

Endothelial Dysfunction and Inflammatory Activation in Patients with
Bicuspid Aortic Valves

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Matthew John Chapman

Student ID: 1218491

Supervisor Professor John Horowitz, Dr Than Ha Nguyen

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Abstract

Bicuspid aortic valve (BAV) is found to affect 1-2% of the Western population and represents the most common congenital cardiac disorder. BAV is associated with valvular dysfunction and aortopathy and its main clinical significance lies in its association with increased variable rates of progressive valve calcification and/or dilatation of the ascending aorta. Often significant aortic stenosis and/or regurgitation ensue. Sometimes BAV is associated with other forms of congenital heart disease particularly that of coarctation of the aorta. Furthermore the natural history of BAV often results in the need for extensive, corrective valvular and/or aortic surgery before the age of 60. Both inflammatory activation and endothelial dysfunction have been considered as potential modulators of these changes; however the predominant pathophysiological bases are unclear. Data from endothelial nitric oxide synthase (eNOS) $-/-$ mice and aortic biopsies in patients undergoing surgery suggest an association between eNOS deficiency and BAV though detailed evaluation of NO signalling in BAV is lacking. Furthermore, valvular and aortic degeneration varies widely among individuals with BAV. Both aortic stenosis and aortic dilatation in the context of BAV have shown to be associated with an inflammatory process. Therefore the relative impacts of inflammatory infiltration and endothelial dysfunction on valvular function and aortic dilatation in a cohort of patients with BAV were examined.

Methods:

A case-control study of patients with BAV was performed together with a multivariate analysis within the BAV group in order to identify factors associated with:

- (a) Development of significant valvular disease.
- (b) Dilatation of the ascending aorta.
- (c) Differential valve: aortic disease.

BAV patients and controls underwent evaluation of endothelial function with flow mediated dilatation (FMD) and plasma concentrations of asymmetric dimethylarginine (ADMA). Correlations with inflammatory markers, myeloperoxidase (MPO) and high sensitivity C-reactive protein (HsCRP), endothelial progenitor cell counts (EPC) were also examined. Morphological and physiological assessment of the valve and ascending aorta was performed with transthoracic echocardiography (TTE) and magnetic resonance imaging (MRI).

Results:

Patients with BAV (n=43) and controls (n=25) were age and gender-matched. FMD was significantly lower in the BAV patient group ($7.85\% \pm 3.48\%$ vs $11.58\% \pm 3.98\%$, $p = 0.001$) and these differences were age-independent on ANOVA. Within the BAV cohort, upon

multivariate analysis, correlates of peak aortic valve velocity (peak AV_{max}) were ADMA and MPO plasma concentrations (both $p < 0.01$), while increasing age was noted as an independent correlate of ascending aortic diameter ($p < 0.05$). Furthermore, both low FMD and inflammatory activation were multivariate correlates of selectivity for valvular over aortic disease.

Conclusions:

While BAV is associated with endothelial dysfunction evident from low FMD and inflammatory activation (specifically MPO release), its structural impact primarily acts on the integrity of the valve, rather than the aortic structure. Confirmatory therapeutic interventions should be directed at reversal of these pathophysiological changes as well as slowing of disease progression.

Declaration

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Publication / presentation list

- 2014** Chapman MJ, Henthorn R, Surikow S, Zoontjens J, Stocker B, Mclean T, Zeitz CJ. Rheumatic mitral valve disease diagnostic tissue quantification (backscatter) *Euro Echo-Imaging* 2014 abstract 90680. Vienna Austria.
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- 2012** NEIL CJ, Nguyen TH, Mahadavan G, Chapman MJ, Kucia AM, Stansborough J, Zeitz CJ, Beltrame JF, Horowitz JD. LV functional recovery from Tako-Tsubo cardiomyopathy is incomplete after 3 months: evidence from 2D speckle-tracking echocardiography. *European Heart Journal* 2012 33 (Abstract Supplement), 480-481.
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- 2011** Sverdlov AL, Ngo DTM, Chapman MJ, Ali OA, Chirkov YY, Horowitz JD: The pathogenesis of aortic stenosis: not just a matter of wear and tear. *Am J Cardiovascular Disease* 2011; 1(2):185-199.
- Sverdlov AL, Ngo DTM, Chan WP, Chapman MJ, Chirkov YY, Gersh BJ, McNeil JJ, Horowitz JD: Progression of Early Aortic Valve Disease: Are ACE Inhibitors Protective? Scientific sessions American Heart association; 2011 Nov 12-16; Orlando Florida. Abstract 12974.
- Ali OA, Chapman MJ, Chirkov YY, Horowitz JD Physiological correlates of progression of aortic and valve disease in patients with type I bicuspid aortic valve. *European Journal Echocardiography* 2011. Abstracts Supplement December 2011. P253.

Presentations Conferences

2014 European echocardiography and other imaging modalities. Vienna Austria 3-7 December 2014. Poster presentation. **Rheumatic mitral valve disease diagnostic tissue quantification (backscatter).**

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Abbreviations

Adenosine 5`-diphosphate	ADP
Angiotensin II	ANGII
Angiotensin converting enzyme	ACE
Angiotensin receptor blockers	AT1
Aortic valve	AV
Aortic valve replacement	AVR
Aortic sclerosis	Asc
Ascending aorta	AscAO
Asymmetric dimethyl arginine	ADMA
Bicuspid aortic valve	BAV
Cardiac magnetic resonance imaging	CMRI
Colour flow doppler	CFM
Continuous wave	CW
Cyclic guanosine monophosphate	cGMP
Electrocardiogram	ECG
Endothelial dysfunction	ED
Flow mediated dilatation	FMD
High sensitivity C-reactive protein	HsCRP
Inflammatory activation	IA
Left ventricular	LV
Low density lipoproteins	LDL's
Left ventricular outflow tract	LVOT
Mast cell	MC
Matrix metalloproteinases	MMP's

Myeloperoxidase	MPO
Nicotinamide adenine dinucleotide phosphate-oxidase	NADPH
Nitric oxide	NO
Pulsed wave	PW
Parasternal long axis view	PLAX
Parasternal short axis	PSAX
Sodium nitroprusside	SNP
Thioredoxin Interacting Protein	TXNIP
Trans-aortic valve implantation procedures	TAVI
Transforming growth factor β_1	TGF β_1
Tricuspid aortic valve	TAV
Two dimensional	2D
Valvular endothelial cells	VECs
Velocity time interval	VTI