Endothelial Dysfunction and Inflammatory Activation in Patients with Bicuspid Aortic Valves

Master of Clinical Science

Faculty of Health Sciences: Discipline of Medicine

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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\textsubscript{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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Signed: Matthew John Chapman

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Publication / presentation list


Presentations Conferences


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
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<td>Myeloperoxidase</td>
<td>MPO</td>
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<td>Nicotinamide adenine dinucleotide phosphate-oxidase</td>
<td>NADPH</td>
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<td>Nitric oxide</td>
<td>NO</td>
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<tr>
<td>Pulsed wave</td>
<td>PW</td>
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<td>Parasternal long axis view</td>
<td>PLAX</td>
</tr>
<tr>
<td>Parasternal short axis</td>
<td>PSAX</td>
</tr>
<tr>
<td>Sodium nitroprusside</td>
<td>SNP</td>
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<tr>
<td>Thioredoxin Interacting Protein</td>
<td>TXNIP</td>
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<tr>
<td>Trans-aortic valve implantation procedures</td>
<td>TAVI</td>
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<tr>
<td>Transforming growth factor β₁</td>
<td>TGFβ₁</td>
</tr>
<tr>
<td>Tricuspid aortic valve</td>
<td>TAV</td>
</tr>
<tr>
<td>Two dimensional</td>
<td>2D</td>
</tr>
<tr>
<td>Valvular endothelial cells</td>
<td>VECs</td>
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<tr>
<td>Velocity time interval</td>
<td>VTI</td>
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