Endothelial Dysfunction and Inflammatory Activation in Patients with Bicuspid Aortic Valves

Master of Clinical Science

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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% ± 3.48% vs 11.58%± 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

I certify that this work contains no material which has been accepted for the award of any other degree or diploma in my name, in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. In addition, I certify that no part of this work will, in the future, be used in a submission in my name, for any other degree or diploma in any university or other tertiary institution without the prior approval of the University of Adelaide and where applicable, any partner institution responsible for the joint-award of this degree.

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Publication / presentation list

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Presentations Conferences

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2011 European echocardiography and other imaging modalities. Budapest Hungary 7-10 December 2011. Moderated poster presentation. **Physiological correlates of progression of aortic and valve disease in patients with type I bicuspid aortic valve.**

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	$TGF_{\beta 1}$
Tricuspid aortic valve	TAV
Two dimensional	2D
Valvular endothelial cells	VECs
Velocity time interval	VTI