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Ascending aortic aneurysm and aortic valve dysfunction in bicuspid aortic valve disease

Ali Aydin [a,1], Nikolaus Desai [a,1], Alexander M.J. Bernhardt [a], Hendrik Treede [a], Christian Detter [a], Sara Sheikhzadeh [a], Meike Rybczynski [a], Mathias Hillebrand [a], Victoria Lorenzen [a], Kai Mortensen [c], Peter N. Robinson [d], Jürgen Berger [b], Hermann Reichenspurner [a], Thomas Meinertz [a], Stephan Willems [a], Yskert von Kodolitsch [a,*]

[a] Centre of Cardiology and Cardiovascular Surgery, University Hospital Eppendorf, Hamburg, Germany
[b] Department of Medical Biometry and Epidemiology, University Hospital Eppendorf, Hamburg, Germany
[c] Medical Clinic II, University of Lübeck, Germany
[d] Institute of Medical Genetics, Charité Universitätsmedizin Berlin, Germany

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ABSTRACT

Background: The relationship of aortic valve dysfunction and ascending aortic aneurysm is unclear in adults with bicuspid aortic valve disease.
Methods: We retrospectively studied 134 consecutive out-patients (98 men, 36 women aged 43 ± 18 years) with bicuspid aortic valve disease. To investigate the relationship of ascending aortic aneurysm and aortic valve dysfunction we exclusively considered severe pathologies that required treatment by surgical or percutaneous intervention.
Results: Of 134 patients, 39 had aortic valve dysfunction without concomitant ascending aortic aneurysm which had been treated previously with isolated valve surgery or percutaneous valvuloplasty comprising 25 patients with aortic stenosis (19%) and 14 patients with aortic regurgitation (10%). Conversely, 26 patients had ascending aortic aneurysm which had been treated previously with aortic surgery (19%). Of these, ascending aortic aneurysm was associated with severe aortic stenosis in 13 patients and with severe aortic regurgitation in 7 patients, whereas aneurysm was unrelated to severe aortic valve dysfunction in the remaining 6 patients including 2 without any degree of aortic valve dysfunction. The maximal aortic diameters were similar at the time of aortic surgery irrespective of presence of severe aortic valve dysfunction ($P = .527$). Other characteristics of patients with ascending aortic aneurysm were also similar irrespective of presence or type of aortic valve dysfunction.
Conclusion: The majority of patients with bicuspid aortic valve disease exhibit ascending aortic aneurysm in conjunction with severe aortic valve dysfunction. However, in our study 6 of 134 (5%) of persons with bicuspid aortic valve disease developed ascending aortic aneurysm without aortic valve dysfunction.

1. Introduction

Bicuspid aortic valve disease is present in 0.5% to 2% of the normal population, and affected adults are at risk for aortic valve dysfunction (AVD) both with severe stenosis and regurgitation [1]. Moreover, the aorta of patients with bicuspid aortic valve disease exhibits larger diameters [2], reduced arterial elasticity [3,4] and increased degeneration of the aortic medial layer [5]. It is unclear, however whether these aortic changes relate to hemodynamic forces from aortic valve dysfunction or whether such aortic abnormalities relate to aortic tissue weakness resulting from genetic defects. Accordingly, there is no consensus whether bicuspid aortic valve disease carries a significant risk for aortic dissection and rupture independently of AVD and whether it is justified to replace the proximal aorta at lower thresholds than in patients with a tricuspid aortic valve even despite the absence of severe AVD [6–8]. We investigated 134 consecutive persons with bicuspid aortic valve disease to elucidate the relationship of ascending aortic aneurysm (ACA) and AVD. To this end we considered ACA and AVD only in those patients who required surgical or percutaneous intervention and we compared their findings to persons with bicuspid aortic valve disease who did not exhibit severe aortic or aortic valve pathology and who did not require surgery or intervention.

* Corresponding author at: Centre of Cardiology and Cardiovascular Surgery, Department of Cardiology/Angiology, University Hospital Hamburg - Eppendorf, Hamburg, Martinistrasse 52, 20246 Hamburg, Germany. Tel.: +49 40 7410 57328; fax: +49 40 7410 54840.
E-mail address: kodolitsch@uke.de (Y. von Kodolitsch).
[1] Both authors contributed equally to this work.

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2. Methods

We considered all patients for inclusion in our analysis that we identified with bicuspid aortic valve disease during a three-year interval at our out-patient unit. Of 190 consecutive out-patients with bicuspid aortic valve disease we excluded 23 individuals because surgical reports of previous aortic valve surgery or percutaneous valvuloplasty were not available, 13 because they fulfilled criteria of syndromes such as Marfan, Turner, Noonan or Down, 12 because they exhibited complex cardiovascular malformations including unrepaired aortic coarctation, and 8 because they had undergone percutaneous valvuloplasty for aortic valve stenosis at an age <16 years. The remaining 134 individuals constituted our study group that comprised 98 men and 36 women with a mean age of 43 ± 18 years (median 43, range 16–77 years, Table 1).

To investigate the relationship of ACA and AVD we exclusively considered severe pathologies that required surgery or intervention. Thus, we screened patient files for any surgery or intervention at the site of the aortic valve or the ascending aorta. Severe AVD was present with previous aortic valve replacement or aortic valve reconstruction or with previous percutaneous balloon aortic valvuloplasty [9] as detailed in Table 1. ACA was present with previous aortic surgery comprising ascending aortic reduction aortoplasty both with (3 patients) or without external reinforcement (7 patients) [10], isolated supracoronary replacement of the ascending aorta (2 patients), supracoronary replacement of the ascending aorta combined with aortic valve replacement according to Wheat (6 patients) [11], replacement of the ascending aorta and aortic valve with a valved conduit and direct reimplantation of the coronary arteries according to Bentall (4 patients) [12], or a valve-sparing root replacement according to David and as classified David-I according to Miller (4 patients; Table 1) [13].

We assessed clinical variables from patient files and original echocardiographic recordings at the time directly before surgery or intervention and in the remaining individuals we assessed these variables from the time of their visit at our out-patient unit during the study period. We present body weight and body height as documented in the files, using these data to calculate body mass index and body surface area [14]. Any documentation of inhalative intake of nicotine for ≥1 year within the last 10 years was considered to be a positive history of smoking. Fasting lipid levels and resting blood pressures had been obtained at our institution, and the use of antihypertensive medication was recorded if there was any documented intake of beta-blockers, angiotensin-converting enzyme inhibitors, or angiotensin-receptor blockers of any dosage and at any combination of these drugs. We screened all patient files for a history of correction of coarctation of the aorta.

We re-evaluated preoperative or ambulatory echocardiographic recordings to assess maximum diameters of the aorta at the level of the aortic root and at the proximal ascending aorta as described by Roman et al [15]. We calculated 95th percentiles of normal diameters at the aortic sinuses and at the level of the ascending aorta as proposed by Biaggi et al [16], and we considered aortic aneurysm with any of the observed aortic diameters >95th percentile of these calculated normal diameters. We diagnosed a bicuspid aortic valve according to classical criteria on 2-dimensional echocardiograms [17], and as recorded during surgery. We documented fusion of the right and left coronary cusp (R–L type), or fusion of the right and non-coronary cusp (R–N type) as described by Fernandez et al.[18]. We identified mild or moderate aortic valve stenosis or regurgitation according to current recommendations [20]. During re-evaluation we resolved incongruent findings by re-evaluating our measurements jointly with 2 additional echocardiographers using a consensus method. When echocardiographic images were not available for reevaluation, we derived echocardiographic data from patient files.

Unless otherwise specified, we expressed quantitative data as means (± standard deviation), and qualitative data as numbers and proportions (percentage). We compared qualitative data by the Freeman-Halton test and quantitative data by the Kruskal-Wallis test (Tables 2 and 3). We considered P values as descriptive measures with a value $P<.05$ as an indicator of inhomogeneity between groups of patients. We used SPSS software (SPSS for Windows, Release 17.0, SPSS Inc. 1993 to 2007, Chicago, Illinois) for all statistical analyses. The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology.

3. Results

Of 134 patients, 39 had severe AVD without ACA which had been treated previously with isolated valve surgery or percutaneous valvuloplasty comprising 25 patients with aortic stenosis (19%) and 14 patients with aortic regurgitation (10%; Table 1). Conversely, 26 patients had ACA which had been treated previously with aortic surgery (19%). Of the remaining 69 patients without severe AVD or ACA, 8 patients had previously undergone surgery for aortic valve endocarditis (6%), whereas the remaining 61 individuals had not undergone any operation or intervention (46%).

Demographic and clinical variables were similar in severe AVD with previous surgery or intervention for aortic stenosis, in severe AVD with previous surgery for aortic regurgitation and in patients without severe AVD (Table 2). However, the ascending aortic diameters tended to be larger in AVD with severe aortic stenosis ($P=.085$), and the R–L type of bicuspid aortic valve was somewhat more frequent in AVD with severe aortic regurgitation ($P=.08$). Interestingly, ACA was present in 13 of 38 patients with severe aortic stenosis (34%), in 7 of 21 patients with severe aortic regurgitation (33%), and in 6 of 75 patients without severe AVD (6%; $P=.001$). The diameters of the aortic root ($P=.004$) and of the ascending aorta were significantly larger in patients with ACA than in patients with severe AVD without ACA ($P<.001$; Fig. 1).

Of the 26 patients with ACA 13 individuals had concomitant severe aortic stenosis, 7 had concomitant severe aortic regurgitation, and 6 did not exhibit any severe AVD. Of these 6 patients 4 exhibited mild

Table 1
Severe aortic valve dysfunction (AVD) or ascending aortic aneurysm (ACA), or both in 134 adults with bicuspid aortic valve disease.

Pathology	All persons	Males	Median age, years (range)	Aortic valve surgery or valvuloplasty		
				Bileaflet device	Biological device	Other
Total number of patients	134	98	43 (16–77)			
Severe aortic valve stenosis	25 (19%)					
- Isolated stenosis	12	5	46 (16–61)	5	3	4[1]
- Leading stenosis	13	10	52 (19–74)	5	6	2[2]
Severe aortic valve regurgitation	14 (10%)					
- Isolated regurgitation	11	10	42 (20–71)	2	5	4[2]
- Leading regurgitation	3	3	34 (17–75)	3		
Ascending aortic aneurysm	26 (19%)					
- With severe aortic valve stenosis[a]	13	10	59 (24–73)	5	7	1[2]
- With severe aortic valve regurgitation[b]	7	5	51 (18–67)	4	2	1[3]
- Without severe aortic valve dysfunction[c]	6	3	43 (35–60)			
Aortic valve endocarditis	8 (6%)	7	26 (17–55)	2	4	2[2]
No severe aortic or aortic valve pathology	61 (46%)	43	39 (16–77)*			

Other AVD comprised:
[1]Percutaneous balloon aortic valvuloplasty.
[2]Ross operation.
[3]Aortic valve resuspension.
PAS comprised:
[a]Ascending aortic aneurysm with previous aortic reduction aortoplasty with (N = 1) or without external reinforcement (N = 6), Wheat procedure (N = 5), or Bentall procedure (= 1). Five of 13 persons exhibited grad II aortic regurgitation in addition to their server aortic valve stenosis.
[b]Ascending aortic aneurysm with previous aortic reduction aortoplasty with (N = 2) or without external reinforcement (N = 1), Wheat procedure (N = 1), or Bentall procedure (N = 3). None of these 7 patients exhibited any degree of concomitant aortic valve stenosis.
[c]Ascending aortic aneurysm with previous supracoronary replacement of the aorta without aortic valve replacement (N = 2), or with a David-I procedure (N = 4).

Table 2
Characteristics of 134 persons according to severe aortic valve dysfunction (AVD).

Characteristic	Severe aortic valve dysfunction			P[3]
	None[1,2] (N = 75)	Stenosis[2] (N = 38)	Regurgitation[2] (N = 21)	
Male sex	55 (73%)	25 (66%)	18 (86%)	.255
Age (years)	41 ± 17	47 ± 18	45 ± 20	.149
Body height (m)	176 ± 11	174 ± 8	178 ± 9	.476
Body weight (kg)	76 ± 16	76 ± 15	76 ± 15	.152
Body mass index (kg/m^2)	24 ± 4	25 ± 4	25 ± 4	.093
Body surface area (m^2)	1.92 ± .24	1.92 ± .19	2 ± .15	.280
History of smoking	17 (37%)	15 (54%)	6 (40%)	.365
Total cholesterol (mg/dl)	191 ± 59	193 ± 58	167 ± 56	.524
High-density lipoprotein cholesterol (mg/dl)	51 ± 12	50 ± 13	39 ± 17	.175
Low-density lipoprotein cholesterol (mg/dl)	118 ± 37	125 ± 62	87 ± 46	.259
Systolic blood pressure (mmHg)	130 ± 20	130 ± 22	133 ± 25	.848
Diastolic blood pressure (mmHg)	78 ± 11	81 ± 15	74 ± 18	.229
Intake of antihypertensive medication	24 (55%)	10 (48%)	6 (50%)	.863
Previous surgery for aortic coarctation	17 (23%)	16 (16%)	3 (14%)	.554
Left ventricular ejection fraction (%)	58 ± 13	54 ± 9	60 ± 7	.561
Aortic root diameter (mm)	36 ± 7	34 ± 7	36 ± 4	.587
Ascending aortic diameter (mm)	38 ± 9	43 ± 8	41 ± 9	.085
Bicuspid valve R–L type (vs R–N type)	37/45 (82%)	16/27 (59%)	9/11 (82%)	.080
Surgery for ascending aortic aneurysm	6 (8%)	13 (34%)	7 (33%)	.001

[1] Including patients with surgery for aortic valve endocarditis.
[2] Including patients with concomitant ascending aortic aneurysm.
[3] Freeman-Halton test for categorical variables and the Kruskal-Wallis test for continuous variables.

Table 3
Characteristics of 26 patients with ascending aortic aneurysm (ACA).

Characteristic	Ascending aortic aneurysm			P*
	No. AVD	Aortic valve stenosis	Aortic valve regurgitation	
	(N = 6)	(N = 13)	(N = 7)	
Male sex	5	10	5	.994
Age (years)	44 (39–60)	59 (24–73)	51 (18–67)	.344
Aortic valve stenosis				.001
- mild degree	1			
- moderate degree				
- severe degree		13		
Aortic valve regurgitation				.001
- mild degree	1	4		
- moderate degree	1	5		
- severe degree			7	
Previous surgery for aortic coarctation	1	1	1	.821
Aortic root diameter (mm)	41 (37–61)	38 (30–46)	43 (38–48)	.204
Ascending aortic diameter (mm)	49 (37–71)	47 (43–57)	52 (35–65)	.852
Bicuspid valve R–L type (vs R–N type)	3/4	6/11	4/5	.549
Aortic root >95th percentile	4/5	3/6	2/3	.583
Ascending aorta >95th percentile	5/6	11/11	6/6	.227
Diameter ascending aorta>aortic root	4/5	6/7	2/3	.788

Quantitative data are given as median and range.
AVD indicates severe aortic valve dysfunction.
* Freeman-Halton test for categorical variables and the Kruskal-Wallis test for continuous variables.

aortic stenosis or mild aortic regurgitation whereas 2 did not exhibit any degree of aortic regurgitation or stenosis (Table 3). Patients with ACA tended to be older with severe aortic stenosis ($P = .347$; Fig. 2, left panel), but the maximal aortic diameters were similar irrespective of presence or type of severe AVD ($P = .527$; Fig. 2, right panel).

4. Discussion

To study the relationship of ACA and AVD we exclusively considered pathologies which were marked enough to require surgery or valvuloplasty. With usage of these criteria we found that ACA developed in three different settings comprising severe aortic stenosis, severe aortic regurgitation, and absence of severe AVD. In the following we discuss these three types of ACA.

In our study 50% of ACA was associated with severe aortic stenosis. Like in other series [1,22] aortic stenosis was the most frequent cause for surgery in the entire group of patients with bicuspid aortic valve. However, ACA was present in 34% of all patients with severe aortic stenosis and in 33% of all patients with severe aortic regurgitation and thus the relative frequency of ACA was similar in both types of AVD. ACA with bicuspid aortic valve stenosis was often addressed as “post-stenotic dilatation” which was typically reported in the mid-ascending aorta [19]. However, we observed that the R–N type of the bicuspid aortic valve was somewhat more prevalent both in severe isolated aortic stenosis and in severe aortic stenosis with ACA. Thus, specific aortic tissue mechanisms [19] yielding distinct flow patterns [20] may have contributed to the formation of ACA in aortic stenosis.

Twenty-seven percent of ACA was associated with severe isolated aortic regurgitation. In total, 33% of our patients with severe aortic regurgitation had ACA, which was similar to the 43% reported by Boodhwani et al [25]. The R–L type of bicuspid aortic valve disease was

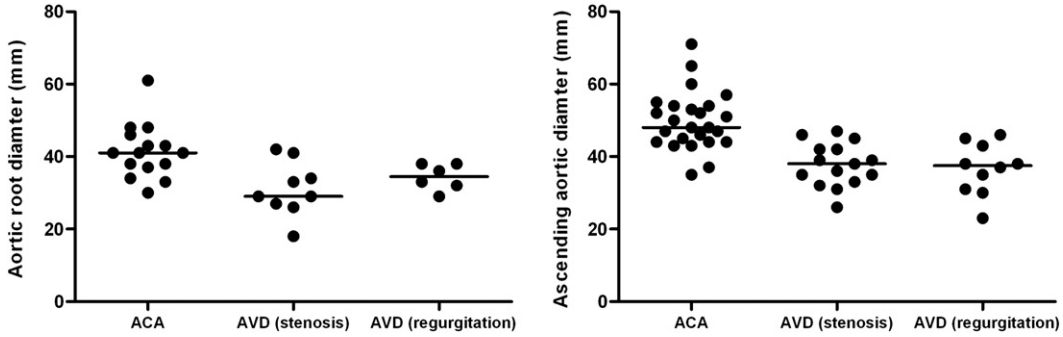

Fig. 1. The scatter dot plot displays aortic diameters and the median is shown as a horizontal line. Patients with ACA (median 41 mm, range 30–61 mm) exhibited increased diameters of the aortic root as compared to patients without ACA but with severe aortic stenosis (median 29 mm, range 18–42 mm) or with severe aortic regurgitation (median 35 mm, range 29–38 mm; $P = .004$; left panel). Similarly, patients with ACA (median 48 mm, range 35–71 mm) had larger diameters of the ascending aorta than patients without ACA but with severe aortic stenosis (median 38 mm, range 26–47 mm) or with severe aortic regurgitation (median 38 mm, range 23–46 mm; $P < .001$; right panel). Measurements of the aortic root were available in 15 (58%), 8 (32%), and in 9 (64%) patients with ACA, and patients without ACA but severe aortic stenosis or regurgitation, respectively. Similarly, measurements of the ascending aorta were available in 25 (96%), 15 (60%), and in 10 (71%) patients with ACA, and in patients without ACA but severe aortic stenosis or regurgitation, respectively.

present in 9 of 11 patients with severe aortic regurgitation (82%), but only in 16 of 27 patients with severe aortic valve stenosis (59%; $P = .080$). These data confirm the finding by Schaefer et al. that the R–L type of the bicuspid aortic valve tends to be more prevalent in aortic valve regurgitation. Thus, we found support for their hypothesis that anatomical subtypes of bicuspid aortic valves may relate to the natural course of bicuspid aortic valve disease[21]. Moreover, our patients with ACA and severe aortic regurgitation did not exhibit any degree of aortic stenosis, some tended to be younger than those with ACA related to severe aortic stenosis, not all had a dilatation at the level of the aortic root, and with a single exception all patients exhibited the R–L type of bicuspid valve. These findings support the notion that ACA in the setting of aortic regurgitation relate to various potential mechanisms [22].

Twenty-three percent of ACA was unrelated to severe AVD. This type represented the smallest group of ACA in our study. Affected persons were nearly all males, they usually exhibited the R–L-type of valve, and their age at surgery was similar to the other patients with ACA. Two patients exhibited ACA with diameters of 65 and 71 mm but they both had well functioning aortic valves with mild regurgitation in one person. Two other individuals with only marginally enlarged ascending aortic diameters of 41 and 44 mm required surgery for rupture of aneurysm of the aortic sinus or for concomitant dilatation of the aortic arch. One of these patients had a mild aortic stenosis which may have accounted for ACA [6–8]. However, another individual with a diameter of 52 mm exclusively exhibited a mild degree of aortic regurgitation, and a person with an aortic diameter of 54 mm did not have any measurable AVD. Thus, ACA without AVD seems to comprise a heterogeneous group of aortic pathologies, of which some form without any degree of AVD. Affected persons may usually be asymptomatic and thus remain unidentified until aortic rupture or dissection.

A majority of patients with severe AVD did not have ACA at the time of aortic valve surgery, which indicates that hemodynamic factors alone may not be enough to cause ACA in all bicuspid aortic valves. However, we did not follow these patients and thus we are unable to exclude that aortic dilatation developed in the postsurgical course. Progression of aortic diameters were described after isolated aortic valve surgery in bicuspid aortic valve disease [23], but Girdauskas et al. concluded from their systematic review of the literature that the available data were not sufficient to elucidate the natural history of the proximal aorta after isolated aortic valve replacement [24].

Some limits of our study need to be mentioned. First, our study was retrospective and we did not have complete data for all variables (Tables 2 and 3). Second, we do not have sufficient follow-up information for postsurgical analyses. Third, a population based study of asymptomatic persons with the incidental finding of bicuspid aortic valve disease and rule-out of moderate or severe AVD presented the mild end of the disease [25]. Conversely, our experience from a tertiary care center focused on the severe end of the disease. However, since we aimed to elucidate the relationship of AVD and severe aortic vessel disease the study of mild phenotypes would not have been informative.

We conclude that a majority of patients with bicuspid aortic valve disease exhibit ACA in conjunction with severe AVD. However, in our study 25 of 38 (66%) of patients with severe aortic valve stenosis and 14 of 21 (67%) patients with severe aortic valve regurgitation did not

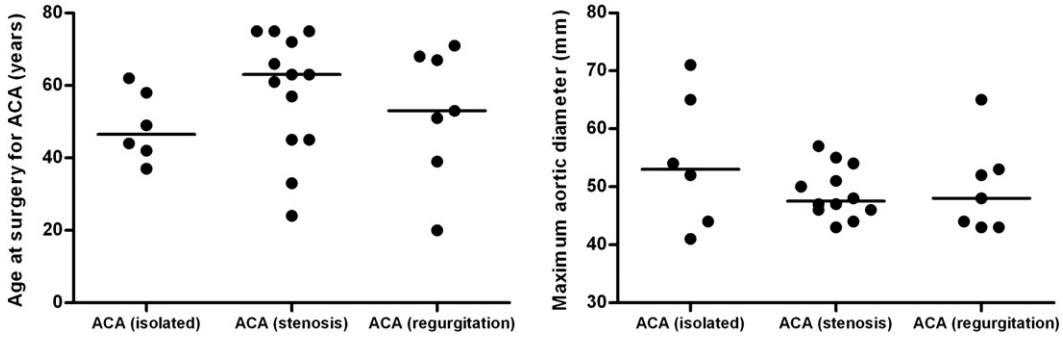

Fig. 2. The scatter dot plot displays age and maximal aortic diameters and their median (horizontal lines) at the time of surgery for ACA. Age was similar although patients tended to be older with ACA combined with severe aortic valve stenosis (median 59 years, range 24–73 years) than in isolated ACA without AVD (median 44 years, range 35–60 years) or in ACA with severe aortic regurgitation (median 51 years, range 18–67 years; $P = .347$; left panel). All maximal aortic diameters were ≥4 cm with no significant difference between patients without AVD (median 53 mm, range 41–71 mm) and patients with severe aortic stenosis (median 48 mm, range 43–57 mm) or regurgitation (median 48 mm, range 43–65 mm; $P = .527$; right panel).

exhibit ACA at the time of aortic valve operation. Moreover, 6 of 134 (5%) of persons with bicuspid aortic valve disease developed ACA without AVD. Thus in bicuspid aortic valve disease ACA is likely caused by a broad variety of factors and it can develop in the absence of any AVD as defined by echocardiographic criteria.

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