Cardiovascular disease burden in thoracic aortopathy

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Part III

Evaluating coronary artery disease in thoracic aortopathy through imaging modalities

Chapter 4

The extent of coronary artery disease in patients with stenotic bicuspid versus tricuspid aortic valves.

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Abstract

Background
Bicuspid aortic valve (BAV) is the most common congenital cardiac malformation, which is often complicated by aortic valve stenosis (AoS). In tricuspid aortic valve (TAV), AoS strongly associates with coronary artery disease (CAD) with common pathophysiological factors. Yet, it remains unclear whether AoS in BAV patients is also associated with CAD. This study investigated the association between the aortic valve morphology and the extent of CAD.

Methods and Results
A single center study including all patients who underwent an aortic valve replacement due to AoS between 2006 and 2019. Coronary sclerosis was graded on preoperative coronary angiographies using the CAGE scoring method, which divides the coronaries in 28 segments and scores non-obstructive (20-49% sclerosis) and obstructive coronary sclerosis (>49% sclerosis) in each segment. Multivariate analyses were performed, controlling for age, sex and CAD risk factors. A total of 1296 patients (931 TAV and 365 BAV) were included, resulting in 548 matched patients. TAV patients exhibited more CAD risk factors (OR 2.66 (95%CI 1.79-3.96); p<0.001). BAV patients had lower CAGE20 (1.61 ± 2.35 vs 3.60 ± 2.79) and CAGE50 (1.24 ± 2.43 vs 3.37 ± 3.49) scores (p < 0.001), even after correcting for CAD risk factors (p < 0.001). TAV patients more often needed concomitant coronary revascularization (OR 3.50 (95%CI 2.42-5.06); p<0.001).

Conclusions
BAV patients who are undergoing surgery for AoS carry a lower cardiovascular risk profile correlating with less coronary sclerosis and a lower incidence of concomitant coronary revascularization as compared to TAV patients.

Introduction

A bicuspid aortic valve (BAV) is the most common congenital cardiac anomaly with a prevalence of 1-2% in the general population (1). BAV is a recognized risk factor for the development of aortic valve and aortic wall alterations, which can result in diseases such as aortic valve stenosis (AoS) or regurgitation, and/or ascending aortic dilation (2). Previous studies showed that a defect in vascular smooth muscle cell differentiation and alterations in extra cellular matrix composition play a key role in the development of aortopathy in BAV patients (3-8).

AoS is thought to reflect a multi-faceted process that shares many pathophysiologic and risk factors with CAD (9-14). Common pathophysiologic factors include lipid deposition, inflammatory processes, and calcifications. Age, smoking, hypertension and dyslipidemia comprise common risk factors of both diseases.

A possible relationship between patients with BAV and CAD has been under debate. BAV patients usually develop AoS at a younger age as compared to patients with a regular tricuspid aortic valve (TAV) (14) Moreover, it has been suggested that AoS in BAV patients essentially relates to an altered hemodynamic flow pattern rather than to CAD risk factors (15-17). This altered flow pattern is considered a result of the divergent cusp morphology, which leads to an increased stress on both the aortic valve cusps and the ascending aorta (4, 15-17).

Although these observations above imply contrasting pathophysiologic backgrounds for AoS in BAV and TAV, conclusions of hitherto conducted studies on this subject are inconsistent (18, 19) and need further research.

This study aims to examine the prevalence of CAD in patients with a BAV versus a TAV morphology. The coronary angiographies of BAV and TAV patients who underwent an aortic valve replacement (AVR) between 2006 and 2019 due to an AoS were studied, in order to identify the prevalence, severity and extent of CAD. Secondly, the presence of CAD risk factors, and the need for CAD related interventions were scored for both groups.

Methods

Study population

This retrospective study was conducted at the Leiden University Medical Center (LUMC) in the Netherlands. Approval for this study was granted by the medical ethics committee of the Leiden University Medical Center (METC LDD, case number G19.113) and patient consent was waived. The data that support the findings of this study are available from the corresponding author upon reasonable request. The surgical database was searched to identify all patients who underwent an AVR because of an

underlying AoS between January 2006 and April 2019. Transcatheter procedures, patients under the age of 18, aortic valve plasty procedures, patients with endocarditis, aortic dissection or aortic valve regurgitation as the primary problem and patients with no preoperative coronary angiograms were excluded. Patients with an AVR in the past were also excluded in those cases were the original aortic valve morphology was non retrievable.

Study parameters

The patients' electronic health records were examined in order to obtain data regarding the patient demographics, medical history (i.e. prior cardiac events, interventions and surgeries), laboratory findings (lipid and creatinine levels) and echocardiographic characteristics of the aortic valve. CAD risk factors were scored for each patient, including family history (any cardiovascular related health issues such as a myocardial infarction before the age of 65), comorbidities (including hypertension and diabetes mellitus), lipid levels, usage of tobacco and/ or alcohol and the body mass index (20). Additionally, the surgical reports were studied to identify the aortic valve morphology and classification of the BAV phenotype according to Sievers, the type of procedure and concomitant CAD related procedures (e.g. coronary artery bypass grafting (CABG)). Aortic diameters were obtained from preoperative echocardiograms or computed tomographies.

Coronary imaging

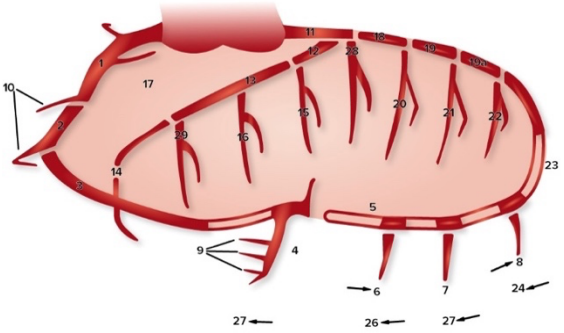
Each patient's last coronary angiography prior to surgery was studied. Only angiographies performed up to one year before the surgery were included. Two independent researchers scored the coronary angiographies of each patient, using the coronary artery greater than or equal to 20 and 50 (CAGE ≥20 and CAGE ≥50 respectively) method (see below for details). The coronary arteries were divided into 28 segments, as previously described in the Coronary Artery Surgery Study (21-23). The extension of the CAD was defined as the number of segments with a stenosis of >20% (non-obstructive + obstructive CAD, CAGE ≥20) and 50% or greater (obstructive CAD, CAGE ≥50). The severity of the CAD was calculated using weight factors per segment as described earlier by Vlietstra e.a. (figure 1) (21). Only the native coronary artery system was scored for patients with a previously performed CABG.

Statistical analysis

The current study presents normally distributed continuous variables as mean ± standard deviation (SD), while continuous variables with a non-normal distribution are presented as median and interquartile range. Continuous variables were analyzed using

a logistic regression. Categorical data are presented as frequencies and percentages and analyzed using the Fischer's exact test. Skewness, kurtosis and normality tests were performed for all variables. Two strategies were followed to correct for the significant differences in baseline characteristics (especially age and sex) between BAV and TAV patients. These strategies included an age and sex based 1:1 matching and a multivariate analyses on the whole (unmatched) cohort. After univariate analyses, multivariate linear regression analyses were performed to model the dependence of the aortic valve morphology (BAV and TAV) on the CAGE ≥20 and CAGE ≥50 scores, controlling for CAD risk factors (e.g. age at surgery, sex, high body mass index, smoking status, alcohol consumption, hypertension, hypercholesterolemia, diabetes mellitus, previous myocardial infarction or angina pectoris, a family history of CAD and the ascending aortic diameter). A p value of <0.05 was considered to be significant. All statistical analyses were conducted using IBM SPSS for Windows version 25.0.

Figure 1: Coronary artery segments (according to CASS) and the corresponding weight factors used for the CAGE score.(22,24)



Segments	Weight factor
11	x5
12,18, 28	x2,5
13	x1,5
1-4, 14, 15, 19, 20, 27	x1
5-10, 16, 17, 21-26	x0,5

Results

A total of 3583 aortic valve replacements were identified between 2006 and 2019, of which 1296 patients were eventually eligible for inclusion. These included 931 TAV and 365 BAV patients, resulting in 548 matched patients (274 BAV and 274 TAV). The group of 365 BAV patients consisted of 30 patients (13%) with a Sievers class 0, 196 (54%) with a Sievers class 1 and 5 (1.4%) with a Sievers class 2 BAV. The Sievers classification was not described for 134 (36.7%) patients. The left-right positioned raphe was the most common variant (n=151, (41.4%)), followed by right-non coronary cusp (n=28,

7.7%) and left-non coronary cusp (n=8, 2.2%). The raphe position was not described for the remaining 9 (2.5%) patients.

Baseline and perioperative characteristics

All baseline characteristics are displayed in table 1.

The matched patients were equally divided into two groups based on age and sex, with no deviation between the groups. Echocardiographic findings regarding the aortic valve showed higher mean gradients (45 vs 37 mmHg, p<0.001) and lower aortic valve areas (0.80 vs 0.90 cm^2, p= 0.004) in BAV patients as compared to the TAV patients (see table 2).

Table 3 shows a detailed list of the perioperative characteristics. TAV patients were more likely to undergo an isolated AVR (odds ratio (OR) 2.43 (95%CI 1.71-3.45); p<0.001), while BAV patients more frequently received concomitant aortic replacement procedures, e.g. full aortic root replacements (OR 5.86 (95%CI 3.68-9.34); p<0.001) or an ascending aortic replacement (OR 12.10 (95%CI 6.29-23.23); p<0.001). Compared to BAV patients, TAV patients were more often in need of concomitant surgery of a second valve (OR 4.62 (95%CI 2.59-8.25); p<0.001).

Coronary artery disease

CAD and CAD risk factors were more common in TAV patients. A history of CAD (e.g. myocardial infarction or instable angina pectoris) was more prevalent in TAV patients (OR 4.15 (95%CI 2.52-6.80); p<0.001), resulting in more coronary revascularization procedures (e.g. percutaneous coronary intervention (OR 5.48 (95%CI 2.86-10.50); p<0.001) and CABG (OR 7.32 (95%CI 1.65-32.54); p=0.004).

Furthermore, TAV patients had a higher count of CAD risk factors compared to BAV patients, e.g. hypertension (OR 2.00 (95%CI 1.41-2.83); p<0.001), diabetes mellitus (OR 3.06 (95%CI 2.01-4.64); p<0.001) and hypercholesterolemia (OR 2.38 (95%CI 1.67-3.39); p<0.001).

Similarly, the CAGE ≥20 and CAGE ≥50 scores, and the number of affected coronary segments were both higher in TAV patients (all p<0.001, see figure 2 and table 4). In line with these results, concomitant CABG at the time of valve replacement was more often performed in TAV patients than BAV patients (OR 3.50 (95%CI 2.42-5.06); p<0.001).

In the light of the differences in the patient characteristics between BAV and TAV patients an additional analysis was performed besides the matched analyses. To control for the effects of CAD risk factors on the CAGE scores, the risk factors were added to a multivariate analysis as confounders or colinear variables. These multivariate analyses were performed on the whole population. After taking the CAD risk factors into account, TAV patients still had higher CAGE ≥20 and CAGE ≥50 scores ((OR 1.15 (95%CI 1.07-1.23); p<0.001) and (OR 1.16 (95%CI 1.09-1.24); p<0.001) respectively).

Table 1: Baseline characteristics of the matched patients

	Aortic valve morphology			
	BAV	TAV		
Characteristic	n = 274	n = 274	OR (95% CI)	*P-value*
Male	182 (66.4)	182 (66.4)	1.00 (0.79-1.27)	1.000
Age at surgery	67 (61-71)	67 (61-71)	1.00 (0.98-1.02)	1.000
Body Mass Index	26.2 (24.1-28.9)	27.5 (25.0-30.9)	1.01 (1.04-1.13)	<0.001
Smoking status	270/274*	264/274*		
Never	120 (43.8)	125 (45.6)	1.08 (0.77-1.51)	0.731
Former	95 (34.7)	97 (35.4)	1.03 (0.73-1.46)	0.929
Currently	55 (20.1)	42 (15.3)	0.72 (0.46-1.12)	0.179
Family history of CAD	32 (11.68)	39 (14.23)	1.25 (0.76-2.07)	0.443
Diabetes	40 (14.6)	94 (34.3)	3.06 (2.01-4.64)	<0.001
Insulin dependent	10 (3.6)	34 (12.4)	1.70 (0.74-3.90)	0.233
Hypertension	142 (51.8)	187 (68.2)	2.00 (1.41-2.83)	<0.001
Hypercholesterolemia†	77 (28.1)	132 (48.2)	2.38 (1.67-3.39)	<0.001
Total cholesterol	4.95 ± 1.18	4.8 (4.00-5.30)	0.91 (0.74-1.12)	0.383
HDL-cholesterol	1.34 (1.1-1.71)	1.3 (1.07-1.52)	1.01 (0.73-1.40)	0.939
LDL-cholesterol	2.82 ± 0.93	2.85 ± 1.21	1.00 (0.76-1.38)	0.871
Preoperative creatinine	82 (72-92.5)	81 (69-99)	1.01 (1.001-1.013)	0.007
Previous CAD				
Previous MI	12 (4.4)	58 (21.2)	5.86 (3.07-11.2)	<0.001
Previous (i)AP	12 (4.4)	21 (7.7)	1.81 (0.87-3.76)	0.150
Previous coronary revascularization				
Previous PCI	12 (4.4)	55 (20.1)	5.48 (2.86-10.50)	<0.001
Previous CABG	2 (0.7)	14 (5.1)	7.32 (1.65-32.54)	0.004
Previous cardiac surgery				
CoA correction	6 (2.2)	0	0.98 (0.96-0.99)	0.030
AVP	1 (0.5)	1 (0.4)	1.00 (0.62-16.1)	1.000
Aorta surgery	2 (0.7)	0	0.99 (0.98-1.00)	0.499

**Denominator represents number of patients for whom this information was known. Data are presented as n (%), mean ± SD or median (interquartile range).*

AVP = Aortic valve plasty, BAV = Bicuspid aortic valve, CABG = Coronary artery bypass grafting, CAD = Coronary artery disease, CoA = Coarctation of the Aorta, HDL = High density lipoprotein, (i)AP = (instable) Angina pectoris, LDL = Low density lipoprotein, MI = Myocardial infarction, PCI = Percutaneous coronary intervention, TAV = Tricuspid aortic valve.

† in mmol/l. ‡ in µmol/l.

Table 2: Echocardiographic characteristics of the matched patients

	Aortic valve morphology			
	BAV	TAV		
Characteristic	n = 274	n = 274	OR (95% CI)	*P-value*
AVA (cm^2)	0.80 (0.60-1.00)	0.90 (0.70-1.10)	2.80 (1.38-5.67)	0.004
Mean AV gradient*	45 (33-58)	37 (27-49)	0.97 (0.96-0.98)	<0.001
Peak AV gradient*	73 (55.3-92.8)	62 (47-78)	0.98 (0.98-0.99)	<0.001
Aortic regurgitation (0-4)	0 (0-1)	0 (0-1.5)	1.00 (0.98-1.01)	0.483

Data are presented as median (interquartile range). AV = Aortic valve, AVA = Aortic valve area, BAV = Bicuspid aortic valve, TAV = Tricuspid aortic valve.
** in mmHg*

Discussion

The primary aim of this study was to identify the prevalence, severity and extent of CAD comparing BAV and TAV patients, by studying the medical histories, surgical reports and scoring the preoperative coronary angiographies. This study showed a lower rate of CAD in BAV patients compared to TAV patients. When assesing the histories of both groups, BAV patients had lower rates of CAD (e.g. myocardial infarction and angina pectoris), coronary artery revascularization (e.g. CABG and PCI) and CAD risk factors (higher age, hypertension, hypercholesterolemia and diabetes mellitus). Additionally, preoperative coronary angiographies showed lower rates of coronary artery sclerosis in BAV patients when compared to TAV patients. Two different strategies were followed to analyse the study population since atherosclerosis is an age dependent process and as the BAV population is younger and more often male. First, the BAV and TAV patients were matched based on age (mean age 66.5 years) and sex (66.4%) and the differences were analysed between the groups. However, as this matched population is relatively young and predominantly male, a secondary multivariate analyses was also performed to correct for the differences in baseline characteristics (i.e. a potential confouding by indication) on the complete (unmatched) population. Conclusions for both strategies (as above mentioned) were very similair, which indicates that the differences between the groups were corrected adequately.

As pointed out previously, AoS is a multi-faceted process which shares both the risk factors and the pathophysiological factors of CAD (9-14). The fact that BAV patients develop AoS at a younger age (14), while they often carry a lower cardiovascular risk profile compared to TAV patients, makes this an interesting group to study. This study endorses the results of previous studies which identified a lower cardiovascular risk profile in BAV patients (9, 18). The manifestation of AoS at a younger age (aproximately 7 years earlier) – while at the same time carrying fewer CAD risk factors – could indicate different etiologies of AoS between BAV and TAV patients. This notion is supported by the lower coronary calcium burden for BAV patients observed in this study, but a higher aortic valve calcium load in BAV patients vs. TAV patients (24). Additionaly,

Table 3: Perioperative characteristics of the matched patients

	Aortic valve morphology			
	BAV	TAV		
Surgery type	n = 274	n = 274	OR (95% CI)	*P-value*
Single AVR	137 (50)	194 (70.8)	2.43 (1.71-3.45)	<0.001
Concomitant CABG	63 (23)	140 (51.1)	3.50 (2.42-5.06)	<0.001
# Distal anastomosis	2 (1-3)	2 (1-3.75)	1.25 (0.99-1.59)	0.064
Concomitant aortic surgery				
Root	107 (39.1)	27 (9.9)	5.86 (3.68-9.34)	<0.001
Ascending	92 (33.6)	11 (4)	12.1 (6.29-23.23)	<0.001
(Hemi)arch	12 (4.4)	1 (0.4)	12.5 (1.61-96.84)	0.003
Other concomitant procedures				
Rhythm surgery	20 (7.3)	21 (7.7)	1.05 (0.56-1.99)	1.000
MVP	13 (4.7)	34 (12.4)	2.84 (1.47-5.52)	0.002
MVR	3 (1.1)	22 (8)	7.89 (2.33-26.67)	<0.001
TVP	6 (2.2)	28 (10.2)	5.08 (2.07-12.49)	<0.001

**Denominator represents number of patients for whom this information was known. Data are presented as n (%), mean ± SD or median (interquartile range).*
AVR = Aortic valve replacement, BAV = Bicuspid aortic valve, CABG = Coronary artery bypass grafting, MVP = Mitral valve plasty, MVR = Mitral valve replacement, TAV = Tricuspid aortic valve, TVP = Tricuspid valve plasty, # = number of

preoperative echocardiographies showed significant differences in aortic valve gradients and AVA between BAV and TAV. These results implicate that CAD risk factors are less contributive to the pathophysiology of AoS in BAV patients than in TAV patients. Instead, higher mechanical stress – which is caused by an abnormal flow pattern that results from the divergent cusp morphology in BAV patients – could be the

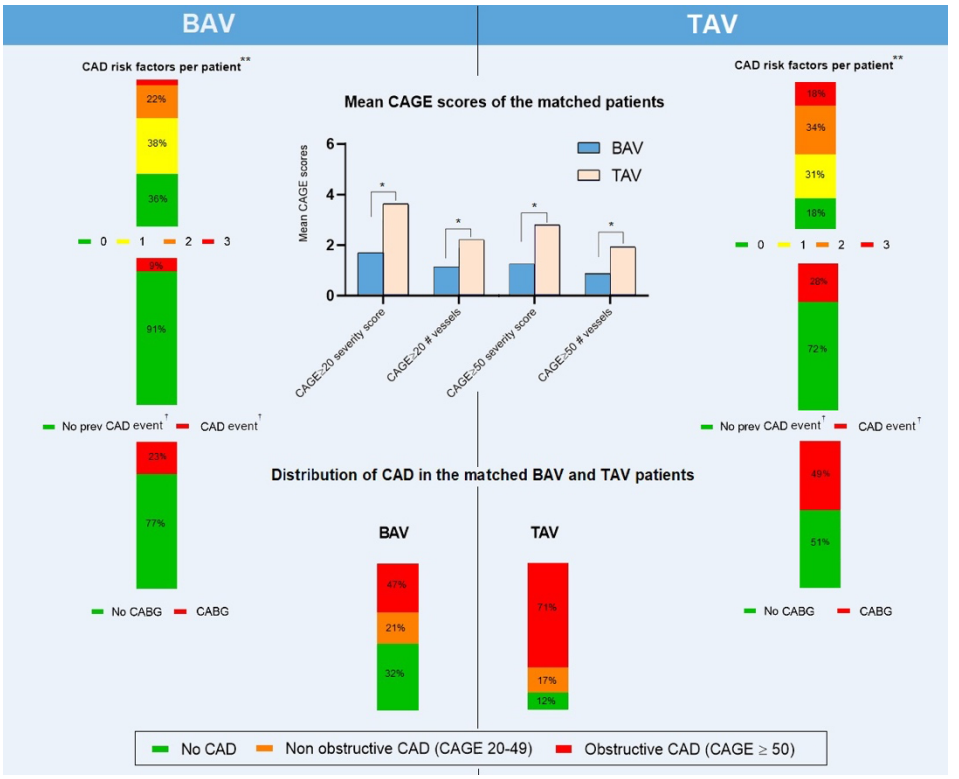
leading cause of the earlier development of AoS in BAV patients (4, 25). BAV cusps display a more excessive bending strain during the cardiac cycle, leading to higher shear stresses on the cusps – especially in the raphal area (15) – which leads to the thickening and early degeneration of the aortic valve (15-17). These observations may reflect the fact that AoS in BAV generally relates to a primary valve defect, whereas AoS in TAV more often relates to a secondary defect. More research is warranted to study the possible differences in the etiology of AoS in BAV and TAV patients.
To our knowledge, the current study – which included a total of 1296 patients – is the largest clinical study yet to examine the relationship between CAD and the aortic valve morphology by directly studying the coronary angiographies of each patient. Hitherto conducted studies regarding the relationship of the aortic valve morphology and the prevalence of CAD have not resulted in consensus. Poggio e.a. performed a meta-analysis in order to identify this relationship (18). This study indicated a higher incidence of CAD in TAV patients, but no significant differences remained between the two groups after correcting for CAD risk factors. However, it is important to point out that non of the included studies in this meta-analysis directly investigated coronary sclerosis by examining the patients' coronary imgaging. Instead, the results found by Poggio e.a. are based on anamnestic or clinical outcomes (e.g. concomitant coronary revascularization), thus only looking at significant coronary sclerosis. Since stenoses of less then 70% are clinically not always revascularized, studying only the clinical outcomes means studying solely the tip of the iceberg (26). On the other hand, another study that explored the associations between AoS and CAD in patients who were planned for an AVR showed a higher incidence of concomitant CABG in TAV patients than BAV patients (62.2% and 26.3% respectively) (9).

Table 4: Mean CAGE scores of the matched patients

	Aortic valve morphology			
	BAV	TAV		
Characteristic	n = 274	n = 274	OR (95% CI)	*P-value*
CAGE 20 severity score	1.61 ± 2.35	3.60 ± 2.79	1.36 (1.26-1.47)	<0.001
CAGE 20 # vessels	0.99 ± 1.34	2.08 ± 1.52	1.71 (1.49-1.95)	<0.001
CAGE 50 severity sore	1.24 ± 2.43	3.37 ± 3.49	1.29 (1.20-1.38)	<0.001
CAGE 50 # vessels	0.86 ± 1.58	2.32 ± 2.28	1.49 (1.34-1.65)	<0.001

Data are presented as mean ± SD.
BAV = Bicuspid aortic valve, TAV = Tricuspid aortic valve, # vessels = number of affected vessels

Figure 2: CAD characteristics of the matched BAV and TAV patients



Assessment of the number of CAD risk factors per patient showed higher amounts of CAD risk factors[1] per patient in TAV patients (top row bar diagrams). The medical histories of TAV patients displayed higher rates of previous CAD events compared to BAV patients (OR 4.15 (95%CI 2.52-6.80); p<0.001), (second row bar diagrams). Concomitant CABG was more often performed in TAV patients (OR 3.50 (95%CI 2.42-5.06); p<0.001) (third row bar diagrams). Preoperative coronary angiographies showed higher rates of coronary sclerosis (both non-obstructive as obstructive) in TAV patients, graded using the CAGE scores (center bar graph). The bottom bar diagrams display the distribution of obstructive and non-obstructive CAD between BAV and TAV patients, which shows higher rates of obstructive CAD in TAV patients. BAV = Bicuspid aortic valve, CABG = Coronary artery bypass grafting, CAD = Coronary artery disease, TAV = Tricuspid aortic valve.

** : P< 0.001*
*** : Diabetes Mellitus, Hypertension and/or Hypercholesterolemia*
† : Previous myocardial infarction or instable angina pectoris

Until now, it is unclear what the mechanism behind the lower rates of CAD in BAV patients is. A recent review even hypothesized that BAV patients are more at risk of developing CAD, by providing an overview of several molecular mechanisms which may promote CAD in BAV patients (27). These included dyslipidemia, which is not in line with the lower cardiovascular risk profile of BAV as found in this study and other previous studies (9, 18), and the activation of pro-inflammatory pathways. To our knowledge, there has not been a histopathological study that has directly assessed the relationship between CAD and the aortic valve morphology. Yet, one could formulate several potential mechanisms which might lead to lower rates of CAD in BAV patients based on other studies. For example, a thinner tunica intima has been observed in BAV patients (8). This might be one of the reasons these patients have lower rates of CAD, since CAD is a disease which primarily develops in this layer of the vessels. Other studies suggested that ascending aortic dilation might have a protective effect on CAD (28-30). Since ascending aortic dilation is a common problem in BAV patients, developing in at least 50% of the BAV population (31, 32), this might also contribute to lower CAD in BAV patients. Another mechanism that might lead to differences of CAD between BAV and TAV patients are the inflammatory pathways, which play a role in the development of CAD (33, 34). Yet, hitherto conducted studies show contradictory conclusions regarding this subject. A study from our laboratory showed lower inflammatory components in the aortic walls of BAV patients (8), while other studies showed the same degree of inflammation between BAV and TAV (35) or even more activated inflammatory pathways in BAV patients (27).
In order to draw conclusions about the complete BAV patients, patients with lower cardiovascular risk profiles need to be studied as well. Future histopathological studies could provide insight into the possible mechanisms underlying this effect.

Limitations

As with all retrospective and observational studies, this study is subject to some limitations due to the research design. This study only focused on the surgical AVR, excluding those patients who underwent a transcatheter aortic valve replacement. This could have led to an inclusion bias, since these patients are often older and carry more comorbidities compared to the surgical AVR group. In order to study the patients with the highest cardiovascular risk profile, the study population only included patients with AoS, which makes it unfit to draw conclusion about the general population including patients without valvular diseases. Despite matching on age and sex, TAV patients still displayed a higher number of confounders (e.g. a higher cardiovascular risk profile) than BAV patients. Yet, these differences in cardiovascular risk profiles could be the result of two different etiologies of AoS. BAV patients who develop AoS at a much younger age while carrying lower amounts of CAD risk factors than TAV patients

indicate different pathophysiological mechanisms leading to a similar disease between these two groups.

Conclusion

BAV patients had significantly lower CAGE scores, resulting in lower rates of concomitant CABG. The patients' medical histories revealed that BAV patients showed lower amounts of CAD and coronary revascularization in the past. Additionally, BAV patients also had lower CAD risk factors at the time of surgery compared to TAV patients. The differences in the cardiovascular risk profile between BAV and TAV suggest different pathophysiological mechanisms of AoS between the two patient groups. Future histopathological studies are mandatory to unravel the possible different mechanisms underlying this effect.

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