**RESEARCH ARTICLE**

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# Ascending aortic wall degeneration in patients with bicuspid versus tricuspid aortic valve

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## Abstract

**Background:** The magnitude of ascending aortic degeneration in patients with bicuspid aortic valves (BAV) is controversial.

**Methods:** The aim of this study was to investigate ascending aortic wall degeneration in patients with BAV as compared with tricuspid aortic valves (TAV). The ascending aortic wall of 67 consecutive patients was processed for histology and immunohistochemistry. The extent of surgery and wall degeneration were investigated. Unadjusted survival was evaluated by Kaplan–Meier analysis. Median follow-up for patients with BAV and TAV was 3.8 years (interquartile range [IQR] 3.5–4.1) and 3.7 years (IQR 3.4–3.9), respectively.

**Results:** There were 33 patients with BAV and 34 with TAV. Mid-ascending aorta diameter was 54 mm (IQR 50–60). Replacement of the aortic valve, together with an ascending aortic prosthesis, was more frequent in BAV vs TAV patients (24% vs. 3%, $P = 0.013$). However, medial fibrosis, elastic fiber thinning, incremental medial degeneration and smooth muscle cell nuclei loss were less prominent in BAV vs TAV patients ($0.1 \pm 0.4$ vs. $0.8 \pm 1.4$, $P = 0.016$; $0.6 \pm 1.4$ vs. $1.6 \pm 2.0$, $P = 0.027$; $1.7 \pm 0.7$ vs. $2.2 \pm 0.8$, $P = 0.045$ and $2.3 \pm 1.5$ vs. $3.2 \pm 1.3$, $P = 0.026$, respectively).

**Conclusions:** Since degeneration of the ascending aortic wall was seldom prominent, histopathology alone may not support the need for surgery of the dilated ascending aorta in BAV patients as compared with TAV patients.

**Keywords:** Aortic wall degeneration, Ascending aorta, Bicuspid aortic valve

## Introduction

Bicuspid aortic valve (BAV) is present in 1–2% of the whole population [1–3]. It has been suggested that patients with BAV are genetically susceptible to early aortic events and poor outcome [2], a conception mainly deduced from circulatory blood flow pattern changes of the ascending aorta [3]. Current recommendations suggest surgery of the ascending aorta without elastopathy, when the aortic root or the ascending aortic diameter exceeds 55 mm [4]. In cases of BAV, surgery of the ascending aorta is also considered (a) if the aortic root or the ascending aortic diameter exceeds 50 mm in the presence of risk factors such as coarctation of the aorta, systemic hypertension, family history of dissection, or an increase in aortic diameter up to 0.3 mm/year, or (b) if the aortic root or the ascending aortic diameter exceeds 45 mm and a surgical aortic valve replacement is scheduled [4]. However, the association of aortic

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wall degeneration with BAV and outcome after surgery remains controversial [5–8].

The Consensus statement on surgical pathology of the aorta from the Society for Cardiovascular Pathology and the Association for European Cardiovascular Pathology was recently launched to clarify the nomenclature and diagnostic criteria of degeneration [9]. The Consensus statement describes detailed means to investigate degenerative aortic wall changes pertinent to the development of an ongoing aortic disease. As the ultimate aim of surgery for the ascending aorta is to prevent aortic events, the aim of this study was to investigate the presence and significance of ascending aortic wall degeneration in BAV patients as compared with tricuspid aortic valve (TAV) patients undergoing surgery for the ascending aorta in a single-center patient cohort.

## Methods

### Study protocol and surgery

After institutional review board approval (Ethical Committee of the Tampere University Hospital, Tampere, Finland, R15013), the need for informed consent was waived and the study conforms to the ethical guidelines of the Declaration of Helsinki. The ascending aortic wall resection of 67 consecutive patients undergoing surgery for dilatation of ascending aorta was obtained and processed for histology. Ascending aortic aneurysm was preoperatively confirmed and evaluated with computer tomography (CT). According to our Institutional policy, aortic aneurysm included an aortic diameter more than 5.0–5.5 cm wide or aortic growth more than 1 cm in a year. This definition was adjusted to the presence of Marfan syndrome, sex, patient size and symptoms according to The Yale Center criteria [10]. Surgery was performed between December 2006 and August 2012.

The decision on the extension of resection and surgical technique was at the discretion of the operating surgeon. When aortic aneurysm, including the sinotubular junction (STJ), was estimated as the reason for aortic regurgitation, STJ was tailored for a suitable graft in a supracoronary fashion. Whenever dilatation included the aorta root, a radical resection of the dilated ascending aorta, together with the root and the aortic valve, was performed. The graft size was estimated by the principal surgeon. Since the surgical procedure was performed upon surgical decision, the sample was procured from the middle of the resected area of the ascending aorta at the vicinity of STJ including the intact aortic wall.

### Histology and immunohistochemistry

Two to five blocks of resected intact ascending aorta were embedded in paraffin, cut to 4 µm thick segments and stained with Hematoxylin and Eosin, Verhoeff-van Gieson, Elastase-van Gieson and Periodic Acid-Schiff. A representative, 1-cm long piece of ascending aortic wall corresponding to all different staining was evaluated systematically for all resected samples procured during surgery (Fig. 1).

Aortic wall histology and immunohistochemistry was performed using Ventana Lifesciences Benchmark XT© Staining module for leukocytes, T- and B-lymphocytes, plasma cells, macrophages, smooth muscle cells, cell proliferation, elastase and van Gieson staining. Ventana Lifesciences Antibody Dilution Buffer© was utilized for dilution media. The heights of different layers (adventitia, media and intima) were calculated for each sample [11].

### Quantification of medial degeneration

Medial degeneration of the ascending aorta was assessed by quantifying 11 different variables describing medial and adventitial damage [9, 12]. These included medial fibrosis, elastic fiber disorganization, elastic fiber loss/ fragmentation, elastic fiber thinning, laminar medial collapse, classification of medial degeneration, mucoid extracellular matrix accumulation, smooth muscle cell disorganization, smooth muscle cell nuclei loss and medial thickness of vasa vasorum, and adventitial fibrosis. According to the consensus, the variables describing medial degeneration were categorized as none, mild, moderate and severe on a scale of 0–3 [9].

### Follow-up protocol

Documentation of mortality and morbidity was available for all the patients. For the included study patients, follow-up consisted of physical examination and echocardiography at three months after surgery, and on-demand thereafter including computed tomography. Morbidity after surgery included documentation of concomitant coronary artery bypass grafting, pacemaker implantation, cerebral stroke, reoperation, and aortic event.
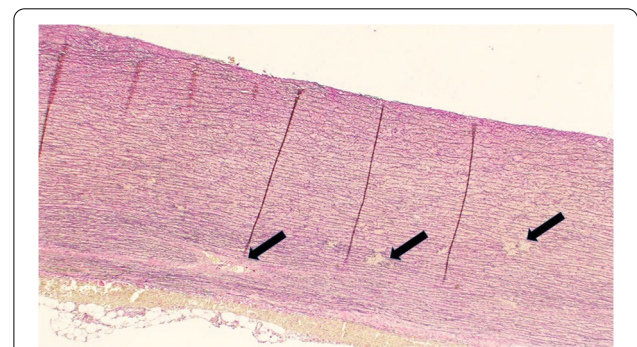


**Fig. 1** Representative histology of ascending aortic wall histology showing disruptions of elastic laminae indicative for degenerative medial layer (black arrows)

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### Statistical analysis

Continuous variables were expressed as medians including interquartile (IQR), incremental variables of media layer degeneration as means with standard deviations, and were compared using the Mann–Whitney test. Categorical variables were presented as numbers and percentages, and were compared using $\chi^2$ or Fisher's exact tests. In order to seek clinical relevance associated with immunohistochemistry, the patients were divided into two groups in accordance with the presence of either BAV or TAV. Unadjusted survival was evaluated by Kaplan–Meier analysis with log-rank tests. All analyses were conducted using the IBM SPSS Statistics version 26.0 (IBM Corporation, Armonk, NY, USA) and R 4.1.2 statistical software (R Foundation for Statistical Computing, Vienna, Austria) with $P < 0.05$ as the criterion for significance.

## Results

### Patient characteristics

Patient characteristics are shown on Table 1. There were 33 patients with BAV and 34 with TAV. The median age for the patients was 66 years (IQR 56–71). Hypertension was frequent in patients with TAV as compared with BAV patients ($P = 0.001$). The median aortic diameter was 53 mm (IQR 50–57) in BAV patients and 55 mm (IQR 52–60) in TAV patients ($P = 0.042$). Median follow-up for patients with BAV and TAV was 3.8 years (IQR 3.5–4.1) and 3.7 years (IQR 3.4–3.9), respectively.

### Operative technique

The operative technique is shown on Table 2. A mechanical valve was implanted with or without a conduit

**Table 2** Operative details according to surgical evaluation of extension of diseased aorta

|  | All patients | BAV | TAV | *P* value |
|---|---|---|---|---|
|  | 67 | 33 | 34 |  |
| Graft replacement of root and ascending aorta |  |  |  |  |
| Mechanical conduit | 10 (15%) | 6 (9%) | 4 (6%) | 0.512 |
| Biological conduit | 32 (48%) | 12 (18%) | 20 (30%) | 0.088 |
| Graft replacement of ascending aorta |  |  |  |  |
| Mechanical valve + prosthesis | **5 (8%)** | **5 (8%)** | **0** | **0.025** |
| Biological valve + prosthesis | 4 (6%) | 3 (5%) | 1 (1%) | 0.356 |
| Prosthesis | 16 (24%) | 7 (11%) | 9 (13%) | 0.776 |

BAV = bicuspid aortic valve; TAV = tricuspid aortic valve

Significant differences between groups are in bold

prosthesis in 11 out of 33 (33%) BAV patients as opposed to only 4 out of 34 (12%) TAV patients owing to patient age. Altogether, replacement of the aortic valve, together with an ascending aortic prosthesis, but without replacement of the aortic root, was more frequent in BAV vs TAV patients (24% vs 3%, $P = 0.013$). The aortic valve, the root and the ascending aorta were replaced using a conduit prosthesis in 55% BAV versus 71% TAV patients ($P = 0.212$). The ascending aorta only was replaced in 16 patients. Concomitant coronary artery bypass grafting was performed in four BAV and three TAV patients.

**Table 1** Patient characteristics

|  | All patients | BAV | TAV | *P* value |
|---|---|---|---|---|
| Number of patients | 67 | 33 | 34 |  |
| Age (years, interquartile) | 66 (56–71) | 64 (55–72) | 68 (61–71) | 0.133 |
| Male, n | 50 (75%) | 26 | 24 | 0.576 |
| Hypertension, n | 44 (68%) | 15 | 29 | 0.001 |
| Diabetes, n | 9 (14%) | 3 | 6 | 0.475 |
| Hypercholesterolemia, n | 17 (26%) | 11 | 6 | 0.166 |
| Vasculitis, n | 6 (8%) | 1 | 5 | 0.198 |
| Arthritis | 6 (9%) | 2 | 4 | 0.673 |
| Asthma, n | 4 (6%) | 0 | 4 | 0.114 |
| Myocardial coronary artery disease, n | 14 (21%) | 7 | 7 | 1 |
| History of stroke | 4 (6%) | 2 | 2 | 1 |
| Earlier abdominal aorta aneurysm surgery | 2 (3%) | 0 | 2 | 0.492 |
| Mid-ascending aorta diameter (mm, interquartile) | 54 (50–60) | 53 (50–57) | 55 (52–60) | 0.042 |
| Moderate to severe aortic valve regurgitation, n | 36 (56%) | 14 | 22 | 0.139 |

BAV = bicuspid aortic valve; TAV = tricuspid aortic valve

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**Table 3** Histology and quantitative immunohistochemistry

|  | All patients | BAV | TAV | *P* value |
| --- | --- | --- | --- | --- |
| Adventitial fibrosis | 0.2 ± 0.4 | 0.1 ± 0.3 | 0.2 ± 0.4 | 0.221 |
| Medial fibrosis | **0.5 ± 1.1** | **0.1 ± 0.4** | **0.8 ± 1.4** | **0.016** |
| Elastic fiber disorganization | 1.0 ± 1.0 | 0.8 ± 0.9 | 1.1 ± 1.1 | 0.191 |
| Elastic fiber loss/fragmentation | 3.6 ± 1.4 | 3.3 ± 1.2 | 3.8 ± 1.6 | 0.206 |
| Elastic fiber thinning | **1.1 ± 1.8** | **0.6 ± 1.4** | **1.6 ± 2.0** | **0.027** |
| Laminar medial collapse | 0.6 ± 1.3 | 0.3 ± 0.9 | 0.8 ± 1.5 | 0.184 |
| Classification of medial degeneration | **1.9 ± 0.8** | **1.7 ± 0.7** | **2.2 ± 0.8** | **0.045** |
| Mucoid extracellular matrix accumulation | 4.6 ± 1.2 | 4.3 ± 0.9 | 4.9 ± 1.2 | 0.051 |
| Smooth muscle cell disorganization | 0.6 ± 0.8 | 0.4 ± 0.7 | 0.8 ± 0.9 | 0.121 |
| Smooth muscle cell nuclei loss | **2.8 ± 1.4** | **2.3 ± 1.5** | **3.2 ± 1.3** | **0.026** |
| Medial thickness of vasa vasorum | 0.2 ± 0.4 | 0.3 ± 0.5 | 0.2 ± 0.4 | 0.407 |

Mean ± standard deviation; BAV = bicuspid aortic valve; TAV = tricuspid aortic valve

Significant differences between groups are in bold

## Perioperative findings, histology and immunohistochemistry

As shown on Table 3, medial fibrosis remained less significant in BAV as compared with TAV patients ($0.1 \pm 0.4$ vs. $0.8 \pm 1.4$, $P = 0.016$, respectively). Elastic fiber thinning was less present in BAV versus TAV patients ($0.6 \pm 1.4$ vs. $1.6 \pm 2.0$, $P = 0.027$). Incremental medial degeneration was $1.7 \pm 0.7$ in BAV as compared with $2.2 \pm 0.8$ in TAV patients ($P = 0.045$). There was a tendency for decreased mucoid extracellular matrix accumulation in BAV as compared with TAV patients ($4.3 \pm 0.9$ vs. $4.9 \pm 1.2$, $P = 0.051$). Smooth muscle cell nuclei loss was less prominent in BAV as compared with TAV patients ($2.3 \pm 1.5$ vs. $3.2 \pm 1.3$, $P = 0.026$).

## Morbidity

Two BAV patients received a pacemaker. During follow-up, one TAV patient had a cerebral stroke, and another TAV patient experienced a B-type aortic dissection. There were no reoperations during follow-up.
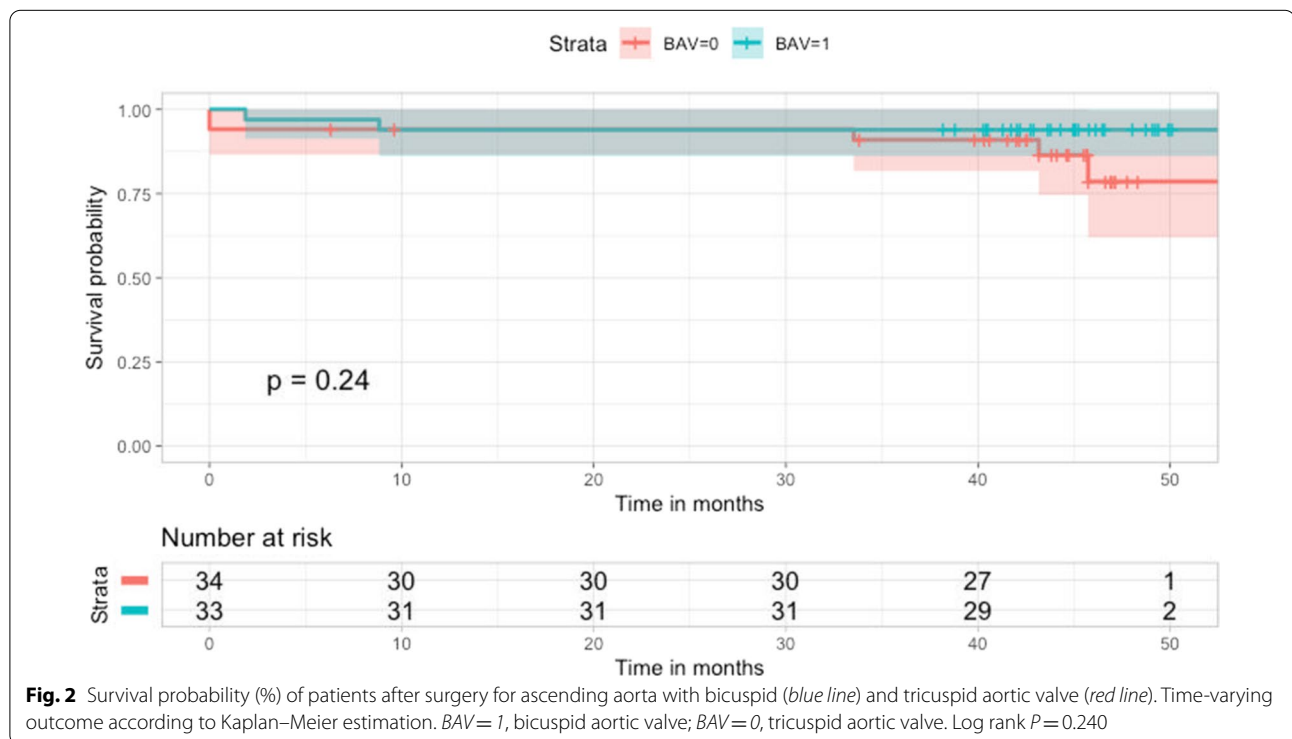


**Fig. 2** Survival probability (%) of patients after surgery for ascending aorta with bicuspid (*blue line*) and tricuspid aortic valve (*red line*). Time-varying outcome according to Kaplan–Meier estimation. *BAV = 1*, bicuspid aortic valve; *BAV = 0*, tricuspid aortic valve. Log rank *P* = 0.240

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### Survival

According to Kaplan–Meier analysis (Fig. 2), survival did not significantly differ between patients with BAV and TAV (log rank $P=0.240$). Two BAV and three TAV patients died during follow-up. Of these, two patients with TAV died during hospitalization.

### Discussion

This study shows that less prominent ascending aortic wall degeneration with increased mid-ascending aorta diameter at a relatively younger age characterized patients with BAV as compared with TAV. The Consensus statement on surgical pathology of the aorta from the Society for Cardiovascular Pathology and the Association for European Cardiovascular Pathology provided a valuable diagnostic platform to evaluate the degree of aortic wall degeneration.

Patients undergoing surgery for the ascending aorta have a multifactorial presentation of clinical symptoms [7, 13]. Despite different patient characteristics, current treatment includes surgical resection of the dilated aortic portion together with surgery for the aortic valve whenever needed. The presence of degenerative histological features would further justify resection of the frail aorta. The detailed evaluation of degenerative aortic wall variables aids objective comparison of different aortic diseases associated with aortic valve morphology and may prevent unnecessary resection in those patients without frail aortic wall.

The almost 50% incidence of BAV in patients undergoing surgery for the ascending aorta seems high in this real-life cohort. However, relatively similar or even higher numbers of aortic surgeries have been reported earlier as many BAV patients undergoing aortic valve surgery have an at least 45 mm ascending aortic diameter [14, 15], a surgical strategy that complies with current recommendations [4]. Many BAV patients received a mechanical aortic valve prosthesis since BAV patients underwent aortic surgery at a relatively early age. The asymmetry of the BAV cusps is often reflected on the configuration of the ascending aorta; the aortic diameter may considerably differ depending on different projections during CT imaging [3]. A slightly increased asymmetric aortic diameter in BAV patients may not indicate prominent and consistent aortic wall degeneration.

Risk factors for aortic dilatation in general may include hypertension, male sex, family history of aortic aneurysm, and atrial fibrillation; in contrast, diabetes, smoking and coronary artery disease are more controversial risk factors for dilatation of the ascending aorta per se [16]. In our study, hypertension and aortic wall degeneration, were statistically more frequent in TAV patients than in those with BAV. The lack of significant difference in age between the patient groups prevents from further speculation whether absolute age correlates with medial degeneration in TAV patients, as previously suggested [15].

Indeed, aortic wall degeneration- as observed by medial fibrosis, elastic fiber thinning, incremental medial degeneration and smooth muscle cell loss of the tissue- was significantly less prominent in BAV as compared with TAV patients. This importantly confirms previous studies suggesting for the degenerative features of the ascending aorta found predominantly in TAV patients [6, 8, 15]. Dilatation of the mid-ascending aorta is not solely associated with the presence of bicuspid aortic valve or increased aortic wall degeneration.

### Conclusions

Ascending aortic dilatation is not associated with increased aortic wall degeneration in BAV patients as compared with TAV patients. The Consensus statement on surgical pathology of the aorta from the Society for Cardiovascular Pathology and the Association for European Cardiovascular Pathology provides an important diagnostic methodology to evaluate the degree of degeneration of the ascending aorta and may correct misconceptions related with aortic valve configuration. This study suggests that the same surgical strategy of resection of the dilated ascending aorta may apply to both patients with either BAV or TAV.

### Limitations

This study represents a real-life single-center contemporary cohort. The limitations of this study include the small number of patients with a relatively short follow-up, and aortic wall histology is obviously only available in patients that underwent surgery.

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## Declarations

### Ethics approval and consent to participate
After institutional review board approval (Ethical Committee of the Tampere University Hospital, Tampere, Finland, R15013), the need for informed consent was waived and the study conforms to the ethical guidelines of the Declaration of Helsinki.

### Consent for publication
Not applicable.

### Competing interests
The authors declare that they have no competing interests.

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