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# Aortopathy and regurgitation in bicuspid valve patients increase the risk of aortopathy in relatives

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ABSTRACT

*Background:* Bicuspid aortic valve (BAV) is the most frequent cardiac congenital valvular disease. Although the BAV risk of first degree relatives (FDR) has been assessed (7–9%), there is little information as to the heritable risk for aortopathy.
*Objective:* Identify the specific risk for regional aortopathy in FDR with tricuspid aortic valve (TAV) of BAV patients according to their aortic phenotype and aortic regurgitation (AR).
*Methods:* Using an international consortium, BAV probands were assessed for aortopathy of the root, ascending aorta and for AR. Aortopathy was defined by the presence of segmental dilatation. The presence of segmental aortopathy and AR in BAV probands was evaluated as predictor for aortopathy in FDR with TAV.
*Results:* We identified 74 FDR related to 49 probands with aortopathy and 66 FDR related to 31 probands without aortopathy. Demographic variables were similar between proband groups. Among FDR, 16 individuals had BAV (11.4%). TAV-FDR of probands with ascending aortopathy had higher incidence of root aortopathy (18.8% vs. 3.6% $p < 0.05$) while TAV-FDR of probands with root aortopathy had higher incidence of aortopathy at all aortic segments (55%vs25%, 55%vs21%, and 4%vs29% at annulus, root and ascending respectively, $p < 0.05$ for all). Independent predictors for root aortopathy in TAV-FDR were: ascending (OR = 6.23;95%CI:1.27–30.5) and root aortopathy (OR = 9.00;95%CI:1.58–51.1) in probands; and for ascending aortopathy: root aortopathy (OR = 4.04;95%CI:1.33–12.3) and AR in probands (OR = 4.84; 95%CI:1.75–13.4).
*Conclusion:* Root and ascending aortopathy in BAV probands are strong predictors of aortopathy in their TAV-FDR. AR in BAV patients has an independent effect on the risk for ascending aortopathy in TAV-FDR.


## 1. Introduction

Bicuspid aortic valve (BAV) is the most frequent cardiac congenital valvular disease with an incidence of 0.5–2% [1]. Patients with BAV have increased risk of requiring surgery during their lifetime for aortic valve dysfunction or aortic dilatation [2,3]. First degree relatives (FDR) are at increased risk for acquiring BAV or aortopathy [4,5]. Although the risk for a FDR to have BAV has been assessed (7–9%), there is limited information as to the risk for aortopathy [6]. Previous data have shown that the incidence of aortopathy in tricuspid aortic valve (TAV) FDR of patients with BAV was 32% [4]. However, our group has previously shown that FDR of BAV probands without aortopathy have similar ascending and root aortic diameters than control patients [7]. Thus, there is no conclusive evidence regarding the aortopathy risk of FDR (of BAV patients) with TAV (TAV-FDR). We hypothesize that the aorta phenotypes and valvular function of BAV probands may associate with the risk of their TAV-FDR developing aortopathy and serve as clinical markers to identify TAV-FDR at higher risk that may require evaluation and monitoring.

Our main objective was to evaluate if the risk for aortopathy in TAV-FDR varied according to the presence or absence of aortopathy (root or ascending aorta) in their probands. Secondarily we evaluated the risk for aortopathy in TAV-FDR according to the presence of valve dysfunction in probands.

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## 2. Methods

A cross-sectional observational study from the Bicuspid Aortic Valve Consortium (BAVCon) was designed. 78 BAV probands were enrolled consecutively from January 2017 until August 2018 with local ethical review board approval and written informed consent at each institution. The overall study was approved by the Uruguay ethical review board. BAV probands were screened at each institution database and classified according to the presence or absence of aortopathy.

FDR (sons/daughters and siblings) of patients with BAV were enrolled and evaluated by each individual site. FDR were grouped according to the existence of aortopathy in their BAV proband. The proband was defined as the index identified BAV patient. Enrollment of FDR of BAV probands was 88% with no significant differences among both groups (85% with aortopathy and 93% without aortopathy).

### 2.1. Clinical evaluation

Demographic and medical history were recorded from each individual before performing the echocardiographic evaluation: age, gender, hypertension, smoking habit, diabetes, dyslipidemia, previous cardiac surgery, use of beta blockers, statins. Physical examination was performed and the following variables were obtained: height, weight, systolic arterial pressure (SAP), diastolic arterial pressure (DAP).

Glucose, creatinine, LDL and total cholesterol levels were measured at each local laboratory.

### 2.2. Echocardiography

Comprehensive transthoracic echocardiograms (TTEs) were performed in all probands and FDRs according to American Society of Echocardiography/European Association of Cardiovascular Imaging guidelines [9]. Aortic annulus, root, sino-tubular junction (STJ) and ascending aorta diameters; aortic valve phenotype, left ventricular ejection fraction, left ventricular end diastolic dimension and the presence and severity of aortic stenosis and regurgitation were measured in each patient. Aortopathy was defined as any of the following: annulus ≥ 14 mm/m$^2$; root ≥ 20 mm/m$^2$; sino-tubular junction (STJ) ≥ 16 mm/m$^2$; ascending aorta (AA) ≥ 17 mm/m$^2$ indexed by body surface area [8]. Root aortopathy was defined as a dilated aortic root diameter greater than ascending aorta diameter [10].

Aortic measurements were obtained in end-diastole and were taken as recommended by published guidelines [9,11]. Measurements were made at parasternal long-axis views at 4 levels: (1) anulus (defined echocardiographically as the hinge points of the aortic cusps); (2) sinuses of Valsalva; (3) STJ and (4) proximal ascending aorta. Measurements were made perpendicular to the long axis of the aorta using the leading edge technique in views showing the largest aortic diameters Parasternal short-axis view is systole and diastole was used to confirm the presence of BAV. Its morphology was classified in 3 types according to the fused cusps: left and right (Type 1), right and non-coronary (Type 2), left and non-coronary (Type 3). Data collection was 100%.

Intra-observer variability was calculated using intra-class correlation coefficient (ICC) in 20 patients. The observer performed measurements in the same patient with 10 days apart and was blinded to the first measurement. Intra-observer variability was extremely low with a ICC of 0,95 for the aortic annulus and aortic root, 0,94 for STJ and 0,92 for ascending aorta ($p < 0.001$).

Inter-observer variability was measured using ICC. Two blinded observers took measurements of the aortic annulus, root, STJ and ascending aorta. Variablity was very low with a ICC of 0,97 for the annulus, 0,97 for the root, 0,83 for the STJ and 0,98 for the ascending aorta.

### 2.3. Statistics

Continuous variables were expressed as mean ± standard deviation and compared using Student's *t*-test or Mann-Whitney. Categorical variables are expressed as absolute value (%) and compared using Fisher exact test or Chi square. In order to evaluate the presence of aortopathy in BAV patients as predictor for aortopathy in FDR, all variables with a $p < 0.1$ in the univariate analysis were entered into a stepwise multivariate logistic regression analysis. Its result was expressed as OR and 95% CI. All analyses were performed using SPSS version 24.0 (SPSS, Inc., Chicago, IL).

## 3. Results

The following sites from BAVCon participated in the study: Centro Cardiovascular Universitario, Uruguay; Mayo Clinic, Rochester, MN; Beth Israel Deaconess Medical Center, Boston; Heart Department, University Hospital "San Giovanni di Dio e Ruggi d'Aragona". Salerno, Italy.

From institutional databases, 78 BAV probands (30 from Hospital "San Giovanni di Dio e Ruggi d'Aragona"; 8 from Mayo Clinic; 23 from Centro Cardiovascular Universitario and 17 from Beth Israel Deaconess Medical Center.) and 140 FDRs participated in the study. Of the BAV probands, 49 (62%) had aortopathy, and of these, 22 patients had root aortopathy (28%). There was no difference in the incidence or phenotype of aortopathy in probands between valvular subtypes of BAV (Supplemental Table 1). Among FDRs, 16 individuals had BAV (11.4%) and 74 (51.4%) had aortopathy. Baseline demographic characteristics of FDRs were similar between those with and without aortopathy (Supplemental Table 2). No incidence of aortic coarctation was registered in any case.

### 3.1. Aortic dimensions

Aortic dimensions of FDRs with BAV were significantly higher at all aortic segments, except for STJ, than in FDRs with TAV (Supplemental Table 3). In 124 TAV-FDRs, aortic evaluation revealed higher indexed root diameter in individuals whose proband had any type of aortopathy (17.9 ± 2.9 vs 16.9 ± 2.5 mm/m$^2$, $p = 0.049$) (Supplemental Table 4) and significantly higher at every level (annulus, root and ascending aorta) in TAV-FDRs whose proband had root aortopathy (Supplemental Table 5).

### 3.2. Incidence of aortopathy in TAV-FDR

The incidence of aortopathy was higher at every level in TAV-FDRs whose proband had any type of aortopathy, but only statistically significant at the aortic root/sinus (19.4% vs 5.3%, $p = 0.019$) (Fig. 1). Furthermore, aortopathy was significantly more frequent at the annulus (55% vs 21.4%, $p < 0.005$), root (25% vs 3.6%, $p = 0.004$) and ascending aorta (55% vs 28.6%, $p = 0.034$) in TV-FDRs of probands with root aortopathy. TAV-FDR of probands with ascending aorta aortopathy had higher incidence of aortic root aortopathy (18.8% vs 3.6%, $p = 0.012$) (Fig. 2).

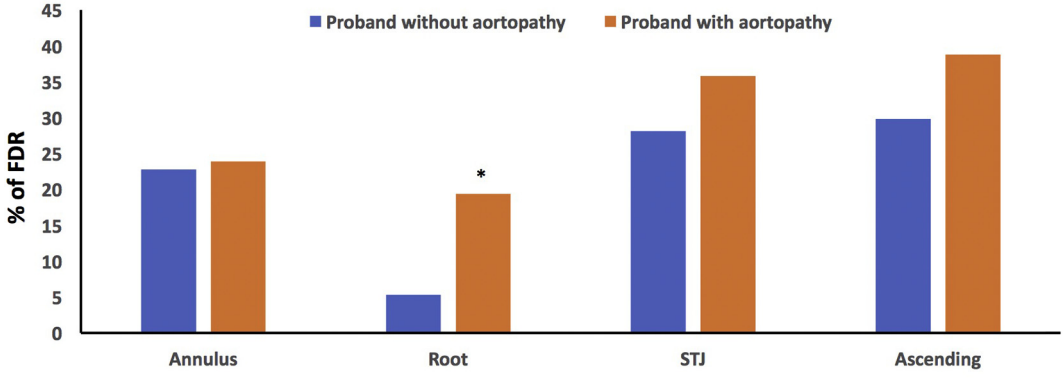


**Fig. 1.** Incidence of aortopathy in TAV-FDR of probands with and without any type of aortopathy.

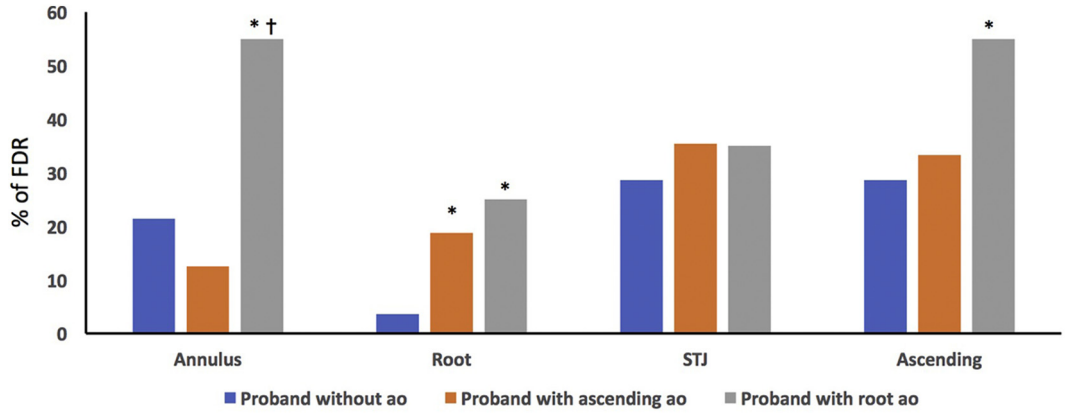


**Fig. 2.** Incidence of aortopathy in TAV-FDR of probands with annulus, root, STJ and ascending aortopathy. Ao – Aortopathy; STJ – Sinotubular junction; FDR – First degree relative. *p < 0.05 vs proband without aortopathy. †p < 0.05 vs proband with ascending aortopathy.

### *3.3. Association with AR in probands (Table 1)*

Lastly, we evaluated the association between moderate-severe aortic regurgitation (AR) in probands and presence of aortopathy in TAV-FDR. We observed that AR in probands was significantly and independently associated with ascending aortopathy in TAV-FDR (61.9% vs 29.1%, p = 0.004). No association was found between aortic stenosis in probands and aortopathy in FDR.

### *3.4. Predictors for aortopathy in TAV-FDRs (Table 2)*

Multivariate regression analysis revealed that independent predictors for root aortopathy in TAV-FDRs were: ascending (OR = 6.23; 95%CI:1.27–30.5), root aortopathy (OR = 9.0; 95%CI:1.58–51.1) in probands and weight in TAV-FDRs (OR = 0.85; 95%CI:0.78–0.92). Independent predictors for ascending aortopathy were: root aortopathy (OR = 4.04; 95%CI:1.33–12.28) and AR in probands (OR = 4.84; 95%CI:1.75–13.44); age (OR = 1.04; 95%CI: 1.01–1.07) and weight (OR = 0.88; 95%CI:0.83–0.93) in TAV-FDRs. Independent predictors for annulus aortopathy in TAV-FDRs were root aortopathy (OR = 5.12; 95%CI:1.67–15.7) in probands and weight (OR = 0.92; 95% CI:0.88–0.96) and age in TAV-FDRs (OR = 1.04; 95%CI:1.01 = 1.07). We further evaluated if the aortic dimension of BAV probes could be associated with aortopathy in FDR. Logistic regression analysis did not reveal an association (p = 0.8).

**Table 1**
Aortopathy in TAV-FDR according to AR in probands.

| | No-mild AR (103) | Mod-Sev AR (21) | p |
|---|---|---|---|
| Annulus | 22 (21.4) | 7 (33.3) | 0.237 |
| Root | 13 (12.6) | 3 (14.3) | 0.836 |
| STJ | 32 (31.1) | 8 (31.1) | 0.530 |
| AA | 30 (29.1) | 13 (61.9) | 0.004* |

AR – Aortic regurgitation. Mod-Sev – Moderate to severe. STJ – Sino-tubuar junction. AA – Ascending aorta.
* p < 0.05.

**Table 2**
Predictors for aortopathy at each aortic segment in TAV-FDR.

| | Annulus AP | Root AP | Ascending AP |
|---|---|---|---|
| Proband with ascending AP | | 6.23 (1.27–30.45) | |
| Proband with root AP | 5.12 (1.67–15.69) | 9.00 (1.58–51.11) | 4.04 (1.33–12.28) |
| Proband with AR | | | 4.84 (1.75–13.44) |
| Weight | 0.92 (0.88–0.96) | 0.85 (0.78–0.93) | 0.88 (0.83–0.93) |
| Age | 1.04 (1.00–1.07) | | 1.04 (1.00–1.07) |

Values are expressed in OR (95%CI). AP – Aortopathy. AR – Aortic regurgitation.

## 4. Discussion

The principal findings of this multicenter study are that FDRs of BAV patients have an increased risk for developing aortopathy if their relative (BAV patient) has aortopathy independently of whether the FDR inherits the BAV or not. The presence of AR, root or ascending aortopathy in probands have a differential effect on the risk for aortopathy in their TAV-FDRs.

Strong evidence supports the risk for FDR of patients with BAV to be affected by the same congenital malformation [12]. Nonetheless, evidence regarding the risk for acquiring aortopathy in the absence of BAV in FDR is lacking. Several studies have shown that FDR of BAV have increased risk of developing aortopathy but there is no specific evaluation for this risk on FDRs of BAV patients without aortopathy [4,5]. Our study adds important data to this unsolved issue.

Biner et al., showed for the first time that FDR (with TAV) of BAV patients have increased risk for developing aortopathy [4]. This study highlighted the importance for echocardiographic surveillance of aortic diameters in these individuals independently of their aortic valve characteristics. Nonetheless, most of the included FDR in Biner's study had their BAV proband with aortopathy. In contrast, Bissell et al. found no ascending aorta dilatation among FDR with TAV. Furthermore, aortic diameters in these individuals were even smaller than healthy controls. In their study, 28% of BAV probands had ascending aortopathy and none had root aortopathy [5].

Our study was designed to identify the specific risk for regional aortopathy in TAV-FDR of patients with BAV according to their aortic phenotype. We divided our FDR sample according to the presence or not of aortopathy in their probands. Both groups were similar in their basal characteristics. The incidence of BAV in FDR of patients with BAV was 11.4% which is similar to already published data [5]. In TAV-FDR, the incidence for root aortopathy was almost 20% when probands had any type of aortopathy as compared to 5% when probands did not have aortopathy.

### *4.1. Aortopathy in TAV-FDRs*

We found that there was a differential risk for acquiring aortopathy which depended on the aortic segment affected in the proband. TAV-FDR whose proband had root aortopathy was the strongest predictor for annulus, root and ascending aortopathy. When we focused our analysis in probands with ascending aortopathy, we found that their TAV-FDR had higher incidence only of root aortopathy. Root phenotype in patients with BAV has been associated with increased genetic

abnormalities and risk for hereditary transmission [13]. Such wide spectrum of genetic pathologic variants in these patients, may explain the increased risk for global aortopathy (annulus, root and ascending) in their TAV-FDR. Although studies evaluating these genetic alterations were performed in patients with BAV, our results suggest that TAV-FDR may share genetic variants which may explain the higher incidence of inherited global aortopathy.

### *4.2. Aortopathy in FDRs with TAV and AR in probands*

Several studies have suggested that BAV patients with AR have increased risk for aortopathy [14,15]. This increased risk has been correlated with molecular alterations in the aortic wall of patients with AR compared with aortic stenosis [16]. Taking into consideration the latter, we evaluated the risk for aortopathy in FDR of probands with AR. Our results showed that TAV-FDR of moderate or severe AR BAV-probands had almost 5 times greater risk of developing ascending aortopathy compared with TAV-FDR whose proband had no AR. These results were independent of the presence of aortopathy in the proband. During the embryologic origin of the ascending aorta and aortic valve, the migration and differentiation of cells from the neural crest have an essential role for the normal development [17,18]. Taking into account their shared embryologic origin, the association between AR in the probands and ascending aortopathy in their FDR could potentially be explained as an inherited molecular alteration in the neural crest cells.

## 5. Limitations

Patients were evaluated with transthoracic echocardiography. CT scan or MRI are considered the gold standard diagnostic modalities, which was difficult to perform due to the multicentric nature of the study. However, in comparison to CT, echocardiography tends to underestimate aortic measurements, in particular the aortic root of BAV patients [19], such that with CT, the differences found could have been even greater but not smaller.

Although it is well known that the mechanisms of AR in BAV are cusp prolapse and annular-root-siontubular junction dilatation, information regarding AR mechanism was not collected during the echocardiographic evaluation.

The number of BAV FDRs is small in order to perform multivariate regression analysis and evaluate predictors for aortopathy exclusively in this group of individuals.

Due to the characteristics of our study and our group (Bicuspid aortic valve consortium), there is selection bias since many BAV patients go undiagnosed throughout their lifetime, and many family members of diagnosed BAV patients also go undiagnosed. Further, there may be other patients diagnosed with BAV at each institution whose family was not evaluated or whose family was evaluated by other physicians.

## 6. Conclusion

Evaluation of risk for segmental aortopathy in FDR with TAV according to aortopathy phenotype and AR in probands has not been previously studied. We were able to show that aortopathy (especially root aortopathy) in BAV patients were strong predictors for aortopathy in their FDR. In addition, AR in BAV patients was shown to have an independent effect on the risk for ascending aortopathy in their FDR. Therefore, our study supports the case for echocardiographic evaluation of all FDR of BAV with aortopathy and/or significant AR.

## Disclosures

None.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2019.03.031.

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