TIME-COURSE CHANGES IN THE ECHOCARDIOGRAPHIC PARAMETERS AND NT-PROBNP LEVELS IN PATIENTS WITH SEVERE MITRAL REGURGITATION UNDERGOING VALVE REPLACEMENT

By

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DECLARATION

I declare that this dissertation is my own unaided work in partial fulfillment for the Degree Masters of Medical Science (Cardiology), University of KwaZulu-Natal.

This has not been submitted before for any degree or examination at any other educational institution.

D.R. Prakaschandra

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ABSTRACT

Conventional echocardiographic parameters are currently used in determining the timing for surgery in patients with mitral regurgitation. Since brain natriuretic peptide (BNP) rises in response to ventricular muscle stretch, and is to detect early heart failure, we hypothesized that BNP would be activated in patients with regurgitant valvular heart disease and concomitant left ventricular dilatation.

Aim/Objectives:

We therefore studied the pattern of changes in NT-pro BNP in patients with chronic severe rheumatic mitral regurgitation who were undergoing mitral valve replacement and compared this with the newer modality of tissue Doppler imaging (TDI).

Setting:

Patients submitted to surgery were prospectively evaluated over 8 months at Inkosi Albert Luthuli Central Hospital, Department of Cardiology. Controls were obtained from the outpatients' follow-up clinic.

Methods:

Simultaneous quantification of the severity of mitral regurgitation (MR), left ventricular (LV) end systolic volume (ESV), left atrial (LA) volume and Doppler filling ratios (mitral (E)/annulus (Ea)) were performed at baseline in all patients and was repeated at 1-week and at the six-week follow-up visit in surgical patients.

Results

Both groups were similar for age and gender and echo-Doppler parameters in all patients preoperatively except LA size ($p< 0.01$) and volume ($p<0.004$) which were more elevated in the surgical group. Mean NT-pro BNP levels were markedly elevated preoperatively (262 pmol/l) in all surgical cases compared to controls (57 pmol/l; $p=0.0001$). NT-pro BNP levels increased further at one week post surgery (395pmol/l) and subsided at the six week follow-up visit (94 pmol/l).These changes were accompanied by significant reduction in LA ($p= 0.003$) and LV chamber dimensions (EDD = 0.004) with an increase in the ejection fraction from 42% at one week to 52 % at six weeks. Four patients had abnormally elevated NT-pro BNP levels (>53pmol/l) at the 6-week follow-up visit. A ROC curve was constructed for all variables to separate surgical cases from controls. The area under the curve was highest for NT-pro BNP (sensitivity= 96%, specificity 45 %).

Conclusion

1. There was a significant difference in the left atrial chamber size and volume, as well as Em/Ea (TDI) and NT-proBNP levels preoperatively between the two groups. The lack of a significant difference in the LV parameters between surgical and control groups suggest an almost total reliance on symptoms in deciding the timing of surgery which was reflected by markedly elevated NT-pro BNP in all surgical patients.
2. Postoperatively, there was a significant reduction in LA and LV dimensions.
3. The high false positivity rate for NT-pro BNP suggests that the test is most likely reflecting early LV decompensation in the less symptomatic control patients who rightly need surgery.

4. Tissue Doppler indices had similar sensitivity but low specificity compared to NT-pro BNP.
5. Serial estimations of NT-pro BNP may prove useful in selecting patients for surgery.

PUBLICATIONS AND PRESENTATIONS

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ABBREVIATIONS

BNP	: Brain Natriuretic Peptide
TDI	: Tissue Doppler Imaging
MR	: Mitral regurgitation
EDD	: End-diastolic Dimension
ESD	: End-systolic dimension
FS	: Fractional shortening
EDV	: End-diastolic volume
ESV	: End-systolic volume
LA	: left atrium
LV	: Left ventricle
EF	: Ejection fraction
ROC	: Receiver operator curve
RHD	: Rheumatic Heart disease
HF	: Heart failure
MRV	: Mitral reurgitant volume
MRF	: Mitral regurgitant fraction
PISA	: Proximal isovelocity surface area
EOA	: Effective orifice area
CMO	: Cardiomyopathy
RV	: Right ventricle
PA	: Pulmonary artery

AF	: Atrial fibrillation
NYHA	: New York Heart Association
Pmol/l	: picomoles per litre
Pg/ml	: picograms per milliliter
m/s	: metres per second
CW	: Continuous wave
MI	: myocardial infarction
ANOVA	: Analysis of Variance
CHF	: congestive heart failure

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CHAPTER 1

BACKGROUND

1. Introduction

Valvular insufficiency may generally be classified as organic when it is due to intrinsic damage to the valve apparatus, or functional when the valve itself is structurally normal, but the regurgitation is due to dilatation of the annulus that prevents leaflet apposition. Whereas organic mitral regurgitation (MR) in the Western world is due to valve prolapse or ischaemic heart disease[1] rheumatic heart disease (RHD) continues to be a predominant cause of morbidity in developing countries. RHD results from organization of the endocardial lesions of acute rheumatic fever. Subsequent scarring from the inflammatory process results in deformation of the valve, and with repeated infection there is progressive valvular damage. The mitral valve is almost always involved in chronic rheumatic valvular disease. The macroscopic hallmark of post-rheumatic valvular disease is commissural fusion associated with leaflet fibrosis. Chronically, scarring of the valve leaflets leads to MR, due to shortening and increased rigidity of the valve leaflets, in combination with shortening and fusion of the valve chordae. These changes lead to inadequate leaflet coaption and apposition. In its early stages valvular regurgitation is without symptoms. At some stage in the natural history of severe regurgitation the clinician has to decide on the need for operation.

1.1. Natural history of Mitral Regurgitation

As indicated above, patients with MR may remain asymptomatic for many years, with an average time from diagnosis to symptoms of 16 years[2]. Once symptoms supervene, outcome is improved with surgical intervention compared to medical therapy, with a reported survival of only 33- 45% at 5 years without surgical intervention [3; 4]. It is well established that some patients with asymptomatic severe MR may develop irreversible contractile dysfunction which is often masked by the after load reducing effect of the regurgitant lesion[5]. Few data are available on the rate of haemodynamic progression of regurgitation severity, the rate of left ventricular (LV) dilatation, or the natural history of patients with mild to moderate regurgitation.

In a study of 74 patients with primary MR of varying aetiology, the severity of MR showed a mean annual increase of 7.4 ml in regurgitant volume, 2.9% in regurgitant fraction and 0.06cm^2 in regurgitant orifice area [6]. Independent predictors of rapid progression included a new flail leaflet and an increase mitral annulus diameter suggesting changes in the valve anatomy contribute significantly to disease progression.

Widely disparate estimates of long term survival in patients with mitral regurgitation between 7–27% at five years have been reported [4, 7]. Patients with severe MR have a mortality rate of 5% annually. In patients with asymptomatic prolapse and severe MR, there is a 10.3% annual risk of developing surgical indications [8]. Most deaths are related to Heart failure (HF), but sudden death has been reported in 5% of patients, even in the absence of severe LV dysfunction, suggesting that arrhythmias may also be an important mechanism of events.

Patients with mild-moderate MR have a much lower rate of cardiac event with a five year event free survival of >95% for those with mild MR, 85% for moderate MR compared to 70% for severe MR[9].

In comparison to the expected survival, Ling et al showed that an excess mortality was noted (6.3% yearly) in the natural history of mitral regurgitation caused by flail leaflets [10]. They showed that conservative management was associated with high morbidity: ten years after diagnosis, 90% of their patients were either dead or had undergone surgery. A high morbidity was also present with a 10 year incidence of atrial fibrillation of 30%, and of heart failure of 63%. Furthermore, at 10 years almost 90% of patients were either dead or had undergone surgery, which means that the valve surgery was almost unavoidable. Patients with New York Heart Association (NYHA) functional class III or IV symptoms, even transient, displayed a considerable mortality (34% yearly) if not operated upon, but even those in class I or II had a notable mortality (4.1% yearly). Patients with ejection fraction < 60% also displayed an excess mortality as compared to those with ejection fraction ≥ 60%, but no group at very low risk under medical treatment could be defined.

Sudden death is a catastrophic event, responsible for approximately a quarter of the deaths occurring under medical treatment. A study of sudden death by Grigioni F et al in 348 patients with mitral regurgitation showed that sudden death occurs at a rate of 1.8% per year overall[11]. The predictors of sudden death were ejection fraction, symptoms, and atrial fibrillation.

While, the determinants of higher rates of sudden death are mostly severe symptoms and reduced ejection fraction, Grigioni found that even in patients without these risk factors, the rate of sudden death was 0.8% per year.

These data underscore the serious prognostic implications of severe mitral regurgitation, suggesting that surgery should be considered timeously in the course of the disease in order to avoid events and assure a successful long term outcome. In particular, they emphasise the need for data in uniform populations of MR where inferences can be made about criteria for surgical intervention in pure uncomplicated MR in the absence of confounding elements that affect the disease progression. Therefore careful evaluation of the patient with MR is critical in determining the need for medical therapy and the timing of surgery. A study of the timing of surgery in patients with rheumatic MR in a population of subjects with low risk for accompanying ischaemic heart disease will provide such information.

1.2. Pathophysiology of Mitral Regurgitation

Mitral regurgitation produces volume overload of the left ventricle and left atrium. If the mitral regurgitation develops slowly over months to years, or if the acute phase can be managed with medical therapy, the individual will enter the chronic compensated phase of the disease. The left ventricle develops eccentric hypertrophy as a result of sarcomere elongation. Preload increases and the left ventricle dilates in order to maintain a normal forward flow. The increase in afterload resulting from left ventricular dilatation is offset by the fact that the ventricle is pumping much of its volume (regurgitant volume) into a low-impedance circuit (the left atrium). Therefore, afterload may be variably reduced initially in MR and typically only becomes elevated in later stages of the disease. An individual may be in the compensated phase of mitral regurgitation for years, but will eventually develop left

ventricular dysfunction, the hallmark for the chronic decompensated phase of mitral regurgitation. It is currently unclear what causes the decompensated phase of this disease.

In the decompensated phase, the ventricular myocardium is no longer able to contract adequately to compensate for the volume overload of mitral regurgitation, and the stroke volume of the left ventricle decreases. The decreased stroke volume causes a decreased forward cardiac output and an increase in the end-systolic volume. The increased end-systolic volume translates to increased filling pressures in the ventricle and the atrium with resultant pulmonary venous congestion. The individual may then develop symptoms of congestive heart failure. With increasing ventricular dilatation, the mitral valve annulus becomes more spherical and dilated, and the degree of mitral regurgitation worsens.

As pointed out, with chronic MR, contractile dysfunction may occur early in the disease course, often before the onset of disease symptoms. Ventricular decompensation is characterized by an increase in the end-diastolic dimension (EDD) and end-systolic dimension (ESD). The ejection fraction (EF) declines, but may still remain in the normal range, making recognition of the onset of contractile failure more difficult. Thus, ejection indices such as ejection fraction are not considered reliable measures of left ventricular contractile function since they remain in the normal range when contractility is already impaired. It has been shown that load-independent measures of contractile function, such as elastance, are more reliable. However, these measurements are both time consuming and invasive to perform and are therefore of limited clinical relevance in patient follow-up [11]. Given its limitations, the EF <60% has been shown to be associated with poorer survival after corrective surgery and likely indicates covert contractile dysfunction in MR patients [13].

Mitral regurgitation enlarges the left atrium (LA), which increases atrial compliance enough to normalise the left atrial pressure, even in the presence of severe regurgitation. Therefore most patients are asymptomatic at diagnosis [14]. Other factors include transmission of the kinetic energy of the mitral regurgitant jet to the left atrial wall and atrial fibrillation [15; 16], followed eventually by changes in the pulmonary circulation [17]. Atrial fibrillation is also associated with adverse cardiovascular and survival end points[18]. Chronic MR leads to elevated pulmonary pressures due to passive elevation in the pulmonary venous pressure. With longstanding disease some patients develop superimposed reactive pulmonary hypertension that becomes irreversible because of the progressive histological changes in the pulmonary vasculature [16]. Pulmonary hypertension ultimately leads to RV dilatation and systolic dysfunction, often in association with tricuspid regurgitation due to the dilated tricuspid annulus.

1.3. Development of Symptoms in Mitral Regurgitation

Symptoms often occur late in chronic MR, most likely as a result of the compliance properties of the left atrium that allow it to accommodate large volumes of blood without a significant rise in pressure. In some instances, pulmonary pressures increase, and although this is associated with poorer survival, it may also protect against the development of symptoms. Cardiac biomarkers such as cytokines and B-type natriuretic peptides, which are reported to be elevated in congestive heart failure, are also increased in patients with chronic MR and cardiac dysfunction. Contractile dysfunction may precede symptoms, and therefore evaluation of symptoms alone is inadequate in determining the timing of surgery in chronic

MR. Delaying surgery until symptoms appear is problematic since the outcome may be sub-optimal at that stage, with excess risk of postoperative mortality and LV dysfunction.

1.4. Compensatory Mechanisms and the development of contractile dysfunction in Mitral Regurgitation

Compensatory mechanisms for chronic MR include the development of catecholamine excess[17], which may also play a role in the genesis of arrhythmias and may explain sudden death that has been reported in patients with longstanding severe MR who are managed without surgery [11]. Studies in asymptomatic patients with severe MR demonstrate the high likelihood of symptoms and risk of sudden death within 10 years of diagnosis and the almost inevitable need for surgery [19].The onset of symptoms and LV impairment heralds an extremely poor prognosis, with an annual mortality of 34% for those in New York Heart Association functional class III or IV.

The development of contractile dysfunction and its relation to the severity of volume overload in MR is not clearly understood. What is clear is that prolonged contractile dysfunction is eventually irreversible even after the MR is relieved and is predictive of both death and congestive heart failure[12]. A number of studies suggest that left ventricular size, particularly in end-systole, is predictive of outcome, presumably mediated through a reduction in left ventricular contractility. A recent study from the Mayo Clinic showed a close link between the quantitative severity of MR and adverse outcome in conservatively managed patients, suggesting that this effect may be mediated through volume loading [20]. It has also been shown that patients with the most dilated ventricles preoperatively are least

likely to regain contractile function even after successful corrective mitral valve surgery. In a series of experiments in which high-fidelity measures of left ventricular contractility such as elastance were used, it was shown that left ventricular contractile dysfunction is present in many patients with severe MR despite a normal ejection fraction and that this returned to normal after corrective mitral valve surgery in some but not all patients [21]. Therefore, when contractile dysfunction occurs, it may be temporary or reversible if detected and treated in time. The duration and determinants of this window of opportunity are not known [12].

1.5. Timing of surgical intervention in MR

Left ventricular dysfunction is a major determinant of poor outcome in MR irrespective of whether treatment is medical or surgical. It is the most frequent cause of late death after surgery[6]. A large study of the outcome of mitral surgery for mitral regurgitation analysed ejection fraction as a function of preoperative left ventricular function[4]. Despite its limitations, ejection fraction was the best predictor of long term survival. As the best outcome is observed in patients with an ejection fraction $\geq$ 60%, it would appear prudent to operate as soon as the EF approaches 60%.

Recent studies recommend elective surgery early rather than late in patients with severe MR [20, 22]. A drawback of both of these studies is that patients were managed by their individual physicians, and it is unclear how frequently they were evaluated or what criteria were used to determine when surgical intervention was appropriate. Although the information in these studies is important and compelling regarding the poor outcome associated with chronic MR

when treated conservatively, it does not necessarily provide us with a comprehensive evaluation of the effectiveness of the current guidelines.

1.6. **Current measures of Global Systolic Function**

Echocardiography is the most commonly used noninvasive method for assessment and estimation of LV function. It provides a good clinical estimate of left ventricular systolic function but its chief limitation lies in the evaluation of contractile function in mitral regurgitation since ejection fraction is often maintained in the presence of LV dysfunction. It is noteworthy that most sudden deaths occur in asymptomatic patients with normal LV function. Furthermore, other limitations include overestimation of the degree of MR and the high interuser variability, particularly in the detection of the subtle early changes of LV impairment.

So, although numerous echocardiographic techniques, both qualitative and quantitative been developed, no single precise method is routinely used as a "reference standard" [23] and previous studies have demonstrated that existing measures of MR severity correlate poorly with clinical signs and symptoms. There are few data on the newer echocardiographic modalities, notably Doppler tissue imaging, the predictive values of which has not been determined.

1.7. New Markers of LV dysfunction

1.7.1. Tissue Doppler Imaging

Current image acquisition from the parasternal short and long axis view allows assessment of myocardial velocity resulting from radial fiber contraction. During systole basal and mid segments are moving not only inwards but also longitudinally towards a center of gravity, which is located between the second and third part of the long axis [24, 25]. Contraction of subendocardial longitudinal fibers can be reliably assessed by Tissue Doppler Imaging (TDI) from the apical views. From base to apex, a velocity gradient with highest velocities at basal segments can be observed; apical segments thicken during contraction while the epicardial apex remains relatively stationary.

Tissue Doppler Imaging has been evaluated in different patient groups for assessment of the ejection fraction. Left ventricular long axis contraction is reflected in mitral annular descent, which can be evaluated by TDI at different sites. In comparison with radionuclide ventriculography the septal and lateral average velocities were well correlated with the ejection fraction under identical conditions. A six-site peak mitral annular descent velocity of >5.4 cm/s identified the ejection fraction within normal range with reasonable sensitivity and specificity [25]. However, as for the ejection fraction it has to be taken into account that mitral annulus-TDI velocities are dependent on loading conditions, atrial haemodynamics and heart rate as well. Yamada *et al* found significant positive correlations of endocardial peak systolic velocity for the LV posterior wall with FS and the ejection fraction in different patient groups but no correlation between Fractional shortening (FS) or the ejection fraction and peak velocity of the ventricular septum [27]. The diastolic filling pattern by TDI very closely resembles the mitral inflow E and A pattern and the E'/A'ratio is quite similar to the E/A

ratio. With normal LV filling early (E') diastolic velocity range is > 10 cm/s in the young and > 8 cm/s in the older patient, late diastolic velocities (A') increase with age.

While the mitral inflow very much depends on preload, thus contributing to problems of interpretation, diastolic tissue velocities are far less influenced by these parameters.

Tissue Doppler Imaging is also useful in the detection of impaired left ventricular relaxation and estimation of filling pressure in patients with atrial fibrillation. In these patients both conventional mitral and pulmonary Doppler indices are limited because of the altered atrial pressure and loss of synchronized atrial contraction. The E/E' ratio correlated with left ventricular filling pressures. The E/E' ratio of ≥ 11 predicted left ventricular filling pressures ≥ 15 mmHg with a sensitivity of 75 % and a specificity of 93%.TDI provides reproducible and complementary measures of left ventricular relaxation and filling pressures, which allow a more comprehensive evaluation of diastolic function[28].

1.7.2 Brain Natriuretic Peptide

B-type natriuretic peptide (BNP) and its inactive N-terminal fragment (NT-proBNP) are neurohormones synthesized and secreted mainly from ventricular myocardium. Stimulus for their release is an increase in ventricular wall stress, ventricular volume expansion and pressure overload. Plasma levels of the natriuretic peptides are elevated with LV systolic dysfunction after myocardial infarction (MI) and are independent prognosticators [29]. We hypothesized that NT-pro BNP levels would be increased in mitral regurgitation, and because this is a validated diagnostic test in heart failure, we were hopeful that it could prove to be an early marker for the development of LV dysfunction.

Previous studies have shown that BNP is an independent predictor of high LV end-diastolic pressure and for assessing mortality risk in patients with congestive heart failure (CHF) [30].

BNP levels rise with age [31]. Mean BNP levels are 26.2 +/- 1.8 pg/mL in the group aged 55-64 years, 31.0 +/- 2.4 pg/mL for the group aged 65-74 years, and 63.7 +/- 6 pg/mL for the group aged 75 years and older. Additionally, women without CHF tend to have somewhat higher BNP levels than their male cohorts of the same age, with women 75 years and older having a mean BNP level of 76.5 +/- 3.5 pg/mL. Although the reason is unknown, aging women possibly have stiffer ventricles than age-matched men.

In the emergency room, BNP testing is helpful in the evaluation of acute CHF. To rule out acute CHF, the cut-point of 300pg/ml had a negative predictive value (NPV) of 98%. To rule in acute HF, age-related cut-points of 450, 900 and 1800pg/ml for ages <50 years, 50-75 years and > 75 years were defined as an optima strategy [32]. BNP levels on admission were the strongest independent predictor of death after 60 days follow-up.

BNP levels also correlate highly with the change in PCWP pressure [33]. It has been proposed that BNP levels may be a useful surrogate indicator of PCWP, although this is not common in clinical practice. BNP may help in tailoring treatment of the decompensated patient.

Furthermore, in heart failure and coronary disease, BNP level reflects the magnitude of hemodynamic and LV alterations and predicts outcome, is linked to the presence of functional MR, and is a major biomarker of risk, so that BNP measurement was recently recommended as integral to clinical management [34].

In chronic organic MR, NT-proBNP physiological determinants and outcome implications are undefined. It remains unclear whether NT-proBNP purely reflects the symptoms, MR severity or whether it is a biomarker of ventricular and atrial alterations due to the MR.

These biomarkers offer an opportunity for the detection of early LV dysfunction and may be useful in identifying high-risk patients. It is possible that natriuretic peptide testing in patients with MR will add to the information obtained from echocardiography, but to date there are only limited published data [35].

1.8. Statement of the problem

Although the aetiology and mechanism of mitral regurgitation are critical factors for the management of patients with severe chronic mitral regurgitation, the left ventricular function is the most powerful predictor of long-term prognosis and the main factor for determining the timing for surgery.

The ejection fraction and end-systolic dimension (ESD), which are echocardiographic parameters, as well as the development of symptoms, have been proposed as the best predictors of long-term mortality. Either an EF <60% or and ESD > 45mm are considered the cut-off values for demonstrating covert LV dysfunction and should be immediately considered as an indication for surgery. This approach however, has inherent limitations, since ejection fraction is often maintained during the compensated phase of chronic MR when LV dysfunction develops with minimal or absent symptoms. Furthermore, when LV dysfunction does develop, the EF may fall, but remains within normal limits due to a reduced afterload from the runoff into the left atrium. Also, an LV ESD > 45mm is rarely seen in the less symptomatic patients.

So, although numerous echocardiographic techniques, both qualitative and quantitative, have been developed, there is no wide consensus on how to measure intrinsic left ventricular function in mitral regurgitation, and previous studies have demonstrated that existing measures of MR severity correlate poorly with clinical signs and symptoms.

So the critical question remains: Is there a load independent parameter that can predict the development of, or detect early LV dysfunction?

1.9. Hypothesis

We hypothesized that patients with worsening mitral regurgitation and/ or left ventricular dysfunction have greater activation of NT-pro BNP compared to a control MR population of stable subjects with severe regurgitation.

1.10. Aims

1. To perform standard assessment of the severity of MR using clinical symptoms, ventricular dimensions and Doppler echocardiography
2. To compare standard assessment with tissue Doppler parameters (obtained at echocardiography) in defining the severity of MR.
3. To determine which parameters (NT-proBNP, TDI, ESD) are predictive of early cardiac decompensation

4. To compare these pre-surgery parameters, with post-surgery values and clinical outcomes.
5. To identify high risk patients (as defined by post-surgery outcomes) and cut-off values for the timing of surgery

CHAPTER 2

METHODS

2.1. Ethics approval

Ethics approval was given by the Biomedical Research Ethics administration at the University of KwaZulu-Natal, Nelson R Mandela School of Medicine in November 2006. Reference No. H112/06. Informed consent was obtained from all subjects *(see Appendix 1)*.

2.2. Study Setting

The study population was selected from Inkosi Albert Luthuli Central Hospital, and included all consecutive patients undergoing surgical correction for mitral regurgitation, as well as all patients with severe MR followed up at the cardiology outpatient clinic.

2.3. Design

The study enrolled patients prospectively during Nov 2006-Sept 2007. Patients with severe, chronic, isolated MR underwent comprehensive quantitative Doppler echocardiography performed by one trained ultrasonographer (RP). Patients were excluded if they had acute MR, MR due to ischaemic heart disease or CMO, previous valve surgery and associated aortic or congenital valve disease. Patients with associated mitral stenosis were excluded if the valve area was less than 2.0cm^2. Clinical evaluation and management of the patients were conducted by their independent clinicians. Assessment of symptoms was determined clinically by the NYHA classification and Atrial fibrillation (AF) was diagnosed by electrocardiography. Doppler echocardiographic recordings and blood samples were collected simultaneously and estimation

of the NT-proBNP level processed independently. The ultrasonographer was blinded to the results of the NT-proBNP and clinical examination. Control subjects with severe MR were selected from the cardiology outpatient follow-up clinic where they were assessed as not requiring surgery in the short term and were receiving medical therapy. Controls were selected as severe MR, but without evidence of ischaemic heart disease (1 patient was found to have ischaemic MR) as it is known that NT-proBNP is activated in the presence of ischaemia. The majority of patients, both in the study and control groups, were receiving diuretic and converting enzyme inhibitor therapy.

2.4 Method: Evaluation of MR

2.4.1. Echocardiographic recordings

Colour Doppler echocardiography was performed on all patients using a Siemens Sequoia machine (Acuson, Germany) with phased array transducer and an emission frequency of 3.0 megaHertz with the patient in the left decubitus position. The images and measurements were reviewed off-line by a trained cardiologist.

2.4.2. Calculation of chamber dimensions

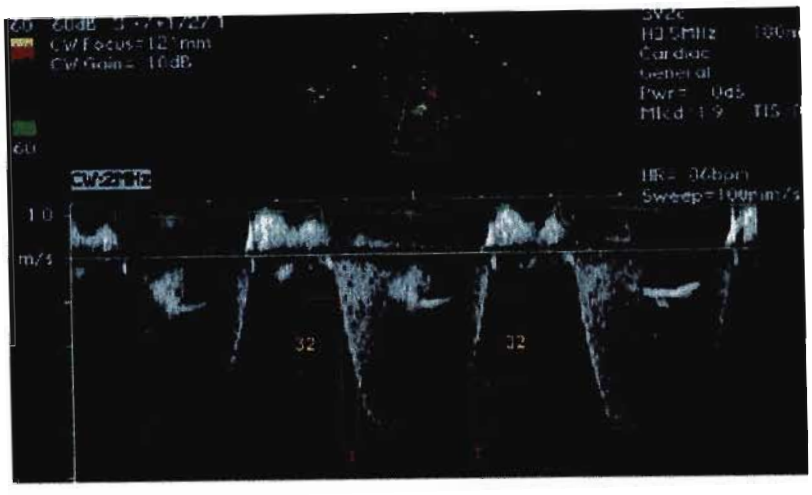
The LV end-systolic and end-diastolic dimensions, LV wall thickness, and left atrial (LA) dimensions were measured according to American Society of Echocardiography guidelines using the leading edge method [36]. All measurements were averaged from three to five cardiac cycles. The LA volume was estimated using the biplane ellipsoid formula [36]. The LV end-systolic and

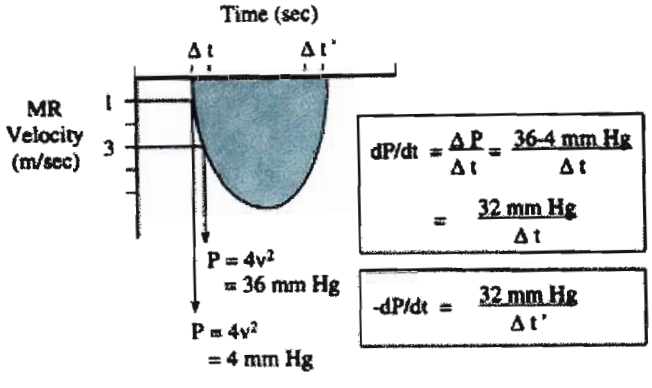
end-diastolic volumes and EF were measured from the apical four-chamber view using the modified Simpson's method [36].

2.4.3. Measurement of the dP/dT

The rate of increase in ventricular pressure in early systole (dP/dt) reflects ventricular contractility. A dP/dt less than 1000mmHg/sec is indicative of impaired ventricular contractility. The dP/dt derived from the continuous-wave Doppler spectrum of the mitral regurgitation jet was determined as follows: the two points on the MR spectrum corresponding to 1 m/s and 3 m/s were identified. These points corresponded to LV-left atrial pressure gradients of 4 mm Hg and 36 mm Hg using the modified Bernoulli equation ($P = 4v^2$). Doppler-derived dP/dt was defined as $\Delta P/\Delta t = 36\text{-}4/\Delta t = 32$ mm Hg/Δt [37]. (See below)

Figure 1: Continuous wave Doppler measurement of dP/dT





2.4.4. **Assessment of severity of mitral regurgitation**

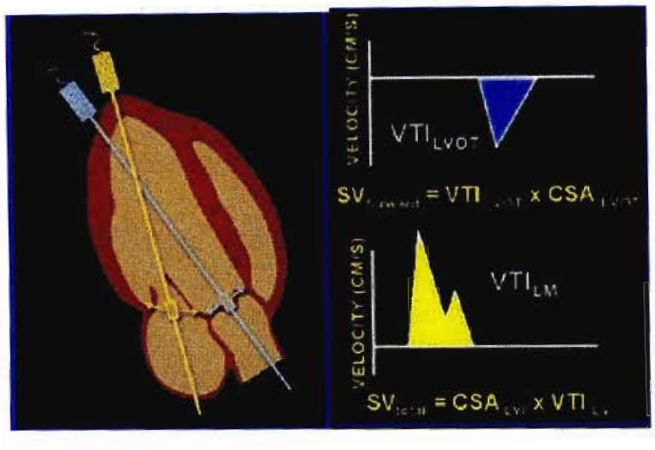
The six frequently applied echocardiographic variables described by Thomas et al [38] were used to evaluate MR. Three of the variables are significantly influenced by the severity of MR; these included jet penetration into the LA, Proximal isovelocity surface area (PISA), Continuous wave (CW) regurgitant jet character and intensity. The other three variables related to the compensatory changes in the heart secondary to MR: pulmonary artery pressure by tricuspid regurgitation velocity, pulmonary venous inflow pattern and LA size. Mitral regurgitation was

quantified by measurement of the regurgitant volume and fraction, as well as the effective orifice area using PISA.

2.4.4.1 Calculation of regurgitant volume and fraction

Quantitative Doppler echocardiography is based on the measurement of the mitral and aortic stroke volumes [38]. Forward stroke volume (Figure 2) in patients with MR was calculated as the product of the left ventricular outflow tract velocity time integral and the LVOT area (regurgitant volume = MV stroke volume − forward stroke volume; Regurgitant fraction (RF) = Regurgitant volume/forward stroke volume).

Figure 2: Calculation of the regurgitant volume

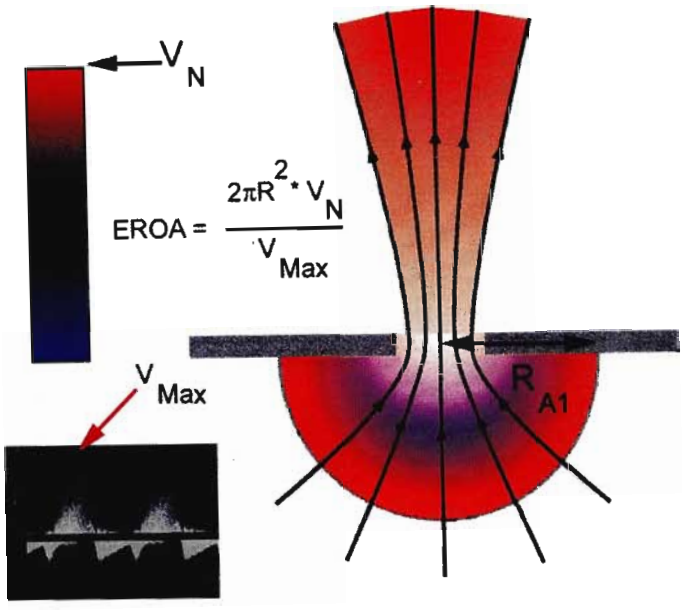


According to published guidelines severe *MR* corresponds to a regurgitant volume >60ml/beat [39].

2.4.4.2 Measurement of Effective orifice area (EROA)

The proximal isovelocity surface area was measured by using proximal flow convergence method[40] and was used to determine the flow rate across the mitral orifice (Figure 3).

Figure 3: Schematic of Effective orifice area (EROA)



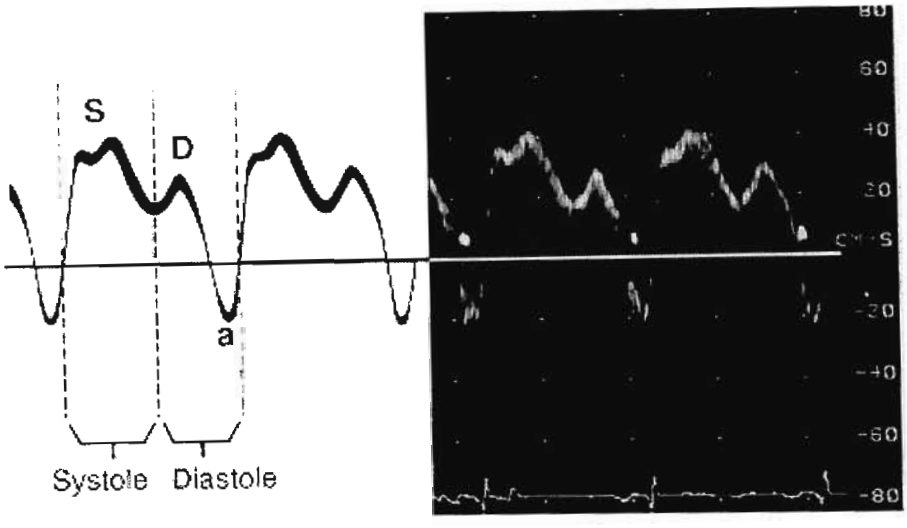
Dividing peak flow rate ($2\pi r^2 v$) by the maximal velocity through the mitral orifice (obtained by continuous-wave Doppler) yields the regurgitant orifice area (ROA), the actual size of the "hole" in the valve and the most fundamental quantitative parameter of severity of regurgitation. An effective orifice area of $0.4cm^2$ corresponds to severe MR.

2.4.4.3 Pulmonary vein (PV) flow

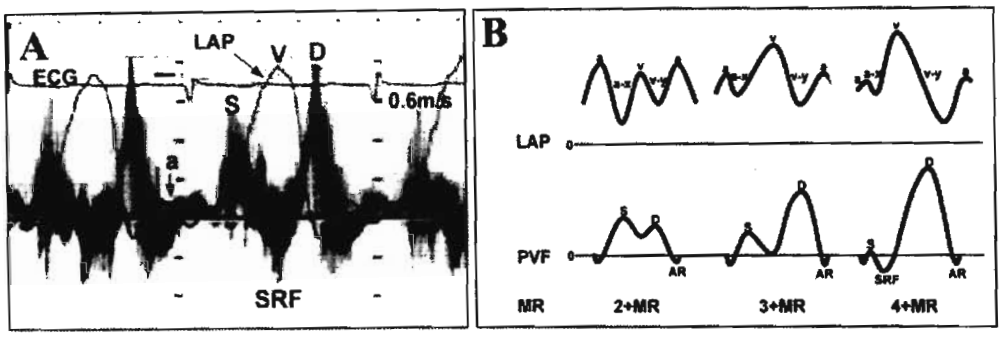
The pulmonary vein flow (Figure 4a) was sampled by the pulsed-Doppler technique. Images were obtained in the apical four-chamber view with transducer angulation to optimally visualize the right upper lobe pulmonary veins as they entered the left atrium. The systolic (S), diastolic (D) and atrial (a) waveforms were measured. Systolic pulmonary vein flow is reduced by increased transmitral flow in mitral regurgitation (Figure 4b)[41]. Pulmonary venous systolic flow reversal was therefore considered an index of severe MR.

Figure 4: Pulmonary vein flow

a) Normal pulmonary vein flow



b) Pulmonary vein flow in mitral regurgitation



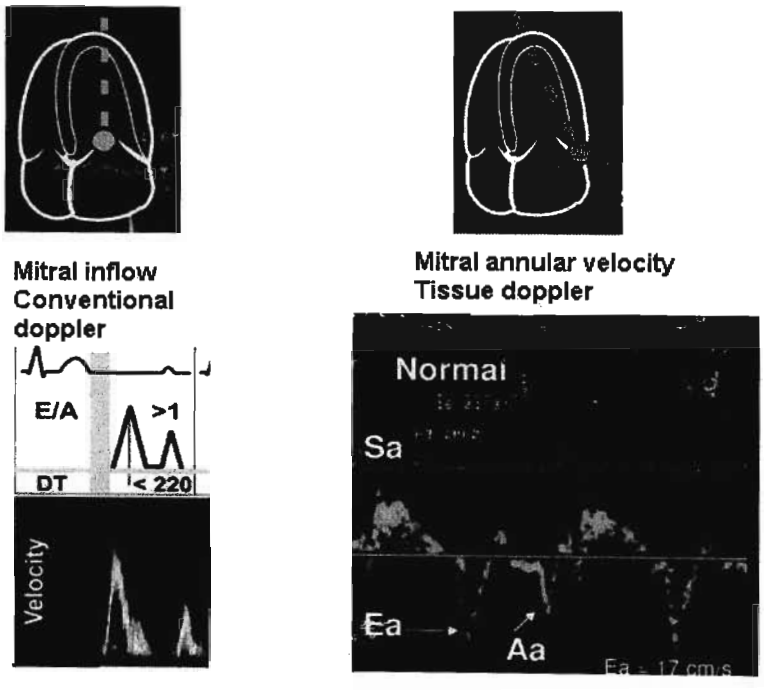
Blunting of the systolic wave (S) and dominance of the diastolic wave (D)

2.5. Tissue Doppler imaging (TDI)

Tissue Doppler Imaging (TDI) was performed with transducer frequencies of 1.8–3.6 MHz with minimum optimal gain as possible to obtain the best signal to noise ratio. In the apical four chamber view, a 5 mm pulsed Doppler sample volume was placed at the level of the lateral mitral annulus. The incident angle between the interrogating Doppler beam and longitudinal motion of the ventricle was kept as small as possible. The myocardial systolic wave (Sm) velocity, the

diastolic indices viz early myocardial (Em) and atrial contraction (Am) peak velocities, Em:Am ratio, and the Em/Ea ratio were measured. Pulse wave (PW) measurements of the mitral E and A wave velocity across the mitral valve were made in the apical 4-chmaber view, with the sample volume placed just beyond the MV leaflet tips. The ratio of the mitral E wave to the annulus E wave on tissue Doppler was used as an estimate of the LV filling pressure (Figure 5).

Figure 5: Estimation of LV filling pressure using diastolic filling ratios: **Emitral/ Eannulus**



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2.6. Measurement of Brain natriuretic peptide levels (NT-proBNP)

Venous blood samples were taken in gel-filled tubes with the patient resting quietly while semi-recumbent at the time of echocardiography. A baseline sample was taken from all subjects, and further samples were taken from subjects undergoing mitral valve replacement at 1-week and 6-weeks post surgery.

The samples were taken and centrifuged within 20 min at room temperature. The plasma was stored at −20°C and NT-proBNP was assayed in batches by standard electrochemiluminescence immunoassay ("ECLIA") using the Modular Analytics E170 (ELECYS module) and Elecsys 1010/2010 analyzer (Roche diagnostics).

Samples from cases and controls were stored for the same duration and were handled together, identically. Resting BNP values considered normal for this methodology lie below 100 pg/mL (11.8pmol/l for NT-proBNP) [42]. The within-assay and total precision coefficients of variation for NT- proBNP (mean 208 pmol/l) is 0.8% and 4.5% respectively. The Reading sensitivity is between 0.6-4130 pmol/l and 5-35000 pg/ml. The functional sensitivity is <5.9pmol/l.

To convert natriuretic peptide levels expressed in pmol/l to pg/ml, multiply by 8.46 for NT-proBNP, and to convert from pg/ml to pmol/l, multiply by 0.118.

2.7. Statistical analysis

SPSS for Windows, version 13.0 was the program used for the statistical analysis. Results are presented as mean +/- SD or percentages. Clinical variables were normally distributed and expressed as mean ± SD. BNP levels were not normally distributed and were therefore log-transformed for statistical analysis. Group comparisons were performed with Analysis of Variance (ANOVA), t-test or chi-square test as appropriate. Associations of baseline NT-proBNP were tested with linear and non-parametric regression (categorical variables) Multivariate analysis with stepwise multiple linear regression was used to define independent determinants of NT- proBNP levels. The time course of NT- proBNP within the cases was evaluated using paired t-tests. The discriminating capacity of the NT- proBNP for separating

surgical cases from controls was assessed by the construction of Receiver Operator Curves (ROC) curves.

2.8.Intra-observer-variability

The intra-observer variability for the measurements of PISA and TDI was <5% .

CHAPTER 3

RESULTS

3.1. Patient population

A total of 55 patients with severe mitral regurgitation were enrolled in the study and surgical cases were followed up for six weeks. Their baseline characteristics are shown in Table 1.

3.2. Baseline demographic Data

All but one of the patients in our study population was of African descent (98%). In the study group, there were seven males and twenty females with a mean age of 20 years, all with a rheumatic aetiology. There was no significant difference between the 2 groups for age, gender or EF (Table 1). There were 28 control patients who were studied from the cardiology follow-up clinic, all with severe rheumatic mitral regurgitation, except one patient who was subsequently found to have ischaemic aetiology.

Patients in the study group were more symptomatic with a predominance of patients in the study group (59%) that had an NYHA classification of 3-4 vs 11% patients in the control group (Table 1). Clinical heart failure was diagnosed in 4 patients in the study group. Both groups had an almost equal number of patients on diuretic therapy. Atrial fibrillation (AF) was present in 10 patients in the study and 6 patients in the control group.

Table 1: Patient demographics and Clinical Findings

	Controls MR n=28	Study Pre-op n=27	P-value
Age	**28**	**20**	**0.72**
Males/Females	**7/21**	**7/20**	**0.937**
NYHA: i-ii	**25**	**11**	**0.001**
NYHA iii-iv	**3**	**16**	
EF	**65 ± 10***	**67 ± 7***	**0.686**
Diuretics	**25**	**21**	
ACE inhibitors	**25**	**25**	
Atrial Fibrillation	**6**	**10**	
Aetiology: Rheumatic	**27/28**	**27/27**	

** mean ± SD*

3.3. Pre-operative data

By design all patients had severe mitral regurgitation as assessed clinically and this was confirmed on echocardiography. Although both control and study groups were equally matched in terms of having severe MR (EOA > 0.35cm^2, regurgitant fraction (RF) and regurgitant volume (RV) of greater than 60% and 60ml respectively) the regurgitant fraction was greatest in the study group (Table 2).

The number of patients with atrial fibrillation and a pulmonary artery (PA) systolic pressure of > 60mmHg were marginally greater in the study group (p=ns). The PA systolic pressure was

elevated in all patients. Significant elevation of the PA pressure was present in seventeen patients in the control and twenty-two in the study group. Only one patient in the control group had markedly elevated systolic pressure (63mmHg) with an NYHA classification of 3. This patient subsequently had a valve replacement seven months after her evaluation.

Table 2: Baseline quantification of severity of MR

	Controls n=28	Study Pre-op n=27
RF : 60-70%	8	2
70-80%	14	4
>80%	3	21
RV > 60ml	27	27
EOA > 0.35	27	27
PAS > 60mmHg	1	4
40-49 mmHg	16	18
30 – 39 mmHg	11	5
Dominant diastolic flow (PWD)	25	24
LA size: < 40mm	4	0
40-49mm	4	2
>49mm	20	25
Systolic flow reversal (colour)**	27	27
Jet density: 50-70% of inflow*	28	27

** Intensity of MR Doppler jet in relation the inflow*

*** Pulmonary vein flow reversal as determined by colour Doppler*

There were no significant differences between the 2 groups for LV dimensions, but the LA size and volume were increased in the study as compared to the control group. ($p<0.001$ and $p = 0.002$ respectively). There was a trend towards slightly higher end-systolic dimensions in the study group.

The systolic wave on tissue Doppler was similar in both groups (Table 3: p=ns). The Doppler early diastolic filling ratios (mitral/ annulus) was elevated in both groups (>10) and was markedly higher in the study group ($p= 0.04$), indicating high LV filling pressures. Likewise a similar pattern was observed with NT-proBNP which was elevated in both groups, and was markedly elevated in the study group (262 ± 224) Table 3: $p<0.001$.

Table 3: Pre-operative evaluation

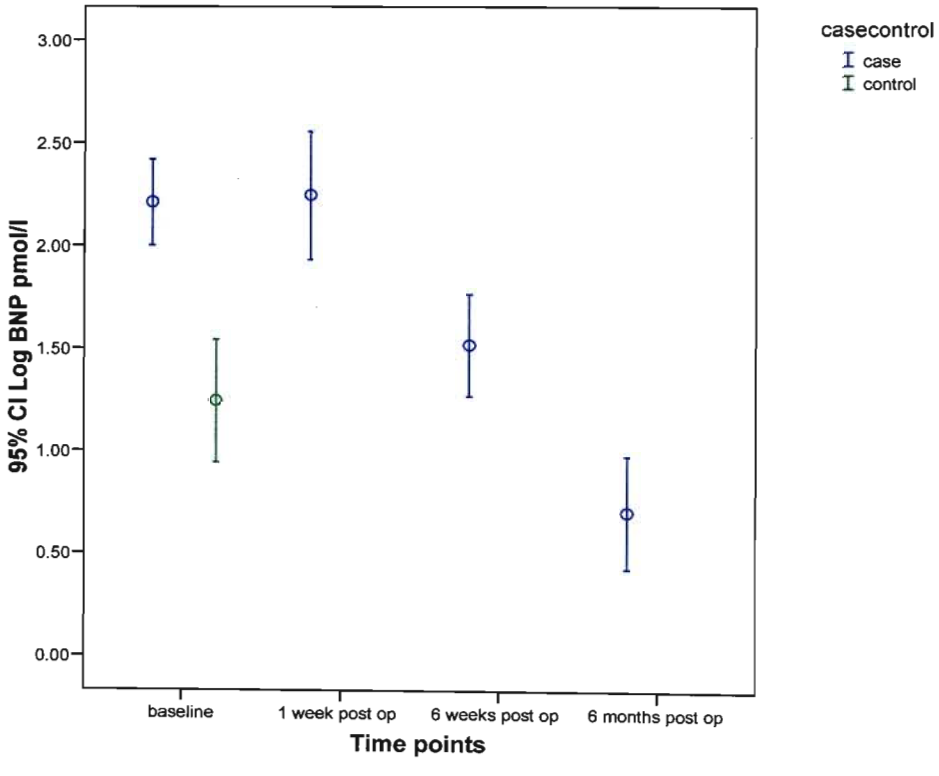
	Controls	Study	p-value
LA size (mm)	**59 ± 13**	**76 ± 16**	**<0.001**
LA volume (ml)	**174.1 ± 118**	**309± 183**	**0.002**
EDV (ml)	**177 ± 69**	**165 ±48**	**0.465**
ESV (ml)	**59 ±26**	**57 ±25**	**0.723**
EDD (mm)	**63 ±10**	**67 ±8**	**0.051**
ESD (mm)	**38 ±9**	**43 ±8**	**0.056**
TDI syst.(m/s)	**0.097±0.03**	**0.1±0.03**	**0.36**
TDI Em/Ea	**14 ±8**	**20±8**	**0.04**
NT-proBNP (pmol/l)	**57 ± 87**	**262 ± 224**	**<0.001**

All values shown as mean ± SD

3.4. Time course patterns of surgical cases and controls

In the surgical cases NT-proBNP time-course patterns showed an initial increase at 1-week after the operation (Figure 6). This was followed by a decrease at the 6-week follow-up visit to values similar to the control population group. A further decrease was documented in 2 patients at the 6-month visit to below control population group.

Figure 6: *NT-proBNP* time course patterns



Values are expressed as mean + SE

3.5. Post-operative data

As expected there was an initial increase in chamber size in patients from the study group who underwent surgical correction and a fall in ejection fraction immediately to a mean of 41% after surgery (one week) (Table 4). This was followed by a decrease in all chamber sizes at 6-weeks

compared to the 1-week evaluation. There was a significant increase in the ejection fraction at 6-weeks which was accompanied by maintenance in the TDI-systolic wave. There were statistically significant changes in the LA dimension, end diastolic diameter of the left ventricle, ejection fraction and NT-proBNP levels. It is noteworthy that inasmuch as there was a slight reduction in the EDV and ESV, these changes were not statistically significant. Although the TDI systolic wave indices were unchanged between the 2 time points, there was a significant increase noted in the early diastolic filling ratios, suggesting a further rise in the left ventricular filling pressures at six weeks.

Table 4: Post-operative data

Means	1wk	6wk	CI	p- value
LA(mm)	64±16	58±16	2.0, 11.2	0.009
LA(ml)	234±152	182±140	21.2, 82.9	0.003
EDV(ml)	139±52	125±55	-15.7, 43.8	0.326
ESV(ml)	86±47	73±47	-10.7, 37.5	0.250
EDD(mm)	59±9	54±8	2.4, 10.2	0.004
ESD(mm)	45.5±14	38.7±9	12.7, 1.0	0.03
EF (%)	42±13	51±13	-17.9, -1.0	0.032
NT-proBNP(pmol/l)	395±460	94±161	87.5, 514.1	0.009
Em/Ea(l)	12±4	15±3	-6.7, -0.2	0.418
TDI- S-wave (m/s)	0.07±0.16	0.07±0.15	-0.01, - 0.2	0.821

CI: confidence interval

In the immediate post-operative period, NT-proBNP levels rose from preoperative levels to a mean level of 395pmol/l and thereafter subsided to 94pmol/l at six weeks. These changes were mirrored by a significant reduction in the LA size and volume, as well as in the LV chamber dimension to the control population group level (Table 4).

Table 5 shows the correlation between mean log NT-pro BNP levels and echocardiographic variables. NT-pro BNP levels were not normally distributed and were log-transformed for this comparison. There were weak correlations at 1-week and stronger correlations at 6-weeks between log NT-proBNP levels and chamber dimensions (Table 5), with the strongest correlation observed between NT-proBNP and TDI- systolic wave.

Table 5: Correlations between log NT-proBNP and Echocardiographic variables

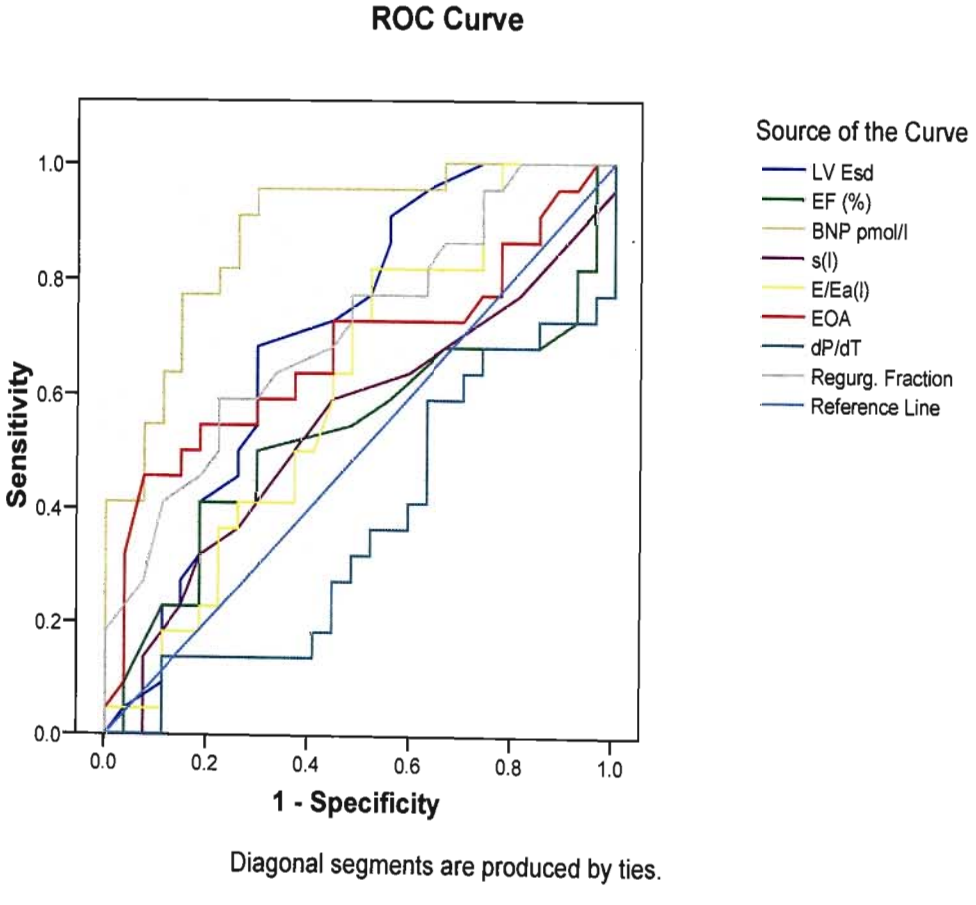
Time points	1-week			6-weeks		
*NTproBNP Pmol/l	395+ 460	r-value	p-value	*94+ 161	r-value	p-value
LA size (mm)	64	0.364	0.115	58	0.32	0.211
LA Vol (ml)	234	0.249	0.290	182	0.24	0.371
EDV (ml)	139	0.217	0.357	125	0.13	0.622
ESV (ml)	86	0.359	0.12	73	0.26	0.353
EDD (mm)	59	0.306	0.177	54	0.47	0.058
ESD (mm)	45	0.164	0.6	39	0.336	0.220
EF (%)	42	-0.18	0.45	51	-0.15	0.554
TDI (systolic)	0.07	0.12	0.6	0.07	0.484	0.049

** Means shown for comparison*

3.6. Discriminating capacity of Echo and NT-proBNP to distinguish cases from controls

A receiver operator curve was constructed for all variables to assess the discriminating capacity of each variable to distinguish between surgical cases and controls (Figure 7). Although the ESD at the established cut-off of 45 mm had a high specificity of 81%, it had a low negative predictive value of 36% (table 6). Of all the parameters studied the area under the ROC curve was greatest for NT-proBNP.

Figure 7: Receiver Operator Curve- Surgical Cases and Controls



At the established the cut-off level of normality for BNP (12pmol/l =125 pg/ml), NT-proBNP yielded the highest sensitivity of 96% and a specificity of 45% (Table 6). Using cut-off criteria established by Januzzi et al [32] for the detection of heart failure, at a level of 53 pmol/l, the specificity for NT-proBNP improved to 74%, and the PPV to 84%.

The two other established markers of systolic function namely, dP/dt and the TDI-systolic wave, had very low specificities and the TDI-systolic wave was elevated in all subjects, both in the study and control groups.

Table 6: Published cut-offs versus study findings

	Cut-offs	Sensitivity	Specificity	PPV	NPV
NT-proBNP (pmol/l)	**12***	**96**	**45**	**79**	**71**
	53	**91**	**74**	**84**	**43**
TDI systolic (m/s)	**0.06****	**96**	**0**	**100**	**34**
	0.085	**64**	**41**	**78**	**36**
TDI: Em/Ea	**10*****	**82**	**45**	**77**	**46**
	13	**63**	**52**	**74**	**32**
ESD (mm)	**45******	**41**	**81**	**78**	**36**
	39	**68**	**70**	**79**	**41**
dP/dt (mmHg/s)	**1000*******	**73**	**7**	**43**	**22**
	1068	**73**	**15**	**45**	**36**

PPV: Positive predictive value, NPV: Negative predictive value

* Cowie MR et al [43]

** Waggoner A[67]

*** Choi YS[28]

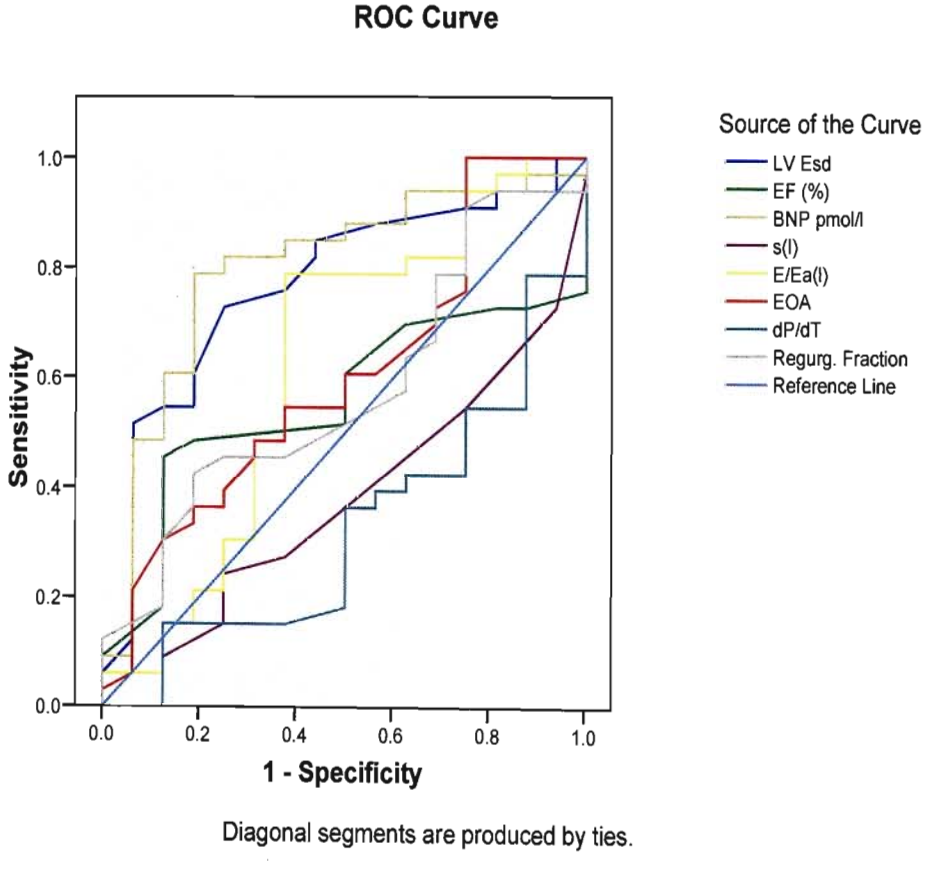
**** Bonow RO et al[36]

***** Chen Cet al[37]

Asterisks refer to published reference values with our values for comparison below.

A second ROC (Fig 8) was constructed using all the variables to separate NYHA class 1and 2 from 3 and 4. Once again, NT-proBNP emerged with the highest area under the curve.

Figure *8*: Receiver Operator Curve – NYHA all classes



3.7. Persistently elevated NT-proBNP levels at 6-weeks

Four patients showed persistently elevated NT-proBNP levels at 6-weeks compared to the other study cases (Table 7). Three patients had a large fall in the ejection fraction post-operatively, accompanied by minimal changes to pre-op ESD and NT-proBNP measurements (Table 7). In

these three cases there was an increase in the diastolic filling ratios (Em/Ea) and a decrease in the TDI-systolic wave.

Two patients (cases 1 and 4 respectively) had a reduced EF < 60% (51% and 56% respectively) preoperatively associated with elevated NTproBNP postoperatively, suggesting that they had been operated upon quite late. As a result the first patient had a marked decline in ejection fraction postoperatively, while the fourth patient had a large drop in the NT-proBNP levels, accompanied by an increase in the TDI-systolic wave, in keeping with return of contractile function.

All four of these patients had atrial fibrillation preoperatively, which persisted at 6-weeks. These four were identified by NT-proBNP levels set by Januzzi's rule in criteria (450pg/ml) for the diagnosis of heart failure patients in the PRIDE study.

Table 7: Four patients with persistently elevated NT-proBNP levels at 6-weeks

	NYHA *Class*		ESD *mm*		EF *(%)*		TDI– S wave *m/sec*		TDI: Em/Ea		NT-proBNP *pmol/l*	
	Pre-op	6 wks	Pre-op	6 wks	Pre-op	6 wks	Pre-op	6wks	Pre-op	6wks	Pre-op	6wks
Case 1	2	2	60	56	51	32	0.07	0.05	19	30	185	184
Case 2	3	2	53	52	65	24	*0.08*	0.06	13	18	612	600
Case 3	4	2	48	51	60	29	0.1	0.05	13	20	81	80
Case 4	3	1	40	36	56	50	0.07	0.1	34	21	497	241

CHAPTER 4

DISCUSSION

This is one of the first studies to evaluate left ventricular function using newer modalities of measuring left ventricular (LV) function. This study examined 55 patients with severe mitral regurgitation and sought to determine the ability of conventional and newer parameters to independently identify the cases that went to surgery. The strength of this study lies in the fact the changes described in relation to surgery could be ascribed purely to the valve regurgitation and not to other confounding factors. In particular ischaemia could not be implicated in the explanation for these changes since all (but one) patients had a clear rheumatic aetiology for their valvular disease and were in an age and ethnic group in which ischaemic heart disease is rare. The clinicians used standard clinical criteria (physical examination, X-ray, ECG, conventional echocardiographic parameters ie ESD >45mm, EF<60%) [36] to decide on surgery. They were blinded to the Tissue Doppler Imaging and the NT-proBNP results. What is clear from this study is that the clinicians are using advanced symptomatology as the prime indictor for surgical intervention. This clearly emerged in the NYHA classification since more than half the patients who went to surgery were severely symptomatic on treatment.

The two groups were matched for LV dimensions; although the LA size and volume were increased in the study as compared to the control group, the number of patients with very large left atria was similar. Despite the fact that all patients had severe mitral regurgitation as assessed clinically and this was confirmed on echocardiography, it is apparent that within this group there were gradations of severity with a significant number of the study patients having RF >80%. It is

clear that there were significant differences between the groups: the study group had larger atria with more elevated filling pressures as reflected by the TDI filling ratio and the NT-proBNP levels. The systolic wave on tissue Doppler, however, was similar in both groups in keeping with their ejection fraction levels. Together with the higher RF all this points to a worse degree of regurgitation in the study group.

This one of the first studies to evaluate time course changes in LV function using newer modalities to assess LV function in a well-defined group of patients with MR. Data on the natural history have been confounded by the varying criteria in the evaluation of the severity of the MR and by the differing aetiologies included in the same study. Since the outcome of patients with MR may be influenced by the underlying disease process rather than the regurgitant severity interpretation of data becomes difficult. For instance, the outcome in patients with ischemic MR may be predominantly affected by the severity of CHD. We therefore excluded patients with ischaemia in this series and can confidently attribute the changes to the regurgitant lesion and to the underlying LV function, and not to ischaemia. There was one patient in the control group, however, that did have ischaemic MR.

In this study of patients with rheumatic mitral regurgitation, we found that NT-proBNP levels were significantly increased in patients undergoing valve replacement surgery, as compared to control patients with similar degrees of mitral regurgitation. In this study we investigated NT-proBNP because it has been shown to be a potential marker of left ventricular dysfunction and could predict diastolic abnormalities in patients with normal systolic function [44] as well as heart failure while limiting the need for expensive cardiac imaging modalities[45, 46]. Moreover, NT-proBNP measurements provide prognostic information in patients with coronary heart disease [47;

[48], and there is evidence that the pharmacotherapy for heart failure might be guided by plasma concentration of NT-proBNP.

It is now well established that the plasma level of BNP is elevated in patients with congestive heart failure and increases in proportion with the degree of left ventricular dysfunction and the severity of symptoms of heart failure [49; 50].

The increase in LV dimensions and fall in the EF in the early postoperative phase that we have documented is well described following mitral valve surgery for MR. Despite symptomatic improvement, postoperative left ventricular dysfunction (ejection fraction < 50%) is frequent, occurring in close to a third of the patients successfully operated upon for organic mitral regurgitation.[51].

In series of experiments in which high-fidelity measures of left ventricular contractility such as elastance were used, it was shown that left ventricular contractile dysfunction is present in many patients with severe MR despite a normal ejection fraction and that this returned to normal after corrective mitral valve surgery in some but not all patients [21]. This was very apparent in all our patients. In fact, all our patients experienced a much higher drop than 10% in the EF immediately post surgery. This improved at the 6-week follow-up visit in all but 3 of our patients (11%). The six-month evaluation will shed more light on the outcome of these patients: whether the LV dysfunction persists, and whether it is related to pre-operative echocardiographic and NT-proBNP measurements in this population.

Postoperative left ventricular dysfunction is associated with diminished survival and a high incidence of heart failure; therefore, timing of the operation to immediately prior to the onset of LV dysfunction is critical in reducing the patients' risk of developing post-operative ventricular dysfunction.

Previous studies have demonstrated a clear inverse relationship between the LV EF and NT-proBNP levels after myocardial infarction (MI) or with cardiac failure [29]. In the current study, we were able to confirm this inverse relationship between natriuretic peptide levels and the EF, and furthermore showed that levels subsided at the six week evaluation with an improvement in the EF. The correlations at 1-week and at 6-weeks between NT-proBNP levels and chamber dimensions suggest that these changes are paralleled by changes in the NT-proBNP levels but not the TDI ratios, suggesting that most of the changes were related to corrections in volume and removal of the diastolic runoff in to the left atrium.

In this study NT-proBNP yielded the highest predictive value for discriminating between study and controls with a sensitivity of 96%. The low specificity of 45% (based on the clinical assessment) indicates a high number of false positives, ie patients selected by NT-proBNP as requiring surgery when in fact they were still being followed up in the clinic on medical therapy. The ESD at the established cut-off of 45 mm for defining the need for surgery had a higher specificity of 81%, but it had a low negative predictive value of 36% (Table 6). The two other markers of systolic function namely, dP/dt and the TDI-systolic wave, had very low specificities and the TDI-systolic wave was elevated in all subjects, both in the study and control groups. When we tried using a different cutoff point of 8.5cm/s, the specificity approached that of NT-proBNP, but the sensitivity dropped from 96 to 64%.

These data indicate that clinicians are placing heavy emphasis on the history to detect the presence of significant symptomatology as a guide to surgical intervention. This has inherent limitation of subjectivity in defining significant valve-related symptoms. Indeed, when the second ROC was constructed using NYHA as the determinant, NT-proBNP again emerged as the strongest discriminator of advanced NYHA class. We believe that the high false positive rate with NT-proBNP suggest that many of the control subjects with symptoms actually require surgery, rendering them true positives. Waiting for more advanced symptoms or signs of early decline of left ventricular function is associated with a real risk of left ventricular dysfunction postoperatively, and cannot be defended unless the mitral regurgitation is not severe enough to warrant immediate surgery. In Western series these patients would have been operated on much earlier since the underlying pathology is non rheumatic, lending a good chance for a successful valve repair and consequently a lower operative risk.

Two studies in particular, both from the Mayo Clinic, have highlighted the poor outcomes in patients with severe MR who were managed conservatively rather than surgically. One of these studies, published in 1996, involved 229 patients with flail mitral valves where flail was used as a surrogate for severe MR in the pre-Doppler era [10]. The 86 patients treated medically in this study had a much higher than expected mortality of 6% per year. At 10 years, the majority of these patients had experienced heart failure, and all but 10% had died or had undergone surgery. Surgery was an independent predictor of better survival in multivariate analysis in this retrospective study. In the second study, Enriquez-Sarano et al prospectively evaluated 456 patients with chronic MR with quantitative MR techniques[20]. Mortality was 22% at 5 years. A major independent determinant of survival was the quantitative severity of the MR assessed by regurgitant orifice area. They found that those patients with a regurgitant orifice area >=0.4 cm^2

had a 5-year survival of 58%, which was inferior to that of a matched control population (78%). Surgical intervention was again a highly significant independent determinant of better survival.

A recent study by Sutton *et al,* found that there was no relation with LV dimensions or ejection fraction and NT-proBNP [52]. In contrast, our study was able to demonstrate a significant correlation between NT-proBNP and the EDV at both assessment points after surgery, and a significant relationship with the EF at 6-weeks. In a study of 84 asymptomatic patients who underwent surgical correction for MR, Agricola et al [53] demonstrated that TDI systolic indices can predict postoperative left ventricular function. A noteworthy point is that the best outcome was observed in patients with an EF > 60% and an LV end systolic diameter < 45 mm [46]. This was also noted in our study. Post-operatively, the changes in NT-proBNP levels were significantly correlated with the TDI- systolic wave (See Table 5). There was a decline in the LA size and ventricular dimensions. We believe that this is most likely related to the combined effect of the severity of regurgitation and declining LV function.

A further possible explanation for the decline in LA size and NT-proBNP is that atrial myocytes synthesize NT-proBNP as well as ANP in response to the chronic increase in LA pressure[54].

Overall, the TDI-systolic wave of 0.06m/s, which has been previously used to rule out systolic dysfunction, had very low sensitivities in separating surgical cases from controls (see Figure7). An increase to 0.085m/s only marginally improved the specificity. From this data, we believe that perhaps different cutoff points should be used in determining impaired LV function, and those cut-points need to be determined with serial evaluations.

Furthermore, an increased E/E(a) ratio (>12) and elevated BNP (>170pg/ml) have been shown to be to be useful parameters in identifying identify patients at heightened risk of developing

paroxysmal atrial fibrillation as well as reflect early left ventricular dysfunction in a population of hypertensive patients [55]. In our study these levels were much higher, even in our control population (see Table 3); suggesting perhaps that our patients need to be evaluated earlier with a view to assessing their risk of developing AF or LV dysfunction.

In this study NT-proBNP could not discriminate preoperatively between the four patients who showed persistently elevated levels at 6-weeks and the rest of the sample. As pointed out three patients had a large fall in the ejection fraction post-operatively, accompanied by minimal changes in pre-op ESD and NT-proBNP measurements. There was an increase in the diastolic filling ratios (Em/Ea) and a decrease in the TDI-systolic wave, all pointing to impaired ventricular function which no parameter could detect preoperatively. All four of these patients had atrial fibrillation preoperatively, which persisted at 6-weeks.

Several early studies have found increased NT-proBNP concentrations in patients with mitral regurgitation but none of these distinguished patients with ischaemic regurgitation from those with non-ischaemic regurgitation. In a population-based study of elderly people living in Finland, N-terminal ANP was significantly increased in those with moderate or severe mitral regurgitation [56]. A study of patients with suspected LV dysfunction also found an association between NT-proBNP and the severity of mitral regurgitation [57]. Another small study found increased plasma BNP concentrations in patients with moderate or severe mitral regurgitation of mixed aetiology [58]. None of these studies excluded or satisfactorily controlled for patients with angina pectoris, LV dysfunction secondary to myocardial infarction, or concomitant valve disease, and all used qualitative methods for assessing mitral regurgitation.

We therefore excluded patients with an ejection fraction lower than 50%, and patients with ischaemia in the study group. There was one patient, however, in the control group who did have ischaemic MR. Aside from this instance, all our patients had chronic, severe rheumatic mitral regurgitation. Further studies will be performed to determine the profile of NTproBNP activation in mitral regurgitation of varying degrees of severity. Furthermore, we plan to study subgroups separately, in order to determine the time course of NT-proBNP in the different stages of MR with/without ischaemia, so that a natural history may be developed for each of these aetiologies.

In this study, we used additional quantitative methods for assessment of the regurgitation severity, as opposed to qualitative methods in previous studies[69]. It was very interesting to see that the surgical group had a significantly higher number of patients with the regurgitant fraction of > 80% (see Table2).

More recently Sutton et al [59] studied 49 patients with varying degrees of isolated mitral regurgitation due to degenerative or rheumatic disease and an ejection fraction of > 55%. Concentrations of NT-proBNP were increased as compared with controls. NT-proBNP levels correlated most closely with clinical and echocardiographic variables and was related to the severity of mitral regurgitation and left atrial dimension as well as age and sex. There was no relation with LV dimensions or ejection fraction but this may reflect the relatively narrow range of LV function and the use of dimensions rather than volumes to assess LV size.

The largest study yet published is that of Detaint et al [60] from the Mayo Clinic, who followed up a relatively unselected group of 124 patients with more than mild organic mitral regurgitation. Just over a third of their patients had severe mitral regurgitation. These authors found that symptoms, the presence of atrial fibrillation, and the extent of both atrial and ventricular remodelling were independently associated with higher BNP concentrations. The severity of

mitral regurgitation, although univariately associated with BNP concentrations, was not an independent predictor. Uniquely, their study examined outcome over a mean of 4.4 years. After age, sex, functional status, LV function, and severity of regurgitation were controlled for, BNP was independently predictive both of death and the combined end point of heart failure or death. The implication of these findings is that BNP is not just a marker for the severity of mitral regurgitation or a surrogate for symptoms. Rather, it seems to reflect the consequences of mitral regurgitation for the heart, including adverse clinical outcome.

A limitation of our study is that we have not evaluated NT-proBNP in normal control subjects. We evaluated patients with severe MR followed up at the outpatient's clinic as control MR subjects, all of whom had baseline NT-proBNP values higher than that reported in normal subjects. Nor have we studied varying degrees of MR, including mild and moderate. In a study of 112 patients with different grades of MR., it was found that only LV ejection fraction ($p = 0.016$) and moderate or severe MR ($p = 0.023$) were significantly associated with NT-proBNP after adjusting for clinical, hemodynamic, and echocardiographic variables [61].

It is apparent that most of the patients in this series had some degree of LV decompensation, as indicated by changes in the TDI ratio and the NT-proBNP levels, despite a preserved EF. In series of experiments in which high-fidelity measures of left ventricular contractility such as elastance were used, it was shown that left ventricular contractile dysfunction is present in many patients with severe MR despite a normal ejection fraction and that this returned to normal after corrective mitral valve surgery in some but not all patients [21]. In our study we had 3 such patients, a high percentage (11%) for a small series. There was no indication of difficulties with myocardial preservation to suggest this as the cause for the decline in postoperative EF by almost

30% form normal pre-operative levels. We have yet to see if the LV function improves at the 6-month follow-up visit.

This is one of the first studies to investigate NT-proBNP and LV function in relation to valve surgery. Two other studies have investigated BNP concentrations pattern following cardiac surgery with cardioplegic arrest and shown enhanced release of BNP after aortic unclamping and termination of cardio pulmonary bypass. Furthermore, besides iatrogenic cardioplegia, cardiac surgery involves other major stimuli such as anesthesia, sternotomia, post-operative hemodynamics, that could influence BNP levels in a non- specific way [62].

Georges et al [63] studied the changes in BNP 12 hours post coronary bypass surgery, and suggested that myocardial ischemia was the cause of the compromised left ventricular function. They also showed that the stunned myocardium was associated with reduced myocardial contraction, increased ventricular pressure and secretion of BNP. They found that ANP and BNP concentrations were elevated when compared to either healthy subjects or coronary heart disease patients, whatever the valvular heart disease (mitral, aortic or tricuspid). The decrease in systolic function after surgery was ascribed to the lack of adequate myocardial preservation during surgery in early studies. Secondly, the loss of the low-impedance systolic runoff into the atrium exposes true ventricular state, increasing the ventricular afterload, unmasking pre-existing contractile dysfunction [64]. Lastly it is now well established that the disruption of the chordal continuity with valve replacement leads to changes in ventricular geometry and impairment of systolic function. In our study we documented a significant fall in ejection fraction postoperatively in four patients. There was no evidence to suggest that any intraoperative complication could have accounted for the deterioration. Although we believe that that our

findings are consistent with changes suggesting that the operation itself contributed to cardiac ischemia from aortic crossclamp and cardioplegic arrest after termination of CPB, there was no documentation to suggest this in the operation notes. In the fourth patient a likely explanation for the decline in LV function lies in the acute afterload changes on the left ventricle consequent upon removal of the regurgitant leak. In this patient there was evidence of improving ventricular contractility from the tissue Doppler and NT-proBNP values.

The current European Society of Cardiology (ESC) guidelines recommend surgery in the asymptomatic patient when the EF falls to <60% and ESD>45mm. Furthermore, surgery is also recommended for patients with AF and PHT with preserved systolic function. There is evidence however, suggesting that a LVESD >40mm is more sensitive to contractile reserve and that its use as an indication for surgery leads to improved postoperative outcomes [16].

Alternate proposed measures include an elevated end-systolic wall stress, an elevated exercise ESD, and EDD greater than 70mm, or an early systolic dP/dt less than 1343mmHg/sec as derived from the Doppler mitral regurgitant jet [68].

In our study, 11 patients in the control group and 18 patients in the study group had a dP/dt lower than 1343mmHg/s. What is very interesting is that the 3 patients (see Table 7) who had persistently elevated NT-proBNP levels and LV dysfunction post-operatively also had dP/dt < 1000mmHg/sec.

CHAPTER 5

CONCLUSION

Long-term survival after mitral valve replacement has been poor, with reported 5-year survival rates between 50% and 85% [61, 4]. Survival is better in later studies, possibly related to improvements in surgical technique [13]. It appears that the two most recognized key factors affecting survival after mitral valve surgery are timing of the operation, and preservation of the chordal apparatus. Improved survival has been documented when surgery is performed before the onset of LV contractile dysfunction. Both ventricular function and survival are improved when at least partial continuity between the mitral annulus and papillary muscles is maintained.

These data provide compelling arguments for earlier and timeous operation in severe MR. The evidence to date points to the most favourable outcomes once symptoms develop or there is evidence of increasing LV dilatation. Both parameters reflect a combination of worsening regurgitation and the onset of LV dysfunction.

In this study we have shown that patients with more advanced symptoms have a higher grade of severe MR and evidence of significant LV decompensation as indicated by markers of filling pressure ie NT-proBNP and E/Ea. In fact NT-proBNP detected advanced disease in a significant number of control subjects designated as false positive against clinical criteria. The false positive rate of 55% suggests that NT-proBNP may actually be detecting early LV decompensation in less symptomatic patients. Although there was no significant difference between the study cases and the controls pre-operatively for LV dimensions or ejection fraction, there was a marked

difference in mean NT-proBNP levels in the two groups. The significant difference in the diastolic filling ratios suggests that the NT-proBNP might be detecting some level of LV decompensation. Because of the ethical issues in randomization, several other studies have adopted a similar approach to ours. Pillai et al70 showed that elevated NT-proBNP levels preoperatively was an indicator of underlying myocardial dysfunction, which was not evident by routine 2-D echocardiography, and sadvocated preoperative assessment of NT-proBNP levels to detect occult myocardial dysfunction. Two other studies examined patients with varying degrees of MR, and showed that changes in ventricular function occur early in the disease process, before they can be detected echocardiographically 35, 71.

The lack of a difference in the LV chamber parameters between surgical and control groups in our study indicates an almost total reliance on advanced symptoms which is worrying, because symptoms sometimes manifest late in the course of the disease, and LV dysfunction may have already set in prior to the onset of symptom development. Furthermore, assessment of symptoms may be difficult in clinical practice. It is likely that in some patients, the symptoms might be as a consequence of severe MR, while others may be classified as asymptomatic because they undertake little activity or ignore subtle symptoms.

The stimulus for NT-proBNP is any increase in intracardiac pressure, dilatation or ischaemia. The fact that patients sent to surgery had markedly elevated NT-proBNP levels, suggests that in this study, the clinical assessment was not satisfactory in determining the correct timing for surgery. In fact, based on these guidelines, our study shows that a portion of the population has already reached the stage where LV dysfunction was fairly advanced.

NT-proBNP levels subsided in the majority of our study cases at 6-weeks. However, our study suggests that its behaviour at the six-week follow-up visit may offer some prognostic information. Inasmuch as NT-proBNP was not able to predict who would fare well, as all our patients had markedly elevated NT-proBNP, where it remained elevated, there was persistent LV dysfunction. The implications of this pattern will be evaluated at the 6-month follow-up visit.

Tissue Doppler systolic indices reflect the EF and are thus subject to the loading conditions[66]. However, the relatively preload independent Doppler filling ratios were unhelpful, as they were *elevated from the onset* in both groups. In fact, the increase in the Doppler filling ratios (see Table 4) at 6-weeks post surgery seems to reflect the lack of changes in the LVEDV and ESV.

All these data allow the supposition that in the natural history of mitral regurgitation, a gradual increase occurs in NT-proBNP levels according to the evolution of the disease. For decision making in the management of patients, the absolute values in each evolution stage cannot be applied, because they are not known. Therefore serial estimations on patients with varying degrees of moderate and severe MR are needed to determine the time points at which the NT-proBNP rises in each evolution stage of MR, to correlate the rise with severity and symptom development and finally, to gauge a NT-proBNP level that should lead to a consideration of surgical intervention.

The dilemma has been defining the onset of contractile dysfunction in patients with MR, given the fact that the loading conditions are altered by the regurgitant lesion. The ideal measure of LV performance should accurately reflect contractility, regardless of loading conditions, and should be precise, reproducible and easily measured. The recommended clinical cut-offs which are

supposed to be closest to meeting these requirements (EF and end-systolic dimensions), may not appear to be very effective in detecting early LV dysfunction, and hence, the timing of surgery is difficult and often delayed.

Our study suggests that severe MR and LV function are closely linked, and that it is difficult to tease out the relevant contributions of each. We feel that NT-proBNP is a composite marker that should become an integral part in the clinical evaluation of patients for surgery, since it is more objective in defining symptomatology, and furthermore, it reflects the culmination of the effects of mitral regurgitation on LV function. The degree of MR by itself is probably not suitable as the sole criterion, nor is the LV dimension, unless this is corrected for body surface area. Indeed, serial NT-proBNP may prove to be the most reliable indicator of the timing for surgery.

We have shown that decision making regarding the timing of surgery in our patients occurs rather late in the course of the disease, exposing many patients to unnecessary morbidity and the risk of permanent LV decompensation. The implications of our findings are that NT-proBNP is not just a marker of the severity of MR, or an objective assessment of symptoms: in fact, it seems to reflect the consequences of severe regurgitation on the heart ie onset of LV dysfunction, and its accompanying sequelae (AF and pulmonary hypertension).We propose that NT-proBNP be an additional marker, particularly in less symptomatic patients, even if the EF is normal. In time, it may prove to be a composite marker for the assessment of LV decompensation.

This study shows that in spite of its limitation as a load-dependent measure, with serial testing in a carefully monitored and screened population, that NT-proBNP identifies early decompensation in patients with apparently preserved ejection fraction in chronic, severe mitral regurgitation. It

supports the finding of Detaint et al in that BNP reflects the severe haemodymamic, ventricular and atrial consequences of MR. It should be considered in patients with severe organic MR to assist in clinical decision making, particularly in patients with severe MR who appears to have mild symptoms.

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APPENDICES

1. Informed Consent Form

INFORMED CONSENT

You have been asked to participate in a research study.

You have been informed about the study by ..... .

The purpose of this study is to determine the function of your heart before and after your operation using ultrasound. In addition, an additional sample of blood will be taken from you to do a special test. This test will measure the level of Brain Naturetic Peptide (BNP) in your blood. It will tell us more about the state of your heart function and whether we need to modify your medication.
We also want to see if the level of the BNP rises or remains the same after your operation (only if you are going for surgery). Therefore an additional blood sample will be taken from you at 1 week, six weeks and six months after the operation.

You may contact the Medical Research Office at the Nelson R Mandela School of Medicine at 031-260 4604 if you have questions about your rights as a research subject.

Your participation in this research is voluntary, and you will not be penalized or lose benefits if you refuse to participate or decide to stop.

If you agree to participate, you will be given a signed copy of this document and the participant information sheet, which is a written summary of the research.

I hereby agree to participate in this test performed on me. This will be used in a study for research purposes. I am aware that the results of this study, including personal details regarding my sex, age, date of birth, initials and diagnosis will be anonymously processed into a study report.
The research study, including the above information, has been described to me orally. I understand what my involvement in the study means and I voluntarily agree to participate.

Ucelwe ukuba ube ngomunye ozosiza ngocwaningo lokwelapha. Unxusiwe ukuba ubengxenye nababye ngu..... inhlosos yocwaningo ngukuthola izinga lesimo senhliziyo yakho, uma kuqhathaniswa ngaphambili nanemuva kokwelashwa nokuhlinzwa kusetshenziswa l-ultrasound.

Kuzodingeka kuthahthwe elinye 'igazi kuwena' oluzosetshenziselwa ukucwaninga izinga le BNP egazini lakho. Kushintshwe indlela owelashwa ngayo.

Kudingeka ulwazi lokuba izinga le BNP liyakhuphuka yini noma cha.

Igazi lizodonswa kuwena emuva kwe-

1. sonto
2. amasonto ayisithupha
3. emva kwezinyanga eziyisithupha emvuva kokuhlinzwa

Ungayicela incazelo ejulile e Nelson R Mandela School of Medice ngaloluhlelo (031-2604604).

Uyacelwa, awuphoqekile ukuba ube kyongxenye yalolucwaningo, futhi ungeke ujesiswe noma uphuma phakathi nendawo.

Ngiyavuma ukuba yingxenye yalolucwaningo kimina. Loku kuzosetshensizwa njengocwaningo kwezemfundo. Ngiazi ukuthi imininingwane yami esese emayelana nobulili bami, iminyaka yami igama lami nesimo sempilo yami ayizuvezwa futhi izosetshenziselwa imfundo nje kuphela.

Lolucwaningo sengitsheliwe ngawo futhi ukuthatha iqhaza kuwo kusho ukuthi ngiyavuma ukuba yingxenye yawo.

Patient: _____ ***KZ No.***_____

_____ _____
Signature of Patient Date

_____ _____
Signature of Witness Date

_____ _____
Signature of Translator Date

PATIENT INFORMATION LEAFLET AND INFORMED CONSENT

(patients going for surgery)

Subject Initials:
Subject Study Number:

Study Title

Timing of Mitral valve Surgery: a comparison of Tissue Doppler Imaging (TDI); Brain Naturetic Peptide (BNP) and echocardiography

Introduction

This information leaflet is to help you decide if you would like to participate in this study which is being conducted for research purposes. Before you agree to take part in this study, you should fully understand what it entails. If you have any questions that are not fully explained in this leaflet, do not hesitate to ask. You should not agree to take part in this study unless you are completely happy about all the procedures involved.

What is the purpose of the study?

You have been diagnosed with severe mitral regurgitation (leaking valve), and therefore, we would like you to consider taking part in this study.
The purpose of this study is to determine the function of your heart before and after your operation using ultrasound. In addition, we would like to take a sample of blood from you to do a special test. This test will measure the level of BNP in your blood. It will tell us more about the state of your heart function and whether we need to modify your medication.
We also want to see if the level of the BNP rises or remains the same after your operation. Therefore an additional blood sample will be taken from you at 1 week, six weeks and six months after the operation.

What are my rights as a participant in this study?

Your participation in this study will be entirely voluntary and you can refuse to participate or stop at any time without stating any reason. The investigator retains the right to withdraw you from the study if it is considered to be in your best interest.

What are the risks involved in this study?

There are no risks involved, as we will be scanning you on a routine basis. The BNP blood sample will be taken when the routine bloods are taken. When you come to clinic for your routine follow-up, a registered phlebotomist will take an extra sample of blood. (about a tablespoon full) for the BNP estimation.

Confidentiality

All the information obtained during the course of this study is strictly confidential. Reported data will not be including information that identifies you as a patient in the study. You will be informed of any finding of importance to your health.

Has the study received ethical approval?

The ethics committee of University of Natal: Nelson R Mandela School of Medicine. has approved this study

PATIENT INFORMATION LEAFLET AND INFORMED CONSENT (for Control population)

Subject Initials:
Subject Study Number:

Study Title

The determinants in the Timing of Mitral valve Surgery: a comparison of TDI; BNP and conventional echocardiography

Introduction

This information leaflet is to help you decide if you would like to participate in this study which is being conducted for research purposes. Before you agree to take part in this study, you should fully understand what it entails. If you have any questions that are not fully explained in this leaflet, do not hesitate to ask. You should not agree to take part in this study unless you are completely happy about all the procedures involved.

What is the purpose of the study?

You have been diagnosed with mitral regurgitation (leaking valve)/ aortic regurgitation (leaking valve)/dilated heart and therefore, we would like you to consider taking part in this study.

We would like to do an ultrasound of your heart to assess the function of your heart. In addition, we would like to take a sample of blood from you to do a special test. This test will measure the level of BNP in your blood. It will tell us more about the state of your heart function and whether we need to modify your medication.

What are my rights as a participant in this study?

Your participation in this study will be entirely voluntary and you can refuse to participate or stop at any time without stating any reason. The investigator retains the right to withdraw you from the study if it is considered to be in your best interest.

What are the risks involved in this study?

There are no risks involved, as we will be scanning you on a routine basis. The BNP blood sample will be taken when the routine bloods are taken. When you come to clinic for your routine follow-up, a registered phlebotomist will take another sample of blood.

Confidentiality

All the information obtained during the course of this study is strictly confidential. Reported data will not be including information that identifies you as a patient in the study. You will be informed of any finding of importance to your health.

Has the study received ethical approval?

The ethics committee of University of Natal: Nelson R Mandela School of Medicine. has approved this study

2. Mitral Regurgitation Index: Grading of Its Six Constituent Variables

1) Jet Penetration:
0 = no jet
1 = central jet; jet does not impinge on lateral wall in any view
2 = eccentric jet which extends up to the first pulmonary vein
3 = eccentric jet which encircles the atrium extending beyond the pulmonary vein
2) PISA:
0 = No PISA
1 = PISA ≤0.5 cm
2 = PISA = 0.5–1.0 cm
3 = PISA ≥1.0 cm
3) CW Jet Intensity and Character:
0 = No jet
1 = Incomplete jet envelope
2 = Complete jet envelope; jet density 20–50% of inflow
3 = Complete envelope; jet density 50–70% of inflow
4) Pulmonary Artery Pressure (PAP)*:
0 = PAP <25 mm Hg
1 = PAP = 25–30 mm Hg

2 = PAP = 31–45 mm Hg
3 = PAP >45 mm Hg
5) Pulmonary Venous Flow Pattern:
0 = systolic dominant flow; systolic impulse exceeds diastolic impulse by 50% or more
1 = systolic dominant flow; systolic impulse exceeds diastolic impulse by <50%
2 = diastolic dominant flow
3 = systolic flow reversal
6) Left Atrial Size:
0 = normal
2 = mild enlargement
2 = mild to moderate and moderate enlargement
3 = moderate to severe and severe enlargement

MR INDEX = Total Score/number of variables.

PISA = proximal isovelocity surface area.