Complex Heart Valve Disease: Functional Capacity and Natriuretic Peptides predict outcomes in mixed and multiple heart valve disease.

Dr Naylin Bissessor

Cardiologist

FRACP (Australia), MBChB, ECFMG

School of Medical Sciences,

Faculty of Medicine, Department of Cardiology,

Griffith University

Submitted in fulfilment of the requirements of the degree of Doctor of Philosophy

Submission date: October 2010
Dedicated to my wife Sandira and children Tyla and Kelan for their, love, understanding and sacrifice made for my career in medicine...
**Synopsis**

Chronic mixed and multiple heart valve disease constitutes a complex group of cardiac pathologies that are prevalent world wide causing significant mortality and morbidity. The American Heart Association and the European Society of Cardiology concede in their guidelines that little data exists in the international literature on this important subject. Patients tend to adopt a sedentary lifestyle in order to cope with this illness and avoid symptoms causing a steady decline in functional capacity. A physically active lifestyle is imperative for a good quality of life and cardiovascular wellness. Significant functional impairment through disease portends an adverse prognosis.

Functional capacity impairment can be objectively measured through formal cardiopulmonary exercise testing through determining the peak oxygen consumption (peakVO2). Exercise intolerance may suggest significant underlying symptoms especially in asymptomatic or mildly symptomatic states with severe heart valve lesions. The onset of symptoms is central to the decision to operate and surgical valve replacement. The peakVO2 measurement is the international gold standard of functional aerobic capacity and is widely used in heart failure and cardiac transplant to predict prognosis and outcome. The role of peakVO2 has not been evaluated in complex heart valve disease.

The haemodynamic complexities of concomitant stenosis and regurgitation cause significant myocardial wall stress. There is release of natriuretic peptides from the myocardial cells in response to myocardial pressure and
volume overload. The resting serum B-type natriuretic peptide (BNP) is measured in a simple blood test and is indicative of the myocardial strain. BNP is fast establishing itself as a prognostic marker of outcome in heart failure, coronary artery disease and single aortic and mitral valve disease. BNP has not been investigated in mixed and multiple valve disease where myocardial wall stress is increased through several volume and pressure related mechanisms.

The research incorporated in this thesis involves the design, study and follow up of a cohort with severe complex heart valve disease referred for the timing of surgery. The predictors of outcome were examined and correlations with functional capacity were made using parameters from the presurgical baseline assessment of asymptomatic and mildly symptomatic patients.

Forty-five surgical candidates (n=45) with severe stenosis and regurgitation of the heart valves disease with asymptomatic or mild symptoms (New York heart association NYHA Class $\leq$ II) were evaluated at presentation. All subjects gave written consent and went on to have a detailed clinical history and physical examination, echocardiographic assessment, resting blood tests (including BNP) and cardiopulmonary exercise testing. Inclusion criteria included the presence two or more heart valve lesions of greater than moderate severity. Patients were excluded if they had $\geq$ NYHA functional class III since this group would need urgent surgery and exercise testing would be inappropriate. Advanced comorbidity that would preclude surgery, significant coronary artery disease, respiratory and renal disease were also exclusion criteria.
Resting measurements of B type natriuretic peptide (BNP) were taken. Functional capacity was assessed through formal cardiopulmonary exercise testing (CPEX) with resting spirometry. The patients were then followed up for nineteen months for outcomes. The study outcomes included the following: valve replacement surgery, major adverse cardiac events, heart failure, death, new arrhythmia and hospitalization (other than for valve surgery). The decision to operate was made independently by members of the cardiosurgical conference who were blinded to BNP and CPEX data.

The simple resting blood test BNP proved to be a sensitive and specific prognostic marker of outcome. The peakVO2 again confirmed its role as a powerful prognostic marker of outcome in complex heart valve disease. Resting BNP combined with resting spirometry were indicators of impaired functional capacity.

Three published clinical papers from this thesis have made a unique scientific contribution to the literature. Journals that have peer reviewed and published this work included the prestigious Journal of Heart Valve Disease, Journal of Congestive Heart Failure and Kardiologica. A fourth review paper on the clinical relevance of BNP, favours publication by the Journal of Heart Valve disease pending minor revisions. Aspects from this thesis were formally presented in the International Society of Heart valve disease in Berlin Germany in June 2009. Posters of each publication were on display at CSANZ 2009, Sydney, Australia; CCT 2009, Kobe, Japan and CRT 2009 Washington DC.
Ethics, disclosures, funding and originality statement

This work has not previously been submitted for a degree or diploma in any university. To the best of my knowledge and belief, the thesis contains no material previously published or written by another person except where due reference is made in the thesis itself. The research and publications in this PHD thesis constitutes my original work. Prior to commencement of this research study regional ethics committee approval and institutional board review endorsement was obtained. All patients gave informed written consent after receiving a detailed explanation of the study (via an interpreter when necessary). The study was funded by the National Heart Foundation and Greenlane Education Research fund. The candidate is the first author of all publications in this thesis which have been peer reviewed by international cardiology journals. There are no other disclosures.
<table>
<thead>
<tr>
<th>Chapter</th>
<th>Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Hypothesis, Executive Summary and Introduction</td>
</tr>
<tr>
<td>2</td>
<td>Functional Capacity testing in heart valve disease</td>
</tr>
<tr>
<td>3</td>
<td>The Development of Natriuretic Peptides in Heart Failure</td>
</tr>
<tr>
<td>4</td>
<td>The role of B-type-Natriuretic Peptide (BNP) and Exercise testing in Aortic Valve Stenosis</td>
</tr>
<tr>
<td>5</td>
<td>The role of B-type-Natriuretic Peptide (BNP) and Exercise testing in Chronic Mitral Valve Regurgitation</td>
</tr>
<tr>
<td>6</td>
<td><em>Accepted for publication</em> The basic science and clinical relevance of B-type-natriuretic peptide in valve disease</td>
</tr>
<tr>
<td>7</td>
<td><em>Publication</em> The role of B-type-Natriuretic Peptide (BNP) in complex mixed and multiple heart valve disease</td>
</tr>
<tr>
<td>8</td>
<td>Review of Cardiopulmonary exercise testing in heart valve disease</td>
</tr>
<tr>
<td>9</td>
<td><em>Publication</em> Presurgical functional capacity evaluation in complex heart valve disease using peak oxygen consumption (peakVO2)</td>
</tr>
<tr>
<td>10</td>
<td><em>Publication</em> Complimentary roles for N-terminal- pro-B-type Natriuretic Peptide (NTproBNP) and spirometry in predicting functional capacity in complex heart valve disease</td>
</tr>
<tr>
<td>11</td>
<td>Conclusion and future direction of research</td>
</tr>
</tbody>
</table>
Acknowledgements

The patients who consented to be part of the research

Griffith University School of Medicine: PHD opportunity, enrolment, support and examination. 2010

Allison Wong and David Liu at UCLA, Los Angeles California for their editorial assistance and scientific contribution 2010

PHD supervisor Prof Rohan Jayasinghe for initiating my cardiology career and scientific review of my thesis. 2007-2010

Allison Gooch for administration and support Department of Cardiology Gold Coast Hospital 2007-2010

Professor Karl Wasserman, Father of cardiopulmonary exercise testing for scientific review of thesis, UCLA- Harbour, 2010

Prof Laurie Howes, Luke Shanahan for scientific Review of clinical papers, Griffith University research Department 2009

Dr Ralph Stewart, Prof John Kolbe, Prof Harvey White, Irene Zing, Statistics Greenlane Clinical Centre Auckland, New Zealand 2006

Prof YK Seedat, Prof DP Naidoo, for early clinical echocardiography and research skills, Nelson Mandela Medical School, Durban, South Africa 1991

Prof Tim Noakes for training in post-graduate sports medicine and functional capacity assessment University of Cape Town. 1993-1996

Heart foundation and Greenlane Education Trust fund Dr Warren Smith. 2006

Lastly my mother Dorothy, sister Melanie, late father Sanjith, late brother Ashwin for a lifelong family culture of academic achievement, belief and divine inspiration...