may be the cause of the larger LVEDV and consecutively greater distension of the ventricle, which might in turn induce a greater preload.

In this study, patients with BAV stenosis showed significantly larger LVOT dimensions as compared with their TAV counterparts, with a mean LVOTd that was 15% larger. To the best of our knowledge, such comparative data of LV metrics have not been published before. An echocardiographic study by Shiran et al. [17] found a larger mean LVOTd in patients with Marfan syndrome as compared with a control group. As expected, the LVOTd of Marfan patients in their study was larger than the BAV stenosis population in this study. One contributing factor for the increased LVOTd in Marfan patients from the Shiran study [17] was their increased BSA compared with controls. In contrast, we did not observe any significant difference in BSA between BAV and TAV patients in this study.

Table 3:   Baseline magnetic resonance imaging measurements of the study population

| Variable | Study population | | P-value |
	BAV-AS (*n* = 154)	TAV-AS (*n* = 36)	
LVOT diameter (mm)	21.7 ± 3.0	18.9 ± 2.7	<0.001
Ventricular area—systolic (mm^2)	1960 ± 873	1699 ± 449	0.039
Ventricular area—diastolic (mm^2)	3369 ± 953	3175 ± 563	0.191
LV end-systolic volume (ml)	82.1 ± 57.9	52.9 ± 25.7	0.008
LV end-diastolic volume (ml)	164.9 ± 68.4	126.5 ± 53.1	0.037
LV anterior wall thickness-diastolic (mm)	15.2 ± 3.0	14.1 ± 1.8	0.026
LV posterior wall thickness-diastolic (mm)	14.0 ± 2.3	13.5 ± 1.8	0.291
LV end-diastolic diameter (mm)	44.3 ± 8.2	42.1 ± 7.8	0.225
LV end-systolic diameter (mm)	27.9 ± 9.3	25.3 ± 7.9	0.169
AML length (mm)	24.0 ± 3.2	22.0 ± 3.5	0.009
Aortic annulus (mm)	27.0 ± 3.1	25.0 ± 2.2	<0.001
Sinus of Valsalva (mm)	36.4 ± 5.7	32.6 ± 3.4	<0.001
Sinotubular junction (mm)	31.3 ± 5.1	28.0 ± 2.6	<0.001

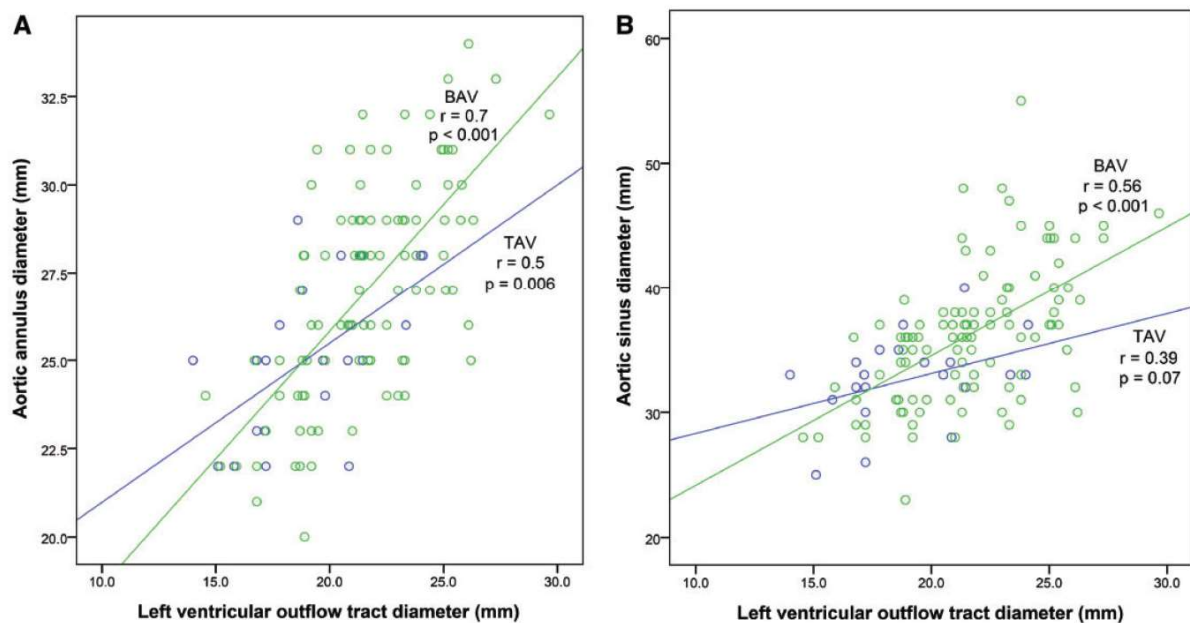Data are presented as mean ± SD, LV: left ventricular.

Figure 3: Correlation analyses between LVOT diameter (LVOTd) and proximal aortic diameters. (**A**) Aortic annulus diameter; (**B**) Sinus of Valsalva diameter.

We found a strong correlation between LVOT and aortic annulus diameters in BAV patients, and this correlation was significantly weaker in TAV patients (i.e. *z*-value showed significant difference in correlation patterns between study subgroups). Of note, correlation patterns between LVOT and sinus of Valsalva/sinotubular junction diameters were not significantly different between both study subgroups.

Anatomic and functional aorto-ventricular junction play a crucial role in the complex interaction between the aortic root and LVOT, which is even more complex in BAV patients, due to the unmethodical spatial arrangement of aortic sinuses and the co-existence of heterogeneous BAV morphotypes. Although rare, the "pure" BAV with two equal sized cusps and without raphe (i.e. Sievers Type 0), represents the most intriguing phenotype in terms of its relation to the LVOT. It might be assumed that along with the diversiform spatial cusp orientation (i.e. antero-posterior or lateral), the triangular intersinusal fibrous extensions and LVOT muscular extensions may become subject to various intraplanar shifting and rearrangements. This assumption is further supported by the observation that from the sub-valvular view, the "commissural area presents rather as an indentation and not as a space" [18]. Moreover, one intersinusal triangle may present either as rudimentary (if there is a BAV phenotype with a raphe) or absent (in the rare BAV phenotype without a raphe) [19]. Thus, BAV patients present with a variety of aortic root deformations which may affect commissures and the aortic annulus as a whole.

The causal chain of interaction between all aortic root components in BAV morphology remains to be further elucidated. The larger LVOTd and strong correlation between LVOTd and aortic root diameter in the setting of BAV morphology may indicate a congenital component of BAV-associated cardiomyopathy. The fact that the cusps and their supporting sinuses are formed from

Table 4: Independent predictors of LVOT diameter >21 mm (as determined by Cox-regression analysis)

Variable	Odds ratio	P-value	95% CI	
Proximal aortic diameter[a]	1.148	0.007	1.039	1.268
Body surface area	0.998	0.775	0.986	1.010
Baseline LVEF	1.017	0.746	0.919	1.125
LV end-systolic diameter	0.993	0.993	0.849	1.163
Ventricular area – systolic	1.002	0.152	0.999	1.004
BAV[b]	9.031	0.041	1.003	81.291

LVEF: left ventricular ejection fraction; CI: confidence interval.
[a]Maximal diameter of ascending aorta (as defined by cardiac MRI).
[b]When compared with tricuspid aortic valve (i.e. categorical variable).

a part of the developing outflow tract [20] along with their anatomical and rheological bond, turns out to affect the postnatal interdependency of the aortic root and LVOT. The combination of valvular and subvalvular characteristics of BAV patients may have an impact on echocardiographic findings [15], that BAV stenosis is more severe for a given anatomic orifice as compared with TAV stenosis. Furthermore, these structural alterations may promote stenosis early in a patient's life. Hence, LV architecture of BAV patients may be exposed to a greater "afterload mismatch" which begins at much earlier stage as compared with TAV patients. It may therefore be assumed that long-standing BAV dysfunction may promote rheologically-triggered BAV-associated valvular cardiomyopathy. In order to address this question, a prospective histological study comparing BAV and TAV cohorts, with and without aortic root dilatation, would be required.

By adding another piece to the puzzle of BAV disease, our prospective study confirms that the "BAV syndrome" consists not only of the valvular impairment and aortic aneurysm/dissection, but with subannular and ventricular features as well, be it subclinical or occult. It is widely accepted that BAVs produce eccentric jets which might contribute in the pathogenesis of BAV aortopathy [12]. By producing different types of eccentric jets, cusp fusion patterns are related to different types of aortopathy (i.e. root phenotype and mid-ascending aortic dilation). As previously shown by Richards *et al.* [21], in eccentric BAVs with smaller LVOT, there is a reduced overall pressure gradient. Moreover, the larger the LVOT, the larger the pressure gradient and the peak velocity, and therefore the greater the eccentricity. It may be postulated that in BAV patients with larger LVOT, due to the greater jet eccentricity, more malign forms of aortopathy may be induced. However, this needs to be verified by further rheological studies involving the analysis of jet eccentricity and the LVOT geometry in BAV and TAV patients.

Another important finding from this study is the significant difference in the length of the AML between BAV and TAV stenosis patients. Similar findings were previously published by Charitos *et al.* [22]. Our results support the previous hypothesis that an elongated AML is an important morphological characteristic of the BAV-associated malformation spectrum. However, none of our study patients in the BAV cohort had significant mitral regurgitation. Therefore, the functional relevance of this finding has to still be clarified.

Study limitations

The most relevant limitation is the small sample size, especially in the TAV group. However, the small sample size is a result of excluding all TAV-stenosis patients >70 years of age in order to achieve a homogeneous and comparable subgroup of TAV patients. Another limitation is our decision to include only those patients presenting with severe aortic valve stenosis referred for AVR surgery. Our findings are therefore not necessarily applicable to the whole spectrum of BAV patients. Although the shape of the LVOT cannot be depicted to be circular, all measurements were conducted in a standard orientation (LV inflow-outflow view) in order to minimize variations. Finally, we did not perform cMRI measurements in control BAV and TAV patients without significant aortic stenosis. It is impossible to determine, therefore, whether our observed differences between BAV and TAV patients precede the development of severe aortic stenosis.

CONCLUSION

Our findings demonstrate that BAV stenosis may be associated with distinct morphological/functional features of valvular cardiomyopathy when compared with TAV stenosis. Moreover, BAV morphology is independently associated with LVOT dilation. Comparable baseline characteristics between the two study groups (i.e. gender, BSA, LVEF and NYHA class) enable us to exclude confounding effect of these variables. Further studies are required to confirm if BAV morphology is associated with a more severe valvular cardiomyopathy when compared with TAV patients.

Conflict of interest: none declared.

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3. Summary (Zusammenfassung)

Dissertation zur Erlangung des akademischen Grades Dr. med.

an der medizinischen Fakultät der Universität Leipzig

Titel: New insights into the left ventricular morphological and functional changes in patients with bicuspid aortic valve disease

Eingereicht von: Kushtrim Disha

Angefertigt in: Zentralklinik Bad Berka GmbH

Betreut von: Prof. Dr. med. Michael A. Borger

Prof. Dr. med. Evaldas Girdauskas

Eingereicht: Februar 2018

The surgical burden of BAV disease is widely acknowledged and is predominantly due to: (i) its predilection for aortic valve stenosis, regurgitation and infective endocarditis even in younger patients; (ii) the fact that it represents the most frequent heart malformation in humans, and (iii) its particular fondness to impact – be it directly or indirectly – the adjacent anatomical structures distal and proximal to the malformed aortic valve. Almost half of the patients who are operated on or die from the aortic valve disease were found to possess this anomaly (2), while almost half of patients with BAV disease present with at least mild-to-moderate ascending aortic dilation (i.e. bicuspid aortopathy) (46, 47). While the bicuspid aortopathy is already subject of intense clinical and basic research, non-valvular changes proximal to the malformed aortic valve are only vaguely and insufficiently addressed. Nonvalvular changes below the aortic valve comprise a wide spectrum of clinical or subclinical,

morphological/functional changes including: left ventricular outflow tract (LVOT), left ventricle (LV), and anterior mitral valve (MV) leaflet.

3.1 Long-term recovery of reduced left ventricular ejection fraction (LVEF) after AVR for BAV disease

Our study is the first to report long-term recovery of impaired systolic LVEF after AVR in patients with BAV disease. Several previous studies have reported similar results to ours, however, without precisely classifying the patients into subgroups with BAV-stenosis (BAV-AS) and BAV-regurgitation (BAV-AR). The rationale for our subgroup analysis of post-AVR recovery of impaired LVEF in patients with BAV disease was the following: 1) younger BAV population (i.e., as compared to TAV), which presents with less comorbidities and consequently results in longer post-AVR survival has a higher likelihood of cardiac-related events, 2) the importance of elucidating long-term results of surgery for the most common congenital heart malformation in humans, 3) the importance of long-standing valvular dysfunction in the case of patients with BAV, which develops earlier in life (32), and therefore may result in earlier LV impairment, 4) the functional severity of aortic valve stenosis is greater in BAV than in TAV patients (81), which results in a more severe 'afterload mismatch' (82) due to the lack of adequate preload for a given level of afterload, 5) few previous studies reported subclinical LVEF impairment in patients with BAV versus TAV even without significant valvular lesions (68), more data on this matter would eventually make the case for prospective evaluation of 'bicuspid cardiomyopathy' as a separate entity of valvular cardiomyopathy.

We found a comparable 10-years post-AVR survival rate between BAV-stenosis and BAV-regurgitation groups. Similarly, no significant between-group (i.e. BAV-AS vs. BAV-AR) differences were found with regard to the mean transvalvular gradient across the aortic valve prosthesis during the follow-up. However, considering the recovery of impaired LVEF, 86% BAV-AS were responders as compared to only 30% BAV-AR patients. We defined our

study patients as 'responders' if their LVEF improved at least 10 pp (percentage points) from the baseline during the post-AVR course. Similarly, BAV-AS improved with a mean of 21 pp their LVEF as compared to the 7 pp in BAV-AR patients. Cox regression analysis identified BAV regurgitation and baseline (preoperative) LVEDD ≥ 60mm as predictors of LVEF non-recovery after AVR surgery. Finally, at 15-years follow-up, a total of 84% BAV-AS patients were free from cardiac-related events, as compared to only 34% in the BAV-AR group.

In patients undergoing AVR for aortic valve stenosis or regurgitation, impaired LVEF is a major prognostic indicator of postoperative outcome (83-88). The pathophysiological mechanisms leading to heart failure differ according to the dominant severe aortic valve lesion (i.e. stenosis or regurgitation). This is crucial to understating the discrepancy of response to AVR in severe AR and AS. In aortic stenosis, an increased LV afterload unfolds the physiologic adaptive process through sarcomere replication, which in turn results in concentric LV hypertrophy (89). This process attempts to normalize wall stress and to preserve the LV systolic function. However, as aortic stenosis progresses, LV gradually fails to maintain a normal stroke volume against the increasing systolic load, thus inducing an overload state known as 'afterload mismatch' (82, 90). Under these circumstances, patients with preoperatively impaired LVEF are supposed to respond to AVR by means of LVEF recovery and survival benefit (83, 88, 91-93). However, some AS patients demonstrate no LVEF recovery post-AVR and are supposed to have reached the state of "fixed myocardial damage" (83).

AR patients differ pathogenically from those presenting with AS, predominantly due to the combination of both pressure- and volume-overload (94). Due to the increased LV diastolic wall stress eccentric hypertrophy develops (94), which in turn triggers the compensatory mechanism of "afterload mismatch, preload reserve" (95). According to the Frank-Sterling principle, the increase in afterload is matched to the increase in preload (i.e. preload reserve), so the force of contraction is augmented to maintain stroke volume. However, in case of long-

standing severe AR, the sufficient forward stroke volume is maintained by increasing the total stroke volume, which is primarily achieved by progressive LV dilation and eccentric hypertrophy (96). LV dilation is frequently combined with aortic root enlargement (37), which may further exacerbate aortic regurgitation induced by aortic valve annular ectasia (97). While left ventricle enlarges, the force required by each myocardial fiber to generate a given intraventricular systolic pressure must be appreciably greater than that developed by the fibers in a normal-sized LV. Consequently, more energy is required in a dilated ventricle to accomplish a given amount of external work as compared to the normal-sized ventricle. While systolic heart failure progresses, the ability of the heart to compensate by Frank-Starling mechanism becomes exhausted as sarcomeres stretch to their maximal length (98). Our data show that the most of BAV-AR patients did not respond to AVR by LVEF improvement, potentially because they had already reached the state of "fixed myocardial damage" prior to AVR. A possible explanation may be the earlier employment and therefore exhaustion of the Frank-Starling mechanism as compared to the BAV-AS patients. Furthermore, BAV-AR patients present at a younger age for AVR surgery and possibly have a long-lasting aortic valve dysfunction. Accordingly, a special care should be taken in this patients' subset, aiming to prevent an irreversible deterioration of myocardial function.

3.2 New-onset relevant mitral regurgitation after previous AVR for BAV regurgitation

Data on the mitral valve pathology in BAV disease are scarce. Myxomatous degeneration of the mitral valve has been described as the most common mitral valve abnormality in patients with BAV disease (77). Another finding is the 'hypermobile' and elongated anterior mitral leaflet in BAV as compared to TAV patients (78). The aim of our study was therefore to assess the prevalence of late new-onset MR in BAV patients who underwent previous aortic valve replacement or aortic root replacement (AVR vs. ARR) for BAV regurgitation and concomitant aortic root dilatation (i.e. BAV root phenotype).

Overall 15-year survival was comparable between two study subgroups (AVR vs. ARR). Postoperative echocardiographic follow-up showed that 15% of AVR patients presented with late-onset relevant MR, whereas none of the patients with ARR developed relevant MR during follow-up. The weak aorto-mitral bicuspid relation (WAMBIRE) comprises a wide spectrum of cardiovascular abnormalities of the embryologically related structures of the fibrous skeleton of the heart (79). This extensive form of BAV disease includes, amongst others, degenerative changes of intervalvular fibrous body and anterior leaflet of the mitral valve, which are anatomically and embryologically tightly related with the fibrous portion of the left ventricular outflow tract (LVOT). Noteworthy, only 38% of patients in AVR subgroup and 100% in ARR subgroup were free from new-onset MR at 15-years postoperatively. Based on our results, we hypothesize that stabilization of fibrous portion of LVOT (i.e. aorto-ventricular junction/intervalvular fibrous body/anterior mitral valve annulus) by means of aortic root replacement in BAV aortic root phenotype, may prevent the progression of degenerative mitral valve disease. Using everting mattress sutures when performing ARR with a composite graft, allows for a subannular placement of the composite graft and tightly positioning of the graft in LVOT, and consequently better stabilization of the fibrous portion of LVOT. We hypothesize that this might be only insufficiently achieved when performing an isolated AVR in BAV root phenotype patients.

3.3 Subannular and LV morphological and functional differences in BAV versus TAV stenosis: MRI-based analysis

The aim of the study was to prospectively assess the subvalvular differences observed in BAV and TAV stenosis patients undergoing AVR surgery. We aimed to test the hypothesis whether the presence of BAV morphology is associated with a more severe subvalvular LV remodeling as compared to the TAV morphology. Patients with BAV-AS presented with significantly larger LVOT diameter (LVOTd) as compared to their TAV counterparts. Larger

LVOTd compared to controls have been also found in patients with Marfan syndrome (99). In contrast to above mentioned study which compared patients' subgroups (i.e., Marfan and controls) with significantly different BSA values, our study cohorts (i.e., BAV vs. TAV) were comparable in terms of their BSA measures. Moreover, we found a strong correlation between LVOTd and aortic annulus diameters in BAV patients. Ascending aortic diameter and presence of BAV were independently associated with LVOTd > 21mm. Additionally, LV end-systolic volume (LVESV), LV end-diastolic volume (LVEDV) and anterior mitral leaflet (AML) were significantly larger in BAV patients.

In BAV patients, anatomic and functional aorto-ventricular junction play a crucial role in the complex interaction between the aortic root and LVOT, principally due to the unmethodical spatial arrangement of aortic sinuses in the presence of heterogeneous BAV morphotypes. It might be hypothesized that along with the diverse spatial aortic valve cusp orientation, various intraplanar shifting and rearrangements of triangular fibrous extensions and LVOT muscular extensions may occur. The strong anatomic interaction of aortic root and LVOT is supported by the finding that cusps and their supporting aortic sinuses are formed from a part of the developing outflow tract (100). A more severe stenosis for a given anatomic residual orifice in BAV versus TAV patients, suggests that LV architecture of BAV patients may be exposed to a greater and an early-onset 'afterload mismatch' as compared with TAV patients. This may in turn promote a rheologically-triggered BAV-cardiomyopathy. Finally, in eccentric BAVs with smaller LVOT there is a reduced transvalvular pressure gradient. On the other hand, the larger the LVOT the higher transvalvular peak gradient and peak velocity which results in a more severe jet-eccentricity (101). This finding may support the hypothesis that in BAV patients with larger LVOT, more malign forms of aortopathy may be induced. However, this assumption remains to be clarified by further rheological studies of jet-eccentricity and LVOT geometry in BAV vs. TAV patients.

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5. Abbreviations (Abkürzungen)

ACC	*American College of Cardiology*
AHA	*American Heart Association*
AML	*Anterior mitral leaflet*
AR	*Aortic regurgitation*
ARR	*Aortic root replacement*
AS	*Aortic stenosis*
AV	*Aortic valve*
AVA	*Aortic valve area*
AVR	*Aortic valve replacement*
BAV	*Bicuspid aortic valve*
BAV-AR	*Bicuspid aortic valve regurgitation*
BAV-AS	*Bicuspid aortic valve stenosis*
CMR	*Cardiac magnetic resonance imaging*
EACTS	*European Association for Cardio-Thoracic Surgery*
ECG	*Electrocardiography*
EDV	*End-diastolic volume*
EROA	*Effective regurgitant orifice area*
LV	*Left ventricle*
LVEDD	*Left ventricular end-diastolic diameter*
LVESD	*Left ventricular end-systolic diameter*
LVEF	*Left ventricular ejection fraction*
LVOT	*Left ventricular outflow tract*
MR	*Mitral regurgitation*
MV	*Mitral valve*
PHT	*Pressure half-time*
R Vol	*Regurgitant volume*
SSFP	*Steady state free precision*
SVD	*Structural valve deterioration*
TAV	*Tricuspid aortic valve*
TEE	*Transoesophageal echocardiography*
VSD	*Ventricular septal defect*

6. Anlagen

6.1 Erklärung über die eigenständige Abfassung der Arbeit

Hiermit erkläre ich, dass ich die vorliegende Arbeit selbstständig und ohne unzulässige Hilfe oder Benutzung anderer als der angegebenen Hilfsmittel angefertigt habe. Ich versichere, dass Dritte von mir weder unmittelbar noch mittelbar eine Vergütung oder geldwerte Leistungen für Arbeiten erhalten haben, die im Zusammenhang mit dem Inhalt der vorgelegten Dissertation stehen, und dass die vorgelegte Arbeit weder im Inland noch im Ausland in gleicher oder ähnlicher Form einer anderen Prüfungsbehörde zum Zweck einer Promotion oder eines anderen Prüfungsverfahrens vorgelegt wurde. Alles aus anderen Quellen und von anderen Personen übernommene Material, das in der Arbeit verwendet wurde oder auf das direkt Bezug genommen wird, wurde als solches kenntlich gemacht. Insbesondere wurden alle Personen genannt, die direkt an der Entstehung der vorliegenden Arbeit beteiligt waren. Die aktuellen gesetzlichen Vorgaben in Bezug auf die Zulassung der klinischen Studien, die Bestimmungen des Tierschutzgesetzes, die Bestimmungen des Gentechnikgesetzes und die allgemeinen Datenschutzbestimmungen wurden eingehalten. Ich versichere, dass ich die Regelungen der Satzung der Universität Leipzig zur Sicherung guter wissenschaftlicher Praxis kenne und eingehalten habe.

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Datum   Unterschrift

6.3 Erklärung über den wissenschaftlichen Beitrag des Promovenden zur Publikation

Erklärung über den wissenschaftlichen Beitrag des Promovenden zur Publikation

Disha, Kushtrim geb. 03.06.1982
Zentralklinik Bad Berka GmbH, Klinik für Herzchirurgie
Promotionsfach: Herzchirurgie
Angestrebte Doktorgrad: Dr. med.

Publikation:

Disha K, Espinoza A, Rouman M, Secknus MA, Kuntze T, Girdauskas E.Long-Term Recovery of Reduced Left Ventricular Ejection Fraction after Aortic Valve Replacement in Patients with Bicuspid Aortic Valve Disease. Thorac Cardiovasc Surg. 2016 Aug;64(5):418-26. doi: 10.1055/s-0035-1557114. PMID: 26251215

Darlegung des eigenen Anteils:
Anteil an der Publikation: 75%
- Planung des Studiendesigns
- Federführung bei der Konzeption des Artikels
- Durchführung der Literaturrecherche und Auswahl der Relevanten Literatur
- Eigenverantwortliche Bereinigung und Analyse der Daten
- Federführung bei der Erstellung der Tabellen und Grafiken
- Interpretation der Ergebnisse in Zusammenarbeit mit den Koautoren
- Federführung bei dem Verfassen der Publikation

Ich bestätige die von Herrn Disha, Kushtrim angegebene Erklärung über den wissenschaftlichen Beitrag in der obengenannten Publikation.

DISHA, KUSHTRIM		BAD BERKA, DEN 22.03.2017
Name, Vorname	Unterschrift	Ort, Datum
ESPINOZA, ANDRES		BAD BERKA, DEN 22.03.2017.
Name, Vorname	Unterschrift	Ort, Datum
Girdauskas, Evaldas		Hamburg, 02.06.2017
Name, Vorname	Unterschrift	Ort, Datum
Kuntze, Thomas		Bad Berka, 2.8.2017
Name, Vorname	Unterschrift	Ort, Datum

Erklärung über den wissenschaftlichen Beitrag des Promovenden zur Publikation

Disha, Kushtrim geb. 03.06.1982
Zentralklinik Bad Berka GmbH, Klinik für Herzchirurgie
Promotionsfach: Herzchirurgie
Angestrebte Doktorgrad: Dr. med.

Publikation:

> Girdauskas E, <u>Disha K</u>, Espinoza A, Misfeld M, Reichenspurner H, Borger MA, Kuntze T.
> Mitral regurgitation after previous aortic valve surgery for bicuspid aortic valve insufficiency.
> J Cardiovasc Surg (Torino). 2016 Mar 24. [Epub ahead of print]. PMID: 27012929

Darlegung des eigenen Anteils:
Anteil an der Publikation: 40%
- Mitarbeit bei der Planung des Studiendesigns
- Mitarbeit bei der Durchführung der Literaturrecherche
- Erstellung der Tabellen und Grafiken in Zusammenarbeit mit dem Erstautor
- Interpretation der Ergebnisse in Zusammenarbeit mit den Koautoren
- Erstellung der Publikation in Zusammenarbeit mit dem Erstautor

Ich bestätige die von <u>Herrn Disha, Kushtrim</u> angegebene Erklärung über den wissenschaftlichen Beitrag in der obengenannten Publikation.

Evaldas Girdauskas
Name, Vorname _____ Unterschrift _____ Homburg, 02.06.2017
Ort, Datum

DISHA, KUSHTRIM
Name, Vorname _____ Unterschrift _____ BAD BERKA, DEN 22.03.2017
Ort, Datum

ESPINOZA, ANDRES
Name, Vorname _____ Unterschrift _____ BAD BERKA, DEN 22.03.2017
Ort, Datum

Kuntze, Thomas
Name, Vorname _____ Unterschrift _____ Bad Berka, 2.8.2017
Ort, Datum

Erklärung über den wissenschaftlichen Beitrag des Promovenden zur Publikation

Disha, Kushtrim geb. 03.06.1982
Zentralklinik Bad Berka GmbH, Klinik für Herzchirurgie
Promotionsfach: Herzchirurgie
Angestrebte Doktorgrad: Dr. med.

Publikation:

Disha K, Dubslaff G, Rouman M, Fey B, Borger MA, Barker AJ, Kuntze T, Girdauskas E.
Evidence of subannular and left ventricular morphological differences in patients with
bicuspid versus tricuspid aortic valve stenosis: magnetic resonance imaging-based analysis.
Interact Cardiovasc Thorac Surg. 2016 Dec 31. pii: ivw363. doi: 10.1093/icvts/ivw363. [Epub
ahead of print]. PMID: 28040769

Darlegung des eigenen Anteils:

Anteil an der Publikation: 80%

- Planung des Studiendesigns
- Federführung bei der Konzeption des Artikels
- Durchführung der Literaturrecherche und Auswahl der Relevanten Literatur
- Eigenverantwortliche Bereinigung und Analyse der Daten
- Federführung bei der Erstellung der Tabellen und Grafiken
- Interpretation der Ergebnisse in Zusammenarbeit mit den Koautoren
- Federführung bei dem Verfassen der Publikation

**Ich bestätige die von <u>Herrn Disha, Kushtrim</u> angegebene Erklärung über den wissenschaftlichen
Beitrag in der obengenannten Publikation.**

DISHA, KUSHTRIM
Name, Vorname   **Unterschrift**   BAD BERKA, DEN 22.03.2017   **Ort, Datum**

GIRDAUSKAS, Evaldas
Name, Vorname   **Unterschrift**   Hamburg, 02.06.2017   **Ort, Datum**

Fey, Beatrix
Name, Vorname   **Unterschrift**   Bad Berka, 22.3.2017   **Ort, Datum**

Dubslaff, Georg
Name, Vorname   **Unterschrift**   Bad Berka, 10.06.2017   **Ort, Datum**

Kuntze, Thomas
Name, Vorname   **Unterschrift**   Bad Berka, 2.8.2017   **Ort, Datum**

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