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Risk of proximal aortic dissection in patients with bicuspid aortic valve: how to address this controversy?

Evaldas Girdauskas[a,*], Kushtrim Disha[a], Michael A. Borger[b] and Thomas Kuntze[a]

[a] Department of Cardiac Surgery, Central Hospital Bad Berka, Bad Berka, Germany
[b] Department of Cardiac Surgery, Heart Center Leipzig, Leipzig, Germany

* Corresponding author. Department of Cardiac Surgery, Central Clinic Bad Berka, Robert-Koch-Allee 9, 99437 Bad Berka, Germany. Tel: +49-3645851101; fax: +49-32121468153; e-mail: egirdauskas@web.de (E. Girdauskas).

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Abstract

The risk of acute aortic events in patients with bicuspid aortic valve (BAV) disease is a controversial issue. The real risk of aortic dissection in patients with BAV disease is unknown. An indirect assessment of this risk, however, could be gained with a more detailed understanding of the pathogenesis of BAV aortopathy. There are two major issues that should be clarified before one addresses the question of aortic dissection risk in BAV patients. The first issue, when analysing the data from previous BAV cohorts, is to determine what stage of BAV disease was present in the described patient population. In particular, was the risk of aortic dissection in BAV patients determined before or after aortic valve replacement (AVR) surgery? The second issue to consider is the functional state of the pathological valve within the observed population. In particular, did patients predominantly suffer from BAV stenosis or BAV insufficiency? Unfortunately, the vast majority of published reports do not separate between the different BAV phenotypes, thereby complicating interpretation of the results. Considering these two important clinical variables (i.e. the stage of BAV disease and the functional phenotype), we herein aim to explain the inconsistency of the published data with regard to the risk of aortic dissection in patients with BAV disease.

Keywords: Bicuspid aortic valve • Aorta • Aortic dissection

INTRODUCTION

The risk of acute aortic events in patients with bicuspid aortic valve (BAV) disease is a controversial issue. Several reports in the literature address distinct clinical aspects of BAV-related aortopathy and contribute even more to the ongoing controversy. However, the real risk of aortic dissection in patients with BAV disease is unknown. Because aortic dissection is an uncommon event, accurate determination of its risk in BAV patients would require following a very large patient cohort for a significant period. An indirect assessment of this risk, however, could be gained with a more detailed understanding of the pathogenesis of BAV aortopathy [1–3]. A reassessment of the genetic and haemodynamic hypothesis for BAV aortopathy may, therefore, be required.

There are two major issues that should be clarified before one addresses the question of aortic dissection risk in BAV patients. The first issue, when analysing data from previous BAV cohorts, is to determine what stage of BAV disease was present in the described patient population. In particular, was the risk of aortic dissection in BAV patients determined before or after aortic valve replacement (AVR) surgery? Considering the recently published evidence on BAV function and effects of transvalvular flow [4–10], AVR surgery may be a key factor in the natural history of BAV-associated aortopathy with considerable influence on the risk of future aortic events.

The second issue to consider when examining studies of BAV patients is the functional state of the pathological valve within the observed population. In particular, did patients predominantly suffer from BAV stenosis or BAV insufficiency? There is increasing support within the literature to advocate the presence of two distinct phenotypes of BAV disease with corresponding valvular stenosis or insufficiency [11–13]. The two distinct entities are characterized by major differences in morphological and clinical characteristics, as well as patterns of associated aortopathy. Such observed differences presumably result in different clinical prognoses [12, 13]. Unfortunately, the vast majority of published reports do not separate between the different BAV phenotypes, thereby complicating interpretation of the results.

Considering these two important clinical variables (i.e. the stage of BAV disease and the functional phenotype), we herein aim to explain the inconsistency of the published data with regard to the risk of aortic dissection in patients with BAV disease.

NECROPSY STUDIES AND AORTIC DISSECTION DATABASES

Large necropsy series were the first clinical data that proposed an increased risk of proximal aortic dissection in the BAV population [14]. A morphologically bicuspid valve was present in 7–15% of unselected cases of fatal aortic dissection in published necropsy studies [15–17]. Compared with an estimated incidence of BAV of 1–2% in the general population, the presence of BAV was associated with a 9-fold increased risk of aortic dissection [16, 18]. Moreover, a bicuspid morphology was found 10-fold more commonly in persons with a type A aortic dissection than in those

without aortic dissection, based on the data of a 21-year necropsy population (i.e. over 21 000 necropsy cases from a single institution) [18]. Patients with BAV and fatal aortic dissection were approximately one decade younger than dissection patients with a tricuspid aortic valve [15, 18].

The above-mentioned necropsy series were 'no intervention' studies and included only those patients who were diagnosed as having BAV at the time of autopsy. These early studies include neither echocardiography data on BAV function nor information on the diameter of the proximal aorta prior to the acute aortic event. Only patients with an unoperated BAV were addressed in these studies. BAV patients who underwent prior AVR surgery were not included in these studies and, therefore, their risk of aortic dissection cannot be addressed with these data. Since these studies come from an earlier era [15–18], one may question their validity in the current era of advanced echocardiographic diagnosis and a rapidly increasing number of BAV patients undergoing AVR surgery [19].

Another important source of information on the prevalence of aortic dissection in the BAV population are the multicentre aortic dissection databases (e.g. IRAD), which include all patients diagnosed with aortic dissections antemortem, i.e. based on imaging data. Unfortunately, there are no data on the functional state of the BAV prior to the aortic event in these studies. In addition, BAV patients who may have undergone previous AVR surgery could not have been classified as BAV in these registries, again making the estimation of aortic dissection risk post-AVR difficult. The prevalence of BAV patients in these large aortic dissection populations ranges between 4 and 12% [20–23], confirming once again a higher prevalence than in the general population. These studies were conducted in the era of easily available echocardiography screening and other imaging techniques, which may explain a lower prevalence of BAV patients in the aortic dissection databases, when compared with the above-mentioned early necropsy trials.

In summary, the aforementioned 'no intervention' studies demonstrate a significantly higher risk of aortic dissection in BAV patients with unreplaced bicuspid valves. Because these patients were not systematically followed for their BAV and/or associated proximal aortic disease prior to the acute aortic event, the statement on increased risk of aortic dissection in the modern era of enhanced clinical awareness of BAV disease may be irrelevant today.

Moreover, the entire hypothesis of a greater risk of aortic dissection in BAV patients from 'no intervention' necropsy studies is based on the assumption that incidence of BAV is in the range 1–2% in the general population. However, these estimates are predominantly derived from necropsy studies from an earlier era [15–18]. As emphasized by the authors of these early studies, the incidence of BAV determined by necropsy reports is unreliable because this anomaly may be easily overlooked [24]. To the best of our knowledge, there are only limited population-based echocardiographic data on the incidence of BAV in the paediatric/young adult population [25–27]. Therefore, the true incidence of BAV in the general population may be underestimated. Moreover, as BAV is a heritable disorder, endemic variations should be encountered with potential accumulation of BAV patients in certain geographic areas.

POPULATION-BASED FOLLOW-UP STUDIES OF BAV PATIENTS PRIOR TO AVR SURGERY

Another source of data that analysed the prevalence of proximal aortic dissection in BAV patients are so-called population-based natural history studies [28–32]. These studies reported on large cohorts of BAV patients with unreplaced bicuspid valves, which were followed for up to 20 years after diagnosis, thus providing data on long-term outcomes. The incidence of proximal aortic dissection was considerably low in two major longitudinal follow-up studies including a total of 854 BAV patients: only three events in 8958 cumulative patient-years [28, 30]. Nonetheless, both of these studies reported a significant and incremental rate of cardiovascular surgery (i.e. 22–27%) with increasing age during the longitudinal follow-up, AVR surgery being the most common event [28, 30]. Two other follow-up studies analysed the natural history of BAV patients with unreplaced valves and a dilated proximal aorta (i.e. diameter >35–40 mm) [31, 32]. A cohort of TAV patients with a comparably dilated proximal aorta served as a control group in both studies. Even in the face of a dilated ascending aorta, these studies demonstrated a low incidence of aortic dissection (i.e. a total of 4 events in 459 cumulative patient-years) with no significant difference compared with TAV patients.

What could be the reasons for these low rates of aortic dissection in BAV population-based studies when compared with the above-mentioned necropsy trials and dissection databases? The most important difference is the type of study design. Although population-based follow-up studies are called 'natural history' trials, these are not in fact 'no intervention' studies. All included patients with (unreplaced) BAV in these studies underwent longitudinal follow-up with periodic examinations during the study period. Since these population-based studies were all performed in the era of advanced echocardiography, BAV patients were monitored for worsening of their aortic valve function and/or increases in their proximal aortic disease with elective surgical intervention, when indicated. The proportion of patients who underwent cardiovascular surgery during the study period ranged from 22 to 77% [28, 30, 31]. Such a study design with appropriate surgical interventions may have significantly contributed to the low aortic dissection rates observed in these studies.

Another important follow-up study, analysing the risk of proximal aortic complications in a large cohort of BAV patients with and without coarctation of the aorta, demonstrated a significant impact of coarctation on the incidence of adverse aortic events [33]. The overall risk of proximal aortic dissection was remarkably low in this series, with only 1 patient developing a type A dissection during the follow-up study of a total of 2436 patient-years [33]. It is important to note that this study was also performed in the modern era of echocardiographic surveillance and surgical management, when required.

In summary, the above-mentioned studies demonstrate that BAV patients with an unreplaced aortic valve have a very low risk of proximal aortic dissection when they undergo appropriate monitoring and intervention. Only BAV patients with simultaneous coarctation of the aorta may be at increased risk of this complication [33].

PROXIMAL AORTIC DISSECTION IN BAV POPULATION AFTER AVR SURGERY

Follow-up studies of BAV patients after isolated AVR

Aortic events after isolated AVR surgery in BAV disease have been the focus of much controversy [34, 35]. There are a limited

Table 1: Follow-up studies of BAV patients after isolated AVR surgery

Authors	Sample size	Study period	BAV disease (AS vs AI)[a]	Proximal aorta (mm)	Follow-up (years)	Type A dissection	Sudden deaths
Russo *et al.* [36]	50	1975–1985	42% AS 18% AI	Normal?	19.5 ± 3.9	5 (10%)	7 (14%)
Borger *et al.* [37]	201	1979–1993	63% AS 22% AI	≤50 mm	10.3 ± 3.8	1 (0.5%)	3 (2%)
Goland *et al.* [38]	252	1971–2000	50% AS 12% AI	≤50 mm	8.9 ± 6.3	0 (0%)	11 (6%)
McKellar *et al.* [39]	1286	1960–1995	77% AS 7% AI	?	12 (0–38)	13 (1%)	?
Dayan *et al.* [40]	60	2000–2003	83% AS 17% AI	≤45 mm	6.2 ± 2	0 (0%)	0 (0%)
Girdauskas *et al.* [41]	153	1995–2001	100% AS	40–50 mm	11.5 ± 3.2	0 (0%)	3 (2%)

[a]Patients with mixed aortic valve lesions were not included.
AS: aortic valve stenosis; AI: aortic valve insufficiency; BAV: bicuspid aortic valve; AVR: aortic valve replacement.

number of follow-up studies that addressed the issue of late aortic events following AVR surgery for BAV disease [36–41]. The corresponding results are very discordant, ranging from a quite benign postoperative course [38–40] to a markedly unfavourable long-term prognosis [36]. All relevant data from these studies are summarized in Table 1. A summary of these data can lead one to quickly conclude that the risk of documented aortic dissection is considerably low in BAV patients post-AVR [36–41]—19 events in 22 852 cumulative patient-years (i.e. 0.8 events/1000 patient-years). Unfortunately, the association between aortic dissection risk and type of BAV disease (i.e. BAV stenosis vs insufficiency) was not assessed in these studies. Moreover, there is no in-depth analysis of the relatively few patients who experienced aortic dissection during the long-term follow-up with regard to the type of BAV disease, diameters of proximal aorta and presence of other well-known risk factors. The high aortic event rate in the study by Russo *et al.* [36] is difficult to explain in view of the data from the other studies.

Proximal aortic dissection after previous AVR surgery

Indirect information on the risk of post-AVR aortic dissection in BAV patients can be obtained from other series [42–44]. An extensive analysis of 33 patients with proximal aortic dissection after previous AVR by von Kodolitsch *et al.* [42] demonstrated that only 5/33 patients (15%) were previously operated on for BAV disease. A subsequent meta-analysis of published reports performed by the same group brought very similar findings—only 8/57 patients (14%) underwent previous AVR for BAV disease [42]. Most importantly, all the 8 BAV patients underwent previous AVR for isolated/predominant BAV insufficiency instead of BAV stenosis [42]. Not a single patient presented with type A aortic dissection post-AVR surgery for isolated BAV stenosis in this meta-analysis. Multivariate analysis identified that only aortic valve insufficiency in combination with fragility/thinning of aortic wall (i.e. regardless of the type of aortic valve disease, BAV or TAV) were independent predictors of late aortic dissection after previous AVR [42]. The remaining two lower volume studies [43, 44] arrived at the same conclusions—previous BAV insufficiency increases the risk of subsequent post-AVR type A dissection.

Other studies that did not differentiate between BAV and TAV disease [45–48] showed similar results: 60–80% of patients with post-AVR aortic dissection underwent their original operation because of isolated/predominant aortic valve insufficiency. Moreover, most of these patients had poorly treated hypertension and a markedly dilated proximal aorta at the time of AVR.

All of the above-mentioned post-AVR dissection series point out the major impact of BAV functional state at the time of AVR on the risk of late aortic events (i.e. clear predominance of patients with previous aortic valve insufficiency) [42–48]. Very few patients suffered proximal aortic dissection late after AVR for isolated aortic stenosis.

Risk of late post-AVR aortic dissection in BAV insufficiency vs BAV stenosis

To the best of our knowledge, the risk of late aortic events post-AVR in BAV insufficiency vs stenosis has not yet been systematically evaluated. However, some indirect comparisons of these 2 patient subgroups may offer some insights.

It has been well documented in the literature that BAV insufficiency and stenosis patients have markedly different clinical and echocardiographic characteristics [11, 12]. The relatively small subset of BAV insufficiency patients (i.e. 10–20% of the total BAV population) is characterized by a significantly younger age, predominance of male gender and a 5-fold higher prevalence of aortic annular dilatation when compared with their stenotic counterparts [12]. Dilatation of the aortic annulus and the entire aortic root has been convincingly demonstrated by thorough echocardiographic analysis of BAV insufficiency patients [11]. In contrast, BAV stenosis is generally associated with asymmetric dilatation at the convexity of the mid-ascending aorta [13].

Obvious differences in the severity of histological changes in the proximal aortic wall have also been identified between BAV stenosis vs insufficiency patients [49, 50]. Major elastin fibre loss in the proximal aorta has been demonstrated in nearly 50% of patients with pure BAV insufficiency vs 10% of BAV stenosis patients in patients who underwent an AVR and proximal aortic surgery [49]. Another recent study, which included a significant proportion of BAV insufficiency patients (i.e. 60% of the total study population), showed a high incidence of moderate/severe histological alterations of the aortic wall even in the absence of clinically relevant proximal aortic dilatation [50].

Moreover, another recent prospective study using the dissectometer, demonstrated a significantly increased tendency towards

aortic media disruption in patients with aortic valve insufficiency vs aortic stenosis [51].

Further indices of the more malignant nature of aortopathy in patients with the BAV insufficiency when compared with the BAV stenosis are presented by the so-called aortoplasty studies [52–54]. Reduction ascending aortoplasty (RAA) is a rather controversial surgical technique with a variety of modifications that have been proposed to overcome its limitations [52]. However, a number of published reports identified BAV insufficiency as a significant risk factor for late redilatation of the proximal aorta after RAA, when compared with BAV stenosis [52–54]. Moreover, BAV insufficiency patients showed a significantly faster growth of the proximal aortic diameter after RAA when compared with those with BAV stenosis (i.e. 1.3 vs 0.2 mm/year, respectively) [54]. However, it must be emphasized that BAV patients included in the aortoplasty series were not really comparable, as they presented with distinct patterns of associated aortopathy. These data were included in our review with the intention to demonstrate that patients with BAV insufficiency vs BAV stenosis are different clinical entities, which may follow different natural history/long-term prognosis.

All of the above-mentioned data indicate that BAV insufficiency is associated with a more malignant form of proximal aortic disease than BAV stenosis. The combined presence of aortic valve annular dilatation and aortic root enlargement at young age suggests a disease process that involves the entire aortic root rather than the aortic valve only. Isolated AVR surgery may therefore not be effective in preventing the progression of aortic disease and risk of subsequent aortic dissection in patients with BAV insufficiency, when compared with their stenotic counterparts.

CLINICAL IMPLICATIONS

The natural history of aortopathy in BAV patients is influenced by the type of BAV disease (i.e. valve insufficiency vs stenosis) and the presence of previous AVR surgery.

BAV patients with unreplaced aortic valves who are not systematically monitored (i.e. community- or hospital-based surveillance strategy) for their aortic valve and proximal aortic disease are at increased risk of aortic dissection, provided the true incidence of BAV is in the range 1–2% in the general population. Clinical surveillance combined with timely surgical intervention may reduce this risk to that of the general population. AVR surgery reduces the risk of future aortic events in BAV stenosis patients, provided the diameter of proximal aorta does not exceed 50–55 mm at the time of AVR. Concomitant mild-to-moderate dilatation of the ascending aorta in these patients is not associated with an increased risk of adverse aortic events at least at 15 years after isolated AVR.

The subsequent risk of aortic events is less affected by AVR surgery in patients with BAV insufficiency. Proximal aortic disease may further progress post-AVR in these patients, which may lead to an increased risk of aortic dissection. A more aggressive treatment of the associated aortopathy is justified in patients undergoing surgery for BAV insufficiency, namely by replacing entire (native) aortic root tissue, whatever surgical approach has been chosen (i.e. valve-sparing root replacement or composite graft procedure).

At this point, it is rather impossible to definitely answer the question about the risk of aortic dissection in BAV, having only mixed BAV cohorts, different stages of BAV disease being lumped together and being analysed by different study designs. In this review, we aimed to define the criteria on which the available literature should be analysed and critically re-evaluated, i.e. functional phenotype, stage of BAV disease and study design. These criteria were implemented in the current review as an assessment tool in order to explain the inconsistency of the published data with regard to the risk of aortic dissection in BAV disease.

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