EFFECT OF MITRAL VALVE REPLACEMENT ON LEFT VENTRICULAR FUNCTION IN SUBJECTS WITH SEVERE RHEUMATIC MITRAL REGURGITATION

by

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DECLARATION

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LIST OF ABBREVIATIONS AND ACRONYMS

ACE-I – angiotensin converting enzyme inhibitor

ARF – acute rheumatic fever

BREC - Biomedical Research Ethics Committee

BSA - body surface area

CABG – coronary artery bypass graft

CI – confidence interval

CPBT – cardiopulmonary bypass time

EDD – end diastolic diameter

EF – ejection fraction

ESC – European Society of Cardiology

ESD – end systolic diameter

HIV – human immunodeficiency virus

IALCH - Inkosi Albert Luthuli Central Hospital

IQR – interquartile range

LA - left atrium

LV – left ventricle

LVEF - left ventricular ejection fraction

LVEDD – left ventricular end diastolic dimension

LVESD – left ventricular end systolic diameter

MR – mitral regurgitation

MVA – mitral valve area

MVR – mitral valve replacement

NYHA – New York Heart Association

OR – odds ratio

PAS – pulmonary artery systolic pressures

RA – right atrium

RHD – rheumatic heart disease

RV – right ventricle

SPAP - systolic pulmonary artery pressure

TR – tricuspid regurgitation

Abstract

Background. The outcome in patients with severe mitral regurgitation (MR) and impaired ejection fraction (EF) is poorly described in the developing world where rheumatic heart disease is endemic.

Objective. This study describes the effects of mitral valve replacement (MVR) on left ventricular (LV) function in patients with rheumatic MR.

Methods. This is a retrospective analysis of all subjects with severe rheumatic MR undergoing MVR over a 9 year period (2005-2013). Clinical and echocardiographic parameters were recorded pre-operatively, at 2 weeks, 6 weeks to 3 months and 6 months to 2 years following MVR.

Results. Of 132 patients included in the study, 66% (n=87) were NYHA class III-IV, 38% (n=50) presented with clinical features of heart failure and 14% (n=19) had atrial fibrillation prior to MVR. The echocardiogram showed increased end systolic diameter (ESD, 39.9±7.2mm), left atrial size (LA, 61.2±12.6mm), and pulmonary artery systolic pressures (PASP, 59.5mmHg, IQR 45-80mmHg). Pre-operatively, 28% (n=37) of subjects had impaired LV function (EF <60%). At 6 months to 2 years following MVR (n=93), 1% of subjects were NYHA III-IV, 1% were in heart failure, and 7.6% had atrial fibrillation. Paired analysis of 83 patients with complete datasets revealed that the EF was >55% in 87% (n=72) pre-operatively, the number of patients with EF >55% dropped to 20% (n=17) at 2 weeks postoperatively ($p<0.001$, 95% CI 0.02-0.09) and thereafter an EF > 55% was recorded in 60% (n=53) at the 6 months to 2 year follow up ($p<0.001$, 95% CI 0.1-0.5). After feeding all clinical and echocardiographic variables into a predictive model only the ESD emerged as a significant predictor of postoperative LV dysfunction (EF< 50%) both on uni- and multivariate analysis.

Conclusion. Most subjects with severe rheumatic MR who were subjected to surgery had advanced disease with heart failure, indicating that preoperatively, impairment of LV function was a frequent finding. The preoperative ESD was the only predictor of postoperative LV dysfunction. This study calls for careful clinical assessment with regular imaging and early referral for surgery in subjects with severe MR according to established guidelines in order to ensure preservation of ventricular function.

CHAPTER 1

LITERATURE REVIEW

Rheumatic heart disease (RHD) is a recognized sequelae of acute rheumatic fever with carditis in the younger population under the age of 25, following an autoimmune response to streptococcal throat infection. It is prevalent in developing countries in Africa, the Middle East, Central and South Asia, the South Pacific, and in poverty-stricken areas of developed countries.[1] The report from the Global, Regional, and National Burden of RHD, 1990-2015, estimated that the age-standardized prevalence of rheumatic heart disease in 2015 was 444 cases per 100,000 population in countries where RHD is endemic and 3.4 cases per 100,000 population for countries with a nonendemic pattern.[2] This has been attributed to the ongoing socio-economic challenges in the developing world, with overcrowding and poverty being major contributors. [2]

In South Africa, the incidence of symptomatic RHD was reported as 24.7 per 100,000 population in the city of Soweto over the past two decades. A much higher prevalence (20.2 cases per 1000) of RHD detected by echocardiography was reported in asymptomatic children in Cape Town.[3] In contrast, Cilliers et al recently demonstrated a decline in the number of paediatric cases of ARF and RHD, from 64 cases in 1993 to only 3 cases in 2010, at Chris Hani Baragwanath Academic Hospital in Soweto, South Africa. This was attributed to improved socioeconomic conditions and better access to health care. [4] There are no published data on RHD from KwaZulu-Natal.

Mitral regurgitation is the predominant valvular lesion in RHD.[5] A systematic review and meta-analysis of 33 articles reported that the mean age of presentation with RHD was 11

years old; 53% of the populations analyzed were of male gender; 65% presented with mitral regurgitation, 21% had aortic regurgitation and 15% had mitral stenosis.[6] Mitral regurgitation results from disruption of any part of the mitral valve apparatus[7]

The mitral valve apparatus is made up of the annulus, the anterior and posterior leaflets, and the chordae, which attach the leaflets to their respective papillary muscles. A normally functioning valve allows blood to flow unimpeded from the left atrium to the left ventricle during diastole and prevents regurgitation during systole. Normal mitral valve function is dependent not only on the integrity of the underlying valvular structure, but on that of the adjacent myocardium as well. Mitral regurgitation is characterized as primary or secondary MR, the former denoting lesions of the valve apparatus itself and includes degenerative disease, rheumatic fever with carditis, rheumatic heart disease, infective endocarditis and papillary muscle rupture.[7,8] Secondary MR refers to regurgitation that occurs as a result of dilatation of the mitral annular ring and left ventricular myopathic processes.[8] The mechanism of mitral regurgitation in rheumatic carditis involves annular dilatation, chordal elongation and anterior mitral leaflet prolapse.[9,10]

As the lesions of MR progress, left ventricular volume overload ensues as a result of an increased regurgitant orifice area.[11] The volume loaded left ventricle increases LV diastolic wall stress which leads to the development of further LV chamber enlargement. During systole the LV decompresses into the compliant low pressure left atrium while at the same time ejecting into the systemic circulation, resulting in a falsely elevated ejection fraction. [7,47] For this reason, though very simply estimated, the ejection fraction is a rather crude indicator of contractile function in mitral regurgitation. Ahmed et al conducted a study of severe degenerative MR in 27 subjects who were largely asymptomatic and had a mean pre-

operative EF above 60%. Immunohistochemical stains of myocardial biopsies and magnetic resonance imaging (MRI) of the heart were performed prior to and at six months following surgery. Oxidative damage as evidenced by xanthine oxidase staining and lipofuscin accumulation was evident, and MRI showed myofibrillar degeneration, the latter two being markers of heart failure.[12] Interestingly, Ahmed's patients selected for MVR had preserved pre-operative left ventricular EF which showed a significant reduction at the 6 month follow up, suggesting that the post-operative EF is the true indicator of the pathophysiologic processes of chronic MR.[12]

With the advent of echocardiography, more cases of RHD can be detected, and analysis of the valve structure and left ventricular dimensions performed.[13] Transthoracic echocardiography is a sensitive diagnostic tool that has been able to detect cases of subclinical and clinical RHD as compared to clinical examination alone.[14,15] Diagnostic echocardiographic criteria were proposed in 2012 by the World Heart Federation to diagnose a rheumatic aetiology (RHD) of valvular heart disease by assessing the morphological characteristics of the valves involved.[16] (Table 1) For the mitral valve, leaflet and chordal thickening, restricted leaflet motion and excessive leaflet tip motion during systole are assessed according to the recommendations.

Table 1. Morphological features of RHD as assessed by echocardiography[16]

World Health Federation: Morphological features of RHD

Features in the MV

■ AMVL thickening* ≥3 mm (age-specific)

■ Chordal thickening

■ Restricted leaflet motion

■ Excessive leaflet tip motion during systole.

AMVL thickness should be measured during diastole at full excursion. Measurement should be taken at the thickest portion of the leaflet, including focal thickening, beading, and nodularity. Measurement should be performed on a frame with maximal separation of chordae from the leaflet tissue. Valve thickness can only be assessed if the images were acquired at optimal gain settings without harmonics and with a frequency ≥2.0 MHz

Abnormal thickening of the AMVL is age-specific and defined as follows:

≥3 mm for individuals aged ≤20 years;

≥4 mm for individuals aged 21–40 years;

≥5 mm for individuals aged >40 years.

Valve thickness measurements obtained using harmonic imaging should be cautiously interpreted and a thickness up to 4 mm should be considered normal in those aged ≤20 years.

Restricted leaflet motion of either the anterior or the posterior MV leaflet is usually the result of chordal shortening or fusion, commissural fusion, or leaflet thickening.

Excessive leaflet tip motion is the result of elongation of the primary chords, and is defined as displacement of the tip or edge of an involved leaflet towards the left atrium resulting in abnormal coaptation and regurgitation. Excessive leaflet tip motion does not need to meet the standard echocardiographic definition of MV prolapse disease, as that refers to a different disease process. This feature applies to only those aged <35 years. In the presence of a flail MV leaflet in the young (≤20 years), this single morphological feature is sufficient to meet the morphological criteria for RHD (that is, where the criteria state "at least two morphological features of RHD of the MV" a flail leaflet in a person aged ≤20 years is sufficient).

Abbreviations: AMVL, *anterior mitral valve leaflet*; AV, *aortic valve;* MV, *mitral valve*; RHD: *Rheumatic heart disease*

Rheumatic heart disease remains the main cause of cardiac morbidity and mortality in children and young adults, the predominant mode of death being heart failure. This notably occurs in the presence of a hemodynamically severe valve lesion, most often mitral regurgitation.[10,17] Heart failure is a very late sequela of mitral regurgitation. Patients tolerate severe regurgitation for years before symptoms become evident, when surgery is usually required. The timing of surgical intervention in mitral regurgitation becomes more difficult when regurgitation is severe and patients have minimal or no symptoms. In general, surgery is performed in asymptomatic patients with mitral regurgitation, when there is evidence of an increase in ventricular size indicating myocardial decompensation.[8,18,48] Surgical correction of the regurgitant valve results in left ventricular reverse remodelling and improvement of heart failure. This suggests that the underlying myocardial factor in rheumatic MR is reversible.[10,17]

Current recommendations for surgical intervention as per International guidelines include all symptomatic patients with severe chronic MR (Class I, level of evidence B), asymptomatic patients with left ventricular dysfunction LVESD≥45mm and/or EF≤60% (Class I, level of evidence B) or asymptomatic patients without LV dysfunction but with the presence of atrial fibrillation or pulmonary hypertension -PASP at rest>50mmHg (Class IIa, level of evidence B).[8] (Tables 2-4) Surgery may be undertaken if it is deemed to benefit the patient in instances of severe LV dysfunction (EF<30%) where the patient is refractory to medical therapy, but has low co-morbidity and high rates of successful mitral valve repair. (Figure 1)

Table 2. Indications for intervention in severe primary mitral regurgitation[8]

Recommendations	Class[a]	Level[b]
Mitral valve repair should be the preferred technique when the results are expected to be durable.	I	C
Surgery is indicated in symptomatic patients with LVEF >30%.[121,131,132]	I	B
Surgery is indicated in asymptomatic patients with LV dysfunction (LVESD ≥45 mm[c] and/or LVEF ≤60%).[122,131]	I	B
Surgery should be considered in asymptomatic patients with preserved LV function (LVESD <45 mm and LVEF >60%) and atrial fibrillation secondary to mitral regurgitation or pulmonary hypertension[d] (systolic pulmonary pressure at rest >50 mmHg).[123,124]	IIa	B
Surgery should be considered in asymptomatic patients with preserved LVEF (>60%) and LVESD 40–44 mm[c] when a durable repair is likely, surgical risk is low, the repair is performed in a heart valve centre and at least one of the following findings is present: • flail leaflet or • presence of significant LA dilatation (volume index ≥60 mL/m^2 BSA) in sinus rhythm.	IIa	C
Mitral valve repair should be considered in symptomatic patients with severe LV dysfunction (LVEF <30% and/or LVESD >55 mm) refractory to medical therapy when the likelihood of successful repair is high and comorbidity low.	IIa	C
Mitral valve replacement may be considered in symptomatic patients with severe LV dysfunction (LVEF <30% and/or LVESD >55 mm) refractory to medical therapy when the likelihood of successful repair is low and comorbidity low.	IIb	C
Percutaneous edge-to-edge procedure may be considered in patients with symptomatic severe primary mitral regurgitation who fulfil the echocardiographic criteria of eligibility and are judged inoperable or at high surgical risk by the Heart Team, avoiding futility.	IIb	C

Table 3. Classes of recommendations[8]

Classes of recommendations	Definition	Suggested wording to use
Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.	Is recommended/is indicated
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure.	
Class IIa	*Weight of evidence/opinion is in favour of usefulness/efficacy.*	Should be considered
Class IIb	*Usefulness/efficacy is less well established by evidence/opinion.*	May be considered
Class III	Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful.	Is not recommended

Table 4. Levels of evidence[8]

Level of evidence A	Data derived from multiple randomized clinical trials or meta-analyses.
Level of evidence B	Data derived from a single randomized clinical trial or large non-randomized studies.
Level of evidence C	Consensus of opinion of the experts and/ or small studies, retrospective studies, registries.

*Tables 2-4, adapted from 2017 ESC/EACTS Guidelines for the management of valvular heart disease

Figure 1. ESC algorithm for management of severe chronic primary MR[8]

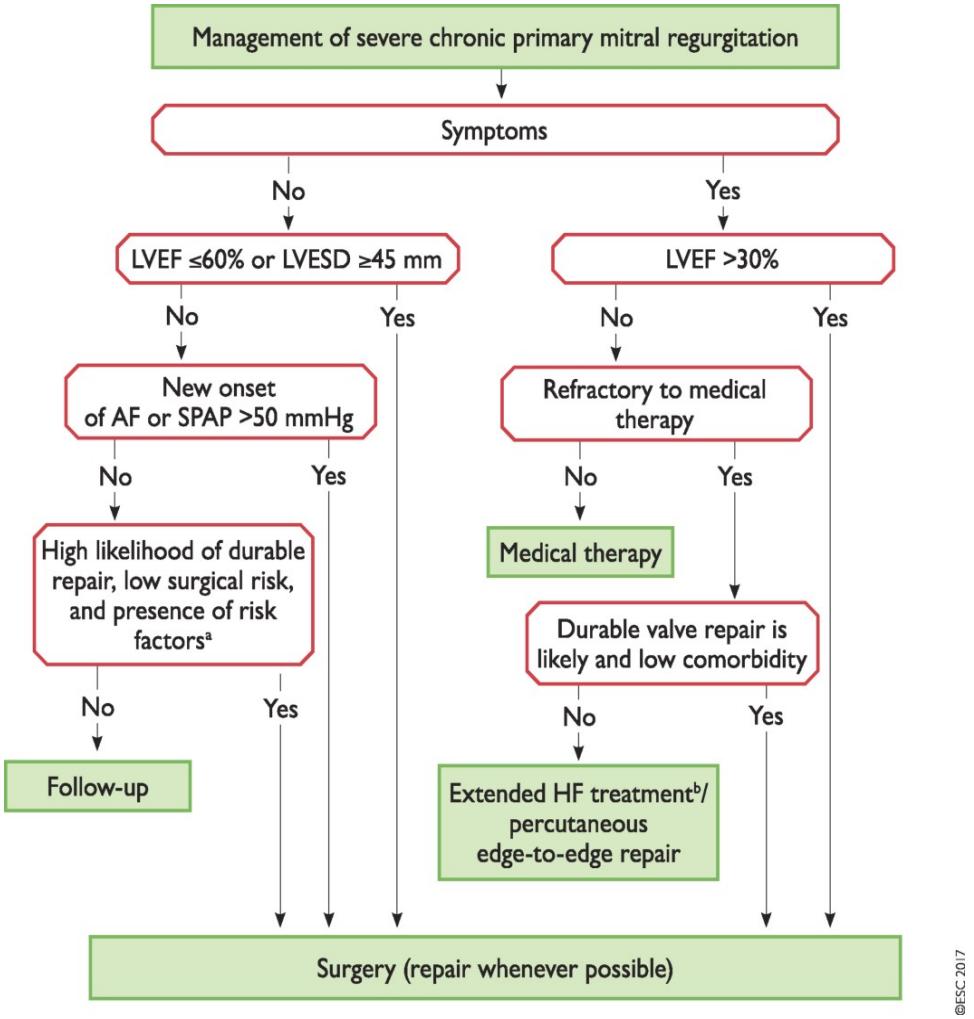

*Figure 1, adapted from 2017 ESC/EACTS Guidelines for the management of valvular heart disease

In review of the literature, most patients with left ventricular dysfunction are usually more symptomatic and have a tendency toward unfavourable post-operative clinical and echocardiographic results.[19,20,21,51] Tribouilloy et al showed that patients with larger LVESD had more symptoms and a higher frequency of atrial fibrillation. They concluded that LVESD >40mm independently predicted higher mortality in patients who were medically managed as well as in those who underwent mitral surgery.[19] Similarly, Wisenbaugh et al studied 66 patients with mostly rheumatic MR who underwent mitral valve replacement.

Their study demonstrated that the probability of death or heart failure increased abruptly at a pre-operative LVESD of 51mm, and that a pre-operative LVESD of 40mm was associated with good outcome. Taking these observations into account, the recommended optimal time for surgery was derived at an LVESD between 40 and 50mm.[22]

Suri et al conducted a retrospective study of patients who underwent mitral valve repair or replacement for mitral regurgitation resulting from leaflet prolapse. They examined the medical records of 1063 patients from 1980 to 1999, which satisfied inclusion criteria. Demographic data, functional class, presence of atrial fibrillation, decade of surgery (1990s vs 1980s), and history of preoperative myocardial infarct or CABG was recorded.[23] Echocardiographic data (EF, LVEDD, LVESD and left atrial size) was noted pre-operatively, at predismissal, 1 year or less, 1 to 3 years, and 3 to 5 years. In their study, ejection fraction declined from the pre-operative to the predismissal value but showed significant recovery at post-operative follow up. The LVEDD showed steady decline over the follow up periods and LVESD showed significant reduction between the predismissal time point and the 3 to 5 year follow up. Suri et al demonstrated that the predictors of preserved left ventricular function following mitral valve repair were pre-operative EF>65% or LVESD<36mm ($p<0.001$). However, these factors could not predict recovery for subjects who underwent mitral valve replacement ($p<0.31$ for EF and $p<0.07$ for LVESD).[23]

In 1994, Enriquez-Sarano et al reported on a retrospective analysis of 409 patients who underwent corrective surgery for organic mitral regurgitation. Multi-variate analysis showed that age>75years (p .0003) and functional class (p .016) were predictors of operative mortality and ejection fraction was a predictor of late survival (EF>60% associated with 100% expected survival at 10 years).[24] Functional class NYHA I-II was associated with

better outcome in the EF>60% cohort as compared to NYHA III-IV (p .0021).[24] In another study the same authors analyzed the pre-operative echocardiographic predictors of post-operative LV dysfunction in 266 patients. Multivariate analysis showed that the most powerful predictor was pre-operative EF (p .0001) followed by end systolic diameter (p .0005).[25] Both studies outline the need for mitral valve surgery in patients with chronic MR prior to the development of left ventricular dysfunction and suggest that clinical and echocardiographic parameters should be carefully monitored to determine the optimal time for surgery.

Because of the inherent limitations of using EF as a marker, several other measures of LV contractile function have been studied. These include exercise haemodynamics, end systolic diameter, end systolic wall stress, Doppler derived dP/dt (rate of rise of LV pressure) and more recently LV strain parameters.[20,26-30,55] The measurement of LV contractile reserve with exercise echocardiography prior to MVR in patients with chronic nonrheumatic MR has been shown to be a better predictor of post-operative LV dysfunction (EF<50%).[26] A 4% decrease in EF had a specificity of 75% and sensitivity of 79%.[26] In 2005, Lee et al also reported that an intact contractile reserve predicts preserved post-operative LV function. [27]. However, bearing in mind the caveats, in clinic practice simple estimation of the EF provides reasonable estimation of LV function in the majority of cases [43], but fails to detect which patients will have impaired LV function postoperatively.

Although left atrial size has not been identified as a predictor of post-operative outcomes in patients with chronic MR, it has been found to reflect the severity and duration of the MR. [31,32] Both left atrial size and PASP are significant predictors of cardiac related mortality. [32,33] Barbieri et al reported the presence of significant pulmonary hypertension (as defined

by PAS>50mmHg at rest) in 20% to 30% of patients with severe MR.[33] Multivariate analysis showed that older age and larger LA size were associated with a higher prevalence of pulmonary hypertension ($p<0.0001$).[33] The presence of pulmonary hypertension depends on the severity of MR, the functional class of the patient and the presence of LV dysfunction.[34,35,52] Yang et al reported that the presence of pulmonary hypertension in patients with primary MR with preserved preoperative EF predicted post-operative LV dysfunction (EF<50%).[36]

Tricuspid regurgitation is common accompaniment in MR. Sani et al showed a prevalence of tricuspid regurgitation as a complication of rheumatic heart disease in 30.2% of 129 patients. [37] To what extent tricuspid regurgitation affects the outcome in patients with chronic rheumatic MR has not been clearly established.[39] In chronic rheumatic MR tricuspid regurgitation may be secondary to left heart dilation and dysfunction, concomitant atrial fibrillation, pulmonary congestion and pulmonary hypertension with subsequent right ventricular dilation, and less commonly, it is due to rheumatic involvement of the tricuspid valve.[577] The entity of late TR that develops years after mitral valve surgery may be due to prosthetic valve dysfunction, left heart disease, right ventricular dysfunction and dilation, pulmonary hypertension, atrial fibrillation, and tricuspid annular dilation.[38,39] As tricuspid regurgitation in mitral valve disease portends a poor outcome, resulting in right heart failure and reduced functional capacity, it is recommended that tricuspid annuloplasty should be performed at the time of mitral surgery if the tricuspid annulus measures more than 35mm. [39]

In addition to preoperative parameters, the cardiopulmonary bypass time (CPBT) has also been to shown to predict post-operative outcome in patients undergoing MVR. In a study

performed by Salis et al, which involved 5006 patients between 2002 and 2008, the mean CPBT was found to be 115 minutes.[43] Multivariate analysis showed that CPBT, considered in 30 minute increments, was significantly associated with postoperative death; pulmonary, renal and neurologic complications; multi-organ failure; and multiple blood transfusions.[44] Madhavan et al calculated that total CPBT should be kept to less than 180 minutes in order to minimize postoperative morbidity and mortality.[45] This was in contrast to recommendations by Nissinen et al in 2009 who advocated 240 minutes.[46] The consensus is that a shorter CPB duration is associated with improved outcomes.

In summary, multiple studies have been conducted with the aim of determining clinical and echocardiographic predictors of postoperative left ventricular dysfunction in subjects with chronic MR, in order to inform timely surgical intervention and improved outcomes. This study describes clinical and echocardiographic characteristics in patients undergoing MVR for severe rheumatic MR in the province of KwaZulu-Natal and examines the response of the left ventricle after surgery using serial echocardiographic analyses.

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CHAPTER 2

EFFECT OF MITRAL VALVE REPLACEMENT ON LEFT VENTRICULAR FUNCTION IN SUBJECTS WITH SEVERE RHEUMATIC MITRAL REGURGITATION

INTRODUCTION

Recent hospital-based studies in South Africa (SA) reveal an incidence of congestive heart failure secondary to RHD of 25 cases/100 000/year.[1,2] Mitral regurgitation (MR) is one of the commonest causes of heart failure in subjects with RHD. Subjects with MR may remain asymptomatic for many years and those with severe MR may only develop symptoms after 6 to 10 years. Symptoms occur late in the natural history of chronic MR since the left atrium dilates to allow it to accommodate large volumes of blood without a significant rise in left atrial pressure.[3] As the lesions of MR progress, left ventricular volume overload ensues as a result of the increase in the regurgitant orifice area.[4] Long standing severe MR eventually leads to impaired LV function with increasing endsystolic volumes and pulmonary congestion. Although there may be underlying LV dysfunction, ejection fraction is maintained until late in the disease process.[4]

At the point when the end systolic diameter increases to above 40mm the EF falls below 60%.[4] International guidelines therefore recommend surgical intervention when the patient develops dyspnoeic symptoms, and/or echocardiography demonstrates evidence of left ventricular dysfunction (EF < 60%) and/or dilatation (ESD > 45mm).[4,5]

Suri et al demonstrated that the predictors of preserved left ventricular function post-operatively were pre-operative EF>65% or LVESD<36mm.[6] An EF less than 60% has been

shown to be associated with poorer survival rates after corrective surgery and is likely to indicate contractile dysfunction in MR patients.[7] Tribouilloy et al showed that left ventricular ESD >40mm independently predicted higher mortality in patients who were medically managed and after mitral surgery.[8] Since most patients with left ventricular dysfunction are usually more symptomatic and are more likely to have an unfavourable post-operative clinical outcome the management of chronic MR demands careful surveillance by the clinician to detect early changes that indicate the need for surgery.[5]

In developing countries, difficulty in access to health care as well as a resource-restricted state health service result in many subjects escaping detection due to the very nature of compensatory haemodynamics in MR, and account for later presentations in the natural history of MR. A recent study of a cohort of patients with severe MR at Inkosi Albert Luthuli Central Hospital (IALCH), a tertiary institution in Kwazulu-Natal, South Africa, has shown that patients with severe mitral regurgitation frequently presented late; many were in heart failure, beyond the optimal period for surgical intervention as judged by the echocardiographic parameters and confirmed on natriuretic peptide estimation.[9] However, this study did not describe the outcome of subjects undergoing surgery for rheumatic MR who have impaired LV function, since few patients had overt impairment of LV function [9]. We hypothesized that in these subjects recovery of contractile function is slow with persistence of heart failure symptoms. Since these subjects are known to have a poorer prognosis [7] and reduced survival rates [8] we examined the clinical and echocardiographic variables in subjects with severe rheumatic MR who underwent MVR in order to define the early surgical outcome in those with impaired LV function, and evaluate the response of the left ventricle after corrective surgery.

METHODS

This retrospective study was conducted in subjects with severe rheumatic MR confirmed at echocardiography in the Department of Cardiology at Inkosi Albert Luthuli Central Hospital (IALCH) over a nine year period (2005 -2013). Patients were selected using the CPT (Common procedural terminology) code for mitral valve replacement (33430) via the Speedminer software program 3 (Speedminer Malaysia), which is a Data Warehouse Management software package, used at IALCH to record and categorise patients' medical details. Patient demographics, HIV status, New York Heart Association (NYHA) classification, presence of atrial fibrillation, chronic medication, and echocardiographic parameters were recorded at their most recent pre-operative visit and subsequent to MVR at 2 weeks, 6 weeks to 3 months and 6 months to 2 years follow up intervals. Data was collected and grouped according to pre-operative EF in each case: EF<40%, EF 40-49%, EF 50-59% and EF>60%.

Patients with pure rheumatic mitral regurgitation were included. Patients with ischaemic and functional MR, concomitant mitral stenosis with mitral valve area (MVA) <2.5cm², aortic valve disease, congenital heart disease, previous MV surgery or other cardiac surgery were excluded. Surgical operative notes were further scrutinized to determine mitral valve pathology and document cardiopulmonary bypass times (CPBT).

Two dimensional directed m-mode and colour Doppler echocardiography was performed on all patients using a Siemens Sequoia machine (Acuson, Germany) with a phased array transducer and an emission frequency of 3.0 megahertz with the patient in the left decubitus position. Images were obtained according to a standardised protocol. The left ventricular end-systolic (LVESD) and end-diastolic dimensions (LVEDD), left atrial (LA) size, pulmonary

artery systolic pressures (PASP) and the presence and severity of tricuspid regurgitation (TR) were measured according to the American Society of Echocardiography (ASE) chamber guidelines.[10] Ejection fraction (EF) was assessed using the Simpson's method.[10]

Mitral regurgitation was considered to be rheumatic in aetiology when the morphology of the valve satisfied the proposed World Heart Federation (WHF) criteria for the diagnosis of chronic RHD.[11] Clinical evaluation of the severity of MR in this unit was supported by colour Doppler estimation of the regurgitant jet into the left atrium, the Doppler intensity of the regurgitant envelope, and the left atrial size using qualitative and semi-quantitative methods as per ASE and European Society of Cardiology (ESC) valvular regurgitation guidelines.[10,12] Calculation of the effective regurgitant orifice using Proximal Isovelocity Surface Area (PISA) was not done because in most cases the regurgitant flow into the left atrium was characterised by an eccentric jet.

The clinical endpoints of this study were to establish whether impaired left ventricular function, as measured by preoperative EF<60%, was associated with a poor surgical outcome in respect of increased rates of mortality and persistent heart failure postoperatively. We also sought to determine which other preoperative echocardiographic parameter/s (LVEDD, LVESD, LA and/or PASP) could predict post-operative left ventricular dysfunction and measured the changes in these echocardiographic parameters at follow up. Comparison between the pre- and postoperative NYHA class was drawn to determine whether surgery improved functional disability and symptoms.

Statistical analysis

Statistical Package for the Social Sciences (SPSS version 23.0) (IBM, Los Angeles) was utilized in the analysis of data for the study. A 95% level of confidence interval (CI) was estimated, and a global significance level of ά = 5% was chosen, to test for the assumptions of the null hypothesis. Simple descriptive analysis was used to highlight clinical characteristics and results were presented as frequencies, means and percentages. Continuous variables are expressed as means ± standard deviations (SDs). The student's t-tests and the chi-square tests were used to compare continuous variables and categorical variables respectively. Paired samples were used to compare changes in echocardiographic variables before and after surgery. A p value of < 0.05 suggested statistical significant findings for the variables being measured. Logistic regression analysis was used to identify preoperative predictors of impaired LV function (EF $< 50\%$), and included CPBT as a potential factor associated with post-operative LV dysfunction.

Ethics

The protocol (Appendix I), was approved by the Biomedical Research Ethics Committee (BREC, BE 055/14). Permission was obtained from the University of Kwazulu-Natal, the Provincial Health Research Committee and Inkosi Albert Luthuli Central Hospital (IALCH) where the data was to be collected (Appendices III-V, VII). Patient's identities were protected as each hospital number was assigned to an ordered numerical system on Microsoft Excel spreadsheets and these records were only available to the principal investigator and supervisor. Data from each file was then recorded following the numerical system and this was made available to the statistician.

RESULTS

Demographic and clinical data. (Table 1)

During the nine year period 788 subjects underwent surgery for severe MR. Based on the inclusion criteria a total of 656 patients were excluded. The exclusions comprised subjects with concomitant aortic stenosis (11%), aortic regurgitation (39%), mitral stenosis (75%), ischaemic MR (4%) and congenital heart disease (3%). This left 132 patients with chronic, severe, isolated MR who were enrolled into the study. There were 97 females (73%) and 35 males. Eighty three percent of patients (n=109) were under the age of 25. In the 75% of subjects who were tested 8% (n=11) were HIV infected. Comorbid conditions were present in 13% of the sample (hypertension (5%), diabetes mellitus (2%), asthma (2%), epilepsy (1%) and Grave's disease (3%).

At baseline, 66% (n=87) of patients were NYHA functional class III-IV (NYHA III 30%, NYHA IV 36%). Heart failure was a common mode of presentation and was present in 38% percent (n=50) of subjects, and 14% (n=19) had atrial fibrillation prior to operative intervention. Medication prescribed to the patients in the study included diuretics (92%), ACE-I (95%), β-blockers (8%), calcium channel blockers (2%), digoxin (21%) and penicillin (72%).

Table 1. Baseline Demographic and clinical data

	EF Group							
	40-49% (n = 7)		50-59% (n = 30)		>60% (n = 95)		Total (n = 132)	
	n	%	n	%	n	%	n	%
Age group								
<12 yrs	1	14%	3	10%	39	41%	43	33%
12-25 yrs	4	57%	20	67%	42	44%	66	50%
>25 yrs	2	29%	7	23%	14	15%	23	17%
Sex								
Male	2	29%	7	23%	26	27%	35	27%
Female	5	71%	23	77%	69	73%	97	73%
HIV								
Negative	4	57%	23	77%	61	64%	88	67%
Positive	1	14%	3	10%	7	7%	11	8%
Not known	2	29%	4	13%	27	28%	33	25%
NYHA class								
I	0	0%	1	3%	9	9%	10	8%
II	1	14%	9	30%	25	26%	35	27%
III	2	29%	8	27%	29	31%	39	30%
IV	4	57%	12	40%	32	34%	48	36%
Heart Failure								
Present	5	71%	13	43%	32	34%	50	38%
Absent	2	29%	17	57%	63	66%	82	62%
AF								
Present	1	14%	4	13%	14	15%	19	14%
Absent	6	86%	26	87%	81	85%	113	86%

AF, atrial fibrillation; *EF*, ejection fraction; *NYHA*, New York Heart Association.

Only 23 subjects were over the age of 25 years. The majority were HIV negative.

Pre-operative echocardiographic data (Table 2)

For the entire group, the median EF was 63% (IQR 58-70%), mean LVEDD 60.7±7.9mm, LVESD 39.9±7.2mm, and LA size 61.2±12.6mm. The median PASP was 59.5mmHg (IQR 45-80mmHg).

Pre-operatively, 84% of patients (n=111) had an EF>55% and the remaining 16% (n=21) had an EF<55%. Five percent (n=7) of patients had an ejection fraction (EF) between 40-49% (median EF 42%, IQR 40-45%) and 23% (n=30) had an EF between 50-59% (median EF 56%, IQR 55-57%). The remaining 72% (n=95) had an EF > 60% (median EF 65%, IQR 62-70). In all, 28% of subjects had an EF<60% ($p<0.001$).

The LVEDD was 62.6±6.5mm in the EF 40-49% group (n=7), 64.3±8.3mm in the EF 50-59% group (n=30) and 59.4±7.6mm in the EF > 60% group (n=95). The left ventricle was significantly more dilated in the EF 40-59% group as compared to the EF>60% group ($p<0.001$). The LVESD was 49±6.6mm in the EF 40-49% group (n=5), 46.4±5.8mm in the EF 50-59% group (n=25) and 37.5±5.9mm in the EF>60% group (n=88). Similarly, the LVESD was significantly higher in the EF 40-59% group compared to the EF>60% group ($p<0.001$).

The left atrium was over 55mm in diameter across all three groups. It was 56.3±9.7mm in the EF 40-49% group (n=7), 65.3±13.8mm in the EF 50-59% group (n=30) and 60.2±12.1mm in the EF>60% group (n=91) (p=0.09). The pulmonary artery systolic pressures (PASP) were elevated in all three groups. The median PASP was 50mmHg (IQR 38-53mmHg) in the EF 40-49% group (n=7), 61mmHg in the EF 50-59% group (IQR 35-79mmHg, n=29) and 60mmHg (IQR 47-80mmHg, n=90) in the EF>60% group (p=0.2). Moderate to severe TR was present in all 7 subjects in the EF 40-49% group, 62% of those in the EF 50-59% group and in 58% of those with the EF>60%.

Table 2. Baseline echocardiographic data across the different EF groups

	EF group			
	EF 40-49% n=7	**EF 50-59% n=30**	**EF>60% n=95**	**p value**
LVEDD (mm)	62.6±6,5	64.3±8,3	59.4±7,6	< 0.001
LVESD (mm)	49.0±6,6	46.4±5,8	37.5±5,9	< 0.001
LA (mm)	56.3±9,7	65.3±13,8	60.2±12,1	0,090
EF (%)*	42(40-45)	56(55-57)	65(62-70)	<0,001
PASP (mmHg)*	50(38-53)	61(35-79)	60(47-80)	0,200

* *median(IQR) EF*, ejection fraction; *LA*, left atrium; *LVEDD*, left ventricular end diastolic dimension; *LVESD*, left ventricular end systolic dimension; *PASP*, pulmonary artery systolic pressure Chamber dimensions were increased in those with EF < 60%.

Most patients responded well to surgery with improvement in NYHA functional class (Table 3). At 6 months to 2 years following MVR (n=93), 1% of patients were NYHA III-IV, 1% of patients had heart failure, and 7.6% had atrial fibrillation.

Table 3. Pre and Postoperative functional class

Pre-operation	**Post-operation 6 months – 2 years**

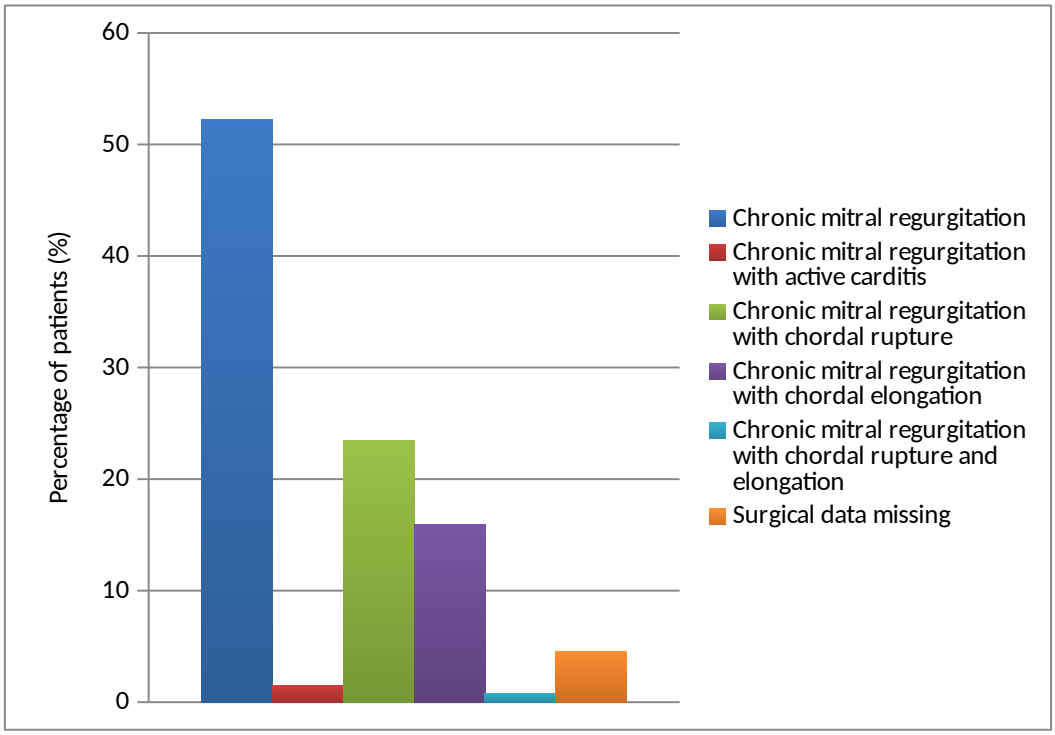
	n (132)	%	n(93)	%
NYHA				
I	10	7.6	79	84.9
II	35	26.5	13	14.0
III	39	29.5	1	1.1
IV	48	36.4	0	0.0

NYHA, New York Heart Association, Significant improvement was noted in functional class after surgery

Operative findings

The patients' operative notes were studied to determine the macroscopic pathology of mitral valve disease as described by the cardiothoracic surgeon. (Fig. 1) All valves displayed varying degrees of rheumatic involvement as assessed by valve thickness and /or calcification. Fifty two percent of patients (n=69) had features of isolated chronic MR with no other findings. In addition to chronic MR, the remaining subjects also had chordal rupture (23%, n=31), chordal elongation (16%, n=21), active carditis (1.5%, n=2) and one subject had both chordal rupture and elongation (1%). Chordal elongation was highly suggestive of active carditis in 21 patients. Chordal rupture was also presumed evidence of active carditis in young subjects in the absence of infective endocarditis. The surgeon also reported active carditis in two patients in whom the pericardium was adherent due to adhesions from fibrinous pericarditis. Two patients (1.5%) had infective endocarditis, both of whom presented in heart failure with EFs > 55%. (Table 4) The first patient, a 23 year old male was found to have grossly impaired LV function (EF 18%) at the 2 week and 6 weeks to 3 months follow up visits and was lost to follow up thereafter. The second, an 18 year old female, had an EF of 70% which fell to 40% at two weeks and she was well (NYHA I) with no clinical features of cardiac failure at 2 years.

Figure 1. Pathology of rheumatic mitral regurgitation at surgery



Active carditis was reported by the surgeon when the pericardium was adherent due to adhesions from fibrinous pericarditis, and /or chordal elongation was present and /or chordal rupture was present in the absence of infective endocarditis.

Outcomes

1. Postoperative morbidity and mortality

Despite being in heart failure the majority of patients underwent uneventful surgery with a median CPBT was 77 minutes (n=111, IQR 64-105 minutes). Of the 12 patients with a persistently low EF (<50%) at the 6 months to 2 year follow up visit, the median CPBT was 98 minutes (IQR 80-106 minutes, p 0.07) and was not significantly different from the remaining patients.

Only 1 out of 94 patients that returned for follow up between 6 months and 2 years post-operatively, remained in heart failure. Despite a pre-operative EF of 56% in this patient, there were already measurements indicating cardiac chamber enlargement, notably a markedly dilated LA of 67mm. At 2 weeks postoperatively, EF was 30% and steadily reduced at the subsequent follow up visits with concomitant increase in left heart chamber dimensions.

In total, there were five postoperative deaths yielding a mortality rate of 4%. (Table 4) These deaths occurred in young patients with advanced NYHA class, grossly dilated left atria (n=2) and PASP>50mmHg (n=3). There was no evidence of infective endocarditis or active rheumatic carditis at surgery. One patient who had a low preoperative EF of 40%, was HIV infected and demised from lobar pneumonia and cardiac failure two weeks after operation. Two patients were in extremis preoperatively, required cardioversion in theatre and demised from a low cardiac output state. The 21yr old male had a good immediate surgical outcome and died from cardiac tamponade a month later. The last patient was a child who died of massive air embolism following removal of the aortic cross clamp.

Table 4. Postoperative deaths

Age	M/F	NYHA	HF	AF	Echo						CPBT (mins)	MV Pathology
			Y/N	Y/N	EF	EDD	ESD	LA	PAS	TR		
24	F	III	Y	N	40	66	52	51	49	severe	-	chronic MR
13	F	IV	Y	N	58	69	-	54	30	severe	68	chronic MR

20	F	IV	Y	Y	62	66	43	78	69	severe	80	chronic MR
21	M	III	N	Y	68	60	37	77	51	moderate	47	chronic MR
9	F	II	N	N	45	53	29	-	60	-	175	chronic MR

AF atrial fibrillation, *CPBT* cardiopulmonary bypass time, *EDD* end diastolic dimension, *EF* ejection fraction, *ESD* end systolic dimension, *F* female, *HF* heart failure, *LA* left atrium, *M* male, *MV* mitral valve, *NYHA* New York Heart Association, *PAS* pulmonary artery systolic pressure, *TR* tricuspid regurgitation

2. Profile and Outcomes in Preoperative Ejection Fraction Subgroups

A subset of 14 patients had a dramatic reduction in EF in the early postoperative period at the 2 weeks review to less than 30%. (table 5)

Table 5. Preoperative data in subjects with EF<30% at 2 weeks post MVR

Age	M/F	NYHA			Echo						CPBT (min)	MV Pathology
			HF	AF	EF	EDD	ESD	LA	PAS	TR		
13	F	IV	Y	N	43	62	45	50	50	severe	150	chronic MR
24*	F	III	Y	N	40	66	52	51	49	severe	-	chronic MR
40	F	II	N	N	55	66	43	64	41	mild	60	chronic MR
23	M	IV	Y	N	56	68	50	39	34	mild	75	chronic MR+active carditis
11	M	II	N	N	56	66	46	78	64	-	165	chronic MR
13	F	IV	Y	Y	59	84	59	75	72	severe	160	chronic MR+chordal elongation
40	M	III	N	Y	53	79	56	88	79	moderate	85	chronic MR
13*	F	IV	Y	N	58	69	-	54	30	severe	68	chronic MR
13	F	IV	Y	N	58	59	-	56	84	severe	40	chronic MR
14	F	II	N	Y	65	78	51	80	63	mild	-	unknown
27	F	II	N	Y	67	66	44	84	53	moderate	40	chronic MR
13	F	IV	Y	N	64	65	42	92	102	severe	75	chronic MR+chordal elongation
54	M	III	N	N	65	64	41	59	53	mild	180	chronic MR+chordal rupture
16*	M	IV	Y	Y	70	65	45	70	74	severe	115	chronic MR

**Deaths, AF* atrial fibrillation, *CPBT* cardiopulmonary bypass time, *EDD* end diastolic dimension, *EF* ejection fraction, *ESD* end systolic dimension, *F* female, *HF* heart failure, *LA* left atrium, *M* male, *MV* mitral valve, *NYHA* New York Heart Association, *PAS* pulmonary artery systolic pressure, *TR* tricuspid regurgitation

Most patients were in advanced NYHA class and had EF < 60%, ESD > 44mm with markedly dilated LA size.

Of these, two thirds (n=9) had a preoperative EF <60% (2 had EF 40-49%), eight patients had clinical features of heart failure (NHYA IV, n=7) and 5 were in atrial fibrillation. (Table 4) Average CPBT in these patients was calculated to be 101 minutes (range 40-180 minutes). Eight patients received inotropic support at the end of mitral valve surgery. Two patients were HIV infected: one had a pre-operative EF of 40% and demised 2 weeks after MVR, and the other had a pre-operative EF of 55% and made an uneventful recovery. In this subset of 14 patients, 5 patients recovered their EF to more than 50% at 6 months to 2 years follow up (pre-operative EF, median 65, IQR 58-67); three died and six were lost to follow up.

i. **Pre-operative EF 40-49% group (n=7)** (Table 6)

Except for two who were middle aged, these were young patients who were in heart failure with moderate to severe tricuspid regurgitation. One was HIV infected and as mentioned earlier, demised from lobar pneumonia 2 weeks after surgery. In three patients the EF recovered (52, 56, and 59%) and was accompanied by fall in the LVESD and resolution of TR at 6 months to 2 years (Table 7); the remaining three patients were lost to follow up.

Table 6. Preoperative Profile of Patients with preoperative EF 40-49%

Age	M/F	Co-morbidities	NYHA	HF	AF	Echo					
				Y/N	Y/N	EF	ED D	ESD	LA	PAS	TR
15	M	Grave's disease	IV	Y	N	40	65	51	57	37	moderate
13	F	nil	IV	Y	N	43	62	45	50	50	severe
57	F	HPT	IV	Y	N	42	73	57	70	52	severe
6	M	nil	III	N	N	49	53	40	41	83	severe
19	F	nil	IV	Y	N	40	62	-	63	38	severe
48	F	HPT	II	N	Y	45	57	-	62	53	severe

24*	F	PIH	III	Y	N	40	66	52	51	49	severe

*HIV infected subject who died at two weeks from lobar pneumonia

AF atrial fibrillation, *EDD* end diastolic dimension, *EF* ejection fraction, *ESD* end systolic dimension, *F* female, *HF* heart failure, *HPT* hypertension, *LA* left atrium, *M* male, *MV* mitral valve, *NYHA* New York Heart Association, *PAS* pulmonary artery systolic pressure, *PIH* pregnancy induced hypertension, *TR* tricuspid regurgitation

Table 7. Follow-up echocardiographic data in subjects with preoperative EF 40-49%

	Pre-operation	**Post-operation**		
		2 weeks	**6 weeks - 3 months**	**6 months - 2 years**
LVEDD (mm)	62.6±6,5	57.3±5,9	58.7±15	59±19,8
LVESD (mm)	49.0±6,6	-	35.0±1,4	40.5±13,4
EF (%)*	42(40-45)	43(18-48)	52.0(10-54)	56.0(52-59)
LA (mm)	56.3±9,7	42.4±6,3	58.0±0	61.5±19
PASP (mmHg)*	50(38-53)	45(37-62)	62.0(40-64)	43.5(35-52)

* *median(IQR) EF*, ejection fraction; *LA*, left atrium; *LVEDD*, left ventricular end diastolic dimension; *LVESD*, left ventricular end systolic dimension; *PASP*, pulmonary artery systolic pressure

ii. **Pre-operative EF 50-59% group (n=30).** (Table 8)

After an immediate fall in the EF to 40% (IQR 30-46%, n=30) at two weeks, it rose steadily to 56% (IQR 47-59%, n=19) at 6 months to 2 years follow up. Moderate to significant TR was present in 62% of patients pre-operatively, in 52% at 2 weeks and 56% at 6 weeks to 3 months. At 6 months to 2 years post MVR only 13% had significant TR. After the initial decrease in echocardiographic parameters at two and six weeks, further decreases became apparent at the 6 month to 2 year visit with significant reduction in LVEDD, LVESD, LA and PASP between the preoperative and 6 month to 2 year follow up visit. (all $p<0.001$).

Table 8. Follow-up Echocardiographic data in subjects with baseline EF 50-59%

	Pre-operation	Post-operation		
		2 weeks	6 weeks - 3 months	6 months - 2 years
LVEDD (mm)	64.3±8,3	56.0±8,7	55.3±10,1	49.0±9,6
LVESD (mm)	46.4±5,8	41.5±6,8	39.8±10,4	36.0±10,9
EF (%)*	56(55-57)	40(30-46)	50.0(28-53)	56.0(47-59)
LA (mm)	65.3±13,8	51.0±13,4	49.3±11,8	44.6±12,4
PAS (mmHg)*	61(35-79)	46.5(35-55)	43.0(37-46)	34(28,5-40)

** median(IQR) EF, ejection fraction; LA, left atrium; LVEDD, left ventricular end diastolic dimension; LVESD, left ventricular end systolic dimension; PASP, pulmonary artery systolic pressure*

iii. **Pre-operative EF>60% group (n=95)** (Table 9)

There was an immediate fall in the EF from 65% (IQR 62-70%) preoperatively to 47.5% (IQR 40-57%, n=92) at two weeks ($p<0.001$); thereafter it increased to 56% (IQR 48.5-60%, n=48) at 6 weeks to 3 months and remained stable at 57% (IQR 43-65%, n=63) at 6 months to 2 years ($p<0.001$). In this group all other parameters steadily reduced over all three time points analysed but most of the decline in LV chamber dimensions appeared complete at the six weeks and remained stable at six months. The LA size and PASP continued to decrease at the six month evaluation. There were significant reductions for LVEDD, LVESD, LA and PASP from the preoperative evaluation to the follow up at 6 months to 2 years (all $p<0.001$). Moderate to severe TR was present in 58% of patients pre-operatively, was present in 31% at 6 weeks to 3 months, and remained in 28% at 6 months to 2 years.

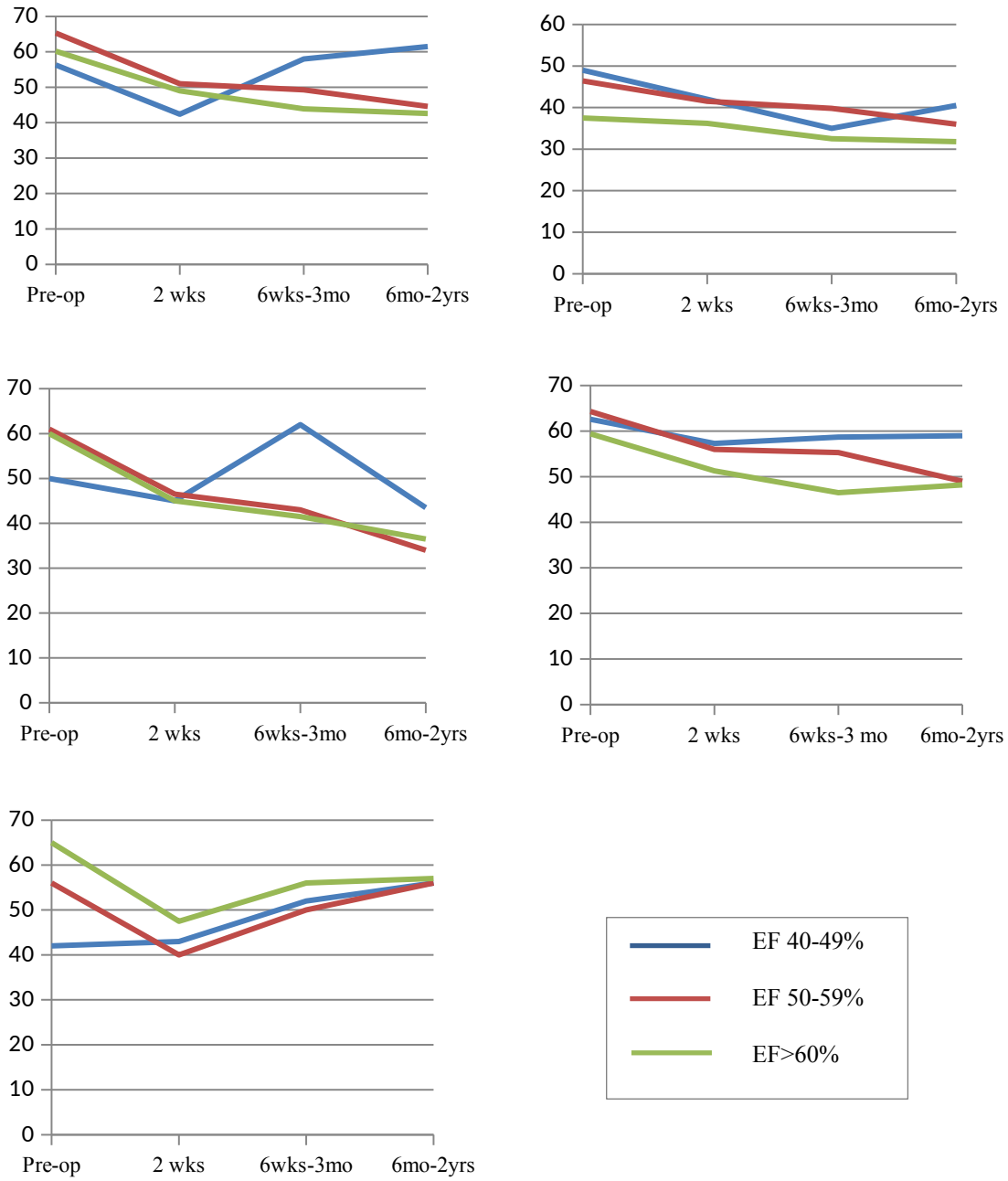
Table 9. Follow–up echocardiographic data in subjects with baseline EF >60%

	Pre-operation	Post-operation		
		2 weeks	6 weeks - 3 months	6 months - 2 years
LVEDD (mm)	59.4±7,6	51.3±7,7	46.5±7,4	48.2±7,4
LVESD (mm)	37.5±5,9	36.2±9,8	32.5±9,4	31.8±6,4
EF (%)*	65(62-70)	47.5(40-57)	56.0(48,5-60)	57.0(43-65)
LA (mm)	60.2±12,1	49.0±11,4	43.9±9,1	42.6±8,7

PASP (mmHg)*	60(47-80)	45.0(38-55)	41.5(36-49)	36.5(31-41)

** median(IQR) EF, ejection fraction; LA, left atrium; LVEDD, left ventricular end diastolic dimension; LVESD, left ventricular end systolic dimension; PASP, pulmonary artery systolic pressure*

Figure 2. Pre- and postoperative echocardiographic data at follow-up



LVESD, LVEDD, LA, EF and PASP depicted as per the pre-operative EF groups over the follow up intervals of 2 weeks, 6 weeks to 3 months and 6 months to 2 years. EF improved steadily in all groups after an initial decline in the immediate postoperative phase. Chamber dimensions, LA size and PASP all decreased after surgery except in the group with EF 40-49%.

Results of paired analysis of echocardiographic parameters

Paired analysis was conducted on 83 subjects with complete datasets for all time points. This revealed that 17/72 (20%) subjects who had pre-operative EF>55% maintained their EF at 2 weeks (p<0.001, 95% CI 0.02-0.09); this number increased significantly to 60% (n=53) at 6 months to 2 years (p<0.001, 95% CI 0.1-0.5) (p<0.001). The median EF in this paired sample was 63% (IQR 58-70%) at pre-operation. (Table 10) At 2 weeks post MVR, there was a significant 20% decrease in EF (median 46%, IQR 38-55) (p<0.001), followed by a significant increase to median EF 57% (IQR 52-63%) at 6 months to 2 years visit (p<0.001). As seen in Table 10, this was accompanied by significant reductions in LVEDD, LVESD, LA and PASP at 6 months to 2 year follow up.

Table 10. Paired analysis showing change in echocardiographic parameters (n=83)

	Pre-operation	**6 months - 2 years**	**Change**	**p value**
EF (%)*	63(58-70)	57(52-63)	-5	< 0.001
LVEDD (mm)	60.2±7,9	48.6±8,3	-11,6	< 0.001
LVESD (mm)	39.9±6,6	33.2±8,4	-6.7	< 0.001
LA (mm)	61.9±10,1	43.7±10,1	-18.2	< 0.001
PASP (mmHg)	63.9±23,4	37.4±8,8	-26,5	< 0.001

* *median(IQR) LA*, left atrium; *LVEDD*, left ventricular end diastolic dimension; *LVESD*, left ventricular end systolic dimension; *PASP*, pulmonary artery systolic pressure; *SD*, standard deviation.

Predictors of postoperative LV dysfunction

In this study 9/14 subjects who had a dramatic decline in LV function immediately postoperatively to EF<30% had a preoperative EF <60% and 8 were in severe heart failure, requiring inotropic support. The 5 subjects who recovered their EF to more than 50% at the 6 month follow up had a median pre-operative EF of 65% (IQR 58-67). Among the seven subjects with EF in the 40-49% range only three recovered their EF to > 50%. The remaining two groups (EF 50-59% and >60%) responded similarly with an initial fall in the EF at two

weeks and a steady increase thereafter to over 55% in both groups, accompanied by a decline in chamber dimensions and pulmonary artery pressure. Of significance, most of the recovery in LV function and chamber diameters was complete at six weeks in the subjects with a preoperative EF>60%, while the PA pressure continued to fall and normalised at six months.

After feeding all clinical and echocardiographic variables into a predictive model only the ESD emerged as a significant predictor of postoperative LV dysfunction (EF< 50%) both on uni- (OR 0.9, 95% CI 0.8-0.9, p 0.04) and multivariate analysis (OR 0.8, 95% CI 0.7-0.9, p 0.04).

DISCUSSION

Rheumatic heart disease remains the major cause of cardiac morbidity and mortality in young adults with cardiovascular disease.[13] Most of our subjects (83%) undergoing mitral valve replacement for severe rheumatic mitral regurgitation were under the age of 25; two thirds presented with severe functional disability (NYHA III-IV) and over a third were in advanced heart failure. Despite this, the overall response to surgery was good: among the 70% who returned to follow-up at 6 months to 2 years: only 1% of patients had signs and /or symptoms of heart failure (NYHA III-IV), with almost complete resolution of tricuspid regurgitation. The finding of persistent TR in the group with preserved LV function suggest the presence of underlying organic tricuspid valve disease in these patients which was not addressed at surgery. [15]

Impaired LV function

A sobering finding of our study is that 37 (28%) subjects underwent surgery with an EF under 60% and ESD over 46mm.ie well beyond the established guidelines recommended for MVR.[5] This pattern is a frequent finding in developing countries where many patients present for the first time with poor prognostic echocardiographic parameters such as an ejection fraction of 60% or an end-systolic diameter of 45 mm. In our paired analysis of 83 patients the majority of subjects had an EF above 55%, which was followed by an immediate fall in the EF after surgery such that only 20% (n=17) had an EF>55% at 2 weeks follow up ($p<0.001$, 95% CI 0.02-0.09), with subsequent improvement to an EF > 55% in 60% (n=53) at 6 months to 2 years. This suggests the majority of subjects had some degree of LV impairment as reflected by the median post-operative EF of 42% which is probably the true EF upon removal of the low pressure runoff into the LA following valve replacement. Despite this the majority of subjects underwent uneventful surgery and postoperative morbidity manifest by heart failure which gradually improved over time. The five documented early deaths in the study occurred in subjects who presented to hospital *in extremis* (n=2) or suffered postoperative complications (n=3).

There were significant differences in LVEDD and LVESD values in the respective EF groups, demonstrating an increase in these chamber dimensions as EF decreased. These findings suggest that there are lesser changes in left ventricular configuration when left ventricular function is preserved in the setting of severe mitral regurgitation. Although we expected the left atrium not to be as dilated in the presence of higher EF (>60%) as compared to the other two groups, in this study the LA was similarly dilated in all EF groups, reflecting both the severity and the duration of mitral regurgitation prior to operation.[16] The EF gradually improved after the initial decline postoperatively while the remaining echocardiographic parameters: LVEDD, LVESD, LA and PASP, decreased steadily at follow

up. Among the seven subjects with EF in the 40-49% range only three recovered their EF to > 50%, and among those subjects who had a sharp fall in the EF to <30% immediately after operation, the five subjects who recovered their EF to >50% at the 6 month follow up had a median pre-operative EF of 65%. It is reassuring that the EF improved steadily, albeit, more slowly in subjects with mildly impaired LV function (EF 50-59%) compared to those with preserved EF (> 60%). This data implies that although impaired LV contractility is encountered in the immediate post-operative period, myocardial function generally improves over time, but only reached normality in subjects with preserved preoperative EF, emphasizing the need for timeous surgical intervention in severe MR. This supports current guidelines recommending surgery in asymptomatic severe MR as soon as the LV begins to dilate (ESD >40mm) or the EF approaches 60%.

The development of contractile dysfunction and its relation to the severity of volume overload in MR is still not clearly understood.[13] It is well recognized that prolonged contractile dysfunction eventually becomes irreversible even after the MR is corrected and is predictive of both congestive heart failure and death.[7] Under these circumstances mitral valve replacement is associated with higher morbidity and mortality due to advanced LV impairment.[9] None of our seven patients in the group with the EF 40-49% (median EF 42%) underwent mitral valve repair which is recommended under these circumstances. The choice of the surgical procedure was dependent on the available expertise at our centre to carry out MV repair which is technically difficult in RHD compared to non-rheumatic MR. [13]

In our study the EF decreased significantly from a median of 63% preoperatively to 45% postoperatively at two weeks. Our findings showing an immediate decline in EF following

surgery is well described.[14] In Enriquez-Sarano's study the EF showed a significant reduction from 58±13% prior to mitral valve surgery to 50±14% following MVR. [14] Several mechanisms explain the decline in EF following surgery in our patients. As pointed out many of these patients had concealed LV dysfunction that was masked by the ventricular loading conditions in severe MR, characterized by increased preload and reduced afterload because of the run-off into the low pressure left atrium during systole. These loading conditions change immediately after valve surgery when the leak has been corrected, exposing the left ventricle to full systemic pressure and unmasking the true state of LV contractility. This explains the immediate fall in EF that was observed after surgery in our patients, which improved in most cases by six months.[6] Another possibility is the presence of underlying coronary artery disease with ischemic LV dysfunction but this was unlikely in our subjects because most of them were young Black African patients. Furthermore, the deleterious effect of ischaemic cardioplegic arrest on the postoperative ejection fraction in subjects is responsible for a transient decline in the early postoperative ejection fraction and must be expected in most subjects with MR. The importance of adequate cardioprotection during cardiopulmonary bypass is a critical factor that cannot be underestimated in subjects with already compromised LV function from long standing severe MR. Myocardial ischemia resulting from a longer duration of cardioplegic arrest was reflected in the prolonged CPBT in our subjects with postoperative LV dysfunction, and no doubt contributed to persistent LV dysfunction.[29] Lastly Essop has emphasised the importance of preserving the chords at surgery since any discontinuity in the chordal-mitral apparatus could lead to further dilatation and impairment of the left ventricle after surgery, thus the non-practice of chordal preservation may allow for misinterpretation of the postoperative EF. [13] This practice was a standard procedure during MVR in our subjects.

Active carditis

An important consideration is the presence of underlying active carditis in young subjects undergoing MVR. Early studies have shown that heart failure is the predominant mode of death in rheumatic carditis, explaining the high early mortality rate among young patients with acute rheumatic carditis.[17,18] Annular dilatation and chordal elongation have been described as the main mechanism leading to mitral valve prolapse and severe regurgitation during active carditis.[17,18] Pure mitral valve regurgitation without stenosis causing heart failure is common in the young who have severe active rheumatic carditis.[13,19] Evidence of active carditis characterised by pericardial inflammation, chordal elongation and /or chordal rupture was present in 55 (42%) patients and may well explain the impairment in ventricular function in these cases. Early surgery is lifesaving is these patients and the underlying ventricular impairment slowly improves in the majority of cases.[13]

Reason for Late surgery

In contrast to developed countries where MR is primarily due to mitral valve prolapse with/ without chordal rupture or coronary artery disease with underlying myocardial ischaemia, in sub-Saharan Africa rheumatic heart disease is responsible for the majority of cases of chronic MR. Because of the compensatory haemodynamics in chronic MR, many of these subjects in the developing world present late in the disease when symptoms are advanced. This difference in disease presentation is largely a result of poor socioeconomic circumstances affecting both the rural and peri-urban communities. Socioeconomic challenges prevent timely access to care; these social inequalities coupled with a resource-constrained health sector all contribute to delayed referrals for specialist assessment and intervention. As a result, most of our subjects with severe MR received operative intervention when their cardiac function has deteriorated beyond the recommended cut-off for surgical intervention

as per international norms. Furthermore over-burdened, understaffed and under-resourced state health institutions contributed to incorrect and delayed diagnoses. These factors led to delayed referral to the single tertiary centre in KZN (IALCH), where bed and theatre constraints resulted in further delays before surgery was undertaken. As a result many patients presented with severe functional disability, often in heart failure, which impacted on postoperative outcomes and contributed to significant morbidity and/or mortality. Wisenbaugh et al documented that patients in developing countries may present for the first time when EF<60% or ESD>45mm.[21] These patients suffer poor outcomes following mitral valve replacement and would likely benefit from mitral valve repair, albeit repair undertaken in rheumatic disease is technically more difficult than with degenerative MR.[4]

Physician related factors

A more worrying explanation for delayed surgery is that clinicians may not be applying established guidelines in referring patients more timeously for surgery. The median EF in our study was 56% suggesting that clinicians are using an EF of 55% to decide on the timing for valve replacement in severe MR, which is not according to the recognized guidelines for mitral valve replacement surgery. Patients with moderate-severe MR are assessed by more junior staff who may not request the echocardiographic assessment because of the demands of a busy clinic; and because such patients are relatively asymptomatic they may be given repeated follow up appointments in the assumption that all is well in stable patients. Symptoms often occur late in the course of MR since the compliance properties of the left atrium allow it to accommodate large volumes of blood before a significant rise in pressure is transferred to the pulmonary circulation. With increasing severity of regurgitation, contractile dysfunction may supervene, often preceding the onset of dyspnoeic symptoms. An EF less than 60% has been shown to be associated with poorer survival rates after corrective

surgery and is likely to indicate underlying contractile dysfunction in MR patients.[3,8,20] The majority of our patients had markedly enlarged LA sizes (n=84, 66% with LA > 55mm) and elevated PASP (n=66, 50% with PASP >60mmHg) indicating that these subjects had severe chronic MR of sufficiently long duration for such advanced changes to have developed. Chronic MR therefore requires careful monitoring by experienced clinicians with repeated echocardiographic assessments which would reveal the onset of ventricular decompensation and the need for early surgery in such cases.

Timing of surgery

The timing of surgery in patients with severe mitral regurgitation (MR) is a critical factor in the preservation of myocardial function. Wisenbaugh et al have shown that the preoperative end-systolic diameter is the only independent predictor of postoperative death.[21] Whereas a good outcome was predicted at a preoperative end-systolic diameter of 40mm, he showed that the risk of severe heart failure and/or death sharply increased when it reached 51 mm. Taking these observations into account, the recommended optimal time for surgery can be derived at an LVESD between 40 and 50mm, mitral valve repair being the preferred surgical intervention when LVESD reaches 50mm.[6,8,13] Despite the median EF being 65% and the median ESD being 37,5mm in our group with preserved EF (>60%), these patients had markedly enlarged left atria (median > 60mm) and elevated PASP (median > 60mmHg) indicating that they also had severe chronic MR of sufficiently long duration for such changes to have developed.

Pulmonary hypertension is another independent predictor of post-operative mortality, with the risk of death or occurrence of heart failure being twice as high as patients without pulmonary hypertension.[22] The presence of pulmonary hypertension depends on the

severity of mitral regurgitation, the functional class of the patient and the presence of LV dysfunction.[23,24] Significant pulmonary hypertension (PAS>50mmHg) has been reported in 20% to 30% of patients with severe MR [22] and 64% of patients with functional class NYHA III-IV.[23] The preoperative PASP was elevated beyond 50mmHg in all EF groups in our study and was lowest in the group with significantly impaired LV function (EF 40-49%). This may be due to an underestimation of the RA pressure in these subjects, most of whom were in advanced heart failure.

The majority of our patients were symptomatic and were receiving heart failure treatment, including ACE inhibitors. Controlling symptoms in these patients with medical therapy in the belief that LV function and cavity size are stable in such patients is a misinterpretation of the evidence-based guidelines for intervention, which recommend surgery in symptomatic severe MR regardless of chamber dimensions.[5,26] The current paradigm for managing severe MR is to offer early surgery in these patients because of the difficulty in diagnosing underlying left ventricular dysfunction and because the long term outcome may be poor even in subjects with good LV function as assessed by the EF. It is already well established that the preoperative EF does not predict the long-term outcome following MVR.[26,27] Furthermore, operative outcomes have improved considerably with better cardioprotection and also using the technique of MV repair in subjects with significantly impaired LV function. We did not include subjects with MV repair in our study as the numbers were few and the operation was not regularly performed at our centre because of the lack of surgical expertise.

Limitations

This study has several limitations, among them being the retrospective design which resulted in incomplete datasets for analysis and the use of raw echocardiographic data which were not

indexed to body surface area. Routine HIV testing prior to surgery was not a prerequisite to surgery in the early years when 25% were not tested. HIV infection was present in 8% of those tested and did not explain the impaired LV function in the group with EF 40-49%. Although there was a low cardiac-related mortality rate in our study (4%) this may not be a true reflection of mortality as nearly one quarter of patients failed to return for follow up. The poor follow-up after the six week visit also resulted in reduced numbers of matched pairs for comparison, thereby reducing the total number of patients whose data could be interrogated for statistical purposes. Also, in our study we did not routinely use quantitative measurements such as calculation of the effective orifice area and regurgitant fraction which are now recommended in both sets of guidelines.[4,5] Our cohort of MR did not include patients with pre-operative EF <40% submitted for MVR as per policy of our surgical unit.

Conclusion

In this study a significant number of subjects with severe MR had advanced symptoms with decompensated HF and their echocardiographic parameters were well beyond the guidelines recommended for surgical intervention. While it is reassuring that operative intervention improved cardiac dynamics and LV function in the ensuing 3 to 6 months in subjects with mildly impaired LV function, a cohort of patients remained with impaired LV function due to delayed operation. The preoperative ESD was the only predictor of postoperative LV dysfunction. Several factors accounted for surgery being performed in the very late stages of the natural history of MR in our patients, among them the primary reason being socio-economic challenges associated with lack of access to health care as a result of a failing public healthcare system. Chronic organic mitral regurgitation (MR) requires careful clinical surveillance and prompt referral for regular echocardiographic assessment to enable early

detection of LV dilatation and timeous surgery in order to achieve preservation of ventricular function.

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Appendix I

RESEARCH PROTOCOL

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Title of study

Effect of mitral valve replacement on left ventricular function in patients with rheumatic mitral regurgitation and impaired ejection fraction

Aim of study

To assess the effect of mitral valve replacement on left ventricular function in patients with rheumatic mitral regurgitation and impaired ejection fraction

Specific objectives

- To determine the effect on cardiac function after mitral valve replacement

  - To determine the cut-off point in terms of pre-operative ejection fraction when surgery will no longer yield a positive effect
- To determine the effect of pulmonary hypertension on outcome

Background and Literature

Information from research in the developed countries describe organic mitral regurgitation secondary to mitral valve prolapse or flail mitral leaflets as these are the common aetiology. In sub-Saharan Africa, rheumatic heart disease is a common occurrence although statistics indicating incidence and prevalence are not known. The difference in spectrum of disease is a result of poor socioeconomic circumstances.

As a result of lack of adequate education in the community, untimely referrals to tertiary institutions for specialist intervention and a resource-restricted state health care service, patients with severe mitral regurgitation receive operative intervention when their cardiac function has deteriorated beyond the recommended cut-off for surgical intervention as per international norms.

Much of research published in the literature and therefore the derived outcome and guidelines for mitral regurgitation pertains to the developed countries. Inasmuch as the aetiology is different, the pathological processes are similar.

Mitral regurgitation results in an increased preload and volume of blood entering the left ventricle. The left ventricle hypertrophies to compensate which maintains the ejection fraction at greater than 60%. As mitral regurgitation persists and worsens, the left ventricle dilates due to oxidative damage to the myocytes as well as left ventricular remodelling. At this point, the end systolic diameter increases to above 40mmHg and the ejection fraction falls below 60%.

According to the American College of Cardiology/American Heart Association guidelines of 2006, patients with severe mitral regurgitation should undergo operative intervention when they become symptomatic, or when echocardiogram demonstrates impaired left ventricular function (ejection fraction < 60%) and left ventricular dilation (end-systolic diameter > 40mmHg).

Studies by Tribouilloy et al and Suri et al in 2009, and Stevens et al in 2012 indicate poor outcomes when surgery is delayed. Tribouilloy et al showed that left ventricular ESD >40mmHg independently predicted higher mortality in patients who were medically managed and in those who received surgery. Invariably, post-operative ejection fraction decreases however if surgery is offered when the patient has a good pre-operative ejection fraction, left ventricular function may improve to normal.

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Study design

Case-control study

The study shall be a retrospective study for a defined term at the tertiary institution, Inkosi Albert Luthuli Central Hospital.

The study will seek to compare all patients with rheumatic mitral regurgitation in terms of their baseline cardiac function and post-operative outcome. There shall be 4 arms to the

study: those patients with ejection fraction less than 40%, 40-49%, 50-59% and greater than 60%, the latter being the control group. The study groups shall be compared with each other and then with the control group. The results shall then be statistically evaluated to determine whether the study groups with impaired left ventricular function have a successful outcome after surgery.

Study population

The study population shall be accessed via a tertiary state institution, Inkosi Albert Luthuli Central Hospital via their computerised database. A list of patients that underwent mitral valve replacement for rheumatic mitral regurgitation between 2007-2011 shall be compiled.

Sampling strategy

Stratified random sampling

Statistical planning (variables / confounders)

The variables shall be the functional class (according to the New York Heart Association classification), ejection fraction, pulmonary artery systolic pressures, electrocardiographic rhythm and clinical signs of heart failure.

Sample size

It is envisaged that over a five-year period, we will harvest fifty patients with severe mitral regurgitation and impaired left ventricular function; and twenty age- and gender-matched controls.

Inclusion / exclusion criteria

Only patients with rheumatic mitral regurgitation shall be considered. The exclusion criteria shall include concomitant aortic valve disease, ischaemic mitral regurgitation and mitral stenosis as these are confounding pathologies. There shall be no restrictions in terms of age, gender, race or social status.

Data collection methods and tools

This shall be a retrospective study where a chart review shall be conducted for all patients who meet criteria for the study, and their clinical and echocardiographic features recorded pre- and post-operatively. Microsoft Access shall be employed to collect the patient data. Four sets of data shall be used for the four arms of the study. The variables that shall be studied for each patient shall be identified and the information recorded for each patient. This will enable ease of reference for statistical analysis for each variable.

Data analysis techniques

Data shall be obtained from a tertiary cardiology centre and cardiothoracic surgery unit. A statistician shall be consulted to analyse and determine the significance of the results. Bias shall be minimised as echocardiography is an objective cardiac investigation. Only charts with adequately documented data will be included in the analysis. Validity in this study depends on the accuracy of measurement of left ventricular function. In this study, left ventricular function was assessed by trained echocardiographers who have at least five years' experience.

Statistical analysis

This shall be a quantitative study. The paired t-Test shall be used to compare pre- and post-operative echocardiographic data, and to compare the study groups to the control group. Confidence intervals, odds ratios and p-values shall be computed for the variables.

Study location

Inkosi Albert Luthuli Central Hospital, Durban, South Africa

Study period

2007-2011

Limitations to the study

This study does not include patients with concomitant aortic valve disease, ischaemic mitral regurgitation or mitral stenosis as these disease processes cause different pathological responses in the myocardium and shall confound the clinical and echocardiographic outcome. No further limitations could be identified at this point.

Ethical considerations

This is a retrospective chart review detailing pre- and post-operative findings around a disease process. Patients shall be identified by their hospital numbers by the principal investigator and the supervisors only. Clinical and echocardiographic outcomes shall be evaluated; there shall be no intervention applied to the patients. Thus patients' identities shall be secured and there shall be no harm inflicted nor benefit derived for the patient as an individual.

Appendix II. Certificate of Completion of NIH Web-based training course

Certificate of Completi n

The National Institutes of He h (NIH) Office of Extramural Research certifies that **Sharen Maharaj** succes ully completed the NIH Web-based training course "Protecting Human R earch Participants".

Date of completion: 09/13/20 3

Certification Number: 12560

Appendix III. Protocol approval by University of Kwazulu-Natal

UNIVERSITY OF
KWAZULU-NATAL
INYUVESI
YAKWAZULU-NATALI

15 January 2014

Prof DP Naidoo
Department of Cardiology

Dear Prof Naidoo

MMED PROTOCOL: "Effect of mitral valve replacement on left ventricular function in patients with rheumatic mitral regurgitation and impaired ejection fraction"
Student: Dr S Maharaj, Student Number: 202501064 (Department of Internal Medicine)

I am pleased to inform you that the abovementioned protocol has been approved. Dr S Ponnusamy has been appointed as co-supervisor.

Please note:

- The Academic Leader: School Research must review any changes made to this study.
- The study may not begin without the approval of the Biomedical Research Ethics Committee.

May I take this opportunity to wish the student every success with the study.

Yours sincerely

for Dr VS Singaram
Academic Leader of Research (Acting)

CC Dr S Maharaj
Dr S Ponnusamy

Biomedical Research Ethics Committee
Westville Campus

Postgraduate, Higher Degrees & Research
School of Clinical Medicine, NRMSM Campus
Postal Address: P/Bag X3, Congella, Durban, 4013, South Africa
Telephone: +27 (0) 31 260 4309 **Facsimilie:** +27 (0) 31 260 4723 **Email:** konar@ukzn.ac.za **Website:** www.ukzn.ac.za

Appendix IV. Permission to conduct research at Inkosi Albert Luthuli Central Hospital

health
Department:
Health
PROVINCE OF KWAZULU-NATAL

Inkosi Albert Luthuli Central Hospital
Ethekwini Health District
Office of the Medical Manager
Private Bag X 03, Mayville, 4058
800 Bellair Road, Mayville, 4058
Tel.: 031 240 1059,
Fax.: 031 240 1050
Email.:ursulanun@ialch.co.za
www.kznhealth.gov.za

Reference: BE 055/14
Enquiries: Medical Management

31 July 2014

Dr S Maharaj
Department of Cardiology
IALCH

Dear Dr Maharaj

RE: PERMISSION TO CONDUCT RESEARCH AT IALCH

I have pleasure in informing you that permission has been granted to you by the Medical Manager to conduct research on: **Effect of mitral valve replacement on left ventricular function in patients with rheumatic mitral regurgitation and impaired ejection fraction.**

Kindly take note of the following information before you continue:

1. Please ensure that you adhere to all the policies, procedures, protocols and guidelines of the Department of Health with regards to this research.
2. This research will only commence once this office has received confirmation from the Provincial Health Research Committee in the KZN Department of Health.
3. Kindly ensure that this office is informed before you commence your research.
4. The hospital will not provide any resources for this research.
5. You will be expected to provide feedback once your research is complete to the Medical Manager.

Yours faithfully

.....
Dr K.E Letebele-Hartell
Medical Manager

Appendix V. Permission to conduct research from the Provincial Health Research Committee

health
Department:
Health
PROVINCE OF KWAZULU-NATAL

Inkosi Albert Luthuli Central Hospital
Ethekwini Health District
Office of the Medical Manager
Private Bag X 03, Mayville, 4058
800 Bellair Road, Mayville, 4058
Tel.: 031 240 1059,
Fax.: 031 240 1050
Email.:ursulanun@ialch.co.za
www.kznhealth.gov.za

31 July 2014

Dr S Maharaj
Department of Cardiology
IALCH

Dear Dr Maharaj

Re: Ref No: BE055/14: Effect of mitral valve replacement on left ventriculare function in patients with rheumatic mitral regurgitation and impaired ejection fraction,

As per the policy of the Provincial Health Research Committee (PHRC), you are hereby granted permission to conduct the above mentioned research once all relevant documentation has been submitted to PHRC inclusive of Full Ethical Approval.

Kindly note the following.

1. The research should adhere to all policies, procedures, protocols and guidelines of the KwaZulu-Natal Department of Health.
2. Research will only commence once the PHRC has granted approval to the researcher.
3. The researcher must ensure that the Medical Manager is informed before the commencement of the research by means of the approval letter by the chairperson of the PHRC.
4. The Medical Manager expects to be provided feedback on the findings of the research.
5. Kindly submit your research to:

   The Secretariat
   Health Research & Knowledge Management
   330 Langaliballe Street, Pietermaritzburg, 3200
   Private Bag X9501, Pietermaritzburg , 3201
   Tel: 033395-3123, Fax 033394-3782
   Email: hrkm@kznhealth.gov.za

Yours faithfully

.....
Dr K.E Letebele-Hartell
Medical Manager

Appendix VI. Approval from Biomedical Research Ethics Committee

UNIVERSITY OF
KWAZULU-NATAL
INYUVESI
YAKWAZULU-NATALI
RESEARCH OFFICE
BIOMEDICAL RESEARCH ETHICS ADMINISTRATION
Westville Campus
Govan Mbeki Building
Private Bag X 54001
Durban
4000
KwaZulu-Natal, SOUTH AFRICA
Tel: 27 31 2604769 - Fax: 27 31 260-4609
Email: BREC@ukzn.ac.za
Website: http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx

14 March 2014

Dr Sharen Maharaj
W203 Palm Gate
11 Centenary Boulevard
Umhlanga Ridge
sharenmaharaj@ymail.com

Dear Dr Maharaj

PROTOCOL: Effect of mitral valve replacement on left ventricular function in patients with rheumatic mitral regurgitation and impaired ejection fraction. REF: BE055/14

PROVISIONAL APPROVAL

A sub-committee of the Biomedical Research Ethics Committee has considered and noted your application received on 21 January 2014.

The study is given **PROVISIONAL APPROVAL** pending a response to the following:

1. Site Permissions

Only when full ethical approval is given, may the study begin. **Full ethics approval has not been given at this stage.**

PLEASE NOTE: Provisional approval is valid for 6 months only - should we not hear from you during this time - the study will be closed and reapplication will need to be made.

Your acceptance of this provisional approval denotes your compliance with South African National Research Ethics Guidelines (2004), South African National Good Clinical Practice Guidelines (2006) (if applicable) and with UKZN BREC ethics requirements as contained in the UKZN BREC Terms of Reference and Standard Operating Procedures, all available at http://research.ukzn.ac.za/ResearchEthics11415.aspx.

BREC is registered with the South African National Health Research Ethics Council (REC-290408-009). BREC has US Office for Human Research Protections (OHRP) Federal-wide Assurance (FWA 678).

Yours sincerely

Ms A Marimuthu
Senior Administrator: Biomedical Research Ethics

Appendix VII. Approval from the Kwazulu-Natal Department of Health

health
Department:
Health
PROVINCE OF KWAZULU-NATAL

Health Research & Knowledge Management sub-component
10 – 103 Natalia Building, 330 Langalibalele Street
Private Bag x9051
Pietermaritzburg
3200
Tel.: 033 – 3953189
Fax.: 033 – 394 3782
Email.: hrkm@kznhealth.gov.za
www.kznhealth.gov.za

Reference : HRKM 230/14
Enquiries : Mr X Xaba
Tel : 033 – 395 2805

Dear Dr S. Maharaj

Subject: Approval of a Research Proposal

1. The research proposal titled **'Effect of mitral valve replacement on left ventricular function in patients with rheumatic mitral regurgitation and impaired ejection fraction'** was reviewed by the KwaZulu-Natal Department of Health.

   The proposal is hereby **approved** for research to be undertaken at Inkosi Albert Luthuli Central Hospital.

2. You are requested to take note of the following:
   a. Make the necessary arrangement with the identified facility before commencing with your research project.
   b. Provide an interim progress report and final report (electronic and hard copies) when your research is complete.

3. Your final report must be posted to **HEALTH RESEARCH AND KNOWLEDGE MANAGEMENT, 10-102, PRIVATE BAG X9051, PIETERMARITZBURG, 3200** and e-mail an electronic copy to hrkm@kznhealth.gov.za

For any additional information please contact Mr X. Xaba on 033-395 2805.

Yours Sincerely

Dr E Lutge
Chairperson, Health Research Committee
Date: 29/05/14

Appendix VIII. Data collection tool

Patient No.	Age	Gender	Co-morbidities	NYHA	Heart failure	AF	Echo						Medication	Comments	HIV
					Y/N	Y/N	EF	LVEDD	LVESD	LA	PAS	TR			
1															
2															
3															
4															
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