

## **Inherited aortopathy assessment in relatives of patients with a bicuspid aortic valve**

**Short title:** Inherited aortopathy assessment in BAV relatives

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### **Abbreviations**

BAV = bicuspid aortic valve  
BSA = body surface area  
CMR = cardiovascular magnetic resonance  
FDR = First degree relative  
HV = Healthy volunteers

MMP = matrix metallo-proteinases  
MRSD = maximum rate of systolic distension  
TAV = tricuspid aortic valve  
WSS = Wall shear stress

## **Background**

Bicuspid aortic valve disease (BAV) is commonly associated with aortopathy which may be in part hemodynamically mediated (1). BAV is known to cluster in families (up to 25% family members affected) (2). Due to this increased incidence in first degree relatives (FDR), many clinicians will screen these. Furthermore, FDR of BAV patients might also have aortic dilation, despite a tricuspid aortic valve (TAV) (3, 4). We therefore examined FDR for evidence of aortic dysfunction. We also examined BAV fusion type in FDR as animal models suggest that fusion type may be genetically determined (5).

## **Methods**

57 BAV patients and 54 healthy volunteers (HV) were recruited from our previous study (1). 142 patient FDR were also enrolled. 14 additional FDR were unable to be contacted or declined. The study was approved by the West Berkshire ethics committee and written informed consent was obtained.

Participants aged >6 years underwent anatomical and functional aortic CMR imaging (n=117) as described (1) including valve function, aortic dimensions, distensibility and maximum rate of systolic distension (MRSD). All BAV patients, HV and 10 FDR from cluster families who had at least 2 identified BAV patients also underwent 4D flow assessment as described (1). Participants < 6 years and claustrophobic participants underwent echocardiography for aortic valve morphology assessment (n=25).

Fasting peripheral venous blood samples were analyzed for matrix metallo-proteinases (MMP) 2 and 9 using R&D Systems ELISA kits. Data were analyzed with Students t-test for comparison of two groups and Anova was used for comparison of the three groups. A p-value < 0.05 was considered significant. No correction was made for observations clustered within families.

## Results

Of 142 relatives, 17 (12%) had a BAV which spread over 10 families (18% of recruited families). Concordant pattern of cusp fusion was only seen in 5 families (Figure 1a). Right-left coronary cusp fusion pattern BAV was observed in 77% and right-non-coronary leaflet fusion pattern in 19% of cases, similar to the incidence in the general BAV population. Variable degree of fusion was observed in 2 families.

The ascending aorta was assessed in 117 FDR with CMR. Index BAV patients had ascending aortic dilation in 16 cases (28%). No patient had aortic root dilation. 5 FDR (33%) with a BAV showed concomitant ascending aortic dilation. In contrast, no FDR with a TAV had ascending aortic dilation. The TAV was normally functioning in all FDR, average age was  $39\pm 19$  (range 7-78) and mean pulse pressure  $57\pm 1.14$  mmHg.

Compared to HV comparable in sex, age and blood-pressure, all FDR had normal aortic diameters in the descending aorta (DA) ( $11.1\pm 1.6$  vs  $10.9\pm 1.6$  mm). The sinuses, sinotubular junction (STJ) and ascending aorta (AA) were even significantly smaller (HV vs FDR: Sinuses  $16.8\pm 2.2$  vs  $15.5\pm 1.9$  mm,  $p<0.05$ ; STJ  $15.1\pm 2.1$  vs  $13.8\pm 1.8$  mm,  $p<0.05$ ; AA  $15.3\pm 2.2$  vs  $14.4\pm 2.1$  mm,  $p<0.05$ ). Aortic function was also comparable (HV vs FDR: AA distensibility  $4.84\pm 3.28$  vs  $5.29\pm 3.64$  1/mmHg; AA MRSD  $0.22\pm 0.13$  vs  $0.23\pm 0.13$  %/ms; DA distensibility  $7.43\pm 3.65$  vs  $7.39\pm 3.96$  1/mmHg; DA MRSD  $0.27\pm 0.07$  vs  $0.28\pm 0.11$  %/ms) (**Figure 1B**).

4D flow measurements in 9 FDR were similar to healthy volunteers (HV vs FDR Systolic flow angle  $7.8\pm 5.4$  vs  $8.8\pm 4.2$  °; absolute rotational flow  $3.6\pm 3.3$  vs  $6.5\pm 8.2$  mm<sup>2</sup>/s; circumferentially averaged mean systolic wall shear stress  $0.59\pm 0.17$  vs  $0.69\pm 0.21$  N/m<sup>2</sup>) (Figure 1a). Both MMP2 and MMP9 concentrations in BAV patients and FDR were similar to healthy

volunteers (BAV vs HV vs FDR: MMP2  $37.6 \pm 5.7$  vs  $36.4 \pm 5.8$  vs  $35.7 \pm 5.8$  pg/L,  $p=0.40$ ; MMP9  $43.4 \pm 22.1$  vs  $36.0 \pm 16.6$  vs  $40.0 \pm 22.0$  pg/L,  $p=0.32$ ).

## **Discussion**

Our cohort revealed a similar percentage of BAV in FDR compared to echocardiography studies, which supports the use of echocardiography for screening. Our BAV population did not include patients with the dilated aortic root phenotype, likely a distinct genetic entity. This may explain the lower incidence of aortic dilation in FDR observed here. The variance in the degree of fusion suggests that partial fusion is a mild form of BAV and if, performing family screening for BAV, this may even be indicated in patients with mild fusion.

Only 16/57 of the index patients had aortic dilation. Of the 10 families with at least one FDR affected with BAV, only 2/10 index patients had aortic dilation who would have been eligible for family screening for aortopathy under the most recent AHA guidelines, which suggests that FDR of all BAV patients should be screened irrespective of presence of aortic dilation. Importantly once a TAV is confirmed, the lack of evidence for aortopathy in FDR with TAV suggests that further screening may not be necessary. However, this may be different in the rarer, genetically distinct aortic root phenotype BAV, where serial family screening for aortopathy may still be indicated.

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## **Figure Legend**

Figure A: Discordant inheritance of BAV fusion type with flow profiles: RN-BAV = right-non-coronary cusp fusion pattern BAV; RL-BAV = right-left coronary cusp fusion pattern BAV; normal flow in FRD with TAV: right-handed helix in FDR with BAV. B: Normal aortic diameters and distensibility in HV and FDR with TAV