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

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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 peak VO2 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.
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Chapter 1

Hypothesis, executive summary and introduction
Hypothesis, executive summary and introduction

Hypothesis

Traditionally imaging has been inadequate as a single modality in evaluating complex (mixed and multiple) heart valve disease, however, the clinical assessment and prognosis of such patients can be optimised using a multimodality approach involving natriuretic peptides, spirometry and functional capacity assessment.

Testing the hypothesis

In this thesis a novel multimodality approach is used to test this hypothesis in patients with mixed and multiple valve disease. Current methods use the clinical findings from the history and physical examination in conjunction with echocardiography to determine the timing of surgery and predict the overall prognosis. This may be adequate for advanced symptomatic disease since these patients require valve replacement surgery promptly. However in the modern era valve disease is often diagnosed earlier due an increased accessibility of medical care infrastructure (especially echocardiography) in first and second world countries. The early detection of moderate to severe valve disease on echocardiography in patients who are asymptomatic or have mild symptoms raises the question of the timing of surgery. The risks of early surgery versus the benefit are an ongoing enigma. The “watchful waiting” approach carries a higher underlying risk for patients with masked symptoms due to a sedentary lifestyle.

A multimodality approach is used in this study to comprehensively assess presurgical valve disease patients at baseline presentation. This approach combines the standard clinical evaluation and, routine echocardiography together with resting biomarkers and cardiorespiratory functional capacity testing. The results are used to determine the predictors of outcome in patients with severe mixed and multiple valve disease.
Executive Summary

A brief synopsis of the methodology and salient findings of the study is discussed below. The facts and figures with a detailed review of each aspect are explained in appropriate subsequent chapters.

The methodology involved an evaluation of forty-five patients (n=45) with complex (mixed and multiple) heart valve disease who were surgical candidates with asymptomatic or mild symptoms (New York heart association NYHA Class ≤ II). Inclusion criteria included the presence two or more heart valve lesions (stenosis or regurgitation) greater than moderate severity. Exclusion criteria incorporated any advanced comorbidity that would preclude surgery, significant coronary artery disease, respiratory and renal disease. Patients generally had at least one severe lesion with up to two other moderate valve lesions on formal echocardiography to meet the study definition of significant mixed or multiple heart valve disease.

Resting measurements of B type natriuretic peptide (BNP) a biomarker of outcome in single valve disease were taken. BNP is released by the heart in response to pressure and volume overload of the ventricle. Functional capacity was assessed through formal cardiopulmonary exercise testing (CPEX) with spirometry. CPEX measures the peak oxygen consumption (peakVO2) the gold standard of cardiovascular functional aerobic capacity. The patients were then followed up for a median period of nineteen months for outcomes. The decision to operate was made independently of BNP and CPEX data. 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). Statistical methods including multivariable regression were used to assess the predictors of outcome.
BNP (a simple resting blood test) proved to be a sensitive predictor of outcome possibly indicating the impact and effect that chronic pressure and volume overload has on the ventricle. The strongest predictors of outcome were obtained from the CPEX measurements and included the peak VO2 and ventilatory efficiency (VE/VCO2). Impaired functional capacity (reduced peak VO2) a proven indicator of prognosis in heart failure and heart transplant once again proved to be a marker of outcome in complex mixed and multiple heart valve disease. Resting BNP and resting spirometry also proved to be an indicator of impaired functional capacity. The baseline resting measurements can be conducted in any clinical setting (urban or remote) which can be used as an adjunct to the clinical assessment and echocardiogram.

Conclusion

In patients with chronic complex mixed and multiple valve disease the role of functional capacity evaluation is critical to the prognosis and timing of valve surgery. Baseline resting BNP and spirometry are useful predictors of impaired functional capacity and prognosis and have a role as adjuncts to the clinical and echocardiographic assessment of mixed and multiple heart valve disease. Further studies in this area are required to firmly establish these predictors across the spectrum of this complex group of patients.

Introduction

Valvular heart disease is a common condition which carries a serious economic burden. (1) The onset of symptoms including shortness of breath is an indication for surgical valve replacement. (1) Mixed valve disease is a combination of stenosis or incompetence co-existing in the same valve. Multiple valve disease is the involvement of
more than one valve by stenosis, or incompetence or both. The mixed and multiple valve
disease is commonly referred to as complex valve disease.(2) The common aetiologies
include rheumatic heart disease and myxomatous valve degeneration.(3) This condition
usually runs a chronic course with concomitant deconditioning a frequent occurrence.(1)
The timing of surgery is difficult in complex valve disease since symptoms may be vague
and lifestyle sedentary despite severe valve lesions detected on echocardiogram.(1,3)
This results in a surreptitious decline in functional capacity which impacts on morbidity,
long term prognosis and quality of life.(1,3)

The guidelines from the American heart association and American College of Cardiology
(AHA/ACC) make the following comments on complex valve disease: “Remarkably few
data exist to objectively guide the management of mixed valve disease. The large number
of combined haemodynamic disturbances (and their varied severity) yields a large
number of potential combinations to consider, and few data exist for any specific
category.” (1)

The management of complex valve disease is multifaceted. Each patient must be
considered individually, and management of the condition must be based on
understanding the potential derangements in haemodynamics and LV function and the
probable benefit of medical versus surgical therapy.(1,3) The focus of this thesis is to
contribute to the international literature on the subject of complex valve disease prognosis
through assessing functional capacity and examining the role of the biomarker
(NTproBNP).
**Pathophysiology**

In mixed mitral or aortic valve disease, one lesion usually predominates over the other. (1) Left ventricular remodelling is expected. The pathophysiology resembles the dominant lesion. (1) In mixed aortic valve disease should aortic stenosis (AS) be the dominant lesion, the pathophysiology and management should follow the management of single valve AS. The left ventricle develops concentric hypertrophy due to pressure overload rather than dilatation. (4) If the concomitant regurgitation is more than mild, volume and pressure overload coexist which may result in pulmonary congestion. (4) The timing of aortic valve replacement AVR is based on symptomatic status. (4) The effect is that neither lesion by itself might be considered severe enough to warrant surgery, but both together produce substantial haemodynamic compromise that necessitates intervention. (1) This mixed lesion causes significant strain on the left ventricle. (4) This results in release of natriuretic peptides to stimulate diuresis. (5) The effect on stroke volume reduces overall blood supply to the muscles and impairs functional capacity. (6)

**Diagnosis**

The diagnosis is usually based on a thorough history, physical examination and an echocardiogram. (3) The severity of the lesion is assessed using mainly non invasive echocardiographic criteria from the table below. (1) The decision to operate is based largely on symptomatic status (NYHA class) and cardiac function. (1,3)

**Two-Dimensional and Doppler Echocardiographic Studies.**

Two dimensional echocardiography is the main modality used to assess the severity of the lesions. (7) Chamber dimensions, doppler flow analysis, left ventricular volumes and parameters of diastolic and systolic function are measured to assess the severity and
effect on the heart.(7) The ACC/AHA have produced criteria that are used to assess the severity of each type of lesion (Table 1 below).(1) Left ventricular dimensions are important in assessing the dominant lesion (stenotic versus regurgitant), and impacts on in management.(1,3) Doppler flow assessment of the aortic valve and mitral valve with mixed disease should provide a reliable estimate of the transvalvular mean gradient; however, there may be a significant discrepancy between the Doppler-derived maximum instantaneous gradient and haemodynamic catheter peak gradient with mixed aortic valve disease. (7)

Table 1. Classification of the Severity of Valve Disease in Adults (adapted from Bonow et al. JACC Vol. 48, No. 3, 2006 ACC/AHA Practice Guidelines August 1, 2006:e1–148)

<table>
<thead>
<tr>
<th>Aortic Stenosis</th>
<th>mild</th>
<th>moderate</th>
<th>severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jet velocity (m/s)*</td>
<td>&lt; 3</td>
<td>3-4</td>
<td>&gt;4</td>
</tr>
<tr>
<td>Mean Gradient (mmHg)</td>
<td>25</td>
<td>25-40</td>
<td>&gt;40</td>
</tr>
<tr>
<td>Valve area (sq. cm)</td>
<td>&gt;1.5</td>
<td>1.0-1.5</td>
<td>&lt;1.0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mitral stenosis</th>
<th></th>
<th></th>
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<tbody>
<tr>
<td>Mean gradient (mmHg)</td>
<td>&lt;5</td>
<td>5-10</td>
<td>&gt;10</td>
</tr>
<tr>
<td>PASP (mmHg)</td>
<td>&lt;30</td>
<td>30-50</td>
<td>&gt;50</td>
</tr>
<tr>
<td>Valve area (sq.cm)</td>
<td>&gt;1.0</td>
<td>1-1.5</td>
<td>&lt;1.0</td>
</tr>
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</table>
**Aortic regurgitation**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angiographic grade</td>
<td>1</td>
<td>2</td>
<td>3-4</td>
</tr>
<tr>
<td>Colour doppler</td>
<td>&lt;25%</td>
<td>25-60%</td>
<td>&gt; 60%</td>
</tr>
<tr>
<td>Central jet width</td>
<td>of LVOT</td>
<td>of LVOT</td>
<td>of LVOT</td>
</tr>
<tr>
<td>Vena contracta</td>
<td>&lt;0.3</td>
<td>0.3-0.6</td>
<td>&gt; 0.6</td>
</tr>
<tr>
<td>Regurgitant volume (ml)</td>
<td>&lt;30</td>
<td>30-59</td>
<td>≥ 60</td>
</tr>
<tr>
<td>Regurgitant fraction (%)</td>
<td>&lt;30</td>
<td>30-50</td>
<td>≥ 50</td>
</tr>
<tr>
<td>Regurgitant orifice area (sq cm)</td>
<td>&lt;0.1</td>
<td>0.1-0.29</td>
<td>≥ 0.30</td>
</tr>
<tr>
<td>Ventricular size</td>
<td></td>
<td></td>
<td>increased</td>
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</table>

**Mitral regurgitation**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angiographic grade</td>
<td>1+</td>
<td>2+</td>
<td>3-4+</td>
</tr>
<tr>
<td>Jet area</td>
<td>Small central</td>
<td>Moderate size</td>
<td>Large jet</td>
</tr>
<tr>
<td>Colour Doppler</td>
<td>&lt;4 sqcm</td>
<td>&lt;20% LA area</td>
<td>&gt;40% LA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>20-40% LA area</td>
<td>Swirling</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Wall impinging</td>
</tr>
<tr>
<td>Vena Contracta width (cm)</td>
<td>&lt;0.3</td>
<td>0.3-0.69</td>
<td>≥ 0.70</td>
</tr>
<tr>
<td>Regurgitant Volume (ml)</td>
<td>&lt;30</td>
<td>30-59</td>
<td>≥60</td>
</tr>
<tr>
<td>Regurgitant fraction %</td>
<td>&lt;30</td>
<td>30-49</td>
<td>≥ 50</td>
</tr>
<tr>
<td>Regurgitant orifice area EROA (sq cm)</td>
<td>0.2</td>
<td>0.2-0.39</td>
<td>≥0.40</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>-----</td>
<td>--------</td>
<td>------</td>
</tr>
<tr>
<td>Left atrial size</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV size</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| **Tricuspid Stenosis**         |     |        |      |
| Valve area (sq cm)             |     | <1     |      |

| **Tricuspid regurgitation**    |     |        |      |
| Vena contracta                |     | >0.7 and systolic flow reversal pulmonary veins |      |

| **Pulmonary valve**            | mild | moderate | severe |
| Stenosis                      |      |          | >4     |
| Jet velocity                  |      |          | Gradient | >60mmHg |

| Regurgitation                  |      |          | Fills outflow tract |
| Colour jet                     |      |          | Dense continuous wave Doppler |
|                                |      |          | Steep deceleration slope |

**Management**

The current approach is to surgically correct disease that produces more than mild symptoms or, in the case of dominant aortic stenosis, to operate in the presence of even mild symptoms.(1,3) In regurgitant dominant lesions, surgery can be delayed until
symptoms develop or asymptomatic LV dysfunction becomes apparent. (1,3)
Development of symptoms or pulmonary hypertension is also an indication for intervention.(1,3)

The study

The study was undertaken for the following reasons:

Prior to this study there were no reported papers in the area of mixed and multiple valve disease. This created an opportunity to make a significant contribution to the international literature. Complex valve disease is endemic in third world countries with a smaller incidence in the first world environment. (1) Migrant populations to first world countries often have medical conditions (e.g. rheumatic heart disease) which are largely left untreated in their home third world countries.(8) This can impact on healthcare economically.(8) The medical condition also provides interesting pathology for academic purposes particularly in relation to prompt diagnosis and optimal management.

The academic facilities available in our first world institutions provide a portal through which medical conditions can be assessed using international guidelines, standards, equipment and budgeted health care funding.(8) These factors are not always available in third world countries despite an abundance of interesting pathological conditions. This is likely to be due to financial issues.

The assessment of functional capacity is crucial to any clinical assessment.(6,9) Prognosis, quality of life, short term and long term outcomes are dependent on the cardiovascular fitness of an individual.(6,9) The progressive failure of the heart as a pump in multiple valve disease is responsible for the significant morbidity and mortality seen in the third world. (6,9) The symptomatic status as determined most commonly by
the onset of shortness of breath decides the timing of surgical valve replacement. (1) History, clinical examination and echocardiography are essential to diagnose the condition. Marked variation in these assessments can sometimes make the prognosis difficult to predict. The use of biomarkers (natriuretic peptides) has shown much promise in predicting prognosis in heart failure of any aetiology. (5) Functional capacity is best evaluated through formal exercise testing. (4) Bedside resting tests like spirometry also provide clues to functional capacity. (9)

Integration of the history, clinical examination and echocardiography with biomarkers and parameters of functional capacity will enable physicians to understand the clinical presentation of complex valve disease and try to predict the prognosis in the best possible way. In this study we try to contribute to the international literature on a topic in which both the American and European guidelines acknowledge as deficient.
References


Chapter 2

Functional Capacity Testing in Heart Valve Disease.
Functional Capacity testing in heart valve disease.

Introduction

The functional capacity of a patient is an important determinant of quality of life. Exercise testing is recommended to determine the functional capacity in heart failure. (1) Advanced levels of chronic heart failure impose significant limitations in exercise capacity due to impaired cardiac output and concurrent physical deconditioning. (2) Cardiopulmonary exercise testing has been widely used to determine the functional aerobic capacity in cardiac disease. (3) Peak oxygen consumption (peakVO2) is reported to be the gold standard in assessing functional aerobic capacity. (3) PeakVO2 has been shown to predict prognosis in heart failure and has an important role in cardiac transplant. (4) Transplant studies have shown that peakVO2 levels less than 15 ml/kg/min was associated with poor long term outcomes. (4)

Functional capacity in heart valve disease

There are only a few studies in the current literature which examine functional capacity and the role of peak oxygen consumption in single heart valve disease. A 2006 Mayo clinic study evaluated the prevalence, determinants, and clinical outcome implications of reduced functional capacity in patients with organic mitral regurgitation. (5) Asymptomatic patients (N=134) underwent cardiopulmonary exercise testing at baseline with follow up for clinical events (death, heart failure, new atrial fibrillation) out to 3 years. They found that reduced functional capacity (< 84%) was an independent predictor of future adverse clinical events. Independent predictors of reduced functional capacity were ERO (effective regurgitant orifice area > 40), impaired diastolic dysfunction E/E’ and a reduction in systolic function.
There have been multiple studies in aortic stenosis and mitral valve disease to determine the effort tolerance in asymptomatic patients. The vast majority used standard treadmill testing to detect effort intolerance. Few studies have used cardiopulmonary exercise testing. There are no studies reported in the literature on complex valve disease. The evaluation and outcomes of this thesis contributes immensely to the literature in the field of valvular heart disease and exercise testing.

**Peak oxygen consumption (peakVO2)**

The amount of oxygen extracted from the atmosphere and delivered to the muscles at the point of maximal effort defines the peak oxygen consumption during exercise. (3) PeakVO2 is assessed in vivo using a gas analyser as part of a metabolic cart during formal exercise testing with electrocardiographic monitoring. The peakVO2 is the highest oxygen consumption achieved during a cardiopulmonary exercise test (CPEX). (3) The well known VO2max assessment is the equivalent of a peakVO2 assessment in athletes. (3) The VO2max curve plotted during exercise forms a plateau since athletes are able to continue high intensity exercise at their peak effort. (3) The units for peakVO2 are expressed in litres/min (l/min) and when corrected for total body mass (total body weight) the units are ml/kg/min. The factors affecting peakVO2 are heart pump function, respiratory disease, muscle blood flow, peripheral vascular disease, muscle deconditioning, and mitochondrial myopathy. (4)

**Symptoms in Heart Valve disease.**

Shortness of breath (dyspnoea) is the commonest symptom limiting physical activity in heart disease. (7) Other symptoms include angina, dizziness, syncope and non specific or vague symptoms like fatigue and lethargy. The diagnosis of having heart disease further generates a
lack of fitness through sedentary lifestyle. This may be through symptom limited activity or psychological reasons (anxiety). In heart valve disease the presence of symptoms is central to the decision to operate. (8) Surgical valve replacement is usually indicated when severe valvular stenosis or regurgitation produces symptoms. Detecting these symptoms may be difficult if the patient has a sedentary lifestyle or if symptoms are vague (fatigue). Formal exercise testing is recommended in the American and European guidelines to detect the presence of dyspnoea or a reduction in effort tolerance. (7,8)

Cardiopulmonary exercise testing is useful to quantify effort intolerance, provides a respiratory or cardiac aetiology for dyspnoea, ensures maximal effort during testing and identifies malingering. (3) When coupled with a thorough history and physical examination a comprehensive assessment of effort tolerance, symptoms and functional aerobic capacity is obtained.

The New York Heart association attempts to classify dyspnoea according to the patient’s symptoms. This has been shown to predict prognosis in heart failure. Weber and Janicki further categorised the functional capacity in heart failure using peakVO2. (9) There is however significant overlap between classes depending on the clinical assessment of functional class and the exercise capacity of the patient.

The exercise testing modality most widely used in cardiology is the standard treadmill test. This exercise time correlates well with the MET capacity as a measurement of functional capacity. When compared to peakVO2, one Metabolic equivalent (MET) is equivalent to 3.5 ml/kg/min assuming the subject is 72kg. (3) Stage I of the Bruce protocol is usually equivalent to 2 METs This provides a gross estimation of functional capacity and becomes
inaccurate depending on the subjects weight and the type of testing protocol used. The treadmill test however is widely available even in remote clinics. There are some standardised protocols which are easily implemented which provide reasonable estimates of exercise capacity.\(^{(3)}\) The exercise test protocol should be appropriate to test the individuals functional capacity hence age and sex matched ramped protocols have been developed.

**Table I.** Dyspnoea is classified into the New York Heart Association (NYHA) functional classes. Each class is then assigned a peakVO2 estimate according to the Janicki Weber classification.\(^{(9)}\)

<table>
<thead>
<tr>
<th>NYHA functional classification</th>
<th>Description</th>
<th>Janicki Weber Classification</th>
<th>PeakVO2 (ml/kg/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td>Asymptomatic</td>
<td>A</td>
<td>&gt;20</td>
</tr>
<tr>
<td>Class II</td>
<td>dyspnoea on moderate levels of exertion</td>
<td>B</td>
<td>16-20</td>
</tr>
<tr>
<td>Class III</td>
<td>dyspnoea on mild levels of exertion</td>
<td>C</td>
<td>10-15</td>
</tr>
<tr>
<td>Class IV</td>
<td>overt heart failure and dyspnoea at rest</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The CPEX test is not as widely available as the standard treadmill test. The metabolic cart and gas analyser is in 2010 a costly equipment expense ($40,000). The test is also expensive
($400). Cardiac scientists who are able to implement the test and interpret the results are not always available. Cardiologists are generally not specifically trained in the interpretation of the results. This creates marked variation in results between different exercise laboratories using the same subject. When the test is accomplished by experienced operators there is good correlation of data with useful adjunct information to the clinical history and examination. The equipment has over the years decreased in size from a cumbersome large metabolic cart to a tidier and smaller console. The number of cardiac scientists with an interest in cardiopulmonary exercise testing has increased in recent times.

Centres without cardiopulmonary exercise testing usually perform standard treadmill tests to monitor exercise tolerance in valve disease. Patients with mild symptoms (NYHA class I or II) can be evaluated by repetitive treadmill exercise testing without a metabolic cart assessment for peakVO2. Total exercise duration (MET capacity) can be used as an objective measure of functional capacity. In comparison, patients who present with or progress to moderate-to-severe heart failure (NYHA class III or IV) should be referred to a center with the capability to perform valve surgery. The specific method used to measure peakVO2 is less important as long as the test is performed and interpreted in a consistent manner. In relation to valve disease the test result interpretation should take into account the presence and treatment of atrial fibrillation, current medical therapy and comorbid conditions.
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Chapter 3
The Development of Natriuretic Peptides in Heart Failure
Natriuretic peptides in heart failure

Introduction

Common risk factors for heart failure include hypertension and coronary disease.(1) In isolated cases, severe aortic and mitral valvular disease can lead to heart failure. More commonly, moderate degrees of valvular disease contribute with other factors to the development of left ventricle decompensation. Obesity is a common contributor to the other heart failure risk factors by directly affecting myocyte triglyceride and fatty acid content, as well as increasing blood pressure and activating the renin-angiotensin-aldosterone system (RAAS) and the sympathetic nervous system (SNS).(1) Diabetes has been associated with heart failure but is confounded by other pathogenic factors such as hypertension and obesity. Finally, chronic kidney disease causes salt and water retention, poor blood pressure control, and is independently related to the development of heart failure.(1)

Figure 1: Pathogenesis of heart failure. (AHA/ACC guidelines)

According to the American College of Cardiology / American Heart Association (ACC/AHA) classification, a Stage A Heart Failure patient has risk factors for heart failure.
Physical changes to the left ventricle, including left ventricular hypertrophy and remodeling, which may be markedly worsened by an acute myocardial infarction are the hallmarks of Stage B Heart Failure. Stage B is most commonly identified as structural abnormalities seen on cardiac imaging. Stage C Heart Failure is a characteristic, symptomatic syndrome with the cardinal features of fatigue, breathlessness, and peripheral edema. Stage D Heart Failure is considered terminal. It has been shown that 90% of those who carry a diagnosis of heart failure will die of the illness within 10 years. (1)

B-type-natriuretic peptide (BNP) is a pro-hormone protein produced by the heart in response to stress and strain on the chamber walls. (2) In the last fifteen years, studies have revealed that natriuretic peptides are important biomarkers of left ventricular dysfunction and outcome in heart failure of any etiology. (3) There are currently multiple reported studies that use plasma natriuretic peptides in the assessment of dyspnea and long term prognosis in heart failure. (4) Atrial natriuretic peptide (ANP) and C-type- natriuretic peptide (CNP) are other commonly used biomarkers of prognosis. (2) The most commonly used biomarker is BNP. The function of BNP is to counteract volume overload by inducing vasodilation, natriuresis, and diuresis. (5) BNP is stored in only limited amounts and increased secretion relies on increased synthesis from activation of the BNP gene. (2) In a normal heart, the atria are the main source of BNP. However, when ventricular wall stress is increased, ventricular BNP production is up-regulated, and ventricular BNP then predominates. (2) Ventricular dysfunction increases plasma concentrations of both ANP and BNP, but the relative increase in BNP is higher. Figure 2 below demonstrates the feedback system.
BNP History

In the 1950s, George Palade MD, developed specialized fractionation techniques, and used electron microscopy to study sub-cellular components while working at the Rockefeller Institute. In 1964, Dr. Palade discovered granules in animal atrial tissue that resembled granules of hormones produced elsewhere in the body. In the 1960’s, researcher Adolfo J. de Bold from Queen’s University in Canada investigated the functional nature of the atrial granules. In 1980, after 12 years of natriuretic peptide research, Atrial Natriuretic Factor (ANF) was discovered and isolated. This showed that the heart has an endocrine function which serves to modulate blood pressure, blood volume, and cardiovascular growth. This discovery triggered worldwide research on ANF, later was known as atrial natriuretic peptide (ANP).
DeBold’s demonstration of diuresis and natriuresis lead to the identification of atrial natriuretic peptide (ANP). (6) At the cellular level, ANP release from atrial cardiac myocytes occurs in response to an increased volume of extracellular fluid. (7) Several studies have localized ANP production to specific granules in atrial cardiocytes. (8,9,10)

Continued research led to the discovery of “Brain Natriuretic Peptide” (BNP) in 1988 by Dr. Sudoh. (11) Although BNP was first isolated in the brain, it was later discovered that BNP originated in the heart, and was a messenger to the brain. BNP was hence appropriately renamed B-type natriuretic peptide. BNP is produced by cardiac myocytes, and since the left ventricle has the most dense tissue mass, the circulating levels of BNP are largely a reflection of left ventricular production.

The single greatest determinant for synthesis and secretion of natriuretic peptides by cardiac myocytes is stretch at the cellular level, and wall tension at the chamber level. Wall tension of any chamber is governed by the Law of LaPlace, with pressure and radius (chamber size) being the most important components.
The Genetics of BNP

The gene for BNP resides on chromosome 1. This gene has a rapid activation sequence and in the setting of an increase in stretch and stimulation of stretch receptors, can markedly up-regulate the production of mRNA for BNP. Thus, in a relatively short period of time, a several hundred fold increase in BNP production can occur. (12)
An important post-translational step is the cleavage of the signal peptide within the Golgi apparatus. After briefly being stored in granules, pro-BNP is released from the cell and then is cleaved by corin (otherwise known as furin) into the mature 32 AA BNP and the inactive 76 AA NT-proBNP. Although BNP and NT-proBNP are produced in a 1:1 manner, the circulatory times and blood pool concentrations are considerably different because each peptide has a relatively different clearance mechanism. At steady state in a stable patient, the ratio of NT-proBNP to BNP is approximately 5 to 8:1.

**BNP Structure and Assay**

BNP is produced as a pro-hormone with a 17 amino acid ring structure. BNP is cleaved in the circulation into active BNP and the N-terminal peptide NT-proBNP. Both can be assayed, but NT-proBNP has a longer plasma half life and higher plasma concentrations. Thus NT-proBNP has become an important blood test since it is readily measurable from obtaining a simple routine venous blood sample at any licensed laboratory or general medical practice. The representative NT-proBNP units are pg/ml or pmol/l. (BNP conversion: 100 pg/mL = 22 pmol/L; NT-proBNP conversion: 300 pg/mL = 35 pmol/L) Levels >600 pg/ml are thought to be highly predictive of ventricular dysfunction.
usefulness also extends to its negative predictive value. NT-proBNP levels within the normal range (<100pg/ml) are interpreted as heart failure being an unlikely cause of dyspnea. (17)

Clearance of BNP

BNP is known to undergo receptor mediated endocytosis and proteolytic degradation by somatic cells via clearance receptors. Mature NP’s (ANP/BNP) have a reduction in blood concentration of approximately 70% as they pass through the kidneys. The remainder of BNP clearance is believed to occur by breakdown by neutral endopeptidase, which is a vascular endothelium-linked enzyme. See Figure 6.

Figure 6

Since fat tissue is vascular and has considerable variability from person to person, the degree of adiposity is related to the NP level with overweight and obese persons having lower steady state NP levels due to enhanced clearance.

Current Role of NT-proBNP in Heart failure

Heart failure is one of the most common cardiovascular diagnoses and has a clear age-dependent increase in incidence (as shown in the Framingham cohort) as well as a cross-
sectional prevalence demonstrated by the National Health and Nutrition Education Study (NHANES). (18) See Figure 7.

![Incidence and Prevalence of Heart Failure (HF) in Framingham & NHANES](image)

**Figure 7 Incidence and prevalence of heart failure (18)**

Trends of NT-proBNP levels are used to monitor the progress of heart failure and the therapeutic response to anti-failure therapy. (14) Figure 8 shows the trends of BNP in heart failure as the stages progress. As a general guideline, in young, healthy adults, 90% will have BNP < 25 pg/ml and NT-proBNP < 70 pg/ml. For acutely dyspneic patients, some have suggested cutoffs of BNP <100 pg/ml and NT-proBNP < 300 pg/ml to rule out heart failure (Figure 8) The Breathing not Properly (BNP) Study displayed the usefulness of NT-proBNP in the Emergency Department to distinguish whether dyspnoea had a cardiac or respiratory etiology. (17) The benefit of NT-proBNP as a prognostic marker in heart failure, atrial fibrillation, cardiac surgery, non cardiac surgery and myocardial infarction is reported in the literature. (3, 4, 15) In single heart valve disease NT-proBNP has been shown to be an important marker of morbidity and mortality. (19)
Figure 8: BNP rises with age over the course of a lifetime but generally stays under 20 pg/ml in the absence of left ventricular dysfunction or structural heart disease. B-type natriuretic peptide <100 pg/ml is the cutoff for diagnosing congestive heart failure in symptomatic patients. Stage A: risk factors; Stage B: asymptomatic structural heart disease; Stage C: symptomatic heart failure; Stage D: refractory heart failure.

**BNP and Heart Valve Disease**
The ACC/AHA guidelines recommend surgery for patients who are symptomatic with severe valve lesions or a significant decline in left ventricular function. (16) The severity of the lesion and the assessment of left ventricular function is accomplished with serial echocardiographic measurements. (16) Symptom onset (most commonly dyspnoea) causes a transition in NYHA class. The onset of symptoms is the turning point in the management of valve disease towards planning surgical valve replacement. (16, 20) Symptoms may be vague or insidious in onset especially if patients are sedentary. (11) The knowledge of having heart valve disease may also create an inactive lifestyle. Patients may also pace their activities to avoid symptoms resulting in an unnoticed decline in functional capacity.
In 160 consecutive patients presenting with heart failure from any cause, Iwanaga and colleagues measured plasma BNP levels and performed echocardiography and cardiac catheterization. Systolic and diastolic wall stress was calculated from echocardiographic and haemodynamic data. This research demonstrated that derived end-diastolic wall stress has the greatest correlation of BNP through a range of measured values. This study clearly showed the blood levels of BNP most closely correlated with left ventricular wall stress. (21)

Recent studies have shown that NT-proBNP concentrations are also increased with disease of the aortic and mitral valves. (20, 22, 23, 24) The plasma NT-proBNP level relates significantly to the severity of the valve lesion and the degree of cardiac remodelling. NT-proBNP concentrations appear to relate to prognosis in these patients and might have a role in identifying suitable candidates for cardiac surgery.

Severe isolated MR usually runs a chronic course. (25) Left ventricular function is masked by dynamic ventricular contractility despite adverse net cardiac output. Monitoring left
ventricular ejection fraction is hence inadequate. The prolonged delay in waiting for a decline in ejection fraction may result in irreversible adverse cardiac remodelling accompanied by a significant deterioration in the patients physical condition. The early detection of underlying LV dysfunction with a biomarker will provide the warning signal of significant stress and strain of the ventricle which can prevent long term permanent adverse remodelling. NT-proBNP levels are known to respond to myocardial wall stress and are shown to be useful markers in such situations. (25)

In similar fashion NT-proBNP is shown to correlate with echocardiographic valve lesion severity, valve area and transvalvular gradient. Wall stress, degree of LVH and decline in ejection fraction also correlate with NT-proBNP. (11, 22) An asymmetric yet wide distribution of NT-proBNP has resulted in a log transformation being used which correlated with ejection fraction, valve area, gradients and wall thickness. (11)

Low NT-proBNP levels are shown to predict a successful postoperative outcome in patients undergoing aortic valve replacement. In a series of patients with aortic stenosis is NT-proBNP was the only independent predictor of survival and of good symptomatic status and along with preoperative ejection fraction was an independent predictor of postoperative LV ejection fraction. (26)

In a study of 12 asymptomatic patients with aortic regurgitation and preserved LV function found a correlation between BNP and the extent of ventricular remodelling. This study is too small to draw any clinically useful conclusions but it is interesting that log transformed concentrations of all three peptides were considerably lower than in equivalent patients with aortic stenosis despite substantial LV dilatation and, by implication, increased diastolic wall stress. (27)

In a study from the Mayo clinic Detaint showed that BNP is not just a marker for the severity of mitral regurgitation or a surrogate for symptoms but also for adverse clinical outcome. In symptomatic patients with an established indication for operation a high BNP concentration predicts a worse late outcome and may be useful in risk stratification. (28) In mitral stenosis NT-proBNP was shown to be predictive of echocardiographic measures of valve lesion severity, mitral valve gradient and decreased post successful valvotomy. (29)
Thus the role of natriuretic peptides has been established as a diagnostic tool for risk stratification, predict prognosis and improve the timing of surgery. In aortic stenosis and in degenerative mitral regurgitation there is evidence that BNP can identify those asymptomatic patients on the verge of developing symptoms or haemodynamic compromise. When used in conjunction with a thorough history and clinical examination NT-proBNP can improve the management and optimise the timing of valve replacement in patients with single valve disease.

The ACC/AHA guidelines admit to the paucity of data on complex mixed and multiple valve disease. (16) The content of this thesis has, for the first time, contributed three important papers to the international literature in the subject of complex mixed and multiple heart valve disease. This includes a contribution of the role of BNP in mixed and multiple valve disease.

**BNP in Obesity**

Despite the lower circulating levels, BNP retains its prognostic capacity in obese patients (30), although lower BNP cut-points are needed for diagnosing HF in patients with a high body mass index (Figure 10) (17).

![Figure 10: B-type natriuretic peptide (BNP) cut-points for 90% sensitivity in diagnosing congestive heart failure in patients with dyspnea, on the basis of body mass index (BMI) subgroup. Specificity at the 90% sensitivity level shown was at least 70% for all 3 groups. Data from the Breathing Not Properly Multinational Study; figure adapted from Daniels et al. (31)
Table 1: Causes of elevated BNP in the absence of overt heart failure.

<table>
<thead>
<tr>
<th>Condition</th>
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<tbody>
<tr>
<td>LV dysfunction</td>
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<tr>
<td>Previous heart failure</td>
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<tr>
<td>Advanced age</td>
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<tr>
<td>Renal dysfunction</td>
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<tr>
<td>Acute coronary syndromes</td>
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<tr>
<td>Pulmonary disease (e.g. acute respiratory distress syndrome, lung disease with right heart failure)</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
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<tr>
<td>High output states (e.g. sepsis, cirrhosis, hyperthyroidism)</td>
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<tr>
<td>Atrial fibrillation</td>
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<tr>
<td>BNP levels lower than expected</td>
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<tr>
<td>Obesity</td>
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<tr>
<td>Flash pulmonary edema</td>
</tr>
<tr>
<td>Heart failure etiology upstream from LV (e.g., acute mitral regurgitation, mitral stenosis)</td>
</tr>
<tr>
<td>Cardiac tamponade</td>
</tr>
<tr>
<td>Pericardial constriction</td>
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</tbody>
</table>

The absence of clinical heart failure in the setting of elevated biomarkers should alert the physician to consider other causes as listed in Table 1 above. These conditions should be excluded before appropriate therapy is implemented. (17) BNP and NT-proBNP are elevated in approximately 25% with acute coronary syndrome. When elevated, they predict increased risk of adverse events during the hospitalization and convalescent period. They have been shown to be complementary to the TIMI and GRACE Global ACS Risk Scores in predicting short and intermediate term outcomes.

Along the stages of heart failure which call for interventions, there are anticipated BNP levels. There is a normal age-related rise in BNP, thus as a general principle, a “normal” BNP is less than or equal to approximately half one’s age. The Food and Drug Administration’s (FDA) approved cut point for abnormal is above 100 pg/ml.
In established heart failure, it is common to witness BNP elevations from 100 to 5000 pg/ml. However, several clinical trials have demonstrated that with evidence-based heart failure therapy e.g. ace inhibitors (ACEI), angiotensin receptor blockers (ARBs), beta-blockers (BBs), aldosterone receptor antagonists, and biventricular pacing--the treated BNP can be normalized in approximately 25% of heart failure patients. As patients progress to the end-of-life, there are persistent BNP elevations over 250 pg/ml and often even over 1000 pg/ml.

**Acute Decompensated Heart Failure**

In the Acute Decompensated Heart Failure National Registry (ADHERE), the study sites were to determine whether admission B-type natriuretic peptide (BNP) levels are predictive of in-hospital mortality in acute decompensated heart failure. B-type natriuretic peptide levels within 24 hours of presentation were obtained in 48,629 (63%) of 77,467 hospitalization episodes.
In-hospital mortality was assessed by BNP quartiles in the entire cohort and in patients with reduced (n=19,544) as well as preserved (n=18,164) left ventricular systolic function using chi-square and logistic regression models. Quartiles (Q) of BNP were Q1 (430), Q2 (430 to 839), Q3 (840 to 1,729), and Q4 (1,730 pg/ml). The BNP levels were 100 pg/ml in 3.3% of the total cohort. Patients in Q1 versus Q4 were younger, more likely to be women, and had lower creatinine and higher left ventricular ejection fraction. There was a near-linear relationship between BNP quartiles and in-hospital mortality: Q1 (1.9%), Q2 (2.8%), Q3 (3.8%), and Q4 (6.0%), P< 0.0001. B-type natriuretic peptide quartile remained highly predictive of mortality even after adjustment for age, gender, systolic blood pressure, blood urea nitrogen, creatinine, sodium, pulse, and dyspnea at rest, Q4 versus Q1 (adjusted odds ratio 2.23 [95% confidence interval 1.91 to 2.62, p  0.0001]). The BNP quartiles independently predicted mortality in patients with reduced and preserved systolic function. (32)
Specificity and Sensitivity of BNP in Dyspnea

In the Breathing Not Properly (BNP) Trial, Maisel and colleagues conducted a prospective study of 1586 patients who came to the emergency department with acute dyspnea and whose B-type natriuretic peptide was measured with a bedside assay. (33)

The clinical diagnosis of congestive heart failure was adjudicated by two independent cardiologists, who were blinded to the results of the B-type natriuretic peptide assay. The final diagnosis was dyspnea due to congestive heart failure in 744 patients (47 percent), dyspnea due to noncardiac causes in 72 patients with a history of left ventricular dysfunction (5 percent), and no finding of congestive heart failure in 770 patients (49 percent). B-type natriuretic peptide levels by themselves were more accurate than any historical or physical findings or laboratory values in identifying congestive heart failure as the cause of dyspnea. The optimal cut point was determined by evaluating BNP using a receiver operating characteristic curve which plots 1-specificity (false positive rate) versus sensitivity (true positive rate) and finds the best overall cut point to optimize the decision statistics.
(sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy. (Figure 13) This cut point of 100 pg/ml also matches the cut point of normal to elevated in the product insert of available BNP assays in the U.S. market in 2010.

**BNP Algorithm**

![BNP Algorithm Diagram]

This important algorithm depicts how BNP should be used in clinical decision making in the urgent care setting in a patient who presents with acute dyspnea and suspected heart failure. After taking a history, physical exam, ECG, and a chest X-ray, if the BNP level is <100 pg/ml and the clinical evaluation does not suggest heart failure, it is very unlikely that heart failure will evolve to be the final diagnosis over the hospital stay or after discharge. Therefore, specific treatments for common causes of dyspnea, such as asthma or congestive obstructive pulmonary disease (COPD), can be employed. If there is no history of heart failure but the BNP is 100-500 pg/ml, this is considered a “grey zone” BNP level, and the clinician should consider other known causes of an elevated BNP including pulmonary embolism (PE), acute coronary syndrome (ACS), cor pulmonale, sepsis, or renal dysfunction.
If BNP is 100-500 pg/ml and there is a prior history of heart failure, then the BNP is largely confirmative of decompensation. Finally, BNP values >500 pg/ml indicate decompensated heart failure is highly likely and appropriate treatments should be initiated.

**Hospitalization and Discharge BNP**

Among those admitted to the hospital with decompensated heart failure and an average BNP of approximately 1000 pg/ml, the follow-up BNP at the time of discharge is predictive of events over the next 6 months. (34)

![Death or Rehospitalization Rates According to Discharge BNP](image)

Figure 15

In general, a greater than 50% reduction in BNP over the course of a hospital admission is a favorable sign, and this group has the lowest rate of death or readmission over the next 6 months.

**Conclusion**
The development of natriuretic peptides as a biomarker of outcome in patients with heart failure and shortness of breath has been established over a considerable period of time. There are multiple other studies in the literature involving various aspects of cardiovascular disease where natriuretic peptides have shown to be useful clinical adjuncts. We expect that natriuretic peptides will continue to grow as a clinical biomarker of outcome in the future.

References
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Chapter 4
The role of B-type-Natriuretic Peptide (BNP) and Exercise testing in Aortic Valve Stenosis
Review on Aortic Stenosis

Introduction
Aortic valve stenosis (AS) is the most common type of valvular heart disease in developed countries. (1) Aortic stenosis develops as a result of progressive inflammation and calcification of the valve leaflets, leading to restriction of leaflet excursion and left ventricular outflow tract obstruction (see Figure 1). Aortic stenosis is gradual in onset and progression, causing chronic left ventricular pressure overload and left ventricular hypertrophy. Replacement of the aortic valve is an effective treatment for symptomatic severe aortic stenosis and improves survival. (1, 2, 3) The optimal timing of aortic valve replacement surgery is determined by analyzing the risks versus benefits. (1, 2)

Cardiologists most commonly diagnose aortic stenosis via echocardiography following a thorough clinical assessment. Cardiologists may perform exercise testing, coronary angiography, and hemodynamic studies to further evaluate the severity of the lesion and functional capacity to detect symptoms and optimize the timing of surgery. (1, 2)

Symptomatic aortic stenosis is the most common indication for surgical valve replacement. In determining whether aortic valve replacement (AVR) is necessary, the cardiologist assesses the symptoms, ejection fraction, severity of the calcification, rate of increase in peak jet velocity (≥0.3 m/s within a year is associated with a poor prognosis), the functional capacity of the patient, concurrent comorbidities, and follow up. The general practitioner’s opinion on the decline of the patient’s functional capacity is also an important clue to the urgency of AVR, and should be included in the referral. The management is ultimately based on the following: assessment of severity, patient education, AVR or periodic echocardiography, cardiac risk factor modification and comorbidities. (2) The management of asymptomatic moderate to severe aortic stenosis is a controversial subject, and has been a subject of debate in the last four decades. (4)

Aetiology of AS
The predicted prevalence of heart valve disease is expected to double within 20 years due to an aging population. (5) The major causes of aortic stenosis requiring valve replacement are: bicuspid aortic valve, degenerative disease of a trileaflet valve, and rheumatic aortic
valve disease. The frequency of the lesions varies with age; patients younger than 50 are more likely to have a bicuspid aortic valve. Between ages 50-70, 66% are likely to have a bicuspid aortic valve and 33% a tricuspid valve. For patients over age 70, 60% are likely to have a tricuspid valve and 40% a bicuspid valve. (6) Congenital AS affects children and young adults. (2)

Figure 1: Severe calcification of a degenerative aortic valve. (6)

Symptoms and findings
Aortic stenosis may be detected from the clinical examination by virtue of its characteristic systolic murmur. This may prompt a referral for further assessment, usually echocardiography. The onset of symptoms is usually the first indication that valve replacement is required. However in critical aortic stenosis, valve replacement may be recommended in the asymptomatic state. (1, 2) The symptoms of aortic stenosis are exertional dyspnea, angina, dizziness or syncope. (1) In general, symptoms in patients with aortic stenosis and normal LV systolic function rarely occur until the valve area is <1.0
cm$^2$, the aortic jet velocity is over 4.0 m/s or the mean transvalvular gradient exceeds 40 mmHg. Many patients do not develop symptoms until even more severe valve obstruction is present, while some patients become symptomatic when the stenosis is less severe, particularly if there is coexisting aortic regurgitation. Sedentary lifestyle or vague symptoms (i.e. fatigue) in early severe aortic stenosis can make symptom assessment difficult. (1, 7) This may delay surgery if the symptoms are not adequately assessed.

Patients may also present with florid heart failure, arrhythmias or aborted sudden death. (2) The annual cumulative risk for sudden death is 1% per year. A detailed patient history and physical examination is hence essential to determine the clinical significance of aortic stenosis.

**Echocardiographic diagnosis**

There are 3 major issues with the diagnosis of aortic stenosis:

1. Diagnosis of AS.
2. Assessment lesion severity.
3. Assessment of underlying LV function and degree of remodeling.

Doppler echocardiography is the cornerstone of aortic stenosis diagnosis.

Echocardiography is used to diagnose and assess the severity of aortic stenosis. (1, 2)

Aortic stenosis is categorised into mild, moderate and severe depending on the values of the echocardiographic parameters (Table 1). (1, 2) The normal aortic valve cross sectional area is 3.0 to 4.0 cm$^2$ in adults. A transvalvular gradient develops when the orifice area narrows down to <50% of normal. (1, 2) In patients with normal LV function, severe AS is defined as a peak aortic valve jet velocity >4 m/s, a mean transaortic pressure gradient >40 mmHg, or an aortic valve area <1 cm$^2$. A valve area index, which takes into account body surface area, of < 0.6 cm$^2$/m$^2$ is also indicative of severe AS. (1)

<table>
<thead>
<tr>
<th>Severity</th>
<th>Aortic jet velocity (m/s)</th>
<th>Mean gradient (mmHg)</th>
<th>Aortic valve area (cm$^2$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>≤1.5</td>
<td>≤5</td>
<td>3.0-4.0</td>
</tr>
<tr>
<td>Mild</td>
<td>&lt;3.0</td>
<td>&lt;25</td>
<td>1.5-3.0</td>
</tr>
<tr>
<td>Moderate</td>
<td>3.0-4.0</td>
<td>25-40</td>
<td>1.0-1.5</td>
</tr>
<tr>
<td>Severe</td>
<td>&gt;4.0</td>
<td>&gt;40</td>
<td>&lt;1.0</td>
</tr>
</tbody>
</table>
The diagnosis of aortic stenosis is made by seeing the restricted excursion of the thickened, calcified aortic leaflets on 2D echocardiography. The aortic valve is best visualised in the left parasternal long axis view and the apical 5 chamber view. Color Doppler ultrasound is used to detect the turbulent jet. Continuous wave Doppler is applied to the outflow tract above the leaflets to determine the jet velocity. Using the continuity equation, which incorporates the jet velocity at specific points, (V1 and V2) the peak gradient and mean gradients across the aortic valve the aortic valve area is estimated. (8)

The short axis view at the base of the heart shows the leaflet structure and mobility. In this view, the aortic valve opening perimeter can be traced in peak systole, when the cusps are fully open. This method is thought to be a crude and less accurate assessment of the AVA than Doppler ultrasound.

Left ventricular hypertrophy (LVH) due to pressure overload from left ventricular outflow tract obstruction frequently occurs in aortic stenosis. (9) LVH is detected as an increase in wall thickness with delayed relaxation. (8) The compliance of the hypertrophied left ventricle is reduced, causing increased filling pressures and impaired relaxation. (8) This causes diastolic dysfunction, which often manifests as shortness of breath. (9)

Pulsed Doppler detects diastolic dysfunction by measuring the E:A ratio of mitral valve inflow velocities. “E” represents the early peak velocity, and “A” the atrial component of mitral inflow during diastole. The E:A ratio increases to >1 in severe diastolic dysfunction. (8) Diastolic dysfunction is also determined from tissue Doppler assessment at the insertion of the mitral leaflets. This generates the E/e’ ratio which can reach values >12 in diastolic dysfunction. The clinical implications of diastolic dysfunction are the onset of dyspnea, which can require medical therapy, and in its severe form, hospitalization may be required.

**Critical Aortic Stenosis**

Critical aortic stenosis has been defined as a valve area <0.75 cm² and/or an aortic jet velocity >5.0 m/sec, after consideration of left ventricular function. (2) However, in patients with severe or critical aortic stenosis who also have a low cardiac output state, the aortic jet velocity and mean gradient may be lower (low-gradient aortic stenosis). This commonly occurs when there is poor left ventricular function.
Mixed and Multiple Valve Disease

Mixed and multiple valve disease can coexist with aortic stenosis. In rheumatic heart disease, often seen in Australian immigrants, the mitral valve is invariably affected when aortic valve disease is present. In chronic untreated aortic stenosis, left ventricular dilatation with mitral regurgitation can coexist. Aortic regurgitation maybe a dominant or non dominant lesion in mixed aortic valve disease. Multiple valve disease in rheumatic heart disease may include concomitant aortic valve, mitral valve, and tricuspid valve disease. When assessing the aortic valve in aortic stenosis, a comprehensive assessment of the other valves should be carried out.

Hemodynamic studies

Hemodynamic studies in the cardiac catheterization laboratory provide a good assessment of valve gradients in aortic stenosis. A pigtail catheter attached to a pressure transducer provides estimates of left ventricular end diastolic pressure (LVEDP), peak LV systolic pressure, peak aortic pressure, peak to peak gradient and mean gradient across the aortic valve. This procedure can be done in severe aortic stenosis when assessing the coronary arteries for disease prior to aortic valve replacement.

It can be difficult to pass a catheter through a tightly stenosed calcified aortic valve. This may require multiple attempts with changes to stiffer crossing wires. There is a risk of stroke from dislodging calcium from the leaflets or perforation of the heart and surrounding vessels. Therefore, recent protocols omit the hemodynamic assessment of the aortic valve if the echo-cardiographic evaluation is deemed adequate. However, the presence of low flow aortic stenosis may render the echocardiographic assessment inaccurate.

Low flow aortic stenosis and pseudostenosis

Low flow aortic stenosis is present when LV function is poor, resulting in a reduced cardiac output and a low transvalvular gradient across a stenosed aortic valve. A severe stenotic aortic valve lesion induces secondary LV dysfunction, and causes a reduction in the transvalvular gradient. This usually is seen as a mean gradient < 30 mmHg on hemodynamic assessment, and aortic valve area <1 cm² on echocardiography. The low flow state produces a lower jet velocity on echocardiography, which may create an inaccurate assessment of aortic valve gradients and the calculation of aortic valve area.
Pseudostenosis is a low flow state where there is primary cardiomyopathy (myocardial disease) coexisting with moderate aortic stenosis. In other words, the myocardial dysfunction is unrelated to the aortic stenosis. In pseudostenosis due to low flow rate conditions, the calculated valve area may mistakenly suggest severe stenosis. (1, 2) Distinguishing between pseudostenosis and true aortic stenosis is important because surgical correction of the valve lesion in pseudostenosis is associated with a high mortality rate and is unlikely to be beneficial.

Table 2: Indications for aortic valve replacement in aortic stenosis. (HYPERLINK "" Vah07"")

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<tr>
<th>Indications</th>
<th>Class</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with severe AS and any symptoms</td>
<td>IB</td>
</tr>
<tr>
<td>Patients with severe AS undergoing coronary artery bypass surgery, surgery of the ascending aorta, or on another valve</td>
<td>IC</td>
</tr>
<tr>
<td>Asymptomatic patients with severe AS and systolic LV dysfunction (LVEF &lt;50 percent) unless due to other cause</td>
<td>IC</td>
</tr>
<tr>
<td>Asymptomatic patients with severe AS and abnormal exercise test showing symptoms on exercise</td>
<td>IC</td>
</tr>
<tr>
<td>Asymptomatic patients with severe AS and abnormal exercise test showing fall in blood pressure below baseline</td>
<td>IIAc</td>
</tr>
<tr>
<td>Patients with moderate AS* undergoing coronary artery bypass surgery, surgery of the ascending aorta or another valve</td>
<td>IIAc</td>
</tr>
<tr>
<td>Asymptomatic patients with severe AS and moderate-to-severe valve calcification, and a rate of peak velocity progression ≥0.3 m/s per year</td>
<td>IIAc</td>
</tr>
<tr>
<td>AS with low gradient (&lt;40 mmHg) and LV dysfunction with contractile reserve</td>
<td>IIAc</td>
</tr>
<tr>
<td>Asymptomatic patients with severe AS and abnormal exercise test showing complex ventricular arrhythmias</td>
<td>IIbC</td>
</tr>
<tr>
<td>Asymptomatic patients with severe AS and excessive LV hypertrophy (≥15 mm) unless this is due to hypertension</td>
<td>IIbC</td>
</tr>
<tr>
<td>AS with low gradient (&lt;40 mmHg) and LV dysfunction without contractile reserve</td>
<td>IIbC</td>
</tr>
</tbody>
</table>

**Natural History**
Chronic calcific aortic stenosis is a progressive condition with a low mortality rate. There is a long latent period during which a patient may be asymptomatic (Figure SEQ Figure \* ARABIC 2). This phase may vary widely among individuals. Sudden death occurs at a rate of ≤1% per year. Symptom-free survival at two years is between 20-50%. (6) The predictors of poor outcomes in asymptomatic patients include the following: (Table 3)

Table 3: Predictors of poor outcomes in asymptomatic aortic stenosis patients. (11)

<table>
<thead>
<tr>
<th>Clinical Factors</th>
<th>Echocardiographic Factors</th>
<th>Exercise Testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Old age, Concurrent atherosclerotic disease</td>
<td>Hemodynamic progression of jet velocity (≥0.3m/s in one year)</td>
<td>Symptom development on exercise testing in physically active patients &lt;70 years of age, Abnormal blood pressure response, Severe ST segment depression</td>
</tr>
<tr>
<td>Severe valve calcification</td>
<td></td>
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</tr>
</tbody>
</table>

There has been a tendency towards early surgery in asymptomatic patients due to the overall risk of death and surreptitious decline in functional capacity. Mortality rates of up to 5% were reported where a rigid policy of not operating on asymptomatic patients were adhered to. (12) The watchful waiting approach is associated with the risk that patients may not seek help promptly when symptomatic and carry a mortality risk while waiting for
surgery when symptomatic. (13) The irreversible remodelling of the left ventricle, in severe left ventricular hypertrophy with fibrosis, may not improve after delayed surgery. The patient may also become a poor surgical candidate if surgery is not performed at an optimal age and time. This may be due to progression of concurrent co-morbidities or new diseases that may develop. These patients have more recently been offered percutaneous AVR.

Patient survival is excellent during the prolonged asymptomatic phase of aortic stenosis. After the development of symptoms, however, mortality exceeds 90 percent within a few years. The onset of symptoms is crucial to the management of the patient with severe AS, as the prognosis is dismal and mortality high within months of the symptomatic state. Aortic valve replacement prevents this rapid downhill course. Exercise testing may play an important role in detecting latent symptoms.

Aortic valve replacement remains the only effective treatment for severe aortic stenosis. The major issue is the optimal timing of surgery. Symptomatic aortic stenosis requires early surgery. Average survival of symptomatic aortic stenosis is 2-3 years. (2) Management involves assessment of rate of disease progression, operative risk, co-morbidities and the clinician’s ability to predict post-surgical outcome after presenting the surgical risks to the patient. The dilemma remains with asymptomatic aortic stenosis, where surgery is delayed until onset of symptoms.

The factors affecting survival include the following: age, left ventricular function, NYHA functional class, low gradient disease, and volume of procedures performed at the hospital. Survival is worse in patients with emergency/salvage procedures, recent infarction, redo-operations, or renal failure. (14) Dobutamine stress echocardiography may be used to stratify patient risk, and to determine the appropriate therapy. Left ventricular contractile reserve in response to dobutamine has been correlated with improved surgical outcomes (15).

Aortic valve replacement (AVR) results in symptomatic improvement and substantial increase in survival. In a study of n=144 patients with symptomatic aortic stenosis, the three-year survival rate was 87% in 125 patients with AVR, and 21% in 19 non-operated patients. (16) A retrospective study of 99 patients with symptomatic aortic stenosis
(NYHA class III or IV), revealed that 91% of survivors were in NYHA class I or II at 5-year follow-up. (7) Patients generally move up in NYHA class post-AVR. (17, 18)

**Age in aortic stenosis**

There is an increasing incidence of aortic stenosis in the elderly. The UK heart valve registry enrolled 1100 patients aged 80 years. They had a 30 day mortality of 4.0%, and all cause mortality of 6.6%. Survival at 1 year was 89% and at 5 years 69%. Higher mortality was associated with advanced NYHA class (III or IV) and preoperative atrial fibrillation. (6)

**Left ventricular function**

The outcome of surgery is dependent on both the systolic and diastolic dysfunction. These are independent risk factors for early and late mortality. (19) Depressed ejection fraction (40-50%) is immediately corrected post AVR. Diastolic asynchrony normalizes later as hypertrophy and fibrosis regress. (2) A severely depressed LV ejection fraction (20-35%) is associated with incomplete resolution of symptoms post AVR but improvement in overall survival. (20)

**Exercise testing**

Exercise testing is contraindicated in severe symptomatic aortic stenosis. There is a risk of sudden death in severe symptomatic AS during treadmill testing. (21) Exercise testing is being assessed as an investigative tool to detect latent symptoms in asymptomatic aortic stenosis patients as well as to determine recommended levels of physical activity. Its role is to determine if exercise intolerance is present. Poor functional capacity and early onset of symptoms during exercise testing may prompt the clinician to recommend valve surgery. Important findings during exercise testing warranting immediate cessation of the test would be the following:

1. Abnormal blood pressure response. This could be a blunted response (a rise in systolic blood pressure of <20 mmHg) or a sudden drop in the recorded blood pressure (a drop in systolic blood pressure of >10mmHg during the exercise test).
2. ST segment depression, which may suggest underfilling of the coronary arteries.
3. Ventricular tachycardia (more than 4 successive premature ventricular beats)
4. Dizziness or presyncope during the test
5. Shortness of breath before five metabolic equivalents (MET) have been achieved in older patients (<70 years old); seven METs in younger patients (>70). (6, 21)

The ability of exercise testing to identify symptomatic patients with severe AS likely to develop symptoms was assessed in a study of 125 patients (mean age 65) with moderate to severe AS (mean valve area 0.9 cm$^2$). No patient with an valve area 1.2 cm$^2$ became symptomatic. Symptom-free survival was 49% in patients with limiting symptoms on exercise testing and 89% in those without symptoms. The sensitivity of exercise-limiting symptoms 72% and specificity 78% to predict outcomes. Exercise-limiting symptoms were the only independent predictor of outcome at 12 months. Other abnormalities on exercise testing such as an abnormal blood pressure response or ST segment depression had no effect. High risk groups include the elderly and patients with a sedentary lifestyle. In these groups the positive predictive value of exercise is reduced. However the surgical risk is also higher. (11)

**Serial testing**

The rate of progression of aortic valve narrowing has to be closely monitored and the patient must be educated about follow up and reporting the onset of symptoms. A change in valve area by 0.1 cm$^2$ per year also carries a poor prognosis. In the asymptomatic patient, exercise stress test should determine the recommended level of physical activity. Follow up visits must include echocardiographic assessments to determine the rate of hemodynamic progression. In moderate to severe calcification and peak jet velocity >4 m/s, re-evaluations every 6 months are recommended to detect the onset of symptoms, decreases in exercise tolerance or changes in echocardiographic parameters. In patients with early mild to moderate aortic stenosis, yearly clinical and echocardiographic re-evaluations are recommended. (1)

**Cardiac biomarkers**

Cardiac biomarkers have been used to assess prognosis and the timing of surgery and are currently under investigation to predict long-term outcomes in AS. The ideal biomarker will
identify a high risk patient with severe disease before the development of symptoms who could undergo valve surgery without increased perioperative morbidity and mortality. The important characteristics of a useful biomarker are the following: (22)

1. Easily and reliably measured.
2. Reflect disease severity
3. Increase with progression of the disease
4. Discriminate between patients who are asymptomatic and identify patients who are likely to develop symptoms in the short to medium term.
5. Reflect subclinical myocardial dysfunction

**Natriuretic peptides in aortic stenosis**
The patient may initially present in NYHA class IV or in the early symptomatic NYHA class II. Dyspnea is the most common symptom of aortic stenosis prompting surgery. (2) The symptomatic state with severe aortic stenosis requires AVR. The urgency of the surgery is usually dictated by the NYHA class. NYHA Class II can have planned elective AVR, whereas Class IV may need emergent surgery. Sedentary patients pose an ongoing risk of their symptomatic status. Exercise testing is recommended for the asymptomatic state but contraindicated for the symptomatic state. Symptomatic subclinical sedentary patients with severe aortic may be subjected to the hazard of undergoing an exercise test to detect symptoms. This includes obese subjects and deconditioned patients with respiratory comorbidities who might have dyspnoea from another etiology. Natriuretic peptides have a significant role in detecting the symptomatic state. (22) High or serially rising BNP predicted the short-term need for valve replacement in asymptomatic severe aortic stenosis. (23)

BNP has an important role in detecting the onset of symptoms and progression to the symptomatic state. (24) BNP mRNA has been shown to be increased in the myocardial tissue of aortic stenosis patients. (25) Increased levels of natriuretic peptides are seen in patients with asymptomatic mild AS compared to normal subjects. (26, 27, 28). Angina and syncope do not produce natriuretic peptide rises, suggesting a different mechanism of symptom development. (24) Natriuretic peptides have been shown to increase in with NYHA class. (29, 24) The asymptomatic state NYHA Class I and early symptomatic state
Class II have important management implications. The identification of NYHA class III and IV can be predicted with diagnostic accuracy of 78% using a cut-off 254.64 pg/ml. (29)

BNP is able to predict an abnormal blood pressure response to exercise, as well as impaired diastolic filling in patients with ejection fraction >50%. (30) This may indicate impaired LV function during exercise testing.

The natriuretic peptides (BNP and NT-proBNP) have been shown to correlate with severity of AS. This includes the mean transvalvular gradient, aortic valve area, peak jet velocity. The peptides also correlate significantly with LV ejection fraction, wall stress, LVH, and left ventricular mass. (22) A cutoff of approximately 500 pg/mL was associated with a high sensitivity to discriminate symptoms (AUC= 0.84). (22) The peptide concentration correlated with shortness of breath but not with angina or presyncope. These peptides are currently under investigation to determine if long term outcomes can be determined from baseline measurements as well as whether progressive increases in natriuretic peptides is associated with poor outcomes.

**Natriuretic peptides and severity of aortic stenosis**

The severity of aortic stenosis is traditionally determined from the echocardiogram, the main parameters being peak aortic jet velocity, mean transvalvular gradient, and aortic valve area. (2). High quality non-invasive imaging has resulted in a reduction in invasive measurements, pressure studies and cardiac output.

Modest correlations are noted between the natriuretic peptides and echocardiographic parameters of valve lesion severity. (26) See Table 4. The range of correlations with parameters of severity and BNP are listed in the table from the comprehensive Steadman Ray review. The range is r = 0.4 - 0.6 with one study demonstrating extremely low correlations (0.18). (31)

The effect of aortic stenosis is initially pressure overload which causes left ventricular hypertrophy (LVH), increase in LV mass and wall stress. LVH causes diastolic filling impairment. The hypertrophy may be concentric or eccentric. The eccentric LVH is associated with significantly impaired systolic function and a poor clinical prognosis (32).
The effect on the cardiac remodelling in structure and function is likely to be responsible for the compensatory release of natriuretic peptides to reduce the pressure and volume overload.
Table 4: Baseline associations in aortic stenosis. (22)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>First Author (Ref. #)/Year</th>
<th>n</th>
<th>Prospective</th>
<th>BNP</th>
<th>NT-proBNP</th>
<th>ANP</th>
<th>NT-proANP</th>
<th>Statistical Methods</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aortic valve area</strong></td>
<td>Pedrazzini et al. (52)/2008</td>
<td>144</td>
<td>Yes</td>
<td>Yes: lower with increasing tertile BNP, p = 0.016 (TTE)</td>
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<td></td>
<td></td>
<td>Kruskal-Wallis</td>
</tr>
<tr>
<td></td>
<td>Cemri et al. (40)/2008</td>
<td>37</td>
<td>Yes</td>
<td>Yes: r = −0.46, p = 0.008 (TTEi)</td>
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<td></td>
<td></td>
<td>Spearman correlation</td>
</tr>
<tr>
<td></td>
<td>Antonini-Canterin et al.</td>
<td>64</td>
<td>Yes</td>
<td>Yes: r = 0.4, p = 0.001 (TTE)</td>
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<td></td>
<td>Univariate regression analysis</td>
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<td></td>
<td>Weber et al. (45)/2006</td>
<td>159</td>
<td>Yes</td>
<td>Yes: r = 0.380, p &lt; 0.001 (TTE)</td>
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<td>Neverdal et al. (44)/2006</td>
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<td>Yes</td>
<td>No: r = 0.18, p = 0.45 (TTE)</td>
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<td>Linear regression</td>
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<tr>
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<td>40</td>
<td>Yes</td>
<td>Yes: r = −0.449, p = 0.006 (TTE)</td>
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<td>Pearson correlation</td>
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<td></td>
<td>Lim et al. (58)/2004</td>
<td>70</td>
<td>Yes</td>
<td>Yes: r = −0.49, p &lt; 0.0001 (TTE)</td>
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<td></td>
<td></td>
<td>Spearman correlation</td>
</tr>
<tr>
<td></td>
<td>Gerber et al. (48)/2003</td>
<td>74</td>
<td>Yes</td>
<td>Yes: r = −0.55, p &lt; 0.05 (TTE)</td>
<td>Yes: r = −0.57, p &lt; 0.05 (TTE)</td>
<td>Yes: r = −0.55, p &lt; 0.05 (TTE)</td>
<td>Pearson correlation</td>
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<tr>
<td></td>
<td>Qi et al. (73)/2002</td>
<td>51</td>
<td>Yes</td>
<td>Yes: r = −0.46, p = 0.037 (TTEi)</td>
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<td>Pearson correlation</td>
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<td></td>
<td>Qi et al. (17)/2001</td>
<td>67</td>
<td>Yes</td>
<td>Yes: r = −0.56, p &lt; 0.001 (TTEi)</td>
<td>Yes: r = −0.52, p &lt; 0.001 (TTEi)</td>
<td>Yes: r = −0.33, p &lt; 0.05 (TTEi)</td>
<td>Pearson correlation and univariate linear regression</td>
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<td><strong>Peak aortic valve velocity</strong></td>
<td>Neverdal et al. (44)/2006</td>
<td>22</td>
<td>Yes</td>
<td>No: r = 0.14, p = 0.54 (TTE)</td>
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<td>Linear regression</td>
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<tr>
<td>Study</td>
<td>Sample Size</td>
<td>Results (TTE)</td>
<td>Statistical Test</td>
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<tr>
<td>Lim et al. (58)/2004</td>
<td>70</td>
<td>Yes: $r = 0.33, p &lt; 0.05$</td>
<td>Spearman correlation</td>
<td></td>
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<tr>
<td>Weber et al. (61)/2004</td>
<td>146</td>
<td>Yes</td>
<td>Weak: $r = 0.04, p &lt; 0.01$</td>
<td>Pearson correlation</td>
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<tr>
<td>Gerber et al. (48)/2003</td>
<td>74</td>
<td>Yes: $r = 0.33, p &lt; 0.05$</td>
<td>Yes: $r = 0.35, p &lt; 0.05$, Yes: $r = 0.38, p &lt; 0.05$</td>
<td>Pearson correlation</td>
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<td>Talwar et al. (39)/2001</td>
<td>15</td>
<td>Yes: $r = 0.53, p &lt; 0.05$</td>
<td>Pearson correlation</td>
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<tr>
<td>Prasad et al. (38)/1997</td>
<td>30</td>
<td>Yes: $r = 0.43, p &lt; 0.02$</td>
<td>NS: $r = 0.31, p &lt; 0.1$</td>
<td>Univariate regression analysis</td>
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<tr>
<td>Pedrazzini et al. (52)/2008</td>
<td>144</td>
<td>Yes</td>
<td>No: 3 tertiles BNP, $p = 0.137$ (TTE)</td>
<td>Kruskal-Wallis</td>
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<tr>
<td>Orlowska-Baranowska et al. (43)/2008</td>
<td>147</td>
<td>Yes: $r = 0.25, p = 0.002$ (TTE)</td>
<td>Linear regression</td>
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<td>Cemri et al. (40)/2008</td>
<td>37</td>
<td>Yes</td>
<td>Yes: $r = 0.38, p = 0.026$ (TTE)</td>
<td>Spearman correlation</td>
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<td>Antonini-Canterin et al. (46)/2008</td>
<td>64</td>
<td>Yes</td>
<td>No: $r = 0.08, p = 0.52$ (TTE)</td>
<td>Univariate regression analysis</td>
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<tr>
<td>Weber et al. (45)/2006</td>
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<td>Yes</td>
<td>Yes: $r = 0.351, p &lt; 0.001$ (TTE)</td>
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<tr>
<td>Weber et al. (72)/2005</td>
<td>109</td>
<td>Yes</td>
<td>Yes: severe &gt; moderate &gt; mild, $p &lt; 0.01$ (TTE)</td>
<td>Kruskal-Wallis test</td>
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<tr>
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<td>Yes</td>
<td>Yes: $r = 0.39, p &lt; 0.01$ (TTE)</td>
<td>Pearson correlation</td>
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<td>70</td>
<td>Yes</td>
<td>Yes: $r = 0.34, p = 0.004$ (TTE)</td>
<td>Spearman correlation</td>
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<td>Yes: $r = 0.36, p &lt; 0.05$ (TTE)</td>
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<td>Yes: $r = 0.38, p &lt; 0.05$ (TTE)</td>
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<td>Year</td>
<td>N</td>
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<td>r, p Value</td>
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<td>r, p Value</td>
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<td>Qi et al. (17)/2001</td>
<td>67</td>
<td>Yes</td>
<td>Yes: r = 0.32, p &lt; 0.01 (TTE)</td>
<td>Yes: r = 0.25, p &lt; 0.05 (TTE)</td>
<td>No: r = 0.15 (TTE)</td>
<td>No: r = 0.09 (TTE)</td>
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<td>Prasad et al. (38)/1997</td>
<td>30</td>
<td>Yes</td>
<td>Yes: r = 0.57, p &lt; 0.001 (TTE)</td>
<td>Yes: r = 0.38, p &lt; 0.04 (TTE)</td>
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<td>37</td>
<td>Yes</td>
<td>Yes: r = 0.49, p = 0.003 (TTEi)</td>
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<td>147</td>
<td>Yes</td>
<td>Yes: r = 0.55, p &lt; 0.0001 (TTEi)</td>
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<td>Linear regression</td>
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<td>Antonini-Canterin et al. (46)/2008</td>
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<td>Yes</td>
<td>Yes: r = 0.49, p &lt; 0.001 (TTEi)</td>
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<td>Poulsen et al. (49)/2007</td>
<td>45</td>
<td>Yes</td>
<td>Yes: r = 0.63, p &lt; 0.001 (TTEi)</td>
<td>Yes: r = 0.53, p &lt; 0.001</td>
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<td>Spearman correlation</td>
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<tr>
<td>Weber et al. (45)/2006</td>
<td>159</td>
<td>Yes</td>
<td>Yes: r = 0.434, p &lt; 0.001 (TTEi)</td>
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<td>Spearman correlation</td>
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<td>Neverdal et al. (44)/2006</td>
<td>22</td>
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<td>Weber et al. (72)/2005</td>
<td>109</td>
<td>Yes</td>
<td></td>
<td>Yes: severe &gt; moderate &gt; mild, p &lt; 0.01 (TTE)</td>
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<td>Kruskal-Wallis</td>
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<td>Yes: r = NQ, p = 0.005 (TTEi)</td>
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<tr>
<td>Qi et al. (17)/2001</td>
<td>67</td>
<td>Yes</td>
<td>Yes: r = 0.6, p &lt; 0.001 (TTEi)</td>
<td>Yes: r = 0.57, p &lt; 0.001 (TTEi)</td>
<td>Yes: r = 0.44, p &lt; 0.001 (TTEi)</td>
<td>Yes: r = 0.52, p &lt; 0.001 (TTEi)</td>
<td>Pearson correlation and univariate linear regression</td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>n</td>
<td>Yes/No</td>
<td>Univariate regression analysis</td>
<td>Ikeda et al. (41)/1997</td>
<td>13</td>
<td>Yes/No</td>
<td>Univariate regression analysis</td>
<td></td>
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</tr>
<tr>
<td>Prasad et al. (38)/1997</td>
<td>30</td>
<td>Yes</td>
<td>Yes: $r = 0.42$, $p &lt; 0.03$</td>
<td>No: $r = 0.15$, $p = 0.05$</td>
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<td></td>
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<td>(TTEi)</td>
<td>(TTEi)</td>
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<tr>
<td>Ikeda et al. (41)/1997</td>
<td>13</td>
<td>Yes</td>
<td>No: values not quoted (TTEi)</td>
<td>No: values not quoted (TTEi)</td>
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</tr>
<tr>
<td>Outcome measure</td>
<td>First Author/Year</td>
<td>N</td>
<td>Biomarker(s)</td>
<td>Subjects</td>
<td>Other Valve Disease</td>
<td>CAD</td>
<td>Comorbidities</td>
<td>Design</td>
</tr>
<tr>
<td>---------------------------------------------</td>
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</tr>
<tr>
<td>Symptoms in unoperated patients</td>
<td>Gerber et al. (66)/2005</td>
<td>29</td>
<td>NT-proBNP</td>
<td>Asymptomatic, at least mild AS (peak velocity ≥2.5 m/s)</td>
<td>Excluded &gt;mild MR or AR</td>
<td>Excluded MI &lt;6 months, RWMA, previous cardiac surgery</td>
<td>Not reported</td>
<td>Prospective cohort mean follow-up 18 months</td>
</tr>
<tr>
<td></td>
<td>Bergler-Klein et al. (51)/2004</td>
<td>43</td>
<td>BNP, NT-proBNP, NT-proANP</td>
<td>Severe AS (peak velocity &gt;4 m/s or AVA &lt;1 cm²)</td>
<td>Excluded &gt;mild MVD or AR</td>
<td>9%; not all had angiography</td>
<td>67% HT</td>
<td>Prospective cohort follow-up 377 ± 150 days</td>
</tr>
<tr>
<td>Survival without AVR</td>
<td>Nessmith et al. (57)/2005</td>
<td>103 total; 24 asymptomatic; 79 symptomatic but unoperated</td>
<td>BNP</td>
<td>AVA &lt;1.2 cm²</td>
<td>Not reported</td>
<td>Excluded MI &lt;6 mo, RWMA, previous cardiac surgery</td>
<td>83% HT, 27% DM</td>
<td>Prospective cohort median follow-up 227 days</td>
</tr>
<tr>
<td>MACE: death/symptom or positive exercise test results-driven AVR</td>
<td>Monini et al. (69)/2009</td>
<td>107</td>
<td>BNP</td>
<td>Asymptomatic AS (mean peak velocity 4.1 m/s)</td>
<td>Excluded more than mild other valve lesions</td>
<td>22%, not all had angiography</td>
<td>56% HT, 12% DM, all SR</td>
<td>Prospective cohort follow-up 24 mo</td>
</tr>
<tr>
<td>MACE: CVS death/hospitalization for HF/AVR</td>
<td>Antonini-Canterini et al. (46)/2008</td>
<td>64</td>
<td>BNP</td>
<td>MeanAVA 0.9 cm² (range 0.3–1.7 cm²); no more than mild AR</td>
<td>Did not exclude other valve disease; severe MR in 3</td>
<td>28%, not all had angiography</td>
<td>55% HT, 17% DM, 9% AF</td>
<td>Prospective cohort median follow-up 8 mo</td>
</tr>
<tr>
<td>MACE:</td>
<td>Poh et (62)/2005</td>
<td>53</td>
<td>NT-proBNP</td>
<td>Variable degrees of AS</td>
<td>Excluded</td>
<td>Known</td>
<td>60%</td>
<td>Prospecti</td>
</tr>
<tr>
<td>MACE: CVS death/symptoms/AVR</td>
<td>Dichtl et al. (68)/2008</td>
<td>47</td>
<td>NT-proBNP, CRP</td>
<td>Asymptomatic patients, at least mild calcific AS (mean gradient &gt;15 mm Hg, peak velocity &gt;2 m/s)</td>
<td>Excluded MS, severe MR, severe AR</td>
<td>No history of CAD</td>
<td>50% HT, 13% DM, 11% AF</td>
<td>Randomized trial of atorvastatin</td>
</tr>
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</tr>
<tr>
<td>MACE: CVS death/hospitalization for HF</td>
<td>Weber et al. (45)/2006</td>
<td>57</td>
<td>conservative ly managed</td>
<td>NT-proBNP</td>
<td>Mild (MPG &lt;30 mm Hg), moderate (30–50 mm Hg), or severe (&gt;50 mm Hg) AS, excluded AR &gt;II</td>
<td>Excluded MR &gt;II</td>
<td>33% of conservatively managed, not all had angiography</td>
<td>11% AF</td>
</tr>
<tr>
<td>MACE: CVS death/symptoms/AVR</td>
<td>Feuchtner et al. (67)/2006</td>
<td>34</td>
<td>BNP</td>
<td>Asymptomatic AS</td>
<td>Excluded &gt;2+ AR</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Prospective cohort follow-up 18–24 months</td>
</tr>
<tr>
<td>MACE: referral for AVR</td>
<td>Weber et al. (61)/2004</td>
<td>146</td>
<td>NT-proBNP</td>
<td>Mild, moderate, and severe AS (mean pressure gradient &lt;30 mm Hg, 30–50 mm Hg, and &gt;50 mm Hg, respectively)</td>
<td>Not reported</td>
<td>25%</td>
<td>74% HT, 21% DM, 13% AF</td>
<td>Prospective cohort</td>
</tr>
</tbody>
</table>
Table 6: Clinical Outcomes in Prospective Studies of Asymptomatic Aortic Stenosis in Adults (22)

<table>
<thead>
<tr>
<th>Study, Year</th>
<th>No. of Patients</th>
<th>Severity of Aortic Stenosis</th>
<th>Age, y</th>
<th>Mean Follow-Up</th>
<th>Group</th>
<th>Event-Free Survival Without Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kelly et al., 1988 (109)</td>
<td>51</td>
<td>Vmax greater than 3.6 m per second</td>
<td>63 ± 8</td>
<td>5–25 mo</td>
<td>Overall</td>
<td>59% at 15 mo</td>
</tr>
<tr>
<td>Pellikka et al., 1990 (114)</td>
<td>113</td>
<td>Vmax 4.0 m per second or greater</td>
<td>40–94</td>
<td>20 mo</td>
<td>Overall</td>
<td>86% at 1 y</td>
</tr>
<tr>
<td>Overall</td>
<td>62% at 2 y</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kennedy et al., 1991 (115)</td>
<td>66</td>
<td>AVA 0.7–1.2 cm2</td>
<td>67 ± 10</td>
<td>35 mo</td>
<td>Overall</td>
<td>59% at 4 y</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Otto et al., 1997 (61)</td>
<td>123</td>
<td>Vmax greater than 2.6 m per second</td>
<td>63 ± 16</td>
<td>2.5 ± 1.4 y</td>
<td>Overall</td>
<td>93 ± 5% at 1 y</td>
</tr>
<tr>
<td>62 ± 8% at 3 y</td>
<td>26 ± 10% at 5 y</td>
<td></td>
<td></td>
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<tr>
<td>Subgroups:</td>
<td></td>
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<tr>
<td>Vmax less than 3–4 m per second</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>84 ± 16% at 2 y</td>
</tr>
<tr>
<td>Vmax 3–4 m per second</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>66 ± 13% at 2 y</td>
</tr>
<tr>
<td>Vmax greater than 3 m per second</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>21 ± 18% at 2 y</td>
</tr>
<tr>
<td>Rosenhek et al., 2000 (96)</td>
<td>128</td>
<td>Vmax greater than 4.0 m per second</td>
<td>60 ± 18</td>
<td>22 ± 18 mo</td>
<td>Overall</td>
<td>67 ± 5% at 1 y</td>
</tr>
<tr>
<td>56 ± 55% at 2 y</td>
<td>33 ± 5% at 4 y</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Subgroups:</td>
<td></td>
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<tr>
<td>No or mild Ca2+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>75 ± 9% at 4 y</td>
</tr>
<tr>
<td>Moderate-severe Ca2+</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>20 ± 5% at 4 y</td>
</tr>
<tr>
<td>Amato et al., 2001 (117)</td>
<td>66</td>
<td>AVA 1.0 cm2 or greater</td>
<td>18–80</td>
<td>15 ± 12 mo</td>
<td>Overall</td>
<td>57% at 1 y</td>
</tr>
<tr>
<td>38% at 2 y</td>
<td></td>
<td></td>
<td>(50 ± 15)</td>
<td></td>
<td></td>
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<tr>
<td>Subgroups:</td>
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<tr>
<td>AVA 0.7 cm2 or greater</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>72% at 2 y</td>
</tr>
<tr>
<td>AVA less than 0.7 cm2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>21% at 2 y</td>
</tr>
<tr>
<td>Negative exercise test</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>85% at 2 y</td>
</tr>
<tr>
<td>Study</td>
<td>N</td>
<td>Criteria</td>
<td>Age Range</td>
<td>Follow-Up</td>
<td>Subgroups:</td>
<td>Positive exercise test*</td>
</tr>
<tr>
<td>--------------------------</td>
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<td>--------------------------------------------</td>
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</tr>
<tr>
<td>Das et al., 2005 (118)</td>
<td>125</td>
<td>AVA less than 1.4 cm²</td>
<td>56–74 (mean 65)</td>
<td>12 mo</td>
<td>Subgroups:</td>
<td></td>
</tr>
<tr>
<td>AVA 1.2 cm² or greater</td>
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<tr>
<td></td>
<td>100% at 1 y</td>
<td></td>
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</tr>
<tr>
<td>AVA 0.8 cm² or less</td>
<td>46% at 1 y</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Pellikka et al., 2005</td>
<td>622</td>
<td>Vmax 4.0 m per second or greater</td>
<td>72 ± 11</td>
<td>5.4 ± 4.0 y</td>
<td></td>
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<tr>
<td>(116)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Overall</td>
<td>82% at 1 y</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>67% at 2 y</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>33% at 5 y</td>
<td></td>
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</tbody>
</table>
Figure 2: NT-proBNP levels versus severity of aortic stenosis. (22)
Figure 3: Flowchart for management of severe aortic stenosis (2)
Coronary artery disease

In patients with aortic stenosis, the prevalence of coronary artery disease is estimated to be > 50%. (33). This can include single vessel to multivessel disease in heavily calcified vessels. This may be higher since these estimations are based on clinical history and angiography, rather than screening all patients with aortic stenosis. Patients with moderate to severe coronary artery disease (more than 50% flow limiting stenosis) are currently recommended for coronary artery bypass surgery (CABG) at the time of AVR. This combined surgery carries a higher risk than isolated valve replacement. Combined AVR-CABG has a higher incidence of postoperative complications versus isolated AVR: permanent stroke (3.2 vs. 1.5%), prolonged ventilation (12.2 vs. 7.1%), and operative mortality (6.8 vs. 4%). (34)

The Mayo clinic reported AVR- CABG outcomes in 154 patients with left ventricular ejection fraction (LVEF) ≤35 %. The thirty day mortality was 9%. The coronary disease predictor of mortality was (Two vessel or left main stem disease). The five year survival was 58%. The NYHA functional class improved by one class in 88%, and two or more classes in 66% of patients. Improvement in LVEF occurred in 76% of patients. (35)

In AS and coronary disease the increased and normal BNP levels have been reported. (36, 37, 38) This is a confounding factor and a recognized limitation when using biomarkers to assess outcomes in aortic stenosis.

In patients undergoing coronary artery bypass surgery for severe coronary artery disease, the presence of moderate to severe aortic stenosis is likely to require concurrent AVR. In patients undergoing percutaneous aortic valve replacement, the severity of underlying disease in the coronary arteries is taken into account. Pre-procedural coronary artery stenting is usually undertaken before percutaneous valve replacement in order to alleviate the need for future angioplasty after the percutaneous valve has been deployed. The percutaneous valve has the potential to obstruct the ostia of the left and right coronary arteries which can result in technical difficulties during coronary angioplasty. This has been shown with both the Edwards sapiens valve and the Core valve, the two types of percutaneous valves.
Aortic stenosis in octogenarians and nonagenarians

There is a higher morbidity and operative mortality associated with surgical AVR in elderly patients. Surgery has, however, been shown to prolong and improve the quality of life. Patients in these age groups usually have multiple comorbidities and are deemed to be a poor surgical risk. This has resulted in the advent of percutaneous valve replacement as a therapeutic option. Cardiothoracic surgery with cardiac bypass carries a risk of stroke, ICU stay, and poor postoperative functional capacity due to deconditioning following major surgery. This can have a significant impact on the long term quality of life of these patients. Age, however, is not considered a contraindication for valve surgery. Decisions should be made on an individual basis taking into account the patient’s wishes, cardiac and noncardiac indicators, and the availability of percutaneous therapy. The timing of surgery in this group is essential as any delay may result in the patient becoming a high risk surgical candidate due to the onset of new pathological conditions or the progression of concomitant clinical disease. (1)

Multiple valve disease

When mitral regurgitation is associated with aortic stenosis, there will be high ventricular pressures, and this may present as increased jet velocities and increased size of the color jet during Doppler echocardiography. The functional mitral regurgitation may resolve after the aortic valve is replaced. This is usually if the severity is less than moderate. Severe mitral valve prolapse or flail leaflets, rheumatic mitral valve disease, or bacterial endocarditis may require concurrent surgical intervention on the mitral valve. (1)

Surgical risks

For surgery to be a viable option, the operative risk must be less than the risk of sudden death (2-3%). AVR does not abolish the risk of sudden death, and insertion of a prosthetic heart valve carries its own morbidity and mortality. Complications of surgery include prosthesis dysfunction, mismatch, paravalvular leak, thrombus formation, arterial embolism, endocarditis, and anticoagulation issues. The frequency of complications is at least 3% per year. Death due valve pathology in the asymptomatic state approximates 1% per year. Thus, even if surgical mortality can be minimized, the combined risk of valve replacement and the late complications of a
prosthetic valve exceed the possibility of preventing sudden death in a truly asymptomatic patient. This further stresses the importance of further investigating the onset of the symptomatic state using exercise testing and biomarkers.

**Aortic valvotomy**

Percutaneous aortic balloon valvotomy is a procedure in which one or more balloons are placed across the stenotic aortic valve and inflated. The aim is to relieve the stenosis by fracturing calcific deposits within the valve leaflets. Stretching of the annulus and separation of the calcified commissures improves the valve area temporarily. The new valve area rarely exceeds 1.0 cm². Early changes reveal a moderate reduction in the transvalvular pressure gradient and an often dramatic improvement in symptoms post-procedure. Serious complications (stroke, aortic regurgitation, myocardial infarction) can occur in 10 -20% of cases. The ruptured valve also has a risk of bacterial endocarditis. Re-stenosis and clinical deterioration occur in most cases within 6 to 12 months, and the long-term outcome resembles the natural history of untreated AS. Repeat balloon valvotomy can be performed, but most patients fail within six months.

**BNP as a predictor of outcome in aortic stenosis**

The onset of symptoms determines the timing of surgery in most cases, except for patients with asymptomatic adverse LV remodelling. (2) Asymptomatic patients who develop symptoms during follow-up have higher levels of BNP (39) and NT-proBNP (39, 40) at baseline. Aortic stenosis patients with a plasma level of NT-proBNP >50 pmol/l at baseline were more likely to have symptoms develop (55%) than patients with levels of NT-proBNP within normal limits (11%) (OR: 9.6, 95% CI: 2 to 64, p <0.02) (40). Routine echocardiographic measures of AVA, peak aortic velocity, and LVEF were less reliable predictors of symptomatic onset (40).

Outcomes and the onset of symptoms have to take into account the following: age, LV function, valve gradients, coronary artery disease, comorbidities, renal function and anaesthetic risk. (2) However studies have shown that those in whom symptoms developed did not differ significantly with regard to age, peak and mean gradients, and the presence of CAD. They had a slightly smaller AVA and slightly lower LVEF. However, by multivariate analysis, only NT-
proBNP (p <0.05) and LVEF (p <0.05) were independent predictors of remaining free of symptoms during follow-up (39). Table 7 shows the symptom free survival over 12 months in patients with severe AS.

Table 7: Symptom-free survival versus NT-proBNP levels at baseline. (39)

<table>
<thead>
<tr>
<th>Time</th>
<th>NT-proBNP &lt; 80 pmol/l</th>
<th>NT-proBNP &gt; 80 pmol/l</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 months</td>
<td>100%</td>
<td>92%</td>
</tr>
<tr>
<td>6 months</td>
<td>88%</td>
<td>58%</td>
</tr>
<tr>
<td>9 months</td>
<td>88%</td>
<td>35%</td>
</tr>
<tr>
<td>12 months</td>
<td>69%</td>
<td>18%</td>
</tr>
</tbody>
</table>

Age is one of the main predictors of survival in aortic stenosis. In an elderly cohort of 124 unoperated patients with moderate to severe aortic stenosis, survival was significantly influenced by the presence of symptoms (relative risk: 7.5, p < 0.01) and BNP tertile (relative risk: 2.9, p < 0.001) (41). The 1-year mortality rate without surgery was 6%, 34%, and 60% with each increasing tertile. No patients with BNP <100 pg/ml died (41). The combination of BNP and symptoms provided a better prediction of survival than symptoms alone (chi-square 13.6, p < 0.001) (41). BNP significantly (relative risk: 2.8, p < 0.01) influenced survival after correction for other univariate predictors: CAD, symptoms, NYHA functional class, LVEF, and AVA (41).

Two other studies in patients with variable severity of AS, many of whom had symptoms or in whom symptoms developed but were still predominantly managed medically, have also shown increased mortality or hospitalization with heart failure in those with elevated BNP (29) or NT-proBNP (42). In the Weber et al. (42) study of the conservatively managed patients with an adverse outcome, only one-third had severe AS, and, compared with event-free survivors, the prevalence of CAD was almost double and LVEF was significantly lower.

Predicting MACE including AVR.

Three relatively small studies in patients with asymptomatic mild-severe AS have shown that those with elevated levels of NT-proBNP are more likely to die, be hospitalized, or need AVR due to the development of symptoms (43, 44, 45). Weber et al. (37) also demonstrated that NT-proBNP using an optimized cutoff of 550 pg/ml is a good indicator (85% accuracy) of the clinician’s decision to refer for AVR in 105 patients with severe aortic stenosis, 84 of whom had American College of Cardiology/American Heart Association indications for surgery. The group from Vienna also showed that low BNP/NT-proBNP/NT-proANP are predictive of short-term symptom-free survival in 43
asymptomatic patients with severe aortic stenosis (39), with NT-proBNP having the best discrimination. Monin et al. (46), from France, recently suggested incorporating BNP levels into a continuous risk score to predict MACE (46). MACE were largely driven by positive exercise tests leading to referral for AVR while still asymptomatic. Although these studies clearly demonstrate the potential of BNP/NT-proBNP as useful prognostic markers in symptomatic AS, they do not give us evidence that operating on asymptomatic patients with high levels leads to a reduction in mortality or better functional outcome.

**Predictors of post-operative outcome.**

Immediately post surgical AVR for AS, there is an increase in BNP (47). BNP then decreases significantly at 6 and 12 months post-AVR but does not return to normal (48, 37). Decreases in BNP parallel decreases in mean transvalvular pressure gradient and left ventricular mass (37). Patients with the largest post-operative valve area index having the largest decrease in NT-proBNP (49).

Elevated BNP levels post-operatively may suggest that BNP is a marker of insufficient reverse remodelling and inadequate recovery. This will continue to stimulate BNP synthesis. Alternatively, because BNP inhibits myocyte growth and fibrosis (50), it may have a more direct role in the reverse remodeling process. Mean myocardial systolic strain increases after AVR, which occurs in parallel with decreases in LVMI, both of which are independently related to changes in NT-proBNP (r =0.67, p < 0.001; R = 0.71, p < 0.001) during 12 months of follow-up after AVR (51). NT-proBNP is a significant predictor of normal post-operative LVEF, along with pre-operative LVEF, by multivariate analysis (39). Post-operative changes in LA volume and LA pressure were reflected in ANP (51) and NT-proANP (49) levels, respectively. Persistently high NT-proANP seems to be predictive of late post-operative atrial fibrillation (AF), consistent with high LA pressure being an important determinant of AF (52).

**Post-operative symptoms**

Three studies demonstrated that high preoperative BNP/NT-proBNP levels are associated with decreased symptomatic improvement in AS patients (39, 53, 54). Patients in whom there is no symptomatic improvement tend to have non-significant decreases in NT-proBNP and LVMI even though the transvalvular pressure gradient decreases (54). Seventeen of 40 patients with symptomatic AS who underwent AVR and in whom symptoms of left-sided heart failure, right-sided heart failure, or hypotension developed in-hospital were characterized by significantly higher baseline pre-operative BNP levels (399 ± 82 pg/ml vs. 124 ± 41 pg/ml, p < 0.011), end-diastolic wall stress, and pulmonary capillary wedge pressure but with similar severity of AS and systolic function (53).
Survival

The prognostic value of BNP/NT-proBNP for survival in operated patients with severe AS (36, 39, 54) and a fourth reported on 70 patients, of whom 43 had AVR (55). Two studies showed that NT-proBNP (39) and BNP (36) were independent predictors of perioperative mortality. The latter study also demonstrated the superiority of BNP in the prediction of perioperative and long-term mortality compared with the commonly used logistic EuroSCORE (36). These results tend to be supported by Lim et al. (55), although the mortality results included death in 7 patients who did not have surgery. The 4 patients who did have AVR and died all had increased BNP (55). In contrast, however, NT-proBNP was not predictive of survival or hospitalization for heart failure in 102 patients with severe AS undergoing AVR (42). There is not a clear explanation why these results differed but may be related to the lower frequency of concomitant coronary artery bypass graft and slightly younger age of patients in the Weber et al. (42) study compared with the Pedrazzini et al. (36) study (29% vs. 42% coronary artery bypass graft, 69 ± 10 years vs. 73 ± 9 years, respectively).

Low-flow, low-gradient aortic stenosis

BNP is higher in patients with truly severe compared with pseudosevere AS and correlates with AS severity and LVEF (56). BNP was a strong predictor of outcome. With BNP levels >550 pg/ml, the cumulative 1-year survival rate of the total cohort when compared with those with BNP levels <550 pg/ml was 47 ±9% versus 97 ± 3% (p < 0.0001), and the postoperative survival rate was 53 % versus 92 ± 7% (56). When subdivided into truly severe and pseudosevere AS, the groups were too small for statistical analysis; however, a consistent pattern of higher mortality was observed in patients with BNP >550 pg/ml. The poorer survival in patients with high BNP/NT-proBNP undergoing AVR does suggest that those patients may have more irreversible myocardial dysfunction, which may be directly related to overt replacement myocardial fibrosis (57).

References


45. Dichtl W, Alber HF, Feuchtner GM, et al. Prognosis and risk factors in patients with asymptomatic...


Chapter 5
The Role of B-type-Natriuretic Peptide (BNP) and Exercise testing in Chronic Mitral Valve Regurgitation
Chronic Asymptomatic Mitral Regurgitation

I. Relevant Clinical Anatomy.

Mitral Valve

The mitral valve (Figure 1) is part of the left heart system, and connects the left atrium to the left ventricle. The valve opens in diastole to allow blood to fill the left ventricle, and closes during systole. The mitral valve system consists of the following components: (1)

1. Annulus
2. Leaflets
3. Commisures
4. Papillary muscles
5. Chordae tendinae

Figure 1: Overall anatomy of the heart, including the mitral valve. MV: Mitral valve, A: Anterior Leaflet, P: Posterior Leaflet (1)
**Annulus**

The annulus is a fibrous ring surrounding the aperture between the left ventricle and atria. The leaflets attach onto the mitral valve. The annulus is anchored to the cardiac skeleton along the side of the anterior leaflet, but is free on that of the posterior leaflet (Figure 2). Therefore, pathological dilation of the annulus usually occurs on the posterior side. This feature is important for mitral repair surgery. (1)

![Figure 2: Diagram of the cardiac skeleton, with mitral annulus. (1)](image)

**Leaflets**

The mitral valve has two leaflets: anterior and posterior, in contrast to the other cardiac valves, which have three. The anterior leaflet is usually one piece, while the posterior leaflet is divided into scallops by minor commisures. The middle scallop of the posterior valve is usually responsible for mitral regurgitation. (1)
Figure 3: Picture of the mitral valve leaflets, with four scallops on the posterior leaflet. A: Anterior leaflet, P: Posterior leaflet, C: Major commisures, *: Minor commisures (1)

Commisures

Two major commisures separate the anterior and posterior leaflets. Minor commisures divide the posterior leaflet into scallops (Figure 3). The anterolateral and posteromedial papillary muscles lie underneath the major commisures. (1)

Papillary muscles

The papillary muscles are located on the left ventricular wall, and contract during systole to keep the mitral valve closed. The two papillary muscles are the anterolateral and posteromedial muscles. The anterolateral muscle has one head, and is supplied by multiple arteries from the left coronary circulation. The posteromedial muscle has multiple heads, and is supplied only by the right coronary artery. An acute myocardial infarction of the right coronary artery can cause mitral valve prolapse of the posterior leaflet due to rupture of the posteromedial papillary muscle. This is the most common cause of post-MI prolapse. (1)

Chordae tendinae

Chordae tendinae connect the mitral valve leaflets to the papillary muscles. The combination of papillary muscles and chordate tendinae prevent mitral valve prolapse. Mitral valve
prolapse may be caused by elongation or rupture of the chordate tendinae, most commonly of the posterior leaflet. (1)

**Left Atrium**

The left atrium (LA) receives oxygenated blood from the lungs via the pulmonary veins. The openings for the pulmonary veins are on the posterior surface of the left atrium.

The left atrium then pumps the blood into the left ventricle through the mitral valve during atrial systole / ventricular diastole. The mitral valve lies on the inferior surface of the left atrium. The backflow of blood is prevented by muscle cuffs that surround the pulmonary veins, which contract like sphincters during left atrial systole, thereby preventing blood from flowing back into the pulmonary circulation. (1)

**Left atrial appendage**

The left atrial appendage is a muscular pouch that lies anterolaterally of the left atrium. The left atrial appendage is often divided into lobes, most commonly two to four. Of clinical significance, the appendage is a common source of emboli in atrial fibrillation. (1)

**Inter-atrial septum**

The inter-atrial septum separates the left and right atria. An opening between the two atria, called the foramen ovalae, exists during fetal development. This closes after birth, becoming a round depression in the inter-atrial septum, known as the fossa ovalis. However, approximately 1/3 of adults have a patent foramen ovalae, where the foramen ovalae remains open. This can potentially lead to an atrial septal defect if the atria become stretched. (1)
Figure 4: Oblique, short-axis cut at the base of the heart. The esophagus (E) is posterior and adjacent to the left atrium (LA) and adjacent to the descending thoracic aorta (DAO). The left upper pulmonary vein (LUPV) and left lower pulmonary vein (LLPV) are clearly seen. (1)

II. Pathophysiology and Natural History

Mitral regurgitation (MR) is the second most common valve abnormality after aortic stenosis. (2) Patients with mild to moderate MR may remain asymptomatic with little or no haemodynamic compromise for many years. However, MR from a primary mitral valve abnormality tends to progress over time, with an increase in volume overload due to widening of the mitral valve orifice. (2) The natural history of severe MR due to a flail posterior leaflet has been documented (3). At 10 years, 90% of patients are dead or require surgical mitral valve repair. The mortality rate in patients with severe MR caused by flail leaflets is 6% to 7% per year.

Types of Mitral Regurgitation

Mitral regurgitation is categorized as either organic or functional (Table 1). Organic MR involves an abnormality of the leaflets or chordal structures. Functional MR is due to the
dilatation of the mitral valve annulus, secondary to weakening of the supporting structures causing failure of leaflet co-aptation (closure). (4)

Table 1: Examples of functional and organic etiologies of mitral regurgitation.

<table>
<thead>
<tr>
<th>Organic</th>
<th>Functional</th>
</tr>
</thead>
<tbody>
<tr>
<td>Degenerative myxomatous valve disease</td>
<td>Ischemic heart disease (most common cause)</td>
</tr>
<tr>
<td>Rheumatic heart disease</td>
<td>LV dilatation secondary to aortic valve disease or primary CMO</td>
</tr>
<tr>
<td>Endocarditis</td>
<td></td>
</tr>
</tbody>
</table>

Natural Progression

Progression of mitral regurgitation is determined by progression of lesions or mitral annulus size (5). Once the MR has become severe, volume overload occurs, causing chamber dilatation and eccentric hypertrophy. In eccentric cardiac hypertrophy, new sarcomeres are created in series, which increases the length of individual myocardial fibers (6, 7). The initial compensatory phase involving eccentric hypertrophy is followed by decompensation and impaired cardiac output.

Compensatory state

The increase in LV end-diastolic volume is compensatory because it permits an increase in total stroke volume, which maintains cardiac output (8). There is a simultaneous increase in LV and left atrial size, which accommodates the regurgitated volume at a lower filling pressure, which protects against pulmonary congestion. (2) In this phase of compensated MR, the patient may be asymptomatic, even during vigorous exercise. It should be noted that in the compensatory phase, augmented preload and reduced or normal afterload (provided by the unloading of the left ventricle into the left atrium) facilitate LV ejection, which results in a large total stroke volume and a normal forward stroke volume. (2) This produces a hyperdynamic state. The duration of the compensated phase of MR is variable, but may last
for many years. However, the prolonged burden of volume overload usually results in LV dysfunction, which can progress to irreversible systolic and diastolic dysfunction. In this phase, contractile dysfunction impairs ejection, and end systolic volume increases. There may be further LV dilatation and increased LV filling pressure. These haemodynamic sequelae result in reduced forward output, pulmonary congestion, and pulmonary hypertension.

**Transition state**

Increased loading conditions often maintain ejection fraction in the low-normal range (0.50 to 0.60) during the transition phase from the compensated to the decompensated state. (2) This occurs in the presence of significant muscle dysfunction, and creates a false sense of normal function (7, 9, 10). Correction of MR should be performed before the advanced phases of LV decompensation set in. This is usually a symptomatic state in keeping with NYHA class III and ambulatory class IV. The transition phase may or may not be symptomatic. When symptomatic, NYHA class II predominates with impaired effort tolerance. Multiple studies indicate that patients with chronic severe MR have a high likelihood of developing symptoms or LV dysfunction over a 10 year period. (5, 11, 12, 13) These symptoms can go unnoticed if the patient has a sedentary lifestyle. A detailed functional capacity history or serial exercise testing can play an important role in detecting a less obvious functional impairment in such patients.

**Decompensation and Sudden Death**

The decompensated state consists of a combination of decreased contractility, increased preload and poor cardiac output. The echocardiographic findings are characterized by severe LV dilatation, elevated end diastolic pressure, and increased wall stress with an impaired ejection fraction. This state is fraught with a wide variety of symptoms, which typically reflect left ventricular dysfunction and volume overload. (4) These include exertional dyspnea, fatigue, listlessness, cough, and generalised weakness and apathy. Weight gain is
common since patients can develop an increasingly sedentary lifestyle. Occupational changes and lifestyle adjustments to accommodate or ward off symptoms are common. Early detection of symptom progression is important since severe symptoms also predict a poor outcome after MV repair or replacement (14). Surgical valve replacement is highly recommended for the symptomatic state with the need to prevent irreversible left ventricular systolic and or diastolic dysfunction. (15) The incidence of sudden death in asymptomatic patients with normal LV function is variable (2). This can be particularly devastating if the patient is still physically active, and able to drive and enjoy a reasonable lifestyle through paced activities. However, patients at risk of sudden death are predominantly those with LV ejection fractions less than 0.60, or with NYHA functional class III–IV symptoms, The risk of sudden death is less in the asymptomatic NYHA class I with normal LV function (5, 14).

III. Diagnosis

The diagnosis of mitral regurgitation is done via a detail history and clinical examination. A well-established estimation of baseline functional capacity is important for gauging the subtle onset of symptoms at subsequent evaluations. (2, 15) Co-morbidities must be documented since they can alter the course of treatment, surgery, and survival.

The physical examination should aim to demonstrate the severity and effect of the valve lesion and chronicity. The factors that need to be detected are the following:

1. Displacement of the left ventricular apex beat from cardiac enlargement and ventricular dilatation.

2. A third heart sound or early diastolic flow rumble may be present, and does not necessarily indicate LV dysfunction.

3. The presence of pulmonary hypertension may indicate advanced disease with worsened prognosis (22).
4. Features of heart failure and fluid overload, including raised JVP, peripheral edema and hepatomegaly.

5. An ECG and chest X-ray are useful in establishing rhythm and for assessing the pulmonary vasculature and pulmonary congestion.

**Echocardiography**

The echocardiogram is central to the diagnosis and assessing the anatomy of the diseased valve and the left ventricle.

<table>
<thead>
<tr>
<th>Class</th>
<th>Indication</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Baseline evaluation of LV size and function, RV and left atrial size, pulmonary artery pressure, and severity of MR in any patient suspected of having MR.</td>
<td>C</td>
</tr>
<tr>
<td></td>
<td>Delineation of the mechanism of MR.</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td>Annual or semiannual surveillance of LV function (estimated by ejection fraction and end-systolic dimension) in asymptomatic patients with moderate to severe MR.</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td>Evaluate the MV apparatus and LV function after a change in signs or symptoms.</td>
<td>C</td>
</tr>
<tr>
<td></td>
<td>Evaluate LV size and function, and MV haemodynamics in the initial evaluation after MV replacement or MV repair.</td>
<td>C</td>
</tr>
<tr>
<td>IIa</td>
<td>Exercise Doppler echocardiography is reasonable in asymptomatic patients with severe MR to assess exercise tolerance and the effects of exercise on pulmonary artery pressure and MR severity.</td>
<td>C</td>
</tr>
</tbody>
</table>

**Transthoracic echocardiogram guidelines**

A baseline, comprehensive, transthoracic, 2D color Doppler echocardiogram is an absolute requirement in the assessment and management of the patient with MR (Table 2). (16) The echocardiogram provides a baseline estimation of left ventricular and left atrial size, and an estimation of the left ventricular contractility and ejection fraction. Qualitative assessment of
the parameters of severity of regurgitation is compulsory (2). Quantification of the severity of MR (Table 3) is strongly recommended. (17, 12, 18, 19) In the majority of patients, an estimate of pulmonary artery pressure can be obtained from the TR peak velocity (20). The structure of the valve leaflets, calcification of the mitral valve apparatus, fibrosis and leaflet excursion determines whether organic or functional valve disease is the aetiology. The severity of echocardiographic lesions should be correlated with the severity on clinical examination. This is documented in a report with a saved, archived set of images available for future reference and emergency if the need arises. Copies are often given to patients for second opinions and safe keeping if they are moving to other states and changing doctors.

**Follow up echocardiogram**

Changes in left ventricular and valve lesion parameters from these baseline values are subsequently used to guide the timing of mitral valve surgery. (2) The heart rate, blood pressure, and medications at the time of each study should be documented, since the afterload and filling time of the ventricle will affect the measured severity of the MR. (16) The rate and rhythm on the electrocardiogram should be documented, especially the presence of atrial fibrillation, which can alter the course of the management.

**Anatomic cause: organic versus functional**

Determining whether the aetiology is organic or functional has important implications for further management, including the type of surgery (repair or replacement). (15) The detailed baseline transthoracic echocardiogram should disclose the anatomic cause of the MR, and classify whether the aetiology as organic or functional.

A central color MR flow jet with a structurally normal mitral valve apparatus in an enlarged ventricle suggests the presence of functional MR. (2) This may be due to annular dilation from left ventricular dilatation, or feathering of the posterior leaflet secondary to regional left
ventricular dysfunction and papillary muscle infarction in patients with ischemic heart disease.

An eccentric color MR flow jet with abnormalities of the mitral valve apparatus suggests organic MR. The echocardiogram should assess the presence of calcium in the annulus or leaflets, the redundancy of the valve leaflets, and the mitral valve leaflet involved (anterior, posterior, or bi-leaflet). Classifications of mitral valve prolapse should also be documented. (16)

Table 3: Classification of the severity of valve disease in adults. AR indicates aortic regurgitation; cath, catheterization; echo, echocardiography; LA, left atrial/atruim; LVOT, left ventricular outflow tract; and MR, mitral regurgitation. * Valve gradients are flow dependent and when used as estimates of severity of valve stenosis should be assessed with knowledge of cardiac output or forward flow across the valve. (17)

<table>
<thead>
<tr>
<th><strong>Aortic Stenosis</strong></th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jet velocity (m per second)</td>
<td>Less than 3.0</td>
<td>3.0–4.0</td>
<td>Greater than 4.0</td>
</tr>
<tr>
<td>Mean gradient* (mm Hg)</td>
<td>Less than 25</td>
<td>25–40</td>
<td>Greater than 40</td>
</tr>
<tr>
<td>Valve area (cm²)</td>
<td>Greater than 1.5</td>
<td>1.0–1.5</td>
<td>Less than 1.0</td>
</tr>
<tr>
<td>Valve area index (cm² per m²)</td>
<td></td>
<td></td>
<td>Less than 0.6</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Mitral Stenosis</strong></th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean gradient* (mm Hg)</td>
<td>Less than 5</td>
<td>5–10</td>
<td>Greater than 10</td>
</tr>
<tr>
<td>Pulmonary artery systolic pressure (mm Hg)</td>
<td>Less than 30</td>
<td>30–50</td>
<td>Greater than 50</td>
</tr>
<tr>
<td>Valve area (cm²)</td>
<td>Greater than 1.5</td>
<td>1.0–1.5</td>
<td>Less than 1.0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Aortic Regurgitation</strong></th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Qualitative</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angiographic grade</td>
<td>1+</td>
<td>2+</td>
<td>3–4+</td>
</tr>
<tr>
<td>Color Doppler jet width</td>
<td>Central jet, width less than 25% of LVOT</td>
<td>Greater than mild but no signs of severe AR</td>
<td>Central jet, width greater than 65% LVOT</td>
</tr>
<tr>
<td>Doppler vena contracta width (cm)</td>
<td>Less than 0.3</td>
<td>0.3–0.6</td>
<td>Greater than 0.6</td>
</tr>
<tr>
<td><strong>Quantitative (cath or echo)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regurgitant volume (ml per beat)</td>
<td>Less than 30</td>
<td>30–59</td>
<td>Greater than or equal to 60</td>
</tr>
<tr>
<td>Regurgitant fraction (%)</td>
<td>Less than 30</td>
<td>30–49</td>
<td>Greater than or equal to 50</td>
</tr>
<tr>
<td>Regurgitant orifice area (cm²)</td>
<td>Less than 0.10</td>
<td>0.10–0.29</td>
<td>Greater than or equal to 0.30</td>
</tr>
</tbody>
</table>
### Additional essential criteria

<table>
<thead>
<tr>
<th>Left ventricular size</th>
<th>Increased</th>
</tr>
</thead>
</table>

### Mitral Regurgitation

<table>
<thead>
<tr>
<th>Qualitative</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angiographic grade</td>
<td>1+</td>
<td>2+</td>
<td>3–4+</td>
</tr>
<tr>
<td>Color Doppler jet area</td>
<td>Small, central jet (less than 4 cm² or less than 20% LA area)</td>
<td>Signs of MR greater than mild present but no criteria for severe MR</td>
<td>Vena contracta width greater than 0.7 cm with large central MR jet (area greater than 40% of LA area) or with a wall-impinging jet of any size, swirling in LA</td>
</tr>
<tr>
<td>Doppler vena contracta width (cm)</td>
<td>Less than 0.3</td>
<td>0.3–0.69</td>
<td>Greater than or equal to 0.70</td>
</tr>
</tbody>
</table>

#### Quantitative (cath or echo)

<table>
<thead>
<tr>
<th>Regurgitant volume (ml per beat)</th>
<th>Less than 30</th>
<th>30–59</th>
<th>Greater than or equal to 60</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regurgitant fraction (%)</td>
<td>Less than 30</td>
<td>30–49</td>
<td>Greater than or equal to 50</td>
</tr>
<tr>
<td>Regurgitant orifice area (cm²)</td>
<td>Less than 0.20</td>
<td>0.2–0.39</td>
<td>Greater than or equal to 0.40</td>
</tr>
</tbody>
</table>

### Right-sided valve disease

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Valve area less than 1.0 cm²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe tricuspid stenosis:</td>
<td>Vena contracta width greater than 0.7 cm and systolic flow reversal in hepatic veins</td>
</tr>
<tr>
<td>Severe tricuspid regurgitation:</td>
<td>Jet velocity greater than 4 m per second or maximum gradient greater than 60 mmHg</td>
</tr>
<tr>
<td>Severe pulmonic stenosis:</td>
<td>Color jet fills outflow tract; dense continuous wave Doppler signal with a steep deceleration slope</td>
</tr>
<tr>
<td>Severe pulmonic regurgitation:</td>
<td></td>
</tr>
</tbody>
</table>

### Repair versus replacement

Echocardiographic assessment and evaluation will help determine the timing and the feasibility of valve repair or replacement if surgery is contemplated. The system proposed by Carpentier (Table 4) allows the echocardiographer to focus on the anatomic and physiologic characteristics of the valve that aid the surgeon in planning the repair. The valve dysfunction is described by the motion of the leaflet’s free edge relative to the plane of the annulus. (21)
The final diagnosis of severe MR for valve surgery should be made by correlating the findings on physical examination with the findings from a comprehensive 2D Doppler echocardiogram. Multiple parameters from the Doppler examination should be used to diagnose severe MR (Table 3) (17), including the color flow jet width and area, the intensity of the continuous-wave Doppler signal, the pulmonary venous flow contour, the peak early mitral inflow velocity, and quantitative measures of effective orifice area and regurgitation volume (2). In addition, there should be enlargement of the left ventricle and left atrium in chronic severe MR. Abnormalities of the MV apparatus are often present if there is severe MR, but ischemic left ventricle dysfunction may also result in severe MR. Non-invasive assessment of MR is usually adequate unless there are poor echocardiographic windows, discrepancies or inconclusive results. If a discrepancy is present, or if the patient has poor windows on trans-thoracic echocardiography, then further evaluation of the severity of MR is required, including magnetic resonance imaging, trans-esophageal echocardiography (Table 5), or cardiac catheterization (Table 6).

**Table 4: Carpentier’s classification of mitral valve leaflet motion (21)**

<table>
<thead>
<tr>
<th>Type</th>
<th>Degree of leaflet free edge motion</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Normal</td>
</tr>
<tr>
<td>II</td>
<td>Increased, as in mitral valve prolapse</td>
</tr>
<tr>
<td>IIIA</td>
<td>Restricted during systole and diastole</td>
</tr>
<tr>
<td>IIIB</td>
<td>Restricted during systole</td>
</tr>
</tbody>
</table>

**Table 5: Indications for trans-esophageal echocardiography (2)**

<table>
<thead>
<tr>
<th>Class</th>
<th>Indication</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Preoperative or intraoperative transesophageal echocardiography is indicated to establish the anatomic basis for severe MR in patients in whom surgery is recommended to assess feasibility of repair and to guide repair.</td>
<td>B</td>
</tr>
</tbody>
</table>
Insufficient information from TTE: severity of MR, mechanism of MR, and/or status of LV function.  

IIa Preoperative transesophageal echocardiography is reasonable in asymptomatic patients with severe MR who are considered for surgery to assess feasibility of repair.

III Transesophageal echocardiography is not indicated for routine follow-up or surveillance of asymptomatic patients with native valve MR.

<table>
<thead>
<tr>
<th>Class</th>
<th>Indication</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Angiographic assessment of MR severity using left ventriculography noninvasive tests are inconclusive regarding severity of MR, LV function, or the need for surgery.</td>
<td>C</td>
</tr>
<tr>
<td></td>
<td>Pulmonary Hypertension: Haemodynamic measurements are indicated when pulmonary artery pressure is out of proportion to the severity of MR or difficult to obtain non-invasively.</td>
<td>C</td>
</tr>
<tr>
<td></td>
<td>Discrepancy between clinical and non-invasive: Left ventriculography and haemodynamic measurements are indicated when there is a discrepancy between clinical and non invasive findings regarding severity of MR.</td>
<td>C</td>
</tr>
<tr>
<td></td>
<td>Coronary angiography is indicated before MV repair or MV replacement in patients at risk for CAD.</td>
<td>C</td>
</tr>
<tr>
<td>III</td>
<td>Left ventriculography and haemodynamic measurements are not indicated in patients with MR in whom valve surgery is not contemplated.</td>
<td>C</td>
</tr>
</tbody>
</table>

**Follow-Up**

Serial testing is required to assess exercise tolerance in the asymptomatic patient, symptomatic status changes in left ventricular function, and progression of disease severity. Exercise testing is especially important if a good history of the patient’s exercise capacity cannot be obtained. Measurement of pulmonary artery pressure and assessment of severity of MR during exercise may be helpful. Interpretation of LV ejection fraction in the patient with MR is made difficult because the loading conditions present in MR facilitate ejection and increase ejection fraction, the standard guide to LV function. Nonetheless, several studies
have indicated that the preoperative ejection fraction is an important predictor of postoperative survival in patients with chronic MR (22, 23, 24, 25, 26).

Ejection fraction in a MR patient with normal LV function is 60% and greater. (2, 15) When the preoperative ejection fraction is less than 60%, postoperative LV function and survival can be adversely affected. (25, 26) This may not hold true for other valve conditions. The hyper-dynamic state is compensatory to the volume overload state. Serial measurements will detect any significant decline in function which will impact on management.

Echocardiographic LV end-systolic dimension (or volume) can be used in the timing of MV surgery. The ACC recommendation for end-systolic left ventricular dimension, (LVESD) should be less than 40 mm preoperatively to ensure normal postoperative LV function (8, 26, 27, 28). The LVESD may be less load dependent than ejection fraction (27). If patients with increased LVESD become symptomatic, they should undergo MV surgery even if LV function is normal.

### Table 7: ACC / AHA follow up recommendations (2)

<table>
<thead>
<tr>
<th>MR Severity</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>Annual follow with appropriate recommendations for antibiotic prophylaxis as required.</td>
</tr>
<tr>
<td>Moderate</td>
<td>Annual follow up, or sooner as directed by symptoms, with antibiotic prophylaxis as required.</td>
</tr>
<tr>
<td>Severe</td>
<td>6- 12 month follow up, or sooner as directed by symptoms, with antibiotic prophylaxis as required.</td>
</tr>
</tbody>
</table>

### IV. Natriuretic peptides

In the last decade there have been multiple studies of the role of natriuretic peptides in valve disease. Natriuretic peptides levels have been shown to be high in patients with MR compared to normal subjects. Sutton showed that in a study of 49 patients with pure MR and
ejection fraction greater than 55%, natriuretic peptides were elevated in both asymptomatic
and symptomatic MR patients compared with controls after adjustment for age, sex, and body
surface area (29). A Mayo Clinic study of 78 patients with varying degrees of both organic
and functional MR also found increased ANP and BNP levels compared with controls (30).

Severity of valve disease and natriuretic peptides

The severity of the valvular lesion has been shown in aortic stenosis to correlate with B-type
natriuretic peptide (BNP) levels (Steadman). However in MR there is an unpredictable
relationship between plasma levels of natriuretic peptides and the severity of MR in
published studies. A number of studies demonstrated a positive correlation between
natriuretic peptides and the severity of both organic and functional MR (31, 32, 33, 34),
whereas others have shown either no correlation or a relationship only on univariate analysis
(30, 35, 36, 37). Findings are summarized in Table 8.

This variability in findings likely reflects heterogeneous patient populations, but the
implication is that natriuretic peptides are not a clinically useful marker of the severity mitral
regurgitation. In practice, this is not a particular issue because the severity can usually be
determined by echocardiography. The volume loaded state is expected to increase with a rise
in the effective regurgitant orifice area (EROA) and other parameters of valve lesion severity.
Table 8: Baseline Association in MR. ANOVA = analysis of variance; EROA = effective regurgitant orifice area; LA = left atrial; LAAI = left atrial area index; LAD = left atrial diameter; LAV = left atrial volume; LV = left ventricular; LVEDD = left ventricular end-diastolic diameter; LVEDVI = left ventricular end-diastolic volume index; LVESD = left ventricular end-systolic diameter; LVESVI = left ventricular end-systolic volume index; RFraction = regurgitant fraction; RVVolume = regurgitant volume; VC = vena contracta.

<table>
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<th>Aetiology</th>
<th>BNP</th>
<th>NT-proBNP</th>
<th>ANP</th>
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<td>0.35</td>
<td>0.001</td>
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<td><strong>Kerr et al. (36)/2008</strong></td>
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<td>Organic</td>
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<td><strong>Detaint et al. (30)/2006</strong></td>
<td>78</td>
<td>Both</td>
<td>&lt;0.01</td>
<td></td>
<td>Univariate regression</td>
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<td><strong>Detaint et al. (35)/2005</strong></td>
<td>124</td>
<td>Organic</td>
<td>0.49</td>
<td>&lt;0.0001</td>
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<td>Organic</td>
<td>0.42</td>
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</table>
Cardiac Structure and Function

Left ventricular function

Multiple mainstream studies in mitral regurgitation fail to show a significant association between any of the natriuretic peptides and left ventricular ejection fraction or fractional shortening. (29, 30, 33, 34, 35, 36) A study including patients with organic MR showed a weak negative correlation between NT-proBNP and left ventricular ejection fraction (r ≥ 0.25) (37), and a study of the BNP/ANP ratio showed a similar finding (94).

Right ventricular function

Similarly, there is no consistent association of natriuretic peptide levels with right ventricular function, LV diastolic filling parameters, or measures of end-diastolic size (30, 34, 36, 37). Increased LV end-systolic dimensions or volumes are important markers of ventricular decompensation in chronic MR, and are associated with BNP and NT-proBNP in most but not all series (30, 33, 34, 37) as are increased pulmonary arterial systolic pressures (30, 33, 36). The most consistent, but not universal, association is with LA dimensions or volumes (29, 33, 34, 36, 37). AF (atrial fibrillation) was an independent predictor of BNP levels in one study (35), but another showed that both ANP and BNP decreased with very large atria in the presence of AF (38).

BNP levels are higher in patients with functional compared with organic MR, but this reflects a greater degree of LV dysfunction with larger end-systolic volumes and greater wall stress (30). Stratification for LV end-systolic volume index (LVESVI) removed the effect of the aetiology of MR. The concept that BNP provides an integrated index of cardiac remodeling including systolic LV dilation, LA dilation, and pulmonary hypertension is an attractive one, but is not supported
by all studies. Again, this is related to the highly heterogeneous patient populations studied.

Table 9 summarizes findings from 4 studies that included data on LVESVI. The majority found that BNP was a marker for increased LVESVI (30, 31, 34), with the one study with negative findings having a small range of LVESVI (36). Thus, BNP is a marker for systolic ventricular remodeling in chronic MR, but only in the context of a wide range of ventricular volumes and hence probably not useful in identifying the earliest stages of ventricular decompensation.

The consistent relationship between BNP and left atrial size suggests that BNP may be produced by left atrial myocardium in response to chronic increases in atrial wall stress, rather than solely by ventricular myocardium (36). The relationship to pulmonary arterial systolic pressure is less easy to explain given the lack of relationship between BNP and measures of right ventricular function.

Table 9: Baseline associations of natriuretic peptide levels and LV end-systolic volume index in MR patients. (17)

<table>
<thead>
<tr>
<th>First Author (Ref. #)/Year</th>
<th>n</th>
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<th>BNP</th>
<th>NT-proBNP</th>
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<td>r = 0.52, p = 0.001</td>
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<td>Detaint et al. (30)/2006</td>
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<td>r² ≥ 0.4, p &lt; 0.001</td>
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<tr>
<td>Detaint et al. (35)/2005</td>
<td>124</td>
<td>Organic</td>
<td>r = 0.26, p = 0.002</td>
<td>Linear regression</td>
<td></td>
</tr>
</tbody>
</table>

Symptomatic Status

BNP, NT-proBNP, and ANP are all higher in symptomatic patients after adjusting for the severity of MR, and the extent of atrial and ventricular remodeling (29). A cut point of BNP >12 pmol/l predicted the presence of symptoms with 75% sensitivity, 85% specificity, and an area under the curve (AUC) of 0.90. AUCs for NT-proBNP and ANP were both 0.89, and all were
superior to LA size, LV size, and severity of MR. Similarly, Potocki et al. (37) demonstrated an AUC of 0.80 for NT-proBNP. Levels of BNP and NT-proBNP increase progressively with worsening symptomatic class, albeit with a considerable degree of overlap (30, 31, 34–37). Shimamoto et al. (38) found that plasma ANP was increased in patients with NYHA functional class II symptoms but then decreased in those with NYHA functional class III and IV symptoms, whereas BNP and hence the BNP/ANP ratio increased progressively. For NYHA functional class II, III, or IV, a cut point of BNP/ANP ratio > 1.2 gave 88% sensitivity, 83% specificity, and an AUC of 0.82. For NYHA functional class III or IV, a cutpoint of 2.97 gave 78% sensitivity, 87% specificity, and an AUC of 0.86.

**Response to Exercise**

Yusoff et al. (34), in a study of 38 patients with severe degenerative MR, identified NT-proBNP levels as a strong independent predictor of maximal oxygen uptake, whereas there were only weak correlations between exercise parameters and resting echocardiographic variables. Kerr et al. (36) performed exercise echocardiography in 33 patients with either moderate-severe or severe MR and preserved LVEF at rest. Increased BNP levels were associated with increased pulmonary arterial pressures at rest and on exercise, and increased LA volumes and lower functional capacity on exercise testing, but not with either resting or exercise measures of LV size and function. The implication of these findings is that although resting BNP levels are clearly related to impaired functional capacity, they may not be a marker of the failure of LV contractile reserve per se.

**Predictors of Outcome**

Detaint et al. (35) followed 124 patients with chronic isolated organic MR for a mean of 4.4 _1.4 years after diagnosis and sampling for BNP. At diagnosis, 35% had severe MR, 69% were
NHYA functional class I, 21% functional class II, and 7% functional class III or IV. After adjustment for age, sex, symptoms, LVEF, and severity of MR, BNP was an independent predictor of survival with a hazard ratio of 1.23 per 10 pg/ml. For death or heart failure, the hazard ratio was 1.09 per 10 pg/ml.

In an elegant study, Pizarro et al. (33) enrolled 269 patients with severe organic MR and normal results of treadmill exercise testing. The first 167 patients were used as a derivation cohort and the second 102 as a validation cohort. BNP was assayed on samples taken as baseline and 1 year, and patients were followed to a combined end point of death, development of LV systolic dysfunction (LVEF <60%), or the onset of heart failure (NYHA functional class III or IV). The AUC for the receiver-operator characteristic curve of BNP as a predictor of the combined end point was 0.80 for the derivation cohort, and 0.81 for the validation cohort. Stratification of baseline BNP into quartiles gave event-free survival rates at 48 months of 99%, 97%, 93%, and 29%.

Using a cut point of 105 pg/ml from the derivation cohort, the combined end point occurred in 66% of the validation cohort with a BNP >105 pg/ml as opposed to 4% with a BNP <105 pg/ml (p < 0.00001) with a hazard ratio of 4.7 on Kaplan-Meier analysis (p <0.0001). In the validation cohort, BNP >105 pg/ml was the strongest independent predictor of the combined end point (OR: 4.1), followed by an effective regurgitated orifice area >55 mm² (OR: 3.7), and an end-systolic diameter/body surface area of >22 mm² (OR: 3.1). In a study of patients with functional MR, NT-proBNP >1,941 pg/ml was second only to a marked increase in the LVESVI (>82 ml/m²) as an independent predictor of death, with a hazard ratio of 2.17 (p <0.026), and was the most powerful predictor of death or hospitalization, with a hazard ratio of 3.19 (p <0.001) (31).
Conclusions

The role of natriuretic peptides as cardiac hormones is clear given their close relationship to cardiac structure and function: reflecting LV wall stress and subclinical myocardial dysfunction. In valvular heart disease, they are correlated with disease severity, although this is more reliable in AS than MR, as well as symptomatic status.

Determining symptomatic status itself can be difficult even with a rigorous clinical history. Breathlessness in particular is very subjective; in a large group of elderly people, one-third of patients were classified as breathless, using the Medical Research Council Scale, but only one-half of them had any identifiable pathology (39). Natriuretic peptides could play a role here.

Perhaps the most exciting prospect for future use comes from their ability to predict outcome. BNP and NT-proBNP show the most promise. In AS, low levels are good predictors of symptom-free survival and high levels are indicative of subsequent mortality, at least in medically managed patients. High levels may also be strong predictors of perioperative and long-term mortality. In MR, high plasma levels are associated with adverse outcomes in both organic and functional MR.

In both AS and MR, the difficulty remains in deciding on the optimum timing of surgery in asymptomatic patients. A reliable biomarker that appropriately risk-stratifies such patients would be invaluable. Natriuretic peptides have been extensively studied in valvular heart disease, and there is preliminary data to suggest that BNP might be a useful predictor of incipient decompensation in asymptomatic patients with organic MR. However, there are no studies that have tested the hypothesis that early surgical intervention in asymptomatic patients with severe
valvular heart disease and elevated levels of natriuretic peptides reduces mortality or improves functional outcome.

Additionally, there are many comorbidities that are not uncommon in valvular heart disease, such as CAD, diabetes, and hypertension, and their impact on natriuretic peptide levels has not been clearly established. Whether natriuretic peptides will have a clinically useful role is yet to be proven. Prospective, randomized, controlled trials in well-described patient populations are needed before they can be incorporated into the routine management of these challenging and increasingly prevalent patient groups.

V. Management

Medical Therapy

In the asymptomatic patient with chronic MR, there is no generally accepted medical therapy. Vasodilators have been suggested as measure to assist the ventricle with adverse remodelling. Use of vasodilators may appear to be logical for the same reasons that they are effective in acute MR. However, there are no large, long-term randomised studies to indicate that they are beneficial. No benefit with use of ACE inhibitors has been seen on left ventricular volume and MR severity. (36, 37, 38, 39)

Afterload reduction

There is a questionable role for afterload reduction. Unless there is hypertension, afterload is usually not affected by organic MR (8, 40, 41, 42). Therapy to reduce afterload is usually intended to ease the strain on the volume-loaded left ventricle. This does not treat the primary problem of regurgitation. Drugs that reduce afterload might produce a physiological state of
chronic low afterload with which there is very little experience. This may affect organ perfusion, and precipitate renal impairment in adverse situations or comorbidities.

In patients with functional or ischemic MR (resulting from dilated or ischemic cardiomyopathy respectively), there is reason to believe that preload reduction may be beneficial. (43) If LV systolic dysfunction is present, primary treatment of the LV systolic dysfunction with drugs such as ACE inhibitors or beta blockers (particularly carvedilol) and biventricular pacing have all been shown to reduce the severity of functional MR. (44, 45, 46, 47). In patients with MR who develop symptoms but have preserved LV function, surgery is the most appropriate therapy. Medication is used only as a “bridge” to planned surgery.

**Atrial fibrillation**

If atrial fibrillation develops, heart rate should be controlled with standard rate-lowering calcium channel blockers, beta blockers, digoxin, or amiodarone. For patients undergoing surgery for severe MR with concurrent chronic atrial fibrillation, a Maze procedure may be added to a mitral valve repair to reduce the risk of post-operative stroke. The embolic risk may be less in MR compared to mitral stenosis with atrial fibrillation (48, 49). The INR is to be maintained at 2 to 3 in this population.

**Surgery**

**Types of Surgery**

There are four different mitral valve (MV) operations are currently used for correction of MR:

1) MV repair;
2) MV replacement with preservation of part or all of the mitral apparatus;
3) MV replacement with removal of the mitral apparatus.
4) Percutaneous Mitraclip insertion.

The final decision is based on the lesion, patient co-morbidities, patient choice, and medication.

**Mitral valve repair**

In most cases, MV repair is the operation of choice when the valve is suitable for repair, and appropriate surgical skill and expertise are available. This procedure preserves the patient’s native valve without prosthesis, and therefore avoids the risk of chronic anticoagulation (except in patients with atrial fibrillation) or prosthetic valve failure late after surgery. (2) Preservation of the native mitral apparatus leads to better postoperative LV function and survival than in cases in which the apparatus is disrupted (18, 50, 51, 52, 53, 54, 55). Improved postoperative function occurs with repair because the mitral apparatus is an integral part of the left ventricle that is essential for maintenance of normal shape, volume, and function of the left ventricle (56). However, MV repair is technically more demanding than MV replacement, may require longer extracorporeal circulation time, and may occasionally fail. Prolonged operations and a suboptimal repair are likely to result in a higher mortality and morbidity rate in low volume centers. Preoperatively a thorough understanding of the valve morphology, and surgical expertise, are of critical importance for the success of valve repair.

**Reoperation rates**

A second sternotomy operation carries a significantly higher risk than the first. Patients may decondition after the first major cardiac surgery, and not quite recover adequately in situations where reoperations are required. This carries a further risk of increased morbidity, prolonged hospitalization and failure to return to a home environment, resulting in nursing home or aged care confinement. The reoperation rate after MV repair is similar to the reoperation rate after MV
replacement (57). There is a 7% to 10% reoperation rate at 10 years in patients undergoing MV repair, usually for severe recurrent MR. (57, 58, 59, 60, 61) This is approximately double the risk of a single procedure. Approximately 70% of the recurrent MR is thought to be due to the initial procedure, and 30% to progressive valve disease. (58) The reoperation rate is lower in those patients who had the initial operation for posterior leaflet abnormalities than in those who had bileaflet or anterior leaflet abnormalities. (5, 60) The advantage of MV replacement with preservation of the chordal apparatus is that this operation ensures postoperative MV competence, preserves LV function, and enhances postoperative survival compared with MV replacement, in which the apparatus is disrupted. (52, 62, 63, 64, 65)

**Repair and replacement: the choice**

Surgical mitral valve replacement using a prosthetic valve is a well understood and requires less skill and surgical experience than mitral valve repair.

The disadvantage is the use of a prosthetic valve, with the long term risk of deterioration inherent in tissue valves, or the need for anticoagulation (associated with risk of haemorrhage) in mechanical valves. MV replacement in which the MV apparatus is resected should almost never be performed. It should only be performed in those circumstances in which the native valve and apparatus are so distorted by the preoperative pathology, i.e. rheumatic disease, that the mitral apparatus cannot be spared. A procedure referred to as artificial chordal reconstruction does extend the opportunities for repair in some such patients with rheumatic MR (66, 67). However, this technique requires a high level of skill and experience.

The ACC guidelines indicate that the advantages of MV repair make it applicable across a wide range of MR cases, including the 2 extremes of the spectrum. Valve repair might be possible in
patients with far-advanced symptomatic MR and depressed LV function, because it preserves LV function at the preoperative level (54); MV replacement, with disruption of the apparatus, in such patients could lead to worsened or even fatal LV dysfunction after surgery. At the other extreme, in the relatively asymptomatic patient with well-preserved LV function, repair of a severely regurgitant valve might be contemplated to avoid the onset of ventricular dysfunction from longstanding volume overload (68). However, failed MV repair would result in the need for a prosthetic valve. This would represent a clear complication because it would impose the risks of prosthesis on a patient who did not previously require it. Hence, “prophylactic” surgery in an asymptomatic patient with MR and normal LV function requires a high likelihood of successful repair.

In many cases, the type of operation: MV repair versus replacement, is important in timing surgery. Repairs are usually done earlier in the natural history course to avoid the valve apparatus from potentially becoming so distorted that it may not be repairable. Although the type of surgery to be performed is never actually established until the operation, most cases lend themselves to preoperative prediction of the operation that can be performed. This prediction is based on the skill and experience of the surgeon in performing repair, and imaging that describes the location and type of MV disease that caused the MR. Nonrheumatic posterior leaflet prolapse due to degenerative MV disease, or a ruptured chordae tendineae can usually be repaired using a resection of the portion of the valve and an annuloplasty. (69, 70) Involvement of the anterior leaflet or both anterior and posterior leaflets diminishes the likelihood of repair because the operation requires other interventions, such as chordal shortening, chordal transfer, and innovative anatomic repairs. (71, 72, 73, 74, 75)
Consequently, the skill and experience of the surgeon, and the results of imaging studies, are likely to be the most important determinants of the eventual operation that will be performed. (2) In general, rheumatic involvement of the MV, and calcification of the MV leaflets or annulus diminish the likelihood of repair, even in experienced hands (76). The number of patients undergoing MV repair for MR has increased steadily over the past decade in the United States and Canada in relation to the number undergoing MV replacement. (2) According to the STS National Cardiac Database from 1999 to 2000 (77), the frequency of repair was only 35.7% (3027) of a total of 8486 procedures, which suggests that MV repair is underutilized. The STS National Database also indicates an operative mortality rate of <2% in patients undergoing isolated MV repair in 2004, which compares favorably to the >6% operative mortality rate for patients undergoing isolated MV replacement (165). Considering the beneficial effect of MV repair on survival and LV function, cardiologists are strongly encouraged to refer patients who are candidates for MV repair to surgical centers experienced in performing MV repair. This requires the prompt detection of onset of symptoms and effort intolerance, reflecting the onset of irreversible cardiac remodeling. It is at these points in the natural history that valve surgery is highly recommended. After detecting these important benchmarks, it is the role of the managing cardiologist to alter the adverse prognosis that occurs if left untreated.
Table 10: Indications for mitral valve operation. (2)

<table>
<thead>
<tr>
<th>Class</th>
<th>Indication</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>MV surgery is recommended for the symptomatic patient with acute severe MR.</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td>MV surgery is beneficial for patients with chronic severe MR and NYHA functional class II, III, or IV symptoms in the absence of severe LV dysfunction (defined as ejection fraction &lt;0.30) and/or end-systolic dimension &gt; 55 mm.</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td>MV surgery is beneficial for asymptomatic patients with chronic severe MR and mild to moderate LV dysfunction, ejection fraction 0.30 to 0.60, and/or end-systolic dimension &gt;40 mm.</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td>MV repair is recommended over MV replacement in the majority of patients with severe chronic MR who require surgery, and patients should be referred to surgical centers experienced in MV repair.</td>
<td>C</td>
</tr>
<tr>
<td>IIa</td>
<td>MV repair is reasonable in experienced surgical centers for asymptomatic patients with chronic severe MR with preserved LV function (ejection fraction &gt;0.60 and end-systolic dimension &lt;40 mm) in whom the likelihood of successful repair without residual MR is &gt;90%.</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td>MV surgery is reasonable for asymptomatic patients with chronic severe MR, preserved LV function, and new onset of atrial fibrillation.</td>
<td>C</td>
</tr>
<tr>
<td></td>
<td>MV surgery is reasonable for asymptomatic patients with chronic severe MR, preserved LV function, and pulmonary hypertension (pulmonary artery systolic pressure &gt;50 mmHg at rest or &gt;60 mmHg with exercise)</td>
<td>C</td>
</tr>
<tr>
<td></td>
<td>MV surgery is reasonable for patients with chronic severe MR due to a primary abnormality of the mitral apparatus and NYHA functional class III–IV symptoms and severe LV dysfunction (ejection fraction &lt;0.30 and/or end-systolic dimension &gt; 55 mm) in whom MV repair is highly likely.</td>
<td>C</td>
</tr>
<tr>
<td>IIb</td>
<td>MV repair may be considered for patients with chronic severe secondary MR due to severe LV dysfunction (ejection fraction &lt; 0.30) who have persistent NYHA functional class III–IV symptoms despite optimal therapy for heart failure, including biventricular pacing</td>
<td>C</td>
</tr>
<tr>
<td>III</td>
<td>MV surgery is not indicated for asymptomatic patients with MR and preserved LV function (ejection fraction &gt; 0.60 and end-systolic dimension &lt; 40 mm) in whom significant doubt about the feasibility of repair exists.</td>
<td>C</td>
</tr>
<tr>
<td></td>
<td>Isolated MV surgery is not indicated for patients with mild or moderate MR.</td>
<td>C</td>
</tr>
</tbody>
</table>
Evaluation of patients after mitral valve replacement or repair

After MV surgery, follow-up is necessary to detect late surgical failure and assess LV function. For patients in whom a bioprosthesis has been inserted, the specter of eventual deterioration is always present and must be anticipated. If a mechanical valve has been inserted, anticoagulation is required, and chronic surveillance of prothrombin time and INR is necessary. After valve repair, follow-up to assess the effectiveness of the repair is indicated early, especially because most repair failures are detected soon after surgery.

Percutaneous mitral valve repair (MitraClip)

Percutaneous valve repair is currently offered only to those patients who are not candidates for surgery. These include: elderly, multiple co-morbidities, compromised functional capacity, high risk for surgical complications including bleeding, significant complication risk, and failure to complete post-operative rehabilitation.

The percutaneous technique has evolved in the last 5 years, causing minimal trauma and good outcomes despite being used in a high risk population. The procedure is fast growing internationally, and will spread to other parts of the world in the next few years. The expected cardiovascular outcomes are: improved quality of life, relief of symptoms, improved functional class, return to pre-morbid activities, reduction in hospital admissions, heart failure prevention, and the notable avoidance of the complications of major cardiac surgery and sternotomy.

The recently reported Everest II trial demonstrated safety, feasibility and effectiveness of this procedure. In a randomized control trial (n=279) the Mitraclip percutaneous repair was compared to surgical valve replacement. Patients had 3+ or 4+ MR on echocardiography, and were
followed up for one year to determine the outcomes, effectiveness, and feasibility of using this device and the less invasive percutaneous approach.

In this trial, the primary safety endpoint being major adverse cardiac events (mace) at 30 days, the MitraClip system demonstrated a superior safety profile compared to surgical repair or replacement (9.6% MitraClip patients vs. 57% of surgical patients, p<0.0001) In the primary effectiveness endpoint, the MitraClip device was non-inferior to surgery at one year. The clinical success rate was 72.4% for MitraClip patients with successful initial treatment, compared to 87.8% for surgery patients. This fell within the 25.4% confidence interval for non inferiority.

At one year MitraClip produced a significant clinical benefit in the following:

1. A reduction in the severity of MR, with 81.5 percent of patients improving to mild (grade 1+) or moderate (grade 2+) MR, whereas at baseline 95.6 percent of patients had moderate-to-severe (grade 3+) or severe (grade 4+) MR (p<0.0001)

2. A reduction in both the end-diastolic volume and dimensions. Left ventricular diastolic volumes decreased a significant 13% (p<0.0001), and left ventricular diastolic dimensions decreased a significant 6.4% (p<0.0001) compared to baseline.

3. Symptom improvement, with 97.5% of patients becoming asymptomatic (NYHA Functional Class I) or mild symptoms (NYHA Functional Class II) (p<0.0001), whereas at baseline, 52.6 % of patients had moderate or severe symptoms (NYHA Functional Class III or IV).

4. Meaningful improvements in both physical and mental quality of life compared to baseline as measured by the SF-36 Survey (increase of 4.7 points in the physical quality
of life score (p<0.0001) and increase of 5.8 points in the mental quality of life score (p<0.0001)).

Management Recommendations

Symptomatic patients with normal left ventricular function

Patients with symptoms of congestive heart failure despite normal LV function on echocardiography (ejection fraction > 0.60 and end-systolic dimension < 40 mm) require surgery. Surgery should be performed in patients with mild symptoms and severe MR, especially if it appears that MV repair rather than replacement can be performed. The feasibility of repair is dependent on several factors, including valve anatomy and surgical expertise. Successful surgical repair improves symptoms, preserves LV function, and avoids the problems of a prosthetic valve. When repair is not feasible, MV replacement with chordal preservation should relieve symptoms and maintain LV function.

Asymptomatic or symptomatic patients with left ventricular dysfunction.

Preoperative variables that are predictive of postoperative survival, symptomatic improvement, and postoperative LV function are summarized in Table 11 (8, 9, 22, 24, 25, 26, 27). The timing of surgery for asymptomatic patients is controversial, but most would now agree that MV surgery is indicated with the appearance of echocardiographic indicators of LV dysfunction. These include LV ejection fraction <0.60 and/or LV end-systolic dimension > 40 mm. (Figure 5) Surgery performed at this time will likely prevent further deterioration in LV function and improve longevity. This is true whether repair or replacement is performed (26), although repair is clearly preferred. It must be emphasized that, unlike with the timing of AVR for AR, LV ejection fraction should not be allowed to fall into the lower limit of the normal range in patients.
with chronic MR (26, 78, 79, 80). The data regarding postoperative survival are much stronger with LV ejection fraction than with end-systolic dimension (22, 24, 25, 26), whereas both ejection fraction and end-systolic dimension strongly influence postoperative LV function and heart failure (8, 9, 22, 26, 27). MV surgery should also be recommended for symptomatic patients with evidence of LV systolic dysfunction (ejection fraction < 0.60, and/or end-systolic dimension > 40 mm).

Determining the surgical candidacy of the symptomatic patient with MR and far-advanced LV dysfunction is a common clinical dilemma. The question that often arises is whether the patient with MR has such advanced LV dysfunction that he or she is no longer a candidate for surgery.
Figure 5: Algorithm Management strategy for patients with chronic severe mitral regurgitation. *Mitral valve (MV) repair may be performed in asymptomatic patients with normal left ventricular (LV) function if performed by an experienced surgical team and if the likelihood of successful MV repair is greater than 90%. AF indicates atrial fibrillation; Echo, echocardiography; EF, ejection fraction; ESD, end-systolic dimension; eval, evaluation; HT, hypertension; and MVR, mitral valve replacement. (2)

Exercise recommendations

Patients with definite LV enlargement (> 60 mm in diastole), pulmonary hypertension, or any degree of LV systolic dysfunction at rest should not participate in any competitive sports.

Primary myocardial disease
It could be difficult to distinguish primary cardiomyopathy with secondary MR from primary MR with secondary myocardial dysfunction. In the latter case, if MV repair appears likely, surgery should still be contemplated (Table 10). Even though such a patient is likely to have persistent LV dysfunction, surgery is likely to improve symptoms and prevent further deterioration of LV function (81). If MV replacement is necessary in such patients, it should be performed only if the chordal apparatus cannot be preserved. The modification of MV geometry by an “undersized” annular ring in patients with severe LV dysfunction and significant functional MR may be beneficial in a subset of patients with primary myocardial disease (82, 83, 84, 85, 86, 87), although the impact on outcomes compared with aggressive medical therapy, including beta blockers and cardiac resynchronization therapy (44, 45, 46, 47), has not been studied in a prospective randomized trial.

**Asymptomatic patients with normal left ventricular function.**

Natural history studies indicate uniformly that asymptomatic patients with severe MR and normal LV function have a high likelihood of developing symptoms and/or LV dysfunction warranting operation over the course of 6 to 10 years (5, 11, 12, 13).

As noted previously, repair of a severely regurgitant valve may be contemplated in an asymptomatic patient with severe MR and normal LV function to preserve LV size and function, and prevent the progression of chronic severe MR (12). Although there is no randomized data with which to recommend this approach to all patients, the committee recognizes that some experienced centers are moving in this direction for patients for whom the likelihood of successful repair is high.
Two recent studies have also addressed the risk of sudden death in asymptomatic patients with severe MR and normal LV function. (12, 13) In a long-term retrospective study in which severity of MR was quantified by Doppler echocardiography (12), 198 patients with an effective orifice area >40 mm² had a 4% per year risk of cardiac death during a mean follow-up period of 2.7 years. However, in the second study of 132 patients followed up prospectively for 5 years, during which the indications for surgery were: symptoms, development of LV dysfunction (ejection fraction <0.60), LV dilatation (LV end-systolic dimension >45 mm), atrial fibrillation, or pulmonary hypertension, there was only 1 cardiac death in an asymptomatic patient, but this patient had refused surgery which was indicated by development of LV dilation (13).

MV repair is often recommended in haemodynamically stable patients with newly acquired severe MR, such as might occur with ruptured chordae. Surgery is also recommended in an asymptomatic patient with chronic MR with recent onset of atrial fibrillation in whom there is a high likelihood of successful valve repair.

Surgery for asymptomatic patients with severe MR and normal LV function should only be considered if there is a > 90% likelihood of successful valve repair in a center experienced in this procedure. Cardiologists are strongly encouraged to refer patients who are candidates for MV repair to surgical centers experienced in performing MV repair.

**Atrial fibrillation**

Atrial fibrillation is a common, potentially morbid arrhythmia associated with MR. In patients with MR due to MVP, there is a high risk of development of atrial fibrillation. The development of atrial fibrillation is independently associated with a high risk of cardiac death or heart failure (88). Preoperative atrial fibrillation is an independent predictor of reduced long-term survival
after MV surgery for chronic MR (26, 88, 89, 90). The persistence of atrial fibrillation after MV surgery can lead to thromboembolism and partially nullifies an advantage of mitral repair by requiring anticoagulation.

### Table 11: Preoperative predictors of surgical outcome in mitral regurgitation. (90)

<table>
<thead>
<tr>
<th>Study, Year</th>
<th>Study Design</th>
<th>Type of Surgery</th>
<th>n</th>
<th>Outcome Assessed</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schuler et al., 1979 (9)</td>
<td>Retrospective</td>
<td>MVR</td>
<td>20</td>
<td>LV function</td>
<td>12 Patients with average LV EF 0.70 had normal postoperative EF; 4 patients with average EF 0.58 had postoperative EF 0.25</td>
</tr>
<tr>
<td>Phillips et al., 1981 (24)</td>
<td>Retrospective</td>
<td>MVR</td>
<td>105</td>
<td>Survival</td>
<td>EF less than 0.50 predicted poor survival</td>
</tr>
<tr>
<td>Zile et al., 1984 (8)</td>
<td>Prospective</td>
<td>MVR</td>
<td>16</td>
<td>Heart failure, LV function</td>
<td>LV ESD index greater than 2.6 cm per m2 (45 mm) and LV FS less than 0.32 predicted poor outcome</td>
</tr>
<tr>
<td>Crawford et al., 1990 (23)</td>
<td>Prospective</td>
<td>MVR</td>
<td>48</td>
<td>Survival, LV function</td>
<td>LV EF less than 0.50 predicted reduced survival; ESV less than 50 ml per m2 predicted persistent LV dilatation</td>
</tr>
<tr>
<td>Wisenbaugh et al., 1994 (40)</td>
<td>Registry</td>
<td>MVR</td>
<td>26</td>
<td>Survival, LV function</td>
<td>ESD, EDD, and FS predicted poor survival and LV function; only ESD significant in multivariate analysis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MVR-CP</td>
<td>35</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enriquez-Sarano et al., 1994 (25)</td>
<td>Retrospective</td>
<td>MVR</td>
<td>214</td>
<td>Survival</td>
<td>LV EF 0.60 or less predicted poor survival whether MVR or CP was performed; EF estimated by echo FS or visual analysis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MV repair</td>
<td>195</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enriquez-Sarano et al., 1994 (26)</td>
<td>Retrospective</td>
<td>MVR</td>
<td>104</td>
<td>LV function</td>
<td>EF, ESD, LV diameter/thickness ratio, and end-systolic wall stress predicted outcome; EF estimated by echo FS or visual analysis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MV repair</td>
<td>162</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Predictors of the persistence of atrial fibrillation after successful valve surgery are the presence of atrial fibrillation for >1 year, and left atrial size >50 mm. (91) In one study, an even shorter duration of preoperative atrial fibrillation (3 months) was a predictor of persistent atrial fibrillation after MV repair. (92) Persistent atrial fibrillation after surgery occurred in 80% of patients with preoperative atrial fibrillation >3 months but in no patient with preoperative atrial fibrillation <3 months. Although patients who develop atrial fibrillation also usually manifest other symptomatic or functional changes that would warrant MV operation, many clinicians would consider the recent onset of atrial fibrillation to be an indication in and of itself for
surgery, if there is a high likelihood of valve repair (Figure 4). (65, 92) In patients presenting for MV operation with chronic atrial fibrillation, a concomitant Maze procedure may prevent future thromboembolic events by restoring normal sinus rhythm. (93, 94, 95, 96, 97, 98, 99) The decision to proceed with a Maze procedure should be based on the age and health of the patient, as well as the surgical expertise, because this procedure may add to the morbidity of the operation.

**Ischemic mitral regurgitation**

The outlook for the patient with ischemic MR is substantially worse than that for regurgitation from other causes. (100, 101) A worse prognosis accrues from the fact that ischemic MR is usually caused by LV dysfunction resulting from myocardial infarction. Furthermore, the MV itself is usually anatomically normal, and MR is secondary to papillary muscle displacement and tethering of the mitral leaflet(s). The mechanism of MR in chronic ischemic disease is local LV remodeling (apical and posterior displacement of papillary muscles), which leads to excess valvular tenting and loss of systolic annular contraction. (102, 103, 104, 105, 106, 107, 108, 109) The indication for MV operation in the patient who undergoes CABG with mild to moderate MR is still unclear, but there is data to indicate the benefit of MV repair in such patients. (110, 111, 112, 113) Patients with ischemic heart disease who have MR have a worse prognosis than those who do not have MR. (114, 115, 116, 117) CABG alone may improve LV function and reduce ischemic MR in selected patients (115, 118), especially those with transient severe MR due to ischemia, in whom myocardial revascularization can eliminate episodes of severe MR. However, CABG alone is usually insufficient and leaves many patients with significant residual MR, and these patients would benefit from concomitant MV repair at the time of the CABG. (109, 110, 111, 112, 113, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128)
Mitral annuloplasty alone with a downsized annuloplasty ring is often effective at relieving MR. (123, 124, 127)

In severe MR secondary to acute myocardial infarction, hypotension and pulmonary edema often occur. Severe MR occurs in 6% to 7% of patients with cardiogenic shock. (129) The cause of the MR should be established, because the MR may be due to a ruptured papillary muscle, papillary muscle displacement with leaflet tethering, or annular dilatation from severe LV dilatation. Those patients with an acute rupture of the papillary muscle should undergo surgery on an emergency basis, with either valve repair or MV replacement. (130) In those patients with papillary muscle dysfunction, treatment should initially consist of haemodynamic stabilization, usually with insertion of an intra-aortic balloon pump. Surgery should be considered for those patients who do not improve with aggressive medical therapy. Correction of acute severe ischemic MR usually requires valve surgery in addition to revascularization. The best operation for ischemic MR is controversial (131, 132), but MV repair with an annuloplasty ring is the best approach in most instances. (110, 111, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128)

**Special Considerations in the Elderly**

Elderly patients with MR fare more poorly with valve surgery than do their counterparts with AS. In general, operative mortality increases and survival is reduced in patients older than 75 years of age, especially if MV replacement must be performed or if the patient has concomitant CAD or other valve lesions. (18, 133, 134, 135, 136, 137, 138) Operative mortality in the elderly is low in experienced centers (139), but the overall operative mortality for MV replacement in this age group in the United States exceeds 14% (134, 137, 138) and is particularly high (>20%) in low-volume centers. (134) Although the risks are reduced if MV repair is performed rather than MV replacement, the majority of patients in this age group
require concomitant CABG (131). The average operative risk for combined MV repair plus CABG in the United States is 8% (140), which will undoubtedly be higher in the older population. These risks are worth taking in patients with significant symptoms. However, under most circumstances, asymptomatic elderly patients or elderly patients with mild symptoms should be treated medically.

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Chapter 6
The Basic Science and Clinical Relevance of B-Type Natriuretic Peptides
Chapter 8
Cardiopulmonary exercise testing in heart valve disease
Cardiopulmonary exercise testing in heart valve disease

Introduction

The assessment of functional capacity reflects the ability to perform activities of daily living and physical activity through anaerobic and aerobic metabolism. (1) The integrated collaboration and condition of the pulmonary, cardiovascular, and skeletal muscle systems determine an individual’s functional capacity. (1) Several studies have demonstrated that the assessment of functional capacity provides important diagnostic and prognostic information in a wide variety of cardiovascular clinical and research settings. (1) The functional capacity of a patient is an important determinant of quality of life. (1) Exercise testing is recommended to determine and quantify the functional capacity in heart failure.(2)

Formal Exercise Testing in Cardiac Failure

Advanced levels of chronic heart failure impose significant limitations in exercise capacity due to impaired cardiac output and concurrent physical deconditioning.( 3) Cardiopulmonary exercise testing has been widely used to determine the functional aerobic capacity in cardiac disease. (4) Peak oxygen consumption (peakVO2) is reported to be the gold standard in assessing functional aerobic capacity. (4) PeakVO2
has been shown to predict prognosis in heart failure and has an important role in
cardiac transplant. (5) Transplant studies have shown that peak VO2 levels less than
15 ml/kg/min were associated with poor long term outcomes. (5)

**Functional capacity testing in heart valve disease**

There are only a handful of studies in the current literature which examine functional
capacity and the role of peak oxygen consumption in single heart valve disease. A
2006 Mayo clinic study evaluated the prevalence, determinants, and clinical outcome
implications of reduced functional capacity in patients with organic mitral
regurgitation.(6) Asymptomatic patients (N=134) underwent cardiopulmonary
exercise testing at baseline with follow up for clinical events (death, heart failure,
new atrial fibrillation) out to 3 years. They found that reduced functional capacity
(< 84%) was an independent predictor of future adverse clinical events. Independent
predictors of reduced functional capacity were ERO (effective regurgitant orifice area
> 40), impaired diastolic dysfunction E/E’ and a reduction in systolic function.

There have been a few studies in aortic stenosis and mitral valve disease to determine
the effort tolerance in asymptomatic patients. The vast majority used standard
treadmill testing to detect effort intolerance. Few studies have used cardiopulmonary
exercise testing. There are no studies reported in the literature on complex valve
disease. The evaluation and outcomes of this thesis contributes immensely to the
literature in the field of valvular heart disease and exercise testing. Table 1 below
describes common terms and tests used to evaluate functional capacity in heart
failure.
Table 1. Commonly used terms and tests to describe functional capacity in heart failure.

<table>
<thead>
<tr>
<th>Descriptor</th>
<th>definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak VO2 (ml/kg/min)</td>
<td>Measured oxygen uptake from CPEX test</td>
</tr>
<tr>
<td>Mets (N)</td>
<td>Multiple of Resting metabolic rate estimated from the work rate</td>
</tr>
<tr>
<td>Weber scale (A,B,C,D,E)</td>
<td>Functional classification</td>
</tr>
<tr>
<td></td>
<td>5-Category scale based on peak VO2</td>
</tr>
<tr>
<td>6 min walk test (metres)</td>
<td>Distance walked in six minutes</td>
</tr>
<tr>
<td>NYHA classification (Class I-IV)</td>
<td>Clinical classification of exertional symptoms</td>
</tr>
</tbody>
</table>

**Peak oxygen consumption (peak VO2)**

The amount of oxygen extracted from the atmosphere and delivered to the muscles at the point of maximal effort defines the peak oxygen consumption during exercise.(4) Functional aerobic capacity is the ability of an individual to perform aerobic work as defined by the maximal oxygen uptake (Peak VO2). Peak VO2 is calculated from, the product of cardiac output (C.O.)and arteriovenous oxygen difference (a-v O2diff) at physical exhaustion, as shown in the following equation:

\[
\text{peakVO2} = (\text{HR} \times \text{SV}) \times ((\text{a} - \text{v}) \text{O2diff})
\]

where:
- \( \text{HR} \) = heart rate
- \( \text{SV} \) = stroke volume

* \(((\text{a}\text{-v})\text{O2diff})\) = arteriovenous oxygen difference
Peak VO2 assessment

Peak VO2 is assessed in vivo using a gas analyser as part of a metabolic cart during formal exercise testing with electrocardiographic monitoring as seen in Fig 1.(4) The peak VO2 result is the highest oxygen consumption achieved during a cardiopulmonary exercise test (CPEX).(4) The units for peak VO2 are expressed in litres/min (l/min) and when corrected for total body mass (total body weight) the units are ml/kg/min. The factors affecting peak VO2 are heart pump function, respiratory disease, muscle blood flow, peripheral vascular disease, muscle deconditioning, and mitochondrial myopathy. (5)

Peak VO2 typically is achieved by exercise that involves only about half of the total body musculature, it is generally believed that peak VO2 is limited by maximal cardiac output rather than peripheral factors. (7)

Fig 1 A treadmill VO2 max test in an athlete

Peak VO2 corrected for weight
There is significant variation in the weight of subjects undergoing cardiopulmonary exercise testing. Although peak VO2 is measured in liters of oxygen per minute, it usually is expressed in milliliters of oxygen per kilogram of body weight per minute to facilitate intersubject comparisons. (1)

**Peak VO2, MET capacity and standard treadmill testing**

In addition, functional capacity, particularly when estimated from the work rate achieved rather than directly measured PeakVO2, is frequently expressed in metabolic equivalents (METs), with 1 MET representing the resting energy expenditure (3.5 mL O2 / kg / min) assuming the subject is 72kg. (1,4) In this instance, functional capacity is commonly expressed clinically as a multiple of the resting metabolic rate. (1,4)

The exercise testing modality most widely used in cardiology is the standard treadmill test. (1) The exercise time correlates well with the MET capacity as the measurement of functional capacity. Stage I of the Bruce protocol is usually equivalent to 2 METs. This provides a gross estimation of functional capacity and becomes inaccurate depending on the subjects weight and the type of testing protocol used. The treadmill test however is widely available even in remote clinics. There are some standardised protocols which are easily implemented which provide reasonable estimates of exercise capacity. (1,4) A distinction should be made between an estimated and directly measured peak VO2. This issue becomes particularly important in patients with cardiovascular disease since slower oxygen uptake on-kinetics can create a large discrepancy between estimated and measured peak VO2. The former dramatically overestimates the latter, especially when aggressive exercise testing protocols are used. (8) Directly measured peak VO2 is more precise and is the preferred measure clinically, but it is less often available, requires secondary expertise to operate, and
includes costs to purchase and maintain the required equipment. Reference equations for normal standards should be specific as to whether peak VO2 was measured or estimated because estimated values require several assumptions and tend to over predict peak VO2. (4)

**Factors affecting Peak VO2**

Peak VO2 is affected by age, gender, muscle conditioning, and the presence of disease or medications that influence its components. Peak VO2 in a young world-class male endurance athlete can exceed 80 mL O2/kg/min, whereas a value of 15 mL O2/kg/min falls within the 50th percentile for a sedentary but healthy 80-year-old woman. (1) Aerobic capacity typically declines an average of 10% per decade in non-athletic subjects, mediated by a decrease in stroke volume and maximal heart rate(9,10). There is also a reduction in blood flow to skeletal muscle and a decline in skeletal muscle function (11,12)

Decline in fitness increases with advancing age, increasing from 3% to 6% per decade in young individuals (20s and 30s) to 20% per decade in the elderly (70s and older). (9)

**Gender differences in Peak VO2**

Peak VO2 in men is 10% to 20% greater than that in women, in part because of a higher haemoglobin concentration, a larger proportion of muscle mass, and a greater stroke volume in men. Consideration of these age and gender differences in Peak VO2
is important when functional capacity in a given individual is interpreted. Population specificity must be considered when assigning a percentage of an age-predicted Peak VO2 achieved for an individual.

**Skeletal muscle conditioning**

Endurance training augments Peak VO2 by 10% to 30% primarily by increasing maximal stroke volume and arteriovenous oxygen difference (13). A background of regular exercise, daily walking or an occupation that requires physical exertion is likely to have a positive effect on the musculoskeletal system. These patients may have the ability to recognise a change in effort tolerance from underlying heart disease earlier. Sedentary patients who have been inactive by choice for most of their lives or those with chronic illness are likely to have poor muscle conditioning which impacts on the exercise test. The test protocol should be well suited to the subject so as to generate the most information and maximal effort.

**Exercise testing: maximal and sub maximal exercise**

Functional capacity, exercise capacity, and exercise tolerance are generally considered synonymous and assumes that a maximal exercise test has been performed and maximal effort has been given by the individual. The measurement of aerobic capacity through ventilatory expired gas analysis is highly recommended when accuracy is essential such as in the heart failure population.(4) There are challenges of precisely estimating VO2 from the exercise workload. A frequent consideration in the assessment of functional capacity, especially in nonclinical settings, is whether to perform maximal or sub maximal testing. Although maximal testing provides the only
accurate determination of aerobic capacity, submaximal testing may be desirable in several situations. These include fitness assessments in facilities in which maximal testing increases subject risk and exposure to potential facility liability, especially in individuals who may be at greater risk for cardiovascular events and particularly when a physician is not on site, and when field testing large numbers of subjects.

A true maximal test is deemed to be achieved when the RER (respiratory exchange ratio) exceeds one. The equation is described as $\text{VCO2/VO2} > 1$. where VCO2 is the maximal CO2 output and VO2 the peak oxygen consumption measured breath by breath. Occasionally in sedentary patients the functional capacity is also used to express an individual’s capacity to perform submaximal activities. The choice of exercise test is important. Using one of a variety of tests; therefore, to avoid confusion, the type of exercise evaluation should be specifically described. The exercise test protocol should be appropriate to test the individuals functional capacity hence age and sex matched ramped protocols have been developed.(1,4)

Submaximal testing typically relies on an extrapolation from the work rate achieved at a given submaximal heart rate relative to an age-predicted maximal heart rate to estimate maximal aerobic capacity. Achievement of 85% of age-predicted maximal heart rate $[0.85 \times (220 - \text{age})]$ and 70% of heart rate reserve $[0.70 \times (220 - \text{age}) - \text{resting heart rate}] - \text{resting heart rate}$ have been proposed as termination criteria for submaximal testing.(14) Percent heart rate reserve tends to more accurately reflect percentage of peak VO2, whereas age-predicted maximal heart rate overestimates volitional effort, leading to the difference in heart rate termination criteria, depending on the equation used.(15) It should be noted that submaximal exercise testing
typically is terminated before the heart rate criteria are achieved, particularly in individuals with a high aerobic capacity in whom the increase in heart rate is lower for each adjustment in work rate. Regardless of the equation used, a significant potential for error exists because of the 10- to 12-bpm SD in the estimate of maximal heart rate in normal subjects. Even greater heart rate variation is encountered in patients with cardiac disease.(16,17)

Patients taking cardiac medications may have an altered heart rate response to exercise, further reducing the ability to accurately predict maximal aerobic capacity.(18) The potential error in estimating maximal heart rate will be compounded by the errors inherent in estimating aerobic capacity from the highest work rate achieved. For these reasons, maximal exercise testing in a clinical laboratory setting is recommended when an accurate assessment of maximal aerobic capacity is imperative. In addition, given the inherent intersubject variability in the heart rate response to exercise, maximal exercise tests should be terminated according to signs/symptoms as opposed to the achievement of a predefined percentage of predicted maximal heart rate.

6 minute walk test

Another form of submaximal exercise evaluation is the 6-minute walk test, which has become widely applied to assess the responses to various treatment interventions. In particular pharmacological therapies or exercise training, in patients with pulmonary disease or heart failure. The distance covered during the time period also can be a powerful prognostic indicator.(19) Additional advantages of such testing protocols
are their simplicity, safety, negligible cost, and applicability to everyday activities. In patients with pulmonary disease, the distance covered in these timed-walk tests is highly reproducible ($r = 0.86$ to $0.95$) and correlates moderately well with peak VO2 ($r = 0.52$ to $0.71$). (20) A similar correlation with peak exercise duration also has been found in patients with heart failure. (21) In patients who have pacemakers, a correlation of 0.74 with cycle ergometry performance has been reported. (22) The reproducibility of timed-walk tests is generally good, with inrasubject coefficients of variation averaging less than 10%. (20) Nevertheless, modest improvements (usually 10%) on repeat testing may necessitate 2 to 3 tests to produce reliable results; most investigators use the best of these efforts as the true measurement. (23) Specific situations in which these timed-walk tests can be appropriately substituted for the traditional, but more demanding, tests of functional capacity in assessing prognosis and responses to therapy are unclear. Studies comparing the prognostic value and the ability to detect meaningful change after an intervention between traditional exercise testing procedures and timed walk tests are required before a more definitive recommendation is made. Some studies, however, have suggested that a threshold value of 300 m during the 6-minute walk test may be prognostically optimal in patients with heart failure. (24, 25, 26). At this time, walk tests should not be considered an equivalent substitute for treadmill or ergometry exercise testing.

**Treadmill vs Cycle ergometer testing**

Assessment of functional capacity typically is performed on a motorized treadmill or a stationary cycle ergometer. In the United States and Australia the treadmill exercise is generally the preferred modality. Furthermore, untrained subjects will usually
terminate cycle exercise because of quadriceps fatigue at a work rate 10% to 20% below their treadmill peak VO2. (27) Cycle ergometry also requires subject cooperation in maintaining pedal speed at the desired level, usually about 60 rpm, although modern ergometers that are electronically braked maintain a steady workload at variable speeds. Several studies have demonstrated a consistent relationship between aerobic capacity determined with a treadmill and a cycle ergometer, although the latter mode of exercise tends to produce a lower peak VO2.(28,29) To rectify the discrepancy between treadmill and cycle ergometry peak VO2, the following formula has been suggested: treadmill METs = 0.98(cycle ergometer METs)x1.85.(30) Multiplication of the value obtained from this equation by 3.5 produces a treadmill peak VO2 value in milliliters of O2 per kilogram per minute.

In addition, cycle ergometry may be preferred in subjects with gait or balance instability, severe obesity, or orthopaedic limitations or when simultaneous cardiac imaging is planned. Although arm ergometry may be used to assess the aerobic capacity of wheelchair athletes or other individuals with lower-limb disabilities, most persons cannot achieve work rates comparable to those obtained with leg exercise because of the smaller, often deconditioned muscle mass.(31)

**Protocol Selection**

The selection of an appropriate exercise test protocol for assessing functional capacity is of critical importance, especially when aerobic capacity is to be estimated from exercise time or peak work rate. Exercise test protocols with large stage-to-stage increments in energy requirements generally have a weaker relationship between measured VO2 and work rate.(8) The Balke and Ware (32) and Naughton et al (33)
protocols, which involve only modest increases in treadmill elevation at a constant speed, are recommended for this reason. Functional capacity also can be accurately determined with the use of a “ramp” protocol in which small increments in work rate occur at intervals of 10 to 60 seconds. Regardless of the specific protocol chosen, the protocol should be tailored to the individual to yield a fatigue-limited exercise duration of 8 to 12 minutes. Even with exercise test protocols using modest increases in workload, results may still indicate a nonlinear relationship between VO2 and work rate when test duration is less than 6 minutes. Conversely, when such protocols result in exercise durations greater than 12 minutes, subjects may terminate exercise because of specific muscle fatigue or orthopedic factors rather than cardiopulmonary end points. In instances in which there is an expectation of greater than 12 minutes of exercise, a test protocol using a more aggressive approach to increasing workload, for example, the Bruce protocol, should be considered. Finally, minimal or no handrail support should be encouraged during treadmill exercise testing secondary to the discrepancy created between estimated (from treadmill speed and grade) and actual VO2 when it is used. Reference equations also should be specific as to whether the test was performed on a treadmill or cycle ergometer because exercise capacity is typically higher on a treadmill.

Cycle ergometer testing also requires a reasonably conditioned subject since quadriceps pain may affect the ability to achieve maximal effort. Treadmill testing requires the subject to walk at a comfortable pace in order to achieve maximal effort. The measurement of peak VO2 implies that an individual’s physiological limit has been reached.
Peak VO2 and VO2max

Peak VO2 describes functional capacity in patients with cardiovascular disease. The well known VO2max assessment is the equivalent of a peakVO2 assessment in athletes. (4) The VO2max curve plotted during exercise forms a plateau since athletes are able to continue high intensity exercise at their peak effort. (4) VO2 max is the most widely used term to describe functional capacity and is known to most cardiologists. True attainment of VO2max (physiological VO2max) has historically been defined by a plateau in VO2 between the final two exercise work rates. Indicating that maximal effort is achieved and sustained for a specified period. (4) Because this determination is subjective, can be difficult to define, and is rarely observed in tests of patients with cardiovascular or pulmonary disease, the term peak VO2 is more commonly used clinically to express exercise capacity.

Conversely, the term VO2max typically is used to describe aerobic capacity in apparently healthy individuals in whom achievement of a plateau inVO2 is more likely. It should be noted, however, that a large proportion of apparently healthy individuals may not reach a plateau inVO2 and that the absence of this response does not necessarily imply submaximal effort.(36)

Anaerobic threshold

Most daily activities do not require maximal effort. A widely used submaximal index of aerobic capacity is the anaerobic or ventilatory threshold, defined by the exercise level at which ventilation begins to increase exponentially relative to the increase in VO2. The term anaerobic threshold is based on the concept that at a given work rate,
oxygen supply to the muscle does not meet the oxygen requirements. (4) This imbalance increases anaerobic glycolysis for energy generation, yielding lactate as a metabolic byproduct (lactate threshold).(37) An increase in ventilation is needed to eliminate the excess CO2 produced in response to a sustained rise in blood lactate.

Whether muscle hypoxia is the major stimulus for increased lactate production remains controversial, and methodologies used to detect anaerobic threshold are not universally accepted.(38) Thus, although the terms anaerobic threshold, ventilatory threshold, and lactate threshold are commonly used interchangeably, they should be considered different but related events. Although the anaerobic threshold usually occurs at 47% to 64% of measured VO2max in healthy untrained subjects, it generally occurs at a higher percentage of VO2max in endurance-trained individuals.(39,40) Exercise training has been shown to increase VO2 at the anaerobic threshold to a degree that is similar to that for VO2max (typically 10% to 25% for previously sedentary individuals); thus, it is an important response to document clinically. Several methods have been proposed for determining the anaerobic threshold, but no universal agreement exists regarding which is best.

The three most common methods of determining the anaerobic threshold are the following:

(1) Point at which a systematic increase in the ventilatory equivalent for oxygen (VE/VO2) occurs without an increase in the ventilatory equivalent for carbon dioxide (VE/VCO2),

(2) Point at which a systematic rise in end-tidal oxygen pressure (PETO2) occurs without a decrease in the end-tidal carbon dioxide pressure (PETCO2),
(3) Departure of VCO2 from a line of identity drawn through a plot of VCO2 versus VO2, often called the V-slope method. When determined visually, these methods on average result in anaerobic values at a similar percentage of VO2max.

Although modern equipment that measures metabolic parameters usually quantifies this point automatically using one of several published or empirical algorithms, it should be validated visually by an experienced reviewer. The confidence in determining the VT may be increased by having 2 or 3 experienced observers independently calculate this point.

**Level of Supervision, Monitoring and Risk of Adverse Events**

Major complications of exercise testing include death, myocardial infarction, arrhythmia, haemodynamic instability, and orthopedic injury. Fortunately, adverse events are rare during properly supervised tests. Among large series of subjects with and without known disease, serious complications (including myocardial infarction and other events requiring hospitalization) have been reported to occur in 1 to as many as 5 per 10 000 tests, and death has occurred in 0.5 per 10 000 tests, although the incidence of adverse events varies depending on the study population.

Among asymptomatic low-risk subjects tested at a single institution, Gibbons et al (47) reported only 5 major complications and 1 death among approximately 70 000 subjects (overall event rate, 0.8 per 10 000 tests), with no complications or deaths in the most recent 45 000 subjects. Finally, in a survey of 570 institutions including 151,949 exercise tests conducted 4 weeks after myocardial infarction, Hamm et al (48) reported fatal, major nonfatal, and other cardiac complication event rates of 0.03%, 0.09%, and 1.4%, respectively. Although the event rate is relatively low regardless of the patient population studied, complications resulting from exercise testing do occur.
It is thus essential that exercise test supervisory personnel are familiar with the clinical indications for the use of such testing, as well as the signs and symptoms of and clinical responses to adverse events to minimize patient risk. The ACC/AHA Clinical Competence statement on stress testing outlines a series of cognitive skills necessary for performance and interpretation of exercise tests.(44) The level of supervision necessary for the individual patient is ultimately determined by the physician overseeing the exercise laboratory who is appropriately trained in testing procedures. In relatively low-risk patients (younger, apparently healthy individuals with no more than 1 cardiovascular risk factor), tests may be directly supervised by specially trained personnel, for example, nurses, nurse practitioners, physician assistants, and exercise physiologists, working under the supervision of a physician who is on site and immediately available. The level of supervision required for moderate-risk patients (individuals with _2 cardiovascular risk factors) varies and is left to the discretion of the physician overseeing the exercise laboratory. In higher-risk patients (signs and symptoms of or known cardiovascular/pulmonary disease), direct physician supervision of the exercise test may be warranted.(49)

**Establishing safety in exercise testing**

A detailed description of risk stratification procedures before exercise testing is to be understood by all personnel.(50) General methodological guidelines for exercise testing in laboratories should be posted on the wall of the laboratory.(51) ECG monitoring of heart rate with multiple-lead ECG waveforms should be continuous throughout exercise and for at least 6 minutes into recovery for diagnostic testing in patients with suspected disease. It must be recognized that activity-compatible body
electrodes may produce significant changes in ECG morphology compared with the
standard limb leads.

Consequently, the former cannot be used as a substitute for, or for comparison with,
the standard resting 12-lead ECG. (52) Blood pressure should be measured
periodically throughout the test, at least at every stage and more frequently in some
high-risk patients, as well as in recovery during ECG monitoring. Patients should be
questioned about symptoms periodically during and after exercise, and for research
and comparison purposes, an angina scale, dyspnea scale, and/or rating of perceived
exertion should be used.

**Ventilatory Expired Gas Analysis**
Ventilatory expired gas techniques during exercise testing, commonly called
cardiopulmonary exercise testing (CPX), have become more widely applied because
they significantly increase the precision and yield of information from the
exercise test. A shortcoming of standard exercise testing is the inherent inaccuracy in
the estimation of exercise capacity from the work rate achieved on a treadmill or cycle
ergometer. (53) Oxygen uptake estimated from the work rate, that is, estimated METs,
is commonly used clinically, but the limitations associated with estimating the MET
level have been widely described.

The accuracy of these estimations is affected by the presence and extent of disease
(the estimate is less accurate when patients with cardiovascular or pulmonary disease
are tested), the exercise protocol used (exercise capacity is more accurately estimated
when more gradual, evenly incremented protocols are used), serial testing
(estimations are more accurate with testing experience), and whether the subject is allowed to hold onto the handrails (holding the handrails significantly decreases the oxygen demands of the work rate, resulting in overestimation of METs).

There is also uncertainty related to defining maximal work capacity because the test usually ends during an incomplete stage. It is recommended that the estimated MET level for a given stage be ascribed for a patient only when more than half the stage has been completed, but the accuracy of this practice depends on the size of the increment in work rate and the relative exercise intensity for a given patient and is inconsistently applied. The direct measurement of $V'_O_2$ obviates these problems because it is more accurate and reproducible than estimated values from the peak work rate achieved.

Information obtained from CPX also has applications for helping to establish the cause of exercise intolerance, estimating prognosis, determining disability, and making judgments concerning therapeutic interventions. Peak $V'_O_2$ is now widely recognized as an important factor in risk stratifying patients with cardiovascular disease. In particular, numerous studies have been published over the past 15 years demonstrating that ventilatory gas exchange responses to exercise predict outcomes in patients with chronic heart failure,\(^\text{53,54,55}\) and these measurements have become a standard tool in the clinical evaluation of these patients.

A large body of research also has evolved regarding cardiopulmonary variables other than peak VO2 in the context of prognosis. Responses such as the anaerobic threshold, VE/VCO2 slope, VE/VCO2 at peak exercise, oscillatory ventilation, oxygen uptake on-kinetics, rate of recovery of VO2, and oxygen uptake efficiency
slope have been used with greater frequency to classify functional limitations and to stratify risk in patients with heart disease. Many of these are expressions of ventilatory efficiency and reflect the various underlying pathophysiological factors that lead to inefficient breathing associated with heart failure or pulmonary disease.

**VE / VCO2 (Ventilatory efficiency)**

There has been a particular focus on the clinical significance of the VE/VCO2 slope in patients with heart failure. This response usually is expressed as the slope of the best-fit linear regression line relating VE and VCO2. Among patients with heart failure, the VE/VCO2 slope has been demonstrated to predict mortality, hospitalization, and major adverse cardiac events. These results may suggest that the ventilatory efficiency may well be equivalent to or at times a better predictor of outcome than peakVO2. (53,54,56,57,58,59,60) Peak VO2 assessment has stood the test of time (30 years) as a measure of functional aerobic capacity. A more thorough review of the host of cardiopulmonary variables has been reported. (61)

**Quality control and calibration**

The accuracy of the data collected by ventilatory expired gas equipment depends heavily on proper maintenance and precise calibration procedures conducted by appropriately trained personnel. Exercise laboratories performing ventilatory expired gas analysis should have quality assurance procedures in place and strictly follow
them. A detailed description of the appropriate use and maintenance of ventilatory expired gas equipment and quality assurance measures can be found in validation and instrumentation studies. (62,63)

**Availability of the CPEX test.**

The CPEX test is not as widely available as the standard treadmill test for multiple reasons. The metabolic cart and gas analyser is a costly equipment expense ($40 000 (2010)). The test is also expensive ($400). Cardiac scientists who are able to implement the test and interpret the results are not always available. Cardiologists are generally not specifically trained in the interpretation of the results unless they have a special interest.

This creates marked variation in results between different exercise laboratories using the same subject. When the test is accomplished by experienced operators there is good correlation of data with useful adjunct information to the clinical history and examination. Patients with mild symptoms (NYHA class I or II) can be evaluated by repetitive treadmill exercise testing without a metabolic cart assessment for peak VO2. Total exercise duration (MET capacity) can be used as an objective measure of functional capacity. In comparison, patients who present with or progress to moderate-to-severe heart failure (NYHA class III or IV) should be referred to a center with the capability to perform valve surgery.

The specific method and protocol used to measure peak VO2 is less important as long as the test is performed and interpreted in a consistent manner. (4) In relation to
valve disease the test result interpretation should take into account the presence and treatment of atrial fibrillation, current medical therapy and comorbid conditions.

The appropriateness of the protocol, availability of emergency equipment experience and qualifications of technicians, scientists and support staff with the presence of a medical practitioner will determine the safety and accuracy of a cardiopulmonary exercise test in heart valve disease.
References


Chapter 11

Conclusion and Future Direction of Research
Conclusion

The importance of assessing functional capacity at baseline is an important aspect of any clinical evaluation in heart valve disease. Our study assessed a rare cohort with mixed and multiple valve disease without coronary artery disease or any severe comorbidity that precludes surgery. The formal cardiopulmonary exercise test (assessing peakVO2) is shown in this study to be a strong predictor of outcome in complex valve disease. The cardiac specific biomarker BNP is shown in this study to be a useful adjunct to the clinical examination and the echocardiogram in predicting outcomes. The BNP test is a simple resting blood test that can be performed in any clinical environment. In complex mixed and multiple heart valve disease, should BNP be combined with spirometry, the study reasons that an impairment in functional capacity can be predicted.

In patients with a sedentary lifestyle, routine activities may not produce symptoms especially if the intensity of the effort is low. Thus an asymptomatic status in these patients does not rule out prognostic disease. In patients who are asymptomatic or mildly symptomatic the results from this thesis proposes a role for biomarkers and formal functional capacity testing to reveal the true severity of the symptoms. The formal peakVO2 measurement quantifies exercise intolerance and can expose a subclinical symptomatic state. Impaired functional capacity (Low peak VO2 measurement) and high BNP levels were both prognostic markers of outcome in our asymptomatic or mildly symptomatic cohort. Detecting the onset of symptoms will aid in the clinical decision regarding the timing of surgery. Optimal timing of valve replacement can lead to prioritised, planned elective surgery as opposed to high risk emergency surgery. Planned surgery has a better chance of recovery of left ventricular function before irreversible adverse remodelling sets in. Future studies
should aim to further consolidate BNP and peakVO2 as proven prognostic markers of outcome in a wider range of valve related conditions.

**Future direction of our valve disease research.**

The advent of percutaneous transcatheter valve replacements is a new and exciting cardiovascular procedure being developed in the last decade. (1) The less invasive technique has created a new option of heart valve replacement in patients who have been refused cardiac surgery. (1) The elderly population (> 75 years) have a high prevalence of valve disease especially calcific aortic stenosis as well as chronic mitral regurgitation. (2) Surgical morbidity and mortality is higher in this patient group as indicated by the surgical risk calculator from the Society of Thoracic Surgeons (STS) and Euroscore. (2) In these two patient groups percutaneous aortic valve replacement or minimally invasive mitral valve repair is an attractive option to avoid major cardiac surgery. International registries and pivotal trials are well underway to thoroughly research percutaneous transcatheter valve replacement technology.

Currently there are two types of percutaneous valves available in Australia and Europe. The CoreValve Revalving System (Medtronic Inc, Minnesota, MN) is currently the most widely used in Australia. The alternative the Edwards Sapiens valve (Edwards Lifesciences, Irvine, CA) has been recently launched in Australia. (1,2) Our interventional cardiologists have demonstrated success in deploying both these valves using international proctors. The CoreValve is not currently in use in the USA due to US FDA (Food and Drug administration) licencing requirements. Both these percutaneous valves are widely used in Europe. The
Edwards Sapiens valve is currently under investigation across the USA as part of the PARTNERS trial (Placement of Aortic Transcatheter valve trial). (3)

Fig 1. CoreValve (Medtronic Inc) showing the self expanding nitinol frame. (1)

Fig 2 Edwards Sapiens (Edwards Lifesciences) percutaneous transcathe ter aortic valve with stainless steel frame. (3)
The Partners Trial (Placement of Aortic transcatheter valve trial)

The Partners trial is a randomised controlled study which commenced in 2007, and combines a “partnered approach” between cardiac surgeons and cardiologists. The purpose of this study is to determine the safety and effectiveness of the device and delivery systems (transfemoral and transapical) in high risk, symptomatic patients with severe aortic stenosis. The device being investigated is the Edwards Sapiens transcatheter aortic valve system (Edwards Lifesciences Menlo Park, CA, USA). The outcome measures are listed below.

Table 1 Outcome measures in Partners trial.

<table>
<thead>
<tr>
<th>Primary Outcome Measures:</th>
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<tbody>
<tr>
<td>Freedom from death (Cohort A: Edwards Sapiens Valve Transfemoral or Transapical vs. other surgical valve) [ Time Frame: 1 year ]</td>
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<tr>
<td>Freedom from Death (Cohort B: Edwards Sapiens Valve transfemoral vs. medical therapy) [ Time Frame: duration of study ]</td>
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<tr>
<th>Secondary Outcome Measures:</th>
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<tr>
<td>Functional Improvement from baseline per NYHA functional classification (Cohort A and Cohort B) [ Time Frame: 30 days, 6 months, 1 year ]</td>
</tr>
<tr>
<td>Freedom from MACCE and expanded safety composite events. [ Time Frame: 30 days, 6 months, 1 year ]</td>
</tr>
<tr>
<td>Evidence of prosthetic valve dysfunction (haemolysis, infection, thrombosis, severe paravalvular leak, or migration) (Cohort A) [ Time Frame: 30 days, 6 months, 1 year ]</td>
</tr>
<tr>
<td>Length of index hospital stay (Cohort A) [ Time Frame: number of days hospitalized ]</td>
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<tr>
<td>Total hospital days from the index procedure to one year post procedure. (Cohort A) [ Time Frame: 1 year ]</td>
</tr>
<tr>
<td>Improved Quality of Life (QOL) from baseline to 30 days, 6 months, and 1 year (Cohort A and Cohort B) [ Time Frame: 30 days, 6 months, 1 year ]</td>
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</table>
Improved valve function demonstrated by a responder analysis showing the percentage of patients in each treatment group who have a greater than 50% improvement in AVA at 30 days, 6 months, and 12 months. (Cohort A and Cohort B) [ Time Frame: 30 days, 6 months, 1 year ]

Total hospital days from the index procedure or randomization in to control arm for medical management patients to 1 year post procedure or randomization (Cohort B) [ Time Frame: 1 year ]

Composite survival, recurrent hospitalisation and NYHA class.

**Eligibility In the Partners trial Inclusion Criteria Cohort A**

Patients must have co-morbidities such that the surgeon and cardiologist Co-PIs concur that the predicted risk of operative mortality is ≥15% and/or a minimum STS score of 10

Patient has senile degenerative aortic valve stenosis with echocardiographically derived criteria: mean gradient >40 mmHg or jet velocity greater than 4.0 m/s or an initial aortic valve area of < 0.8 cm²

Patient is symptomatic from his/her aortic valve stenosis, as demonstrated by NYHA Functional Class II or greater

The subject or the subject's legal representative has been informed of the nature of the study, agrees to its provisions and has provided written informed consent as approved by the IRB of the respective clinical site

The subject and the treating physician agree that the subject will return for all required post-procedure follow-up visits

Cohort B All candidates for Cohort B of this study must meet #2, 3, 4, 5 of the above criteria and

The subject, after formal consults by a cardiologist and two cardiovascular surgeons agree that medical factors preclude operation, based on a conclusion that the probability of death or serious, irreversible morbidity exceeds the probability of meaningful improvement. Specifically, the probability of death or serious, irreversible morbidity should exceed 50%.
**Exclusion Criteria**

Evidence of an acute myocardial infarction ≤ 1 month before the intended treatment

Aortic valve is a congenital unicuspid or bicuspid valve; or is non-calcified

Mixed aortic valve disease (aortic stenosis and aortic regurgitation with predominant aortic regurgitation > 3+)

Any therapeutic invasive cardiac procedure performed within 30 days of the index procedure, (or 6 months if the procedure was a drug eluting coronary stent implantation)

Pre-existing prosthetic heart valve in any position, prosthetic ring, or severe (greater than 3+) mitral insufficiency

Blood dyscrasias as defined: Leukopenia, acute anemia, thrombocytopenia, history of bleeding diathesis or coagulopathy

Untreated clinically significant coronary artery disease requiring revascularization

Haemodynamic instability requiring inotropic support or mechanical heart assistance.

Need for emergency surgery for any reason

Hypertrophic cardiomyopathy with or without obstruction

Severe ventricular dysfunction with LVEF < 20

Echocardiographic evidence of intracardiac mass, thrombus or vegetation

Active peptic ulcer or upper GI bleeding within the prior 3 months

A known hypersensitivity or contraindication to aspirin, heparin, ticlopidine, or clopidogrel, or sensitivity to contrast media, which cannot be adequately pre-medicated

Native aortic annulus size < 16mm or > 24mm per the baseline echo as estimated by the LVOT

Patient has been offered surgery but has refused surgery.

Recent (within 6 months) CVA or a TIA

Renal insufficiency and/or end stage renal disease requiring chronic dialysis

Life expectancy < 12 months due to non-cardiac co-morbid conditions.

Significant aortic disease, including abdominal aortic or thoracic aneurysm defined as maximal luminal diameter 5cm or greater; marked tortuosity (hyperacute bend), aortic arch atheroma or narrowing (especially with calcification and surface irregularities) of the abdominal or thoracic aorta, severe "unfolding" and tortuosity of the thoracic aorta (applicable for transfemoral patients only).
Iliofemoral vessel characteristics that would preclude safe placement of 22F or 24F introducer sheath such as severe obstructive calcification, severe tortuosity or vessels size less than 7 mm in diameter(applicable for transfemoral patients only). Currently participating in an investigational drug or another device study.

The current downside of percutaneous valve replacement therapy is the cost (percutaneous valves cost $40000-60000 per unit depending on the type). There are also vascular access and bleeding issues, with the risk of malposition and embolisation at final deployment. (1) Successful procedures have a minimum time to discharge in 2-3 days as opposed to a week in intensive care, ward observation, rehabilitation and nursing home discharge with cardiac surgery. There is an immediate and impressive reduction in valve gradients to normal levels. Patients in the older age category also have a higher stroke risk, longer hospital stay and prolonged recovery period with major surgery. (1) Mortality and morbidity risks from registries using percutaneous valve therapy have shown to be equal to predicted major cardiac surgery risks in feasibility studies. (1) World wide there have been more than ten thousand different percutaneous valves inserted in the last few years. Whether or not the percutaneous procedure is non inferior or better than surgical valve replacement needs to be tested in a randomised control trial (hence the role for the pivotal Partners Trial). It is hypothesized from its inception that as the percutaneous procedure becomes more refined there will a tendency to more frequent percutaneous replacements. This may be by clinical decision or through patient choice.

The improvement in quality of life is central to the decision for valve replacement whether this is by percutaneous or surgical technique. Functional capacity improvement is a significant aspect of quality of life especially for the elderly patient.
who might be living alone. The pre-procedural predictors of outcome will ultimately help determine which procedure will be chosen. The procedure should produce a functional capacity improvement with the shortest possible recovery period and return to home conditions. The Partners trial is currently addressing a comparison between both methods of valve replacement (surgical versus percutaneous) in a randomised fashion to address outcomes and technical complications. Unfortunately functional capacity assessment beyond the clinical NYHA (New York Heart Association) functional class is not one of the major outcomes.

We demonstrated that the peak oxygen consumption is a useful predictor of outcome in complex mixed and multiple valve disease. BNP and spirometry were strong predictors of poor functional capacity. These parameters together with clinical predictors, co morbidities, demographic data and investigational data needs to be assessed in percutaneous valve therapies to improve the timing of surgery, functional capacity status and post procedural recovery.

It is important to remember that the Partners trial is currently being conducted in the USA. The Edwards Sapiens valve is already widely used in Europe and has shown much promise. (1,3) . Smaller but similar CoreValve studies are currently being conducted to ensure that a reasonable alternative will be available to the Edwards. There are multiple registries world wide in both percutaneous valve type that provide important outcome data and technical issues to aid proper further development.(1)

The impact of this therapy is expected to revolutionise our thinking in valve replacements with considerable focus on the timing of surgery. Given our greater experience with the CoreValve in Australia, we endeavour to produce data to supplement landmark trials like the Partners Study albeit in a small way. We hence
conducted a retrospective study of our initial cohort of patients receiving percutaneous aortic valves to assess outcomes of the expensive and technologically advanced procedure.

**A retrospective study of transcather aortic valve replacement in Queensland**

Despite concerns, percutaneous aortic valve replacement is well underway in Australia for patients who are poor surgical candidates. The first percutaneous aortic valve replacement in Australia was successfully completed at the St Vincent’s hospital in Sydney, NSW in early 2009 using an 18Fr CoreValve revalving system. Percutaneous aortic valve replacements started in Queensland in 2009 at the Prince Charles hospital in Brisbane. We hence conducted a small retrospective study from our registry to examine short term outcomes in patients who have already had percutaneous aortic valve replacements in Queensland. This retrospective study does not assess the predictors of outcome but provides a foundation from which a more detailed study which includes BNP and functional capacity testing can be assessed. The abstract is described below.

**ABSTRACT :Percutaneous Aortic Valve replacement (PAVR) using 18F Core Valve prosthesis: Short term outcomes.**

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**Aim:** To report short term outcomes of PAVR after transcatheter retrograde implantation of the 18-Fr Core Valve prosthesis.
Background: PAVR is an emerging therapeutic alternative for patients with severe symptomatic aortic stenosis who are high risk surgical candidates.

Method: Mandatory inclusion criteria were: 1) Symptomatic state 2) Severe aortic valve disease (ACC criteria 2006) 3) Logistic EuroSCORE > 15%, 4) inoperable. Exclusion criteria included severe peripheral vascular disease, Preprocedure all patients had the following: clinical and surgical assessment, echocardiographic evaluation, iliac, aortic and coronary angiogram ± aortic valvuloplasty and written consent. The approach included transfemoral vascular access under local anaesthesia in a mildly sedated conscious patient. To optimise safety an intensivist, surgeon and proctor, provided in-lab technical assistance, surgical cutdown if needed and critical care support.

Results: Intention to treat N=21. The cohort had a mean age of 84.2±5.4 years and mean logistic EuroSCORE of 21.4 ±4.5%. N= 20 patients with AS with a mean valve area of 0.68± 0.18 cm² were recruited. Overall mortality 30 days was 9.5% . Intra-procedural mortality was 4.5% from ventricular perforation (Core valve was not used). Post PAVR one patient with advanced renal failure died in ICU two days later. One patient had vascular access failure despite surgical cutdown (Core valve not used).

A 90 % deployment success rate was achieved (19 Core Valves) including one valve–in–valve procedure for Severe AR . Mean Aortic transvalvular gradients decreased significantly (pre-procedure 47 mm Hg vs. post-procedure 9.0 mm Hg, p<0.001). Mean aortic valve area increased to 2.1± 0.5 cm², p<0.001. Residual aortic regurgitation grade ≤ 2 at 30 days. Major bleeding 4,7%. One patient required intubation to avoid restlessness during valve deployment. The combined rate of death, stroke, and myocardial infarction was 14%. Two patients required repositioning
using a snare to reduce paravalvular leak. No embolization of deployed valves occurred. Device positioning was considered optimal without compromise of coronary flow in 100%. Mortality from 30 -210 days of follow up was 0%. Post PAVR there are 18(94%) patients who are alive and 61% achieved an NYHA class improvement.

**Conclusions**: Initial outcomes from implantation of the 18F-Core Valve prosthesis suggest a safe and feasible option in patients who are refused surgery in our centre. Our results compare favourably with international registries with PAVR.

This abstract has been submitted to various conferences for poster presentation. The numbers in our study are too small to draw any definite conclusions. Our future studies after acceptance of this thesis will include cardiopulmonary exercise testing both pre and post procedure. A summary of this future study is presented below.

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**Study 1 Aortic Stenosis in the elderly undergoing percutaneous aortic valve replacement (PAVR) in Queensland Australia:**

**Background**

Percutaneous valve replacement is technically a less traumatic procedure which does not warrant a sternotomy or cardiac bypass anaesthesia. (1) Percutaneous valve replacement is shown to reduce blood loss and suffering from major cardiac surgery. The therapeutic procedure improves valve area (from 0.7 to 1.3 cm sq). The ultimate
goal is to relieve the stenosis and increase the stroke volume and cardiac function in a group of patients whose functional capacity and quality of life is compromised.

The project aims to describe the preprocedural predictors of adverse outcome in percutaneous valve replacement and compares this to conventional surgical valve replacement. We will assess the following predictors: Euroscore (includes co-morbidities and concurrent illness), clinical functional class assessment, echocardiographic parameters of valve lesion severity, natriuretic peptides and spirometry. Percutaneous valve replacements are currently offered only to those patients who are not candidates for surgery. This may be the elderly, with multiple comorbidities, compromised functional capacity, and high risk for surgical complications including bleeding, complication risk and failure to complete post operative rehabilitation. The percutaneous technique has evolved in the last 8 years causing minimal trauma and good outcomes despite being used in a high risk population.(1) The procedure is fast growing internationally and will grow in Australia in the next few years. The expected cardiovascular outcomes are improved quality of life, relief of symptoms, improved functional class, and reduction in hospital admissions, heart failure prevention and the absence of the complications of major cardiac surgery.

**Aims**

To define the predictors that lead to adverse cardiovascular outcome in patients undergoing percutaneous aortic valve replacement compared to surgical valve replacement in the following respects:

1.1 Clinical assessment Comorbidities and Euroscore

1.2 Clinical functional Class (New York Heart Association Classification)

1.3 peakVO2 (peak oxygen consumption)

1.4 Resting b type natriuretic peptide levels (Ntpro-BNP)
1.5 Echocardiographic parameters of valve lesion severity, systolic function (Ejection Fraction), Diastolic function (E/E’ and E:A ratio), the presence of mixed/multiple valve pathologies.

1.6. The presence of coronary artery disease requiring coronary intervention.

2. To assess the sensitivity and specificity of each of the above predictors at 30 days 6 months and 1 year post procedure to predict the primary end points of cardiac mortality and recurrent hospital admissions and secondary end points: procedural blood loss, stay in hospital (duration), heart failure, new arrhythmia, quality of life, device failure (paravalvular leak or embolisation)

**Method:** N= 50 patients who are declared unfit for surgery will undergo PAVR. They will be matched with 50 patients with surgical valve replacement. The patients will be assessed at baseline 30 days, 6 months and 1 year post procedure. They will undergo clinical assessment, NYHA class, peak VO2, BNP, euroscore and echocardiogram at the respective intervals. Comparisons will be made between the groups regarding their outcomes.

**Conclusion:** The results will be interpreted to generate further safety and efficacy data. The predictors of outcome will be obtained using multivariable regression. The data will be written up and presented for publication in peer review journals. The data will guide future development and experience with modern percutaneous technology.
**Percutaneous mitral valve repair**

Mitral valve regurgitation affects 1-2 % of the US population. (4,5) It is the second most common valve condition after aortic stenosis. (4,5) Mitral valve repair is primarily used to correct valve pathology related to degenerative disease (myxomatous) and functional disease MR secondary to ischemic heart disease or dilated cardiomyopathy. (5) Percutaneous edge to edge repair of the mitral valve is expected to commence in 2011 in Australia. Percutaneous mitral valve replacements unlike aortic valve replacements are in phase 1 of development with a few of the first in-human valve replacement studies being conducted. Percutaneous mitral valve repair is currently offered only to those patients who are not candidates for surgery. (6) Patients include the following: elderly with multiple comorbidities, compromised functional capacity, high risk for surgical complications including bleeding, (6) significant complication risk and failure to complete post operative rehabilitation.

Fig. 3 Percutaneous mitral valve repair involves a transeptal approach used to deliver a clip device that can grasp the central mitral leaflet edges to create a double orifice. A Clip device. B Schematic diagram of the clip just below leaflets. C Echocardiographic view of the open clip positioned just below leaflets. D Echocardiographic view of double orifice valve. LA—left atrium; LV—left ventricle (4)
We are currently developing protocols in preparation for the development of this procedure which has been developed in the USA. Here again the safety and feasibility needs to be established together with the predictors of outcome. Using the same principles adopted in this thesis we are developing protocols to optimise outcomes. These protocols are still subject to ethics review and will be modified in the future. An outline of the protocol investigating our approach to percutaneous mitral valve procedure when it is approved for use in Queensland is presented below.
Study 2 Protocol Outline: Mitraclip (E-valve Menlo park CA)

Safety, feasibility and predictors of outcome in percutaneous mitral valve edge to edge repair using the Mitraclip (E-valve, Menlo Park, CA) for severe mitral regurgitation.

Background: Valvular heart disease (mitral regurgitation) is a common cause of morbidity and mortality in the elderly.(1,6) Patients who are elderly or have multiple comorbidities, carry a high surgical risk and may not be offered surgery. In recent years these patients are shown to have improved outcomes with percutaneous valve replacement compared to the complications of major cardiac surgery. (1,6) There is a growing population of elderly patients in this high risk surgical category. Percutaneous valve replacement and repair is technically a less traumatic procedure which does not warrant a sternotomy or cardiac bypass . (1,6) The Everest II trial has proved that percutaneous mitral valve edge to edge repair is shown to reduce the blood loss and suffering of major cardiac surgery and is a useful therapeutic measure to improve mitral regurgitation.(7)

The procedure generates an improvement in the stroke volume and cardiac output through a reduction in the mitral regurgitation volume in a group of patients whose functional capacity and quality of life is compromised by having a regurgitant mitral valve. The procedure essentially involves the insertion of one or two Dacron clip(s) at the leaflet edges through a percutaneous delivery system. (6) The clips bring together the leaflet edges reducing the orifice size and the regurgitant volume. The procedure is conducted under transoesophageal imaging with concomitant
fluoroscopy. The patient is given a general anaesthetic with haemodynamic monitoring. (6,7) The infrastructure to carry out this procedure includes access to Cardiac Catheterisation laboratory and Cardiothoracic surgical unit, transoesophageal echocardiography, ward facilities, Intensive care, on site back up surgery.

The project aims to describe the safety and efficacy and preprocedural predictors of adverse outcome in percutaneous mitral valve repair. We will assess the following predictors: STS and Euroscore (includes co-morbidities and concurrent illness), clinical functional class and functional capacity assessment, echocardiographic parameters of valve lesion severity, natriuretic peptides, spirometry and pre repair haemodynamic measurements.

The percutaneous technique has evolved in the last 5 years causing minimal trauma and good outcomes despite being used in a high risk population. (6) The procedure is fast growing internationally and will definitely reach other parts of Australia in the next few years. The expected cardiovascular outcomes are improved quality of life, relief of symptoms, improved functional class, return to premorbid activities, reduction in hospital admissions, heart failure prevention and the notable avoidance of the complications of major cardiac surgery and sternotomy,

The recently reported Everest II trial demonstrated safety, feasibility and effectiveness of this procedure. (7) In this randomised control trial (N=279) the Mitraclip percutaneous repair was compared to surgical valve replacement. (7) Patients had 3+ or 4+ of MR on echo. Patients were followed up for a year to determine the
outcomes, effectiveness and feasibility of using this device and less invasive percutaneous approach.

In the Everest trial the primary safety endpoint of major adverse events at 30 days demonstrated a superior safety profile (p<0.0001) of the MitraClip compared to surgical repair or replacement (9.6% MitraClip patients vs 57.0 %of surgery patients. (7) In the primary effectiveness endpoint, the MitraClip device was non-inferior to surgery at one year (clinical success rate of 72.4 percent for MitraClip patients with successful initial treatment compared to a clinical success rate of 87.8 percent for surgery patients).(7) This fell within the 25.4% confidence interval for non-inferiority.(7)

At one year Mitraclip produced a significant clinical benefit in the following:
A reduction in the severity of MR, with 81.5 percent of patients improving to mild (grade 1+) or moderate (grade 2+) MR whereas at baseline 95.6 percent of patients had moderate-to-severe (grade 3+) or severe (grade 4+) MR (p<0.0001)
A reduction in both the end diastolic volume and dimensions. Left ventricular diastolic volumes decreased a significant 13 % (p<0.0001) and left ventricular diastolic dimensions decreased a significant 6.4 % (p<0.0001) compared to baseline.

Symptom improvement with 97.5 percent of patients becoming asymptomatic (NYHA Functional Class I) or mild symptoms (NYHA Functional Class II) [p<0.0001], whereas at baseline, 52.6 % of patients had moderate symptoms (NYHA Functional Class III) or severe symptoms (NYHA Functional Class IV. PeakVO2 however was not measured.
SF 36 : Meaningful improvements in both physical and mental quality of life compared to baseline as measured by the SF-36 Survey (increase of 4.7 points in the physical quality of life score \([p<0.0001]\) and increase of 5.8 points in the mental quality of life score \([p<0.0001]\)).

There is thus a significant need to report such data of the Mitraclip procedure in order to further reinforce safety, efficacy and usage in the interventional arena.

**Overview of our future study- MitraClip**

**Hypothesis:**

The Mitraclip provides meaningful and sustained clinical benefit and predictors of adverse events can be recognised pre procedurally.

**Objectives**

- To establish the safety and feasibility of the percutaneous mitral valve edge to edge technique.
- To define the predictors that lead to adverse cardiovascular outcome in patients undergoing percutaneous valve replacement compared to surgical valve replacement in the following respects:

1. Clinical assessment, Comorbidities, STS and Euroscore
2. Clinical functional Class (New York Heart Association Classification), Cardiopulmonary exercise testing with peakVO2 measurements
3. Resting Btype natriuretic peptide levels (Nt-BNP)
4. Echocardiographic parameters of valve lesion severity, systolic function (Ejection Fraction),
5. Diastolic function LV volumes and dimensions (E/E’ and E:A ratio), the presence of mixed /multiple valve pathologies.
6. The presence of coronary artery disease requiring coronary intervention.
7. Characteristic of the mitral valve lesion, lesion subtype, structure of the leaflets
8. Interatrial septal abnormalities
9. Structure of the cardiovascular system relevant to the procedure - vessel tortuosity, structural abnormalities of the heart, atria, and mitral valve
10. Preprocedural Imaging of the relevant structures including the echocardiography, transoesophageal echocardiography, Fluroscopy and angiography
11. Haemodynamic factors and anaesthesia risk

Follow up: To assess the sensitivity and specificity of each of the above predictors (1-5) at 30 days and 6 months and 1 year post procedure to predict the primary end points of cardiac mortality, recurrent hospital admissions and mace. Secondary end points: procedural blood loss, stay in hospital (duration), heart failure, new arrhythmia, device failure severity of MR, embolisation, dislodgement, radiation duration, contrast usage, quality of life, procedural success defined as optimal placement of the mitraclip with ≤ moderate mitral regurgitation (2+)

Statistics: IRB review will be obtained. An institutional board review will be conducted to permit the publication of results. A statistical analysis will be performed. These include univariate and multivariable regression to determine the predictors of outcome. T tests will be used to compare age groups (elderly and young) and disease groups (poor ejection fraction vs normal ejection fraction).

Conclusion: Safety, feasibility and preprocedural predictors of outcome are vital to the continued usage of minimally invasive percutaneous mitral valve technology. This study attempts to optimise patient selection and report overall morbidity and mortality.
Summary and final conclusions

Establishing a clear role for percutaneous valve replacement as an alternative to surgery is important. International registries and pivotal trials are of paramount importance in establishing safety of new technologies. Trained personnel, with a process of establishing safety and feasibility in all prospective centres that plan to undertake these procedures is absolutely essential. The predictors of outcome will help identify high risk groups and pre-empt an adverse prognosis. The studies currently underway are important in addressing the technical aspects, complications, adverse events and outcomes. Such trials provide the foundation data which justify the use of costly minimally invasive valve therapies. The clinical assessment and diagnostic work up coupled with preprocedural risk factors guide the planning and execution of the technologically advanced procedure. The ultimate aim of such a procedure should be to reduce morbidity and mortality and above all improve the quality of life of the patient.

The functional capacity of the patient is central to the quality of life of a patient. The peak VO2 measurement is an international gold standard that has stood the test of time. Symptoms are sometimes hidden in the patient’s functional capacity especially in sedentary patients. Patients may become sedentary in lifestyle through personal choice or as an effect of disease. Detecting the presence of these symptoms at the earliest onset will impact on outcome. In first world countries the availability of technology allows for early detection and close monitoring of pathological valve disease. When the prognosis is unclear then biomarkers may provide clues as to the potential outcome. The cardiac specific biomarker B type natriuretic peptide has been proven repeatedly as a useful clinical adjunct.
As we delve into the future with exciting technologies especially in valve disease we have to bear in mind that patient selection and the timing of minimally invasive surgery will drastically affect the risk to benefit ratios and complication rates. Reducing the morbidity and mortality rates will instil confidence in our ability to successfully accomplish percutaneous valve replacement. This will create strong financial support to further enhance our research in the human body. Improvement in the quality of life of our patients through functional capacity improvement will definitely result in greater patient confidence and enhance the trust in the doctorpatient.

As we investigate the genetic basis of disease and identify more biomarkers of outcome we should ensure that they are assessed in the context of the clinical assessment. We should strive for perfection in the timing of valve surgery but never forget the choices of the patient. We should embrace new and well researched therapies with courage and caution but always respect the knowledge, therapeutic procedures and modalities of the past that have brought us to these very exciting times.

_Naylin Bissessor_

_Cardiologist_
References


3. www.clinicaltrials.gov Indentifier NCT00530894


