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ASSESSMENT OF MYOCARDIAL MECHANICS IN CHRONIC RHEUMATIC MITRAL REGURGITATION

Ruchika Meel

A thesis submitted to the Faculty of Medicine, University of the Witwatersrand, for the degree of Doctor of Philosophy

Johannesburg 2016

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Declaration

I declare that this thesis is my own, unaided work. It is being submitted for the degree of Doctor of Philosophy in the Faculty of Medicine, University of the Witwatersrand, Johannesburg. The work contained in thesis has not been submitted for any degree or examination in this university or any other university.

.....

Ruchika Meel

10 Day of June 2016

I certify that the studies contained in this thesis have the approval of the Ethics Committee of the University of the Witwatersrand, Johannesburg. The approval number was M140114.

.....

Ruchika Meel

10 Day of June 2016

.....

M.R. Essop (Supervisor)

10/6/16

.....

E.N.Libhaber (Supervisor)

10/6/16

ii Dedication

This thesis is dedicated to my husband Ricardo, my parents Prof. BL Meel and Veena Meel, my brother Piyush and my sisters Anita, Swati, Anita Tetarwal, and last, but not least, all the patients who participated in this study.

iii Acknowledgements

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American Society of Echocardiography 26th Annual Scientific Sessions in Boston, Massachusetts, June 12-16, 2015 (Visited the imaging laboratory and observed cardiac MRI cases at the Boston Medical Centre, Boston, USA, under the supervision of Dr F. Ruberg)

v List of Abbreviations

2-D: two-dimensional

ACEI: angiotensin converting enzyme inhibitor

ARB: angiotensin receptor blocker

ARF: acute rheumatic fever

ASE: American Society of Echocardiography

AF: atrial fibrillation

AML: anterior mitral leaflet

BMI: body mass index

BSA: body surface area

CHBAH: Chris Hani Baragwanath Academic Hospital

CRMR: chronic rheumatic mitral regurgitation

CMR: cardiac magnetic resonance

CV: conduit volume

CVS: cardiovascular

DBP: diastolic blood pressure

Ɛ: strain

$Ɛ_{CT}$- peak contractile (negative) strain

$Ɛ_{R}$: peak systolic (positive) longitudinal strain or strain in the reservoir phase

ECM: extracellular matrix

ECV: extracellular volume

EDD: end-diastolic diameter

EDP: end-diastolic pressure

EDV/EDVi: end-diastolic volume/ end-diastolic volume indexed

EF: ejection fraction

ELISA: enzyme-linked immunosorbent assay

EROA: effective regurgitant orifice area

ESC: European Society of Cardiology

ESV/ESVi: end-systolic volume/ end-systolic volume indexed

GLS: global longitudinal strain

FAC: fractional area change

HF: heart failure

HIV: Human immunodeficiency virus

HR: heart rate

HRP: horse radish protein

IVSD: interventricular septal diameter

LA: left atrium

LAEF: left atrial emptying fraction

LA AEVi: left atrial active emptying volume index

LA exp index: left atrial expansion index

LAVi: left atrial volume indexed

LGE: late gadolinium enhancement

LV: left ventricle

LVEF: left ventricular ejection fraction

LVMi: left ventricle mass indexed

Max-LAVi /LA_{max}: maximum left atrial volume indexed/ maximum left atrial volume

Min- LAVi /LA_{min}: minimum left atrial volume indexed/ minimum left atrial volume

MMP-1: matrix metalloproteinase 1

MR: mitral regurgitation

MRI: magnetic resonance imaging

MS: mitral stenosis

MV: mitral valve

MVA: mitral valve area

NYHA: New York Heart Association

PASP: pulmonary artery systolic pressure

PBS: phosphate buffered saline

PEF: passive emptying fraction

PEV: passive emptying volume

PHT: pulmonary hypertension

PIIINP: procollagen III N-Terminal propeptide

PIP: procollagen Type IC-Peptide

PISA: proximal isovelocity surface area

PML: posterior mitral valve leaflet

Pre-A LAVi /V_{pre-A}: pre-atrial contraction volume indexed/ pre-atrial contraction volume

PSS: peak systolic strain

PWD: posterior wall diameter

RAAS: renin angiotensin aldosterone system

RegV: regurgitant volume

RF: regurgitant fraction

RHD: rheumatic heart disease

ROI: region of interest

RV: right ventricle

RWT: relative wall thickness

SBP: systolic blood pressure

SD: standard deviation

SNS: sympathetic nervous system

STE: speckle tracking echocardiography

SV: stroke volume

TAPSE: tricuspid annular plane systolic excursion

TDI: tissue Doppler imaging

TIMP-1: tissue inhibitor metalloproteinase 1

TMBZ: 3,3ˈ,5,5ˈ-Tetramethylbenzidine

TR: tricuspid regurgitation

TV: tricuspid valve

VC: venae contracta

WHF: World Heart Federation

WHO: World Health Organization

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viii Abstract

Chronic rheumatic mitral regurgitation (CRMR) is a commonly encountered lesion in the developing world, yet it remains an understudied disease in comparison to degenerative MR. There are several unresolved issues in CRMR ranging from limited data on the current demographic and clinical profile of the contemporary patient with CRMR, to the evaluation of this lesion with sophisticated techniques utilising strain (Ɛ), magnetic resonance imaging (MRI) and biomarkers. Furthermore, the role of medical therapy has been mainly restricted to studies pertaining to degenerative MR. Thus, in this thesis the aim was to address some of the aforementioned deficiencies in the field of CRMR. In the process of studying the atrioventricular functional parameters in CRMR, we established age and vendor-specific (Philips QLAB 9) normative data for left atrial (LA) functional and volumetric parameters in a normal black population.

Eighty four subjects with CRMR were studied at Chris Hani Baragwanath Hospital (CHBAH) and compared with a prior landmark study by Marcus et al conducted at this institution. Mean age was 44.0±15.3 years, compared to 19 years in the study by Marcus et al. Acute rheumatic fever (ARF) was rare compared to the previous study. Hypertension and human immunodeficiency virus (HIV) were present in 52% and 26% respectively. Echocardiography showed leaflet thickening and calcification, restricted motion and sub-valvular disease, as opposed to pliable leaflets with predominant prolapse and chordal rupture in the study by Marcus et al.

One hundred and twenty normal black subjects from 18 and 70 years of age were studied. Maximum LA volume indexed (LAVi) was 19.7±5.9 mL/m^2. LA pump function increased with age (r=0.2, p=0.02), and the conduit function decreased with

age (*r*=-0.3, p< 0.001). LA Ɛ in the reservoir phase was 39.0±8.3%. LA Ɛ in the reservoir phase declined with age (p<0.001). Two studies were conducted using speckle tracking in 77 patients with CRMR. The first study found that 86% had decreased LA peak reservoir Ɛ and 58% had depressed left ventricular (LV) peak systolic Ɛ. In the second study, right ventricle (RV) peak systolic Ɛ was lower in the MR group compared to controls (-16.8±4.5% vs -19.2±3.4%, p=0.003). LV peak systolic Ɛ was an independent predictor of RV peak systolic Ɛ (r=0.46, p<0.004).

CRMR is a disease characterised by eccentric jets due to distorted leaflet architecture. Thus, the echocardiographic proximal isovelocity surface area (PISA) method, to assess MR severity, is suboptimal. In CRMR there may be involvement of the LV by the rheumatic process especially in the postero basal region. To study these issues, 22 patients without comorbidities underwent MRI. On comparison of MR severity assessment by echocardiography (using an integrated approach) and MRI, there was concordance between the two techniques in all but seven patients. Six patients were reclassified as severe MR after MRI and one patient was re-categorised as moderate MR. Only four patients had fibrosis on late gadolinium enhancement. No particular regional involvement was noted. We also studied markers of collagen degradation and synthesis in CRMR and their relation with MRI parameters. Matrix metalloproteinase-1 was increased compared to controls (log MMP-1 3.5±0.68 vs 2.7±0.9, p=0.02), implying increased collagen degradation rather than synthesis in CRMR. This supports the paucity of fibrosis found on MRI.

Effects of combination medical therapy in heart failure (HF) secondary to severe CRMR in 31 patients was studied. On optimal therapy no HF-related admissions or deaths were noted. There was improvement in LA peak systolic strain. LV and RV functional indices remained unchanged on maximal therapy.

In conclusion, the contemporary CRMR patients are older, have comorbidities and less ARF. Upper limits of maximum LAVi are lower in the black population compared to Caucasians, and age needs to be considered when interpreting abnormalities of LA function. LA dysfunction was noted with or without involvement of the LV, therefore perhaps in CRMR, LA dysfunction precedes LV dysfunction. RV peak systolic Ɛ was useful for assessment of subclinical RV dysfunction in CRMR, therefore quantitative measurement of RV systolic function should not rely solely on conventional indices. Cardiac MRI was a useful adjunctive tool for MR severity assessment in 32% of CRMR patients when echocardiography alone was insufficient. CRMR is characterised by predominant collagen degradation and is associated with low prevalence of fibrosis. Finally, there may be a role for combination anti-remodelling therapy in HF secondary to MR. Finally, we have provided normal reference ranges for LA volume and strain parameters that would serve as platform for future studies in this population. Our findings pertaining to imaging, biomarkers and role of combination anti-remodelling therapy in CRMR may aid in the clinical assessment and management of patients with CRMR, and serve as a base for further research in these fields.

Chapter 1

Introduction

Demographics of chronic rheumatic heart disease, current knowledge and pertinent concepts in strain imaging, And therapy for chronic rheumatic mitral regurgitation

1.1 Introduction

Chronic rheumatic heart disease (RHD) is common in the developing world (World Health organization (WHO) 2001). WHO statistics show that about 15 million people suffer from RHD worldwide and which is associated with 250 000 deaths annually (WHO 2001). Across Africa RHD accounts for 6.6-34% of cardiovascular (CVS) disease-related hospital admissions or echocardiographic examinations (Sliwa and Mocumbi 2010b). From surveys of school-going children the prevalence of chronic RHD varies from 2.7/1000 in Nairobi to 14.3/1000 in Kinshasa (Essop and Nkomo 2005). The prevalence of RHD in Sub-Saharan Africa is estimated at 5.7/1000 (Nkomo 2007). From data derived from older surveys from the 1970s, predominantly from school children, the estimated prevalence of RHD in sub-Saharan Africa was high at 5.1/1000 (Nkomo 2007). From older literature, McClaren et al. in 1975, reported an incidence of 6.9/1000 among school children in Soweto (McClaren et al.1975). More recently, Engel et al. reported an incidence of 20.2/1000 cases among scholars in the Bonteheuwel and Langa communities of Cape Town, with the prevalence being higher in poorer communities (Engel et al. 2015). Recently Sliwa et al. reported a high incidence of 23.5/100 000 of RHD among adults at Chris Hani Baragwanath Hospital (CHBAH) and chronic rheumatic mitral regurgitation (CRMR) was noted to be the most common lesion (59%) (Sliwa et al. 2010a). A declining incidence (64 cases per year in 1993, to 3 per year in 2010) in ARF in the paediatric population of Baragwanath Hospital has been reported (Cilliers 2014). The recent global heart disease registry (REMEDY study) reported contemporary data on presentation, complication and treatment of RHD but the incidence or prevalence of RHD in South Africa was not clearly addressed (Zuhlke et

al. 2015). However, 25.8% (86/3343) participants were from upper middle income countries (SA/ Namibia) (Zuhlke et al. 2015. In the present study we specifically analysed a subgroup of RHD patients, specifically those with isolated CRMR, as it is one of the most commonly encountered valvular lesions in the adult patient with RHD at CHBAH (Sliwa et al. 2010a). Even though it is a commonly encountered lesion and an important cause of mitral regurgitation (MR) in the developing world, it remains an understudied disease compared to MR of degenerative aetiology (Mohan J and Mohan S 2012, Essop and Peters 2005). Additionally, it is uncertain whether current guidelines derived mainly from literature pertaining to degenerative MR can be applied to rheumatic MR (Mohan J and Mohan S 2012). While the body of knowledge expands in the field of degenerative MR, rheumatic MR constantly lags behind, although this disease afflicts a large proportion of the world population (Haub and Kaneda 2012). Thus, in this thesis we will attempt to address some of the aforementioned deficiencies in the field of CRMR.

From the limited studies done in the past, CRMR tended to be a lesion of the young, who presented with acute, fulminant carditis and no comorbidities (Clur 2006, Marcus et al. 1994). In contrast, currently a decline in ARF and increase in number of new cases of RHD (predominantly CRMR) among the adult population; alongside the emergence of diseases such as HIV and hypertension among the predominantly older black population has been reported (Sliwa et al. 2010a, Sliwa et al. 2008). There is a paucity of literature which has systematically documented the change in the demographic and clinical characteristics of contemporary patients with CRMR and the impact of these emerging comorbidities in this patient group. Thus, one of my aims was to document the prevalence of these comorbidities in the current cohort

of patients with CRMR at CHBAH and compare and contrast our finding with an earlier cohort of patients reported by Marcus et al. from the same institution as ours.

The timing of surgical intervention for MR is critically influenced by imaging criteria. There is limited data regarding imaging in the developing world for CRMR. The most commonly used modality to assess MR is two-dimensional (2D) rest echocardiography. Cardiac magnetic resonance imaging (CMR) and newer 2D strain imaging techniques constitute important emerging imaging modalities (Van De Heyning et al. 2012). Current valvular heart disease guidelines recommend surgery based on left ventricular (LV) ejection fraction, dimensions or presence of symptoms (Nishimura et al 2014, Lancelloti et al 2013, Zoghbi et al. 2003). The former, volume-based parameters have limited value for assessment of contractile LV function (Marciniak et al. 2007). Strain imaging using speckle tracking echocardiography has emerged as a valuable tool for myocardial and left atrial (LA) function assessment and for prognostication in various disease states at a subclinical stage (Hoit et al. 2014, Fine et al. 2014, Dandel et al. 2009). In degenerative MR LV global longitudinal strain (GLS), LA volume of ≥60mL/m^2 and depressed peak global LA strain are important predictors of postoperative outcomes, five-year survival and worse prognoses (Yang L et al. 2015, Le Torneau et al. 2010, Lancellotti et al. 2008). Recently, Le Torneau et al. emphasised the importance of biventricular function impairment on postoperative outcomes in degenerative MR (Le Torneau et al. 2013). Right ventricular peak systolic strain (RV PSS) has been shown to be an important parameter for evaluation of subclinical RV dysfunction and is of prognostic significance in various disease states such as MR and low-flow, low-gradient aortic stenosis (Dahou et al. 2016, Fine et al. 2014, Le Torneau et al. 2013). Limited studies in CRMR prompted us to initially establish normative data for LA

volumetric and strain parameters in a black population, to study the extent of abnormality in these parameters in CRMR. A previous study pertaining to the LV functional parameters in a normal black population, allowed me to study the LV parameters in patients with CRMR (Maharaj et al. 2013). Further, we studied RV function in CRMR and healthy controls.

Chronic MR is associated with progressive left ventricular (LV) dysfunction and, eventually death if left untreated (Enriquez-Sarano et al. 2005). This disease has a long silent period before symptoms manifest. During this latent period LV function progressively deteriorates, and results in poor outcomes for patients even if surgery is performed (Bonow et al. 2012, Gaasch and Meyer 2008). Little data exists with regard to imaging, biomarkers and medical therapy for CRMR in the context of the developing world. Accurate delineation of the severity of MR with multimodality imaging and risk stratification with the aid of biomarkers could prove to be valuable non-invasive tools in accurate timing of surgery (Banerjee et al. 2014, Bergler-Klein J et al. 2014, Van De Heyning and Magne 2012, Lee and Marwick 2007). Early referral for mitral valve surgery has been shown to improve long term clinical outcomes. Given the general insufficient availability of adequate cardiothoracic surgical services, effective medical therapy for chronic MR would be ideal. This may, at the very least, serve as a bridge to surgery.

1.2 Demographics of chronic rheumatic mitral regurgitation: current and past observations at Chris Hani Baragwanath Academic Hospital

Previous studies have documented the high prevalence of rheumatic fever and RHD in the population of Soweto and have provided a detailed description of the echocardiographic findings in these patients (Sliwa et al. 2010a, Marcus et al. 1994). In developed countries, degenerative disease is the major cause of chronic MR and when surgery is indicated, repair of the valve is the preferred therapy (Enriquez-Sarano et al. 2009). In geographically low and middle income areas, chronic MR is still due predominantly to rheumatic disease and when severe, mitral valve replacement is often required (Essop et al. 2005). While the demographic profile and echocardiographic features of degenerative MR have been well documented, there remains uncertainty regarding rheumatic MR ranging from diagnostic echocardiographic criteria to optimal management (Essop and Peters 2014, Enriquez-Sarano et al. 2009, Essop and Nkomo 2005).

CRMR is a frequently encountered lesion in which the mitral valve is not inherently stenotic and must be distinguished from a mixed lesion which is characterised by varying degrees of mitral stenosis (Sliwa et al. 2010a, Marcus et al. 1994). Rheumatic valvular regurgitation was predominantly a disease of the young, as documented in earlier literature and stenotic lesions tended to occur in older patients (Essop and Peters 2014, Sliwa et al. 2010a, Marcus et al. 1994). In clinical practice we have observed that in recent years the demographic profile of patients presenting with CRMR appear to have changed. The two major factors contributing to this may be related to the decline in rheumatic fever, likely secondary to improvement in socioeconomic status and access to penicillin, with a concomitant emergence in diseases associated with a western lifestyle (Stewart et al. 2008). A

third potential confounding variable is the pandemic of HIV which adds to the comorbidity of patients with CRMR in this era (Essop and Peters 2014). We hypothesised that these changes may have a significant impact on the clinical presentation, assessment and management of patients with CRMR. Thus, we embarked on this study to systematically document the clinical and echocardiographic features of the current patients with moderate or severe CRMR and compare them to the study by Marcus et al. done at CHBAH thirty years ago. A second objective was to compare the clinical presentation and echocardiographic assessment of CRMR in patients with and without comorbidities. This topic will be addressed in Chapter 2 of this thesis.

Additionally, due to the prognostic role of the LA in MR, we studied the LA and myocardial deformation parameters in CRMR after establishing age-related normative data on LA volumetric and deformation parameters in a black population.

1.3 Left atrial volumetric and strain parameters

1.3.1 Left atrial function assessment using traditional parameters

LA size and volume are altered in many disease states and are important predictors of morbidity and mortality in many CVS diseases such as hypertension, valvular heart disease, diabetes and sleep apnoea (Hoit 2014, Seward and Hebl 2014, Cameli et al. 2012, Leung et al. 2008). Additionally, LA volume is independently associated with adverse CVS outcomes such as atrial fibrillation, acute coronary events, HF and stroke (Tsang et al. 2012).

The LA has multiple functions. It is a contractile chamber that also acts as a reservoir, conduit and volume sensor (Bonow et al. 2012). The LA acts as a reservoir to receive blood from the pulmonary veins during ventricular systole (Viera

et al. 2014, Tsang et al. 2012). During the ventricular early diastolic phase, it acts as a conduit and transfers blood passively into the LV and during end-diastole it contracts and pumps the blood actively into the LV (Viera et al. 2014, Tsang et al. 2012). All the aforementioned phases are influenced by compliance of the LA chamber and thus by LA relaxation and contraction (Viera et al. 2014). The anatomy and pathophysiology of the LA is complex, its multifaceted profile cannot be effectively defined by a single anatomical, functional or clinical feature (Seward and Hebl 2014). Thus, optimal quantification of its function is difficult (Seward and Hebl 2014, Cameli et al. 2009).

The traditional parameters of LA function assessment such as LA size, volume and functional parameters and Doppler flow assessment across the mitral valve and pulmonary veins have proved useful and are readily available to most imagers (Viera et al. 2014). However, they are limited by factors such as poor echocardiographic windows, foreshortening, errors in volumetric measurement using biplane Simpson's method and no reference gold standard of LA function measurement (Viera et al. 2014). Recently, three dimensional LA volumetric assessment showed promise, but it too is limited by problems of gain settings and extensive variability between observers (Viera et al. 2014).

1.3.2 Overview of basic concepts in strain imaging

Knowledge in the field of myocardial deformation imaging has advanced rapidly with various techniques utilising velocity imaging, displacement imaging and deformation imaging (strain and strain-rate imaging) (Shah and Solomon 2012, Gorcsan et al. 2011). Strain is less load-dependent compared to the traditional parameters such as EF (Shah and Solomon 2012, Dandel et al. 2009).

Strain measures myocardial deformation and is expressed as a percentage (Shah and Solomon 2012, Gorcsan and Tanaka 2011, Dandel et al. 2009). The concept of Lagrangian strain not only takes into account the initial and final length of an object before and after deformation, but also during the process of deformation (Dandel et al. 2009). It can be stated using the following formula: $\varepsilon = L - L_0 / L_0$ and was initially used to measure LV deformation but now it can be applied to the LA; where ε = strain, L = baseline length and L = final length after myocardial deformation (Shah and Solomon 2012, Dandel et al. 2009). By convention, thickening and shortening of a given myocardial segment related to its initial length is described by positive and negative strain values, respectively (Dandel et al. 2009). As the myocardium contracts, shortening and thickening of the wall occurs and thus one can measure the radial thickening or positive radial strain, circumferential shortening or negative circumferential strain as well as longitudinal shortening, or negative longitudinal strain during ventricular systole (Figure 1.1 and 1.2) (Shah and Solomon 2012, Dandel et al. 2009).

Different echocardiographic techniques can be used to measure myocardial strain (Marwick 2006). These include M-mode techniques, tissue Doppler and speckle tracking methods. There are inherent challenges with each of the aforementioned modalities. The main limitations of tissue derived strain include signal noise, underestimation, angle dependence, through–plane motion and respiratory drift. These technical limitations can be minimised by careful image acquisition. Further, this technique has been validated with sonomicrometry and correlation with magnetic resonance imaging (MRI) has been confirmed. To overcome the aforementioned limitations, the speckle tracking technique emerged (Dandel et al. 2009, Marwick 2006). Speckles are natural acoustic markers (20 to 40

pixels in size), distributed throughout the myocardium (Dandel et al. 2009). The movement of the speckles represents motion of the tissue. Speckles can be tracked from frame to frame in the 2D ultrasonic image with the aid of specialised software. Thus, 2D strain and strain-rate can be calculated by tracking the motion of these speckles. The major limitation of this technique is the necessity of high image quality and adequate frame rate. Additionally, strain values derived from speckle tracking echocardiography (STE) have low inter-observer variability (Dandel et al. 2009). The overall limitation of all the aforementioned techniques is a lack of consensus regarding normal reference values for strain due to considerable inter-vendor measurement variability (Lang et al. 2015).

Strain imaging in contrast to traditional parameters of LA, LV and RV functions such as volume and ejection fraction is able to detect subclinical disease in these chambers in pathologic states such as MR, aortic regurgitation and stenosis, hypertension, diabetes, ischaemic heart disease, chemotherapy induced cardiac dysfunction and cardiomyopathies (Moustafa et al 2016, Dandel et al. 2009).

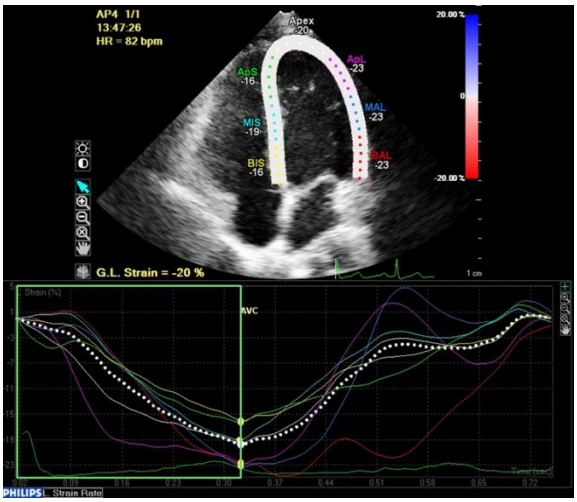


Figure 1.1 Apical 4C view depicting LV peak longitudinal strain.

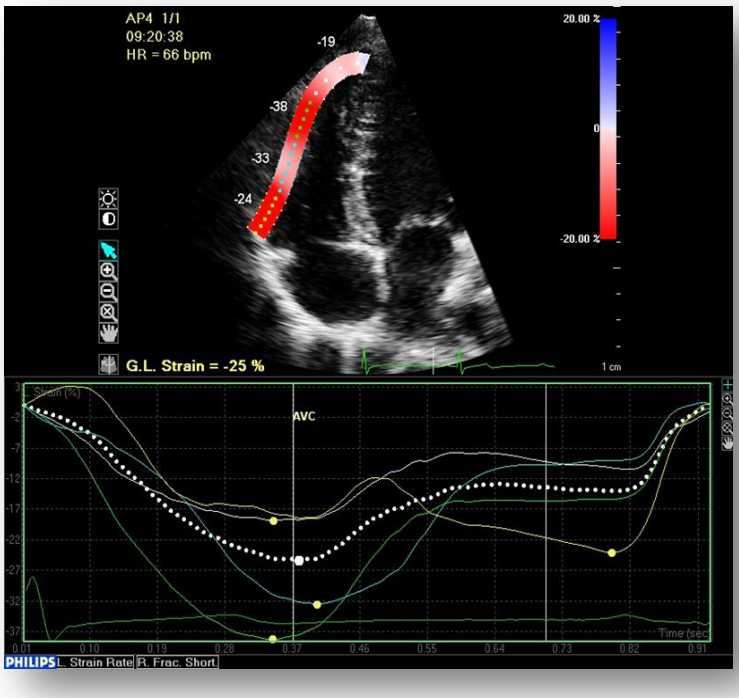


Figure 1.2 Apical 4C view depicting RV free wall peak longitudinal strain.

1.3.3 Left atrial speckle tracking echocardiography

The physiology of the LA can be depicted in the LA strain curves derived by speckle tracking echocardiography (Figure 1.3) (Viera et al. 2014). The reservoir phase, which corresponds to isovolumetric contraction, ejection, and isovolumic relaxation of the LV, results in stretching of the LA as it receives blood from the pulmonary veins (Viera et al. 2014). This results in an increased LA longitudinal strain (Ɛ), ultimately reaching a positive peak at end of ventricular systole, as the LA filling ends (Viera et al. 2014). The descent of the mitral annulus as the LV contracts in systole also influences this phase (Viera et al. 2014). During the conduit phase as the LA empties its contents passively into the LV in early diastole the LA Ɛ plateaus (LA diastasis) (Viera et al. 2014). Finally, as the LA contracts and actively pushes blood into LV the LA wall shortens resulting in decrease in LA Ɛ (Viera et al. 2014).

Speckle tracking echocardiography has been found to be a feasible and reproducible technique in the evaluation of longitudinal LA strain (Ɛ) thus providing an additional new parameter for LA function assessment (Kowallick et al. 2014, Pinton et al. 2009). This may enable earlier identification of subclinical LA dysfunction which has additional prognostic implications in various disease states (Hoit et al. 2014).

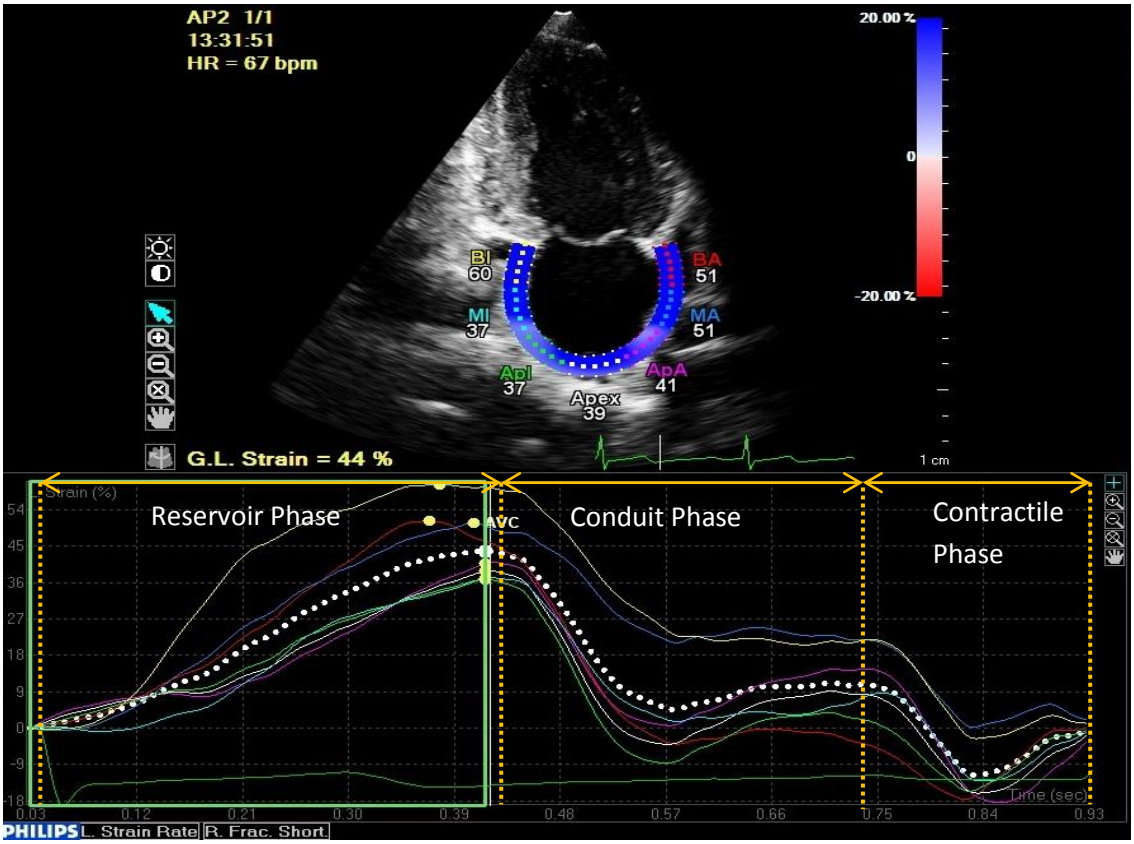


Figure 1.3 Apical 2C view of the LA depicting reservoir, conduit and contractile phases.

1.3.4 LA volumetric and strain parameters in a normal black population - Do data exist?

Recent data from the EchoNoRMAL study has highlighted the possibility that echocardiographic measurements of LA size may differ among various ethnic populations with black Africans having lower LA diameters than Caucasians (Aune et al. 2015). For example; in a 50-year old African men the average LA size was 4.0 cm compared to 4.5 cm in a Caucasian male of the same age. Reference values for LA parameters in the recent chamber guidelines have been derived largely from studies done in Caucasians (Lang et al. 2015). Additionally, there is still no consensus on normal values pertaining to LA Ɛ, as there are limited multi-ethnic

studies on different vendor platforms. There are no studies which have documented normative data on LA volumes indexed to body surface area in black Africans. This is required to ensure that application of current cut-off values for LA parameters defined in guidelines can be accurately applied to this population. Further, there is no current evidence that ethnicity may affect Ɛ values of the LA since this has not been studied previously. Thus, we sought to establish normal reference ranges of LA volumetric parameters and peak positive LA Ɛ ($Ɛ_{R,}$ LA reservoir function) and peak negative LA Ɛ ($Ɛ_{CT,}$ LA contractile function) in a black African population. This aspect of the study will be addressed in Chapter 3 of the thesis. Further, the impact of healthy aging has not been studied in a normal black population in relation to the LA size and function.

1.3.5 Effects of age on LA volumetric and strain parameters

As the number of older individuals increase in our population it becomes relevant to develop reference values for various cardiovascular parameters to accurately risk-stratify these individuals. This would help to correctly distinguish normal aging from pathological states. In healthy humans, aging is associated with progressive cardiac structural and functional alterations. Aging is associated with LV diastolic dysfunction secondary to increase in LV wall thickness and HF with resultant LA enlargement and functional abnormalities such as atrial fibrillation (Lakata and Levy 2003, Gerstenblith et al. 1997). Further, aging per se causes intrinsic LA dysfunction (Casaclang-Verzosa et al. 2008). Due to these changes, the need for age-related reference values for CVS risk stratification becomes imperative (Lakata and Levy 2003, Gerstenblith et al. 1997).

Age-related changes in the LA have been studied extensively in white populations using traditional parameters such as LA size, volumes, and more recently, 2D strain (Boyd et al. 2011, Aurigemma et al. 2009, Thomas et al. 2002, Spencer et al. 2001). The data from the aforementioned studies have been discrepant with reference to LA volumetric parameters. Thomas et al. attributed the lack of change in volumes in their study to normal healthy aging whereas others have demonstrated increase in LA volumes and size with normal aging ((Aurigemma et al. 2009, Casaclang-Verzosa 2008, Spencer et al. 2001). The limited data regarding LA Ɛ have shown a decline in LA peak systolic Ɛ with aging (Boyd et al. 2011).

There are no age-related reference values for LA volumes or strain in Africans. Thus, we sought to determine the effects of healthy aging on LA function in a black population with the aid of both traditional and newer echocardiographic techniques of 2D strain and this will be elaborated further in Chapter 4. Establishing the normative data was crucial for us to study atrioventricular mechanics in CRMR.

1.4 Atrioventricular mechanics in chronic rheumatic mitral regurgitation

The consequence of the chronic volume overload of MR on the LA and the LV results in chamber dilatation of these chambers (Bonow et al. 2102). The LV develops eccentric hypertrophy as a result of neuro-hormonal activation resulting in a compensated state (Bonow et al. 2012, Gaasch and Meyer 2008). During this period the patient remains asymptomatic at the expense of the compensatory mechanisms (Bonow et al. 2012). However, there are certain deleterious effects, such as toxic effects of noradrenalin, resulting in cell loss secondary to myocyte

necrosis and apoptosis (Tsutsui et al. 1994). Additionally, LV dilatation results from myocardial slippage secondary to loss of interstitial collagen (Bonow et al. 2012, Tsutsui et al. 1994). Ultimately, LV dysfunction supervenes and the transition to a decompensated ventricle and HF occurs (Bonow et al. 2012, Tsutsui et al. 1994).

Similarly, the LA dilates secondary to neuro-hormonal activation. Volume overload is a stressor that results in numerous adaptive and maladaptive changes (Casaclang-Verzosa et al. 2008, Cohn et al. 2000). On a microscopic level these comprise increased myocyte hypertrophy and growth, necrosis, apoptosis and increase extracellular matrix production with interstitial fibrosis (Casaclang-Verzosa et al. 2008, Cohn et al. 2000). There are also changes at the cellular ionic channel level and in energy generation and consumption (Casaclang-Verzosa et al. 2008, Cohn et al. 2000). Finally, activation of the fetal gene programme results in an increase in atrial hormone expression (Casaclang-Verzosa et al. 2008, Cohn et al. 2000). All of these processes eventually culminate in LA remodelling with resultant structural and functional alterations including changes in LA size, compliance and atrial fibrillation (Casaclang-Verzosa et al. 2008, Cohn et al. 2000). The LA eventually decompensates and fails, as it becomes fibrotic and noncompliant and reaches the descending limb of the Frank-Starling curve. Additionally, in rheumatic MR the LA may be directly involved by the rheumatic process and result in a giant, fibrotic, calcified and noncompliant LA as a result of ongoing inflammation (Shriki et al. 2011, Edwards et al. 2006, Roberts and Vermani 1978, Plaschkes et al. 1971).

Imaging has been used to study the compensated and transition states of the LV and the LA. In degenerative MR there is an initial increase in LV peak global strain due to volume overload with later decline as LV decompensation occurs (Klein 2013, Witkowski et al. 2012). Strain is able to detect subclinical changes in the LV in the

asymptomatic phase before decline in EF and thus may be a more sensitive marker for follow-up of LV function (Gunjan et al. 2012, Yurdakal et al. 2011, Lee and Marwick 2007). In rheumatic MR, LV dysfunction may be a result of not just volume overload but also due to intrinsic myocardial involvement by the rheumatic process (Choi et al. 2006, Barlow 1987, Stollerman et al.1975). There are limited data pertaining to the LV deformation parameters in CRMR. In a study of patients with rheumatic MR, LV longitudinal strain was found to be diminished (Gunjan et al. 2012). We thus studied LV deformation with strain imaging in a black population with rheumatic MR.

Several studies have evaluated the three LA mechanical phases in MR by non-invasive tools using 2D echocardiography and strain imaging (Borg et al. 2009, Ren et al. 2014, Yurdakul et al. 2014, Debonnaire et al. 2013, Mustafa et al. 2011, Aksakal et al. 2012). Discrepant findings were noted in the aforementioned studies. LA reservoir function was depressed in most studies Debonnaire et al. 2013, Aksakal et al. 2012, Mustafa et al. 2011) while conduit function was increased in others (Mustafa et al.2011, Borg et al. 2009). Results regarding booster function show conflicting results between studies (Ren et al.2014, Askakal et al. 2012, Mustafa et al.2011, Borg et al. 2000). Ren et al, Yurdakul et al. and Borg et al. reported preserved booster function based on volumetric parameters, whereas Mustafa et al. and Askakal et al. reported decline in booster function. The possible reasons for the discrepant observations may be due to a variable combination of MR severity, aetiology, LA and LV compliance as well as their intrinsic characteristics.

Few studies have evaluated LA mechanics in MR of rheumatic origin. A study of rheumatic MR showed a decrease in reservoir and booster function in these patients but preserved conduit function on volumetric analysis (Askakal et al. 2012). Further,

their study showed a decrease in longitudinal strain in all three LA mechanical phases (Askakal et al. 2012). Therefore, strain imaging may prove useful for detection of subclinical LA dysfunction in MR, before a change in the more traditionally used marker of adverse outcome such as LA volume; and thus aids in earlier risk stratification for surgery.

The current guidelines, largely derived from literature around degenerative MR, recommend surgical intervention based on LV dimensions and EF (Nishimura et al. 2014). An enlarged LA has been known to be associated with adverse outcome in MR (Le Torneau et al. 2010, Borg et al. 2009). Recent valvular heart disease guidelines recommend new onset atrial fibrillation as an indication for surgery (Nishimura et al. 2014). However, LA size or volume does not feature prominently, although they are likely earlier markers of LA dysfunction. Further, the current guidelines do not as yet include strain cut-off values for the LA or LV as indications for surgery.

In a normal individual LA and LV chambers interact synergistically to maintain adequate cardiac output and this interaction becomes of utmost importance in disease states where LV dysfunction is present as the atrial contribution to total stroke volume (SV) becomes significant (Todaro et al. 2012). This intimate physiologic interaction in systole and diastole between these chambers results from their close anatomic connection (Silbiger et al. 2012). LA and LV longitudinal fibres insert into the common mitral annulus and hence the descent of the annulus during LV systolic contraction, allows filling of the LA during LA diastole. The contraction of the LA fibres during LA systole contributes to LV filling at end-diastole (Silbiger et al. 2012). It would seem more insightful to study both chambers simultaneously with strain imaging due to interdependence of each chamber in systole and diastole on

each other and to determine the dysfunction of LA and LV in MR. We therefore, sought to study LA and LV mechanics in moderate or severe CRMR with the aid of traditional volumetric parameters and newer echocardiographic techniques of 2D strain. We further hypothesised that LA dysfunction may precede LV dysfunction in CRMR due to both the fact that its thinner wall would make it more susceptible to haemodynamic stress and that it may be directly involved in the rheumatic process. The above-mentioned aspects will be discussed in detail in Chapter 5 of the thesis.

In addition to the intimate anatomic relationship between the LV and the LA, there exists a strong interdependence between the RV and LV since both share a common septum. We therefore decided to study the RV function in CRMR and explore LV-RV interaction in this disease. The reason for this will be elaborated further in the following section.

1.5 Right ventricular functional assessment in chronic rheumatic mitral regurgitation

RV function is an important prognostic determinant in various cardiovascular and pulmonary diseases, including MR (Hyllen et al. 2014, Fine et al. 2014, Burgess et al. 2002, D'Alonzo et al.1991). The RV has been poorly studied compared to the LV, which has established normative data for dimensions, volumes, mass and function (Hyllen et al. 2014, Rudski et al. 2010). The complex geometry of the RV presents challenges to its accurate structural and functional assessment, and there is limited data on RV function in MR (Hyllen et al. 2014, Rudski et al. 2010). The

prognostic value of RV functional assessment and its utility in guiding indications for surgery in MR do not feature in the standard guidelines (Nishimura et al. 2014). Multiple methods exist for assessment of RV systolic function. These include tricuspid annular plane systolic excursion (TAPSE), tissue Doppler derived S' and RV fractional area change (FAC). One or more of these parameters can be used to assess RV function (Lang et al. 2015). These parameters have several limitations. TAPSE is unable to measure global RV function, is influenced by tricuspid regurgitation and image quality (Finel et al. 2014, Rudski et al. 2010). S' only measures the longitudinal function of the RV. S' is also dependent on image quality, the volume of tissue sampled, and myocardial tissue motion - all potentially resulting in measurement variability (Fine et al. 2014, Rudski et al. 2010). Additionally, RV FAC is reliant on good image quality (Lang et al. 2015).

Thus RV strain imaging is increasingly being used, as it enables assessment of global RV function and detection of subclinical disease, in a reproducible manner (Fine et al. 2014, Rudski et al. 2010). RV strain analysis by speckle tracking echocardiography has been shown to be useful for the assessment and management of congenital heart disease, valvular heart disease, and various interventional procedures such as cardiac resynchronisation therapy and balloon mitral valvuloplasty (Todaro et al. 2015, Forsha et al. 2014, Kumar et al. 2014). There is however a paucity of data regarding RV functional and strain parameters in CRMR.

The RV and the LV have an interdependent relationship. This relationship stems from the anatomic continuity between the superficial fibres of the RV and LV (Ho et al. 2006). This anatomic relationship between the RV and LV represents the physiological basis for RV free wall traction caused by contraction of the LV (Haddad

et al. 2008). Assessment of RV function provides incremental information for the decision making process regarding surgical intervention in MR (Hyllen et al. 2014). Thus, we felt it useful to study the RV using traditional and newer strain imaging techniques, in patients with CRMR. Further, we explored the RV and LV interaction in CRMR using strain imaging, given that biventricular functional impairment is a predictor of both CV and overall survival postoperatively (Le Torneau et al. 2013a,b). CRMR results in pulmonary hypertension (PHT) and secondary RV remodelling. The RV function is usually maintained until the latter stages of its function when LV dysfunction occurs. Neuro-hormonal factors from the LV abnormality and secondary PHT may also influence development of RV dysfunction. Further, the RV akin to the LV myocardium may be directly involved by the rheumatic process (Barlow 1987, Roberts and Vermani 1978, Stollerman et al.1975). These concepts shall be discussed further in Chapter 6 of this thesis.

Multimodality imaging and biomarkers are increasingly being used in MR for accurate quantification of valve lesion severity, especially in cases incompletely evaluated by echocardiography alone (Banerjee et al. 2014, Bergler-Klein et al. 2014, Rajani et al. 2014, Leong et al. 2013, Van De Heyning et al. 2012, Lee and Marwick 2007). Increasingly, cardiac MRI is being utilised in MR for: assessment of regurgitant fraction (RF) using phase contrast mapping and evaluation of cardiac chamber volumes; and prognostication and surgical risk stratification based on the presence or absence of LV fibrosis on late gadolinium enhancement (LGE) and T1 mapping (Kammerlander et al. 2016, Uretsky et al. 2015, Edwards et al. 2014, Van De Heyning et al. 2014). We therefore investigated the role of echocardiography, cardiac MRI and biomarkers of collagen turnover in CRMR in the thesis and these aspects are elaborated below.

1.6 Role of cardiac magnetic resonance imaging in evaluation of LV function and assessment of mitral regurgitation severity

CMR is advantageous over conventional echocardiography in assessment of valve lesions (Kar and Sharma 2015). It has higher spatial and temporal resolution and is less operator dependent (Kar and Sharma 2015). There is no dependence on body habitus (Kar and Sharma 2015). Quantification of LV volumes is much more accurate (Kar and Sharma 2015). Furthermore, it can be used as a surrogate for LV fibrosis (Kammerlander et al. 2016, Doltra et al. 2013, Di carli et al. 2012). The main limitations of MRI are related to cost, lengthy study time, and lack of compatibility with magnetic devices (Kar and Sharma 2015).

1.6.1 Role of CMR in evaluation of cardiac volumes and function

CMR is regarded as a gold standard for the quantification of LV volumes and function (Myerson 2012). In this regard it is highly accurate and reproducible. Unlike echocardiography it measures volumes in three dimensional planes. Semi-automated algorithms make the measurements of volume and function more reliable and reproducible compared to echocardiography, where measurements are largely operator-dependant and thus prone to variations (Kar and Sharma 2015) (Figure 1.4). However, CMR requires the correct placement of the basal ventricular image slice and careful contour placement while post-processing, to accurately differentiate atrial and ventricular chambers (Myerson 2012). Erroneous inclusion or exclusion of the basal slice, incorrect contour placement and chamber delineation can result in

significant errors in volume calculation. The prognostic role of increased LV volumes and dimensions in MR is well recognised (Nishimura et al. 2014, Gaasch and Meyer 2008). Thus, accurate quantification of volumes by CMR makes it a useful tool for ventricular function assessment and especially, serial follow-up of MR as it has a long asymptomatic period (Bonow et al. 2012, Myerson 2012).

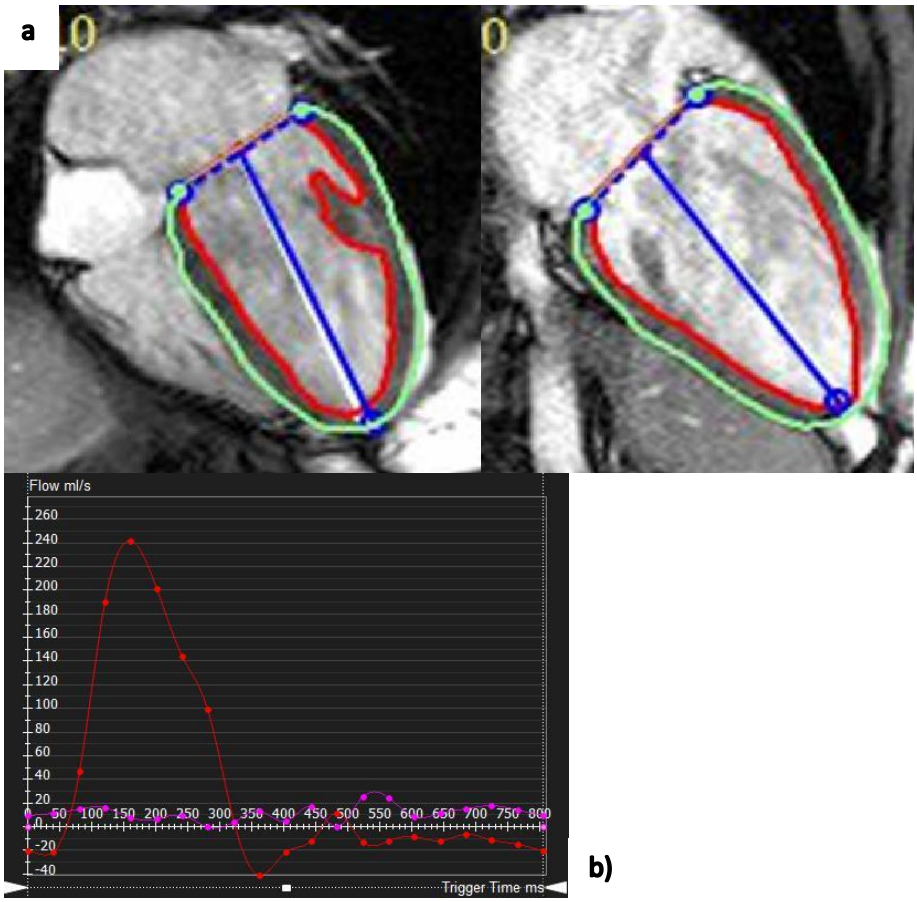


Figure 1.4 a) Measurement of LV end-diastolic and end-systolic volumes on cardiac MRI. b) Measurement of aortic flow using phase contrast Imaging.

1.6.2 CMR for quantification of mitral regurgitation

CMR is a useful adjunctive tool to echocardiography in assessment of valve lesions (Kar and Sharma 2015, Myerson 2012). In MR its main use is for accurate quantification of regurgitation severity and assessment of ventricular volume and function (Myerson 2012). Additionally, it can provide anatomical information pertaining to leaflet morphology and function equivalent to trans-oesophageal echo. The effective regurgitant orifice area can be directly planimetered in some patients with less complex mitral valve morphology. Cine imaging is useful for directly visualising valve anatomy and motion and hence provides information regarding mechanism of regurgitation. Additionally, the direct visualisation of flow allows one to assess location, direction of jet as well as measurement of jet width and vena contracta. CMR, in contrast to echocardiography has the ability to directly quantify flow and velocity using through–plane phase contrast velocity mapping (Figure 1.4). This technique unlike echocardiography or invasive catheterisation does not require complex equations to calculate regurgitant volumes (RegV) and fractions. MR severity can be easily assessed by quantifying RF using the following simple formulae: (regurgitant volume/forward volume × 100%) (Edwards et al. 2014, Myerson 2012). The difference between LV, SV and the aortic forward stroke volume is used to derive the RegV. A regurgitant fraction greater than 40% is regarded as significant regurgitation. Quantification of flow by CMR has shown accuracy when compared to in vitro studies and has a good correlation with in vivo measurements. CMR has a few limitations when assessing valve lesions which include the need to acquire images over several cardiac cycles resulting in suboptimal visualisation of small objects such as vegetations. The thin nature of

valve leaflets makes them prone to partial volume effects resulting in poor visualisation and inaccurate effective regurgitant orifice area (EROA) assessment may result from misalignment of imaging plane at the true mitral leaflet tips. However, CMR still remains advantageous over echocardiography in MR assessment, whereas, a single CMR scan is able to provide pertinent information regarding valve anatomy, function, severity of regurgitation, LV volumes and function; and the presence of myocardial scarring.

Recently, CMR has been used as an adjunctive non-invasive imaging modality to characterise the severity of degenerative MR (Kar and Sharma 2015, Uretsky et al. 2015, Van De Heyning et al. 2013). Discordance was noted between the two techniques (CMR and echocardiography) in one study, with MRI classifying a significant 30% of the lesion as moderate that were assessed as severe by echocardiography (Uretsky et al. 2015). The results from prior smaller studies have shown equivalence or superiority of MRI in assessing MR severity (Van De Heyning et al.2013, Sukpraphute 2012, Uretsky et al. 2010, Cawley and Otto et al. 2009, Hellgren et al. 2008, Gelfand et al. 2006). No studies have examined whether similar discrepancies in the assessment of MR severity applies to rheumatic MR, where the MR jets are predominantly eccentric and the proximal isovelocity surface area (PISA) method is thus not always reliable in assessment of MR severity (Enriquez-Sarano et al.1993). Therefore, we studied a subgroup of patients with CRMR using both echocardiography and MRI.

1.7 CMR for detection of fibrosis

CMR technology has enabled us to characterise tissue in various cardiac pathologies (Doltra et al. 2013, Di Carli et al. 2012). LGE is a widely used technique for detection and quantification of fibrosis in myocardial tissue. Extracellular volume (ECV) expansion may have prognostic value in predicting mortality and other composite end-point (Wong et al. 2012). Gadolinium is an extracellular agent (Doltra et al 2013, Di Carli et al. 2012). The extracellular space expands as a result of an infiltrative disease process, fibrosis or oedema, and this resultant increase in the ECV allows gadolinium to accumulate in the extracellular space. The gadolinium washes out slowly and is seen as an area of enhanced myocardium on delayed T1-weighted imaging compared to normal myocardium (Di Carli et al. 2012). Therefore, diseases that result in diffuse fibrosis of the myocardium may be missed by this technique as there a lack of a normal reference myocardial region. To overcome this limitation, contrast-enhanced T1 mapping has been developed to detect diffuse fibrosis (Jellis et al. 2010). Additionally, T1 mapping has proven to be a useful technique for assessment of both macroscopic and microscopic fibrosis (Kammerlander et al. 2016).

In chronic degenerative MR detection of fibrosis by LGE may help risk-stratify patients for earlier surgery before irreversible myocardial damage supervenes (Van De Heyning et al. 2014, Edwards et al. 2014). The prevalence of fibrosis has not been studied in CRMR; previous studies have noted involvement of the posterobasal region of the LV by the rheumatic process (Barlow 1987). Sepulveda et al. and Choi et al. reported diffuse, mesocardial and heterogeneous enhancement of myocardium by LGE in ARF and patchy delayed enhancement of the LV in chronic rheumatic in a

case report, respectively (Sepulveda et al. 2013, Choi et al. 2006). Therefore, based on the above-mentioned observations and findings we speculated that there may be LV fibrosis in CRMR and this may have a similar relevance as in degenerative MR.

1.8 Biomarkers of collagen turnover in mitral regurgitation

It is well known that increased morbidity and mortality is associated with myocardial remodelling and chamber dilation irrespective of aetiology (Bonow et al. 2012). The LV geometry and structural integrity of myocardial cells is maintained by myocardial fibrillar collagen matrix (Bonow et al. 2012, Li et al. 2000, Spinale et al. 2000). The two most abundant collagen precursors in the heart include procollagen I and III (Lopez et al. 2010). Circulating biomarkers of collagen metabolism are generally divided into two broad groups; these include biomarkers of collagen degradation and biomarkers of collagen synthesis (Lopez et al. 2010). Alteration in collagen matrix occurs in various cardiac diseases (Bonow et al. 2012, Li et al. 2000, Spinale et al. 2000). LV remodelling results from alterations in collagen volume and collagen organization due to a complex interplay between matrix metalloproteinase (MMP) activation and tissue inhibitors of metalloproteinase (TIMP) expression (Mann and Taegtmeyer 2001). Fibrosis is characterised by decreased collagen breakdown and increased collagen synthesis (Bonow et al. 2012). MMPs are endogenous enzymes involved in the degradation of collagen (Bonow et al. 2012, Lopez et al. 2010, Li et al. 2000, Spinale et al. 2000). Their action is inhibited by TIMPs. MMP activity is controlled by endogenous physiological inhibitors and substrate interaction (Bonow et al. 2012, Lopez et al. 2010, Li et al. 2000, Spinale et al. 2000). They are

also regulated at pre- and post - transcriptional levels (Li et al. 2000, Spinale et al. 2000). Therefore, the progression of the fibrotic process in the myocardium is determined by the interplay of MMPs, the tissue inhibitors of MMPs (TIMPs) and their regulators (Bonow et al. 2012, Lopez et al. 2010, Li et al. 2000, Spinale et al. 2000). Increased MMP activity leads to excessive degradation of extracellular matrix (ECM) and lead to slippage of myocyte bundles and/or individual myocytes within the LV wall resulting in LV remodelling, dilation and dysfunction (Mann and Taegtmeyer 2001). The MMPs rise in the HF state and contribute to the matrix remodelling process (Bonow et al. 2012, Lopez et al. 2010). The MMPs increase in HF of any aetiology (Bonow et al. 2012, Li et al. 2000). The following MMPs increase more than others in heart failure: MMP-9, 3, 13 and 14 (Bonow et al. 2012, Li et al. 2000, Spinale et al. 2000).

Chronic MR results in volume overload which in turn activates a series of downstream pro-fibrotic pathways (Chemaly et al. 2013). The exact pathophysiology of fibrosis in MR still remains poorly understood (Van De Heyning et al. 2014). Histopathology studies have shown the presence of extensive interstitial fibrosis in the hearts of patients with severe MR; sometimes even greater than that in pressure overloaded states such as severe aortic stenosis and hypertensive heart disease (Fuster et al. 1977). In contrast more recent work in animals, report increased fibrosis in pressure loaded ventricles as opposed to volume loaded ventricles (Chemaly et al. 2013). This is explained on the basis of increased oxygen supply-demand ratio in the pressure loaded ventricle resulting in ischaemia and fibrosis, as well as reduced activation of pro-fibrotic pathways in reactive fibrosis (Chemaly et al. 2013).

The increase in wall stress in chronic MR has also been implicated in ventricular fibrosis as a result of neuro-hormonal activation (Edwards et al. 2014). Yet other studies have attributed lack of fibrosis in volume overload states to activation of alternative pathways such as the Kallikrein-kinin system resulting in an increase in enzymes such as matrix metalloproteinase (MMP). This activation results in collagen degradation rather than synthesis as the primary abnormality in MR (Wei et al. 2012, Janicki et al. 2005). A study on CRMR and biomarkers found increased MMP-1 activity in patients with chronic MR (Banerjee et al. 2014).

Novel biomarkers, in the context of rheumatic valve disease, are procollagen type1C-peptide (PIP) and procollagen III N-Terminal propeptide (PIIINP) (Banerjee et al. 2014). Type-I collagen, which is ubiquitous in valve and other tissues, is initially synthesized as procollagen I (Bonow et al. 2012, Lopez et al. 2010). This protein undergoes cleavage of amino-terminal and carboxy-terminal ends, to produce the triple helical monomers (Bonow et al. 2012, Lopez et al. 2010). PIP is released into the blood stream during collagen synthesis (Bonow et al. 2012, Lopez et al. 2010). PIP has been shown to increase in hypertensive heart disease, HF, and hypertrophic cardiomyopathy (Lopez et al.2010, Morillas et al. 2013, Ho et al. 2010). Procollagen III undergoes similar metabolism by collagen proteinases and the propeptide PIIINP is released into the blood stream. In ischaemic heart disease and idiopathic dilated cardiomyopathy, an association has found between PIIINP concentrations and myocardial collagen type II content (Lopez et al. 2010). Banerjee et al. reported an increase in activity of PIP and PIIINP in CRMR (Banerjee et al. 2014). Therefore, we studied biomarkers of collagen synthesis (PIP and PIIINP) and breakdown (MMP-I and TIMP-I) in CRMR.

In summary, a paucity of data exists in CRMR on:

1) Presence of myocardial fibrosis by LGE and biomarkers of collagen turnover on MRI and;

2) A comparison of CMR and echocardiographic techniques for assessment of rheumatic MR severity. These findings are presented in Chapter 7 of the thesis.

The aforementioned biomarkers may be used as non-invasive tools for the diagnosis of asymptomatic valve disease, therapeutic targets for anti-remodelling therapy and follow-up of patients with valvular heart disease such as MR (Banerjee et al. 2014, Lopez et al. 2010, Khan et al.2006, Mann and Taegtmeyer 2001, Spinale et al. 2000). Anti-remodelling therapy in hypertension and HF with angiotensin-receptor blockers (ARB) and aldosterone-receptor antagonists have been shown to decrease levels of PIP and PIIINP (Lopez et al. 2010). Therefore, anti-remodelling therapy may be used in MR to halt cardiac remodelling and thus prevent progression to HF. These findings are presented in Chapter 7 of the thesis.

1.9 Anti-remodelling therapy for heart failure secondary to chronic rheumatic mitral regurgitation

In chronic MR the persistent volume overload results in activation of compensatory mechanisms which include activation of SNS-RAAS, the Frank-Starling mechanism and eccentric hypertrophy (Bonow et al. 2012, Tsutsui et al. 1994). Over the long-term, these compensatory mechanisms are deleterious and culminate in myocardial dysfunction and failure (Bonow et al. 2012, Tsutsui et al. 1994). These pathways have provided the rationale for benefit of medical therapy in MR. Most of above-mentioned trials were small studies involving vasodilators such

as ACEI and beta-blockers in degenerative MR and have been inconclusive (Ahmed et al. 2012, Carabello 2008, Evangelista 2007).

Beta-blockade has demonstrated efficacy in reducing mortality in patients with cardiac failure due to non-valvular causes (Yancy et al. 2013). In canine models with chronic experimental MR chronic beta-blocker therapy improves LV function (Tsutsui et al. 1994). A pilot study involving patients with moderate to severe MR on beta-blocker therapy (metoprolol) was conducted over a 2-week period. CMR was used to follow-up this cohort. No reduction in RegV was demonstrated, however, LV work was reduced by beta-blocker therapy (Stewart et al. 2008). A larger study was therefore proposed to assess the effect of beta-blockers on LV function and symptoms due to MR (Stewart et al. 2008). A subsequent trial was published, involving patients with moderate to severe, degenerative MR on beta-blocker therapy, (metoprolol) over a 2-year follow-up. LV function was assessed using CMR. Improvements were found in LVEF and LV early diastolic filling rate. No change in LV end-diastolic volume (EDV) or LV end-systolic volume (ESV) was noted (Ahmed et al. 2012).

In addition to beta-blockers, the introduction of ACEIs or ARBs and spironolactone have resulted in further dramatic declines in mortality due to systolic HF due to non-valvular causes (Yancy et al. 2013). Limited data exist on their use in valvular heart disease.

ACEIs have been used in the treatment of systolic HF with significant reductions in morbidity and mortality (Yancy et al. 2013). In the context of MR, benazepril was used in dogs with moderate to severe MR and showed improved survival (Kittelson et al. 2009). Wisenbaugh et al. studied the effects of captopril in

thirty-two patients with severe isolated MR over a 6-month period, and found no difference in LV diameters or EF when compared to placebo (Wisenbaugh et al. 1994b). In a trial on humans assessing a combined population of patients with moderate to severe aortic regurgitation and MR, a significant reduction in regurgitant fraction, LV end-systolic and EDVs and LV mass, was noted when quinapril was used (Schön et al. 1994).

ARBs seem to produce a similar beneficial effect. In a, small study on the use of losartan for the treatment of MR, a modest but variable improvement in the severity of MR was noted. Specifically, the RegV and the effective regurgitant orifice decreased and the effect was durable for one month (Dujardin et al. 2001). Another trial assessing moderate degenerative and rheumatic MR also found a beneficial effect with losartan over a 6-week period with regards to MR severity, LA size, and LV function (Sekuri et al. 2008).

Spironolactone has been evaluated in the context of systolic HF resulting in favourable LV remodelling and a decline in morbidity and mortality through aldosterone antagonism (Yancy et al. 2013, Soberman and Weber 2000). The mortality reduction in HF was attributed to a decrease in sudden death and progression of HF (sudden death has not been reduced by any other agent used in systolic HF) (Soberman and Weber 2000). No human trials with spironolactone in MR have been noted in the literature. In dogs however, a study investigating spironolactone in moderate to severe MR resulted in a significant reduction (55%) in a composite end-point of cardiac-related death, euthanasia, or severe worsening of MR (Bernay et al. 2010).

Studies have not evaluated the effects of combination therapy (ACEI/ARB, beta-blockers, aldosterone-receptor antagonist) in HF secondary to MR. There is proven reduction of mortality and morbidity with combination anti-remodelling therapy in HF resulting from ischaemia and cardiomyopathies (Yancy et al. 2013, Merlo et al. 2011). Therefore, we hypothesised that a similar benefit may be derived in HF secondary to rheumatic MR. Our patients' clinical profiles differ significantly from those of the western world. Timeous surgical intervention is hampered by late presentation to a tertiary care centre as a result of misdiagnosis at a primary health care level, as well as a general lack of cardiothoracic services. A substantial proportion of these patients are thus admitted in HF and are treated with medical therapy. We studied the effect of combination anti-remodelling therapy in terms of clinical outcome; and traditional as well as newer echocardiographic parameters such as 2D strain in a subset of patients with CRMR. Combined anti-remodelling therapy would potentially offer an alternative option to these patients who are at high risk for need for surgery or are not inclined to undergo surgical intervention. Further, the benefit of anti-remodelling therapy may extend to asymptomatic patients with significant MR to stabilise the disease process and thus delay the time to surgery or perhaps even obviate the need for surgical intervention. The finding of this study are presented in Chapter 8 of this thesis.

In summary, CRMR is a commonly occurring, unique disease associated with significant morbidity and mortality. In this thesis I, have studied the demographic and clinical profiles of an evolving disease because the population with rheumatic MR ages and ARF recedes in a peri-urban hospital. We also established age-related normative data in a black population regarding LA volumetric and strain parameters. This allowed me to study the atrio-ventricular mechanics in CRMR. RV

plays an important prognostic role in MR and therefore part of this thesis focused on the study of RV function in CRMR. Older literature has alluded to rheumatic MR not only being a disease of the mitral valve, but also the myocardium, however this concept has not been extensively explored by modern imaging and biomarkers. Therefore, we studied CRMR with not only conventional echocardiography, but with cardiac MRI also which entailed two main aspects - quantification of CRMR severity and prevalence of LV fibrosis by LGE. We further evaluated the role of biomarkers in CRMR and their relation to imaging parameters. There have been a few studies that aimed to provide answers regarding the use of medical therapy in degenerative MR but patients with CRMR were under represented and thus the role of combination anti-remodelling therapy in CRMR was explored.

1.10 Study aims

The aims of this study were:

a) To examine our contemporary patient population with moderate or severe rheumatic mitral regurgitation specifically to detect the changing demographic and echocardiographic profile at Chris Hani Baragwanath Academic Hospital (Chapter 2).

b) To establish normal reference ranges of left atrial volumetric parameters and peak positive LA ε ($\varepsilon_{R,}$ left atrial reservoir function) and peak negative left atrial ε ($\varepsilon_{CT,}$ left atrial contractile function) in a black African population (Chapter 3).

c) To determine the effects of healthy aging on left atrial function in a black population with the aid of both traditional and newer echocardiographic techniques of two-dimensional strain (Chapter 4).

d) To study the left atrial and left ventricular mechanics in moderate or severe chronic rheumatic mitral regurgitation with the aid of traditional volumetric parameters and newer echocardiographic techniques of 2D strain (Chapter 5).

e) To study right ventricle function using traditional and the newer two-dimensional strain imaging techniques in chronic rheumatic mitral regurgitation (Chapter 6).

f) To study the echocardiographic and cardiac magnetic resonance characteristics of patients with chronic rheumatic mitral regurgitation and their association with biomarkers (Chapter 7).

g) To study the effect of anti-remodelling therapy in chronic rheumatic mitral regurgitation, in terms of clinical outcome and echocardiographic parameters (Chapter 8).

Chapter 2

The changing spectrum of chronic rheumatic mitral regurgitation in Soweto, South Africa

2.1 Abstract

2.1.1 Background

Previous studies have documented the high prevalence of rheumatic heart disease in the population of Soweto and have provided a detailed description of the echocardiographic findings. We sought to determine whether the clinical and echocardiographic characteristics of rheumatic mitral regurgitation (MR) had changed in a more contemporary population.

2.1.2 Methods and Results

This cross-sectional study included 84 subjects with moderate or severe rheumatic MR. It comprised 84% females with a mean age of 44±15.3 years. Acute rheumatic fever (ARF) was documented in only one patient. Hypertension and HIV were present in 52% and 26% respectively. Echocardiography showed leaflet thickening in 41%, calcification in 25% and restricted motion and sub-valvular disease in 34% of the study population. Carpentier IIIa leaflet dysfunction occurred in 80%. Leaflet prolapse was seen in 20%. Patients older than 30 years had hypertension (69% vs 9% $p<0.01$) and HIV (32% vs 9% $p=0.03$) more commonly. These findings are in marked contrast to previous literature, in which younger patients (mean=19 years), commonly presented with rheumatic carditis, and had no comorbidities. In that study, leaflets were pliable, with 84% having isolated leaflet prolapse, and no commissural fusion. Elongated (92%) and ruptured (25%) chordae predominated.

2.1.3 Conclusion

Contemporary patients with rheumatic MR are older, have less ARF and greater associated comorbidities. Further, the echocardiographic features have evolved to greater leaflet thickening, calcification and reduced motion with little prolapse. These findings may have significant implications for the management of rheumatic disease in the modern era and serve to inform strategies for future management.

2.2 **Introduction**

The epidemiology of mitral regurgitation (MR) shows striking regional variation (Essop and Nkomo 2005, Enriquez-Sarano and Sundt 2010). In developed countries, degenerative disease is the major cause of MR and when surgery is indicated, repair of the valve is the preferred therapy (Enriquez-Sarano and Sundt 2010). In geographically low and middle income areas MR is still predominantly due to rheumatic disease and when severe, mitral valve replacement is often required (Essop and Nkomo 2005). While the demographic profile and echocardiographic features of degenerative MR have been well documented, there remains uncertainty regarding rheumatic MR ranging from diagnostic echocardiographic criteria to optimal management (Essop and Nkomo 2005, Enriquez-Sarano and Sundt 2010, Adams et al. 2010). This uncertainty is compounded by several factors including: the declining incidence of acute rheumatic fever (ARF), the rising incidence of comorbidities such as human immunodeficiency virus (HIV) infection and chronic lifestyle diseases associated with increasing urbanisation (Essop and Peters 2014, Stewart et al. 2008). In a landmark study of 700 patients with rheumatic valvular

disease from CHBAH, published approximately 30 years ago, Marcus et al. provided detailed echocardiographic and surgical data. The demographic profile and echocardiographic features of patients with rheumatic MR within that cohort were characterised by a disease afflicting predominantly young individuals with a high burden of concomitant acute rheumatic carditis. We therefore chose to examine our contemporary patient population with severe rheumatic MR specifically to detect the changing demographic and echocardiographic profile in a hospital serving the large community of Soweto in South Africa.

2.3 Methods

We conducted a prospective cross-sectional study at the Chris Hani Baragwanath Academic Hospital (CHBAH). Patients were enrolled from January 2014 and October 2014 from the valvular heart disease clinic. This study formed part of an ongoing study of rheumatic mitral regurgitation. All patients were screened and those deemed to have moderate or severe rheumatic MR were referred for possible inclusion in the study. Ninety-one patients with presumed rheumatic MR underwent clinical evaluation, resting electrocardiogram and detailed echocardiographic assessment according to a pre-determined protocol.

Patients aged 14 years or older with echocardiographic features of moderate or severe rheumatic MR were included. Patients were excluded if they had significant aortic valve disease, concurrent mitral stenosis (MS) with a valve area of less than 2.0 cm^2 (as assessed by planimetry), documented ischaemic heart disease, pre-existing non-valvular cardiomyopathy, prior cardiac surgery, congenital or pericardial disease, pregnancy, severe systemic disorders such as renal failure, uncontrolled

hypertension (systolic blood pressure >140mmHg and diastolic blood pressure >90mmHg) on medication or severe anaemia (Haemoglobin <10g/dl). Seven patients were excluded because of anaemia, renal dysfunction, mild MR, and MR of non-rheumatic etiology. The final study group included 84 patients. We performed sub-group analysis of patients younger than 30 years and those greater than 30 years (based on the mean age of the patients in the study by Marcus et al of patients with isolated CRMR of 19±11 years with 89% of patients being less than 30 years of age). Additionally, clinical and echocardiographic characteristics of patients with and without hypertension were compared and contrasted. The study was approved by the University of the Witwatersrand Ethics Committee (M140114).

After obtaining voluntary consent, all patients underwent a detailed clinical evaluation, 12 lead electrocardiogram followed by transthoracic echocardiography. The assessment of previous heart failure (HF) was made based on a combination of the patient's prior history, as well as available clinical records. Acute or recurrent rheumatic carditis was diagnosed using the modified Jones and the World Health Organization criteria (Dajani et al. 1992, WHO 2001). The HIV status was available for all patients from prior medical records.

Transthoracic echocardiography was performed on all patients in the left lateral position using a S5-1 transducer on a Philips iE33 system (Amsterdam, the Netherlands). Images were obtained according to a standardised protocol. Data was transferred and analysed off-line using the Xcelera workstation (Philips).

All linear chamber measurements were performed according to the American Society of Echocardiography (ASE) chamber guidelines (Lang et al. 2015). Left atrial (LA) volume was measured using the biplane area length method (apical 4 and 2 chamber for LA), and was indexed to body surface area (BSA). Left ventricular (LV)

end-diastolic- volume (EDV), end-systolic volume (ESV) and ejection fraction (EF) were assessed using the Simpson's method (Lang et al. 2015). LV mass was calculated according to ASE recommendations and was indexed to BSA (appendix). LV diastolic function measurements were performed in accordance with the ASE guidelines on diastolic function and included pulse-wave Doppler at the mitral tips and tissue Doppler of both medial and lateral mitral annuli (Nagueh et al. 2009). Measurements relating to the right ventricle were based on the ASE guidelines on the RV (Rudski et al. 2010).

MR severity was assessed using qualitative, semi-quantitative and quantitative methods as per ASE and ESC valvular regurgitation guidelines (Lancelloti et al. 2013, Zoghbi et al. 2003) (appendix). In equivocal cases the echocardiographic data was integrated with the clinical evaluation by an experienced cardiologist to distinguish moderate from severe MR.

MR was considered of rheumatic aetiology when the morphology of the valve satisfied the proposed World Heart Federation (WHF) criteria for the diagnosis of chronic RHD (Reményi et al. 2012) (appendix). The Carpentier classification was used to assess leaflet motion (Chauvaud et al. 2001). The extent of morphological abnormality of the valve was determined using the Wilkins score (Wilkins et al. 1998). The Wilkins score was used to characterise the mitral valve due to the absence of an alternate scoring system. Although it was originally designed for prediction of success for balloon mitral valvotomy in MS, its systematic classification of structural changes to the mitral valve was considered useful to characterise the morphology of chronic rheumatic valve disease, and thus was utilised in this study.

The Wilkins score is divided into four components:

1) leaflet thickening,

2) leaflet mobility,

3) leaflet calcification,

4) sub-valvular apparatus involvement.

The individual components are then graded from 0 (absent) to 4 (severe) depending on the extent of involvement ranging from none to severe (Wilkins et al. 1998).

Statistical analysis was performed with Statistica version 12.5 series 0414 for Windows. Continuous variables are expressed as means ± standard deviations (SDs) or medians (IQRs). Student's t test or Mann-Whitney U test were used to compare continuous variables. Categorical variables were evaluated by the chi-square and Fisher's exact test when necessary. A p value of < 0.05 was recognised as statistically significant.

2.4 Results

The baseline characteristics of the study patients are listed in Table 2.1. All patients were black South Africans, predominantly from Soweto. MR was moderate in 59 (68%) and severe in 25 (32%) of patients. The mean patient age was 44±15.3 years with 84% female patients. Two-thirds of patients were NYHA II or III, with 26% having been hospitalised for HF in the preceding year. One patient presented with features of acute rheumatic carditis two years prior to this study. No patients had recurrent rheumatic carditis despite 6% being on penicillin for secondary prophylaxis for ARF. Four (5%) patients presented with atrial fibrillation (AF).

Hypertension was the most important comorbidity present in 52% of patients. Concomitant HIV infection occurred in 26% of patients and 19% were on highly active antiretroviral therapy. Eighty-five percent (85%) of patients were on varying

combinations of medical therapy for either hypertension or HF and AF with 15% not on any drug therapy. None of the eight patients who underwent coronary angiography during their surgical workup had occlusive coronary artery disease.

The mean LVEF was 58±12.7% with 43% of patients having a LVEF <60%. The EDV and ESV were 93.8±31.4 mL/m^2 and 39.7±22.3 mL/m^2, respectively. Pulmonary hypertension was present in 38 (45%) subjects with none having contributing pulmonary abnormality. Concomitant organic rheumatic tricuspid valve (TV) disease was present in 29% of patients with the mean tricuspid annulus diameter of 38±7.2 mm. Of the 64% of patients presenting with tricuspid regurgitation (TR), 31% had moderate or severe disease (Table 2.1).

Table 2.1 Baseline clinical and echocardiographic characteristics*

Characteristics	n=84
Age (years)	44±15.3
Gender %	
Females	84
Clinical	
SBP, mmHg	124.1±11.4
DBP, mmHg	77.2±8.8
HR, beats/min	78.2±12.7
BMI, kg/m^2	27.1±6.1
BSA. m^2	1.7±0.2
NYHA functional class %	
I/II/III/IV	34/42/24/0

Comorbidities %	
Hypertension	52
Diabetes mellitus type 2	3
HIV	26
Medication %	
HAART	19
Diuretics	71
Spironolactone	21
ACE inhibitors	40
Beta Receptor Antagonists	25
Calcium Channel Antagonists	29
Aspirin	12
Warfarin	5
Digoxin	5
Amiodarone	1
Left ventricle	
LV EDD, mm	55.3±9.5
LVESD, mm	41.4±10.3
IVSD, mm	8.9±3.5
PWD, mm	8.6± 1.6
EDV indexed, mL/m^2 †	93.8±31.4
ESV Indexed, mL/m^2 †	39.7±22.3

LV mass, g	175.7±64.2
LV mass indexed, g /m^{2} †	77.9±22.5
LVEF %	58.8±12.8
Average E/E', cm/s	18±10.0
Dec time, cm/s	214.2±63.3
E', cm/s	8.6±3.3
E/A ratio	1.5±0.7
Left atrium	
LA indexed, mL/m^{2} †	69.5±50.7
Right ventricle	
RV S', cm/s	12.8±11.0
PASP, mmHg	36.2±18.9
TR (none/mild/mod or sev) %	36/33/31

* Data are presented as mean± SD or %. † Values are indexed to BSA.

ACE – *Angiotensin converting enzyme*. BSA – *Body surface area*. BMI – *Body mass index*. DBP - *Diastolic blood pressure.* Dec. time – *Deceleration time.* EDV – *End-diastolic volume*. EROA – *Effective regurgitant orifice area*. ESV – *End-systolic volume*. HAART – *Highly active antiretroviral therapy*. HIV – *Human immunodeficiency virus.* HR- *Heart rate*. IVSD – *Interventricular septal diameter*. LA – *Left atrium*. LV – *Left ventricle*. LV EDD – *Left ventricular end-diastolic diameter.* LVEF – *Left ventricular ejection fraction*. LVESD – *Left ventricular end- systolic diameter*. NYHA – *New York Heart Association*. PASP - *Pulmonary artery systolic pressure*. PWD – *Posterior wall diameter*. RV – *Right ventricle*. SBP - *systolic blood pressure.*

The mean mitral annulus diameter was 43±8.5 mm with 71 (84.5%) having an annulus greater than 35 mm. A Wilkins score of 4-8 was present in 26%, and 8-12 present in 74% of patients with chronic rheumatic MR. Sub-valvular apparatus thickening contributed the most to the total score (34.4%), followed by leaflet

calcification (27%) (Figure 2.1). Figure 2.2 depicts the overall distribution of subjects in each component of the Wilkins score. Chordae were not elongated and echocardiographic features suggestive of calcification within the leaflets were found in all subjects. Significant commissural fusion was present in 30% of cases.

Eighty percent of (80%) cases were classified as having restrictive-Carpentier type IIIa leaflet dysfunction while the remaining 20% had a mixed lesion which was a combination of type II (excessive leaflet motion) and type IIIa dysfunction. All patients had greater degrees of restriction of the posterior mitral leaflet (PML) except in three cases where the anterior mitral leaflet (AML) was restricted to a greater degree than the PML. A posteriorly-directed eccentric MR jet was present in 96% of cases except for three subjects that had anteriorly directed jets secondary to posterior mitral leaflet prolapse (Figure 2.3).

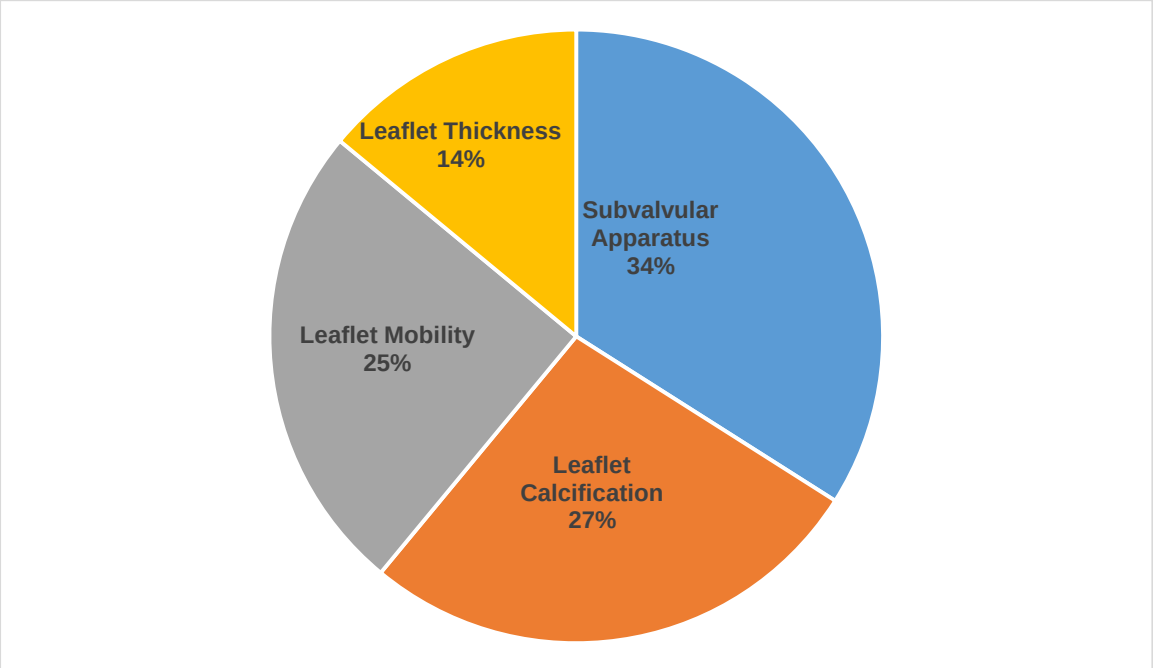


Figure 2.1 Distribution of valve abnormality according to the Wilkins score components.

Patients younger and older than 30 years of age were compared (Table 2.2). Twenty-six percent (26%) were younger than 30 years of age. There was no significant difference in the proportion of individuals having moderate or severe MR ($p>0.05$). The remodelling parameters of the LV, LVEF and LA volume were similar in both groups ($p>0.05$). Older patients were more likely to have comorbidities including hypertension (69% vs 9%, $p<0.01$) and HIV (32% vs 9%, $p=0.03$), and a greater degree of impairment of early diastolic relaxation (E' = 11.4±3.3 vs 7.6±2.3, $p<0.01$). The comparative analysis of the morphology of the mitral valve revealed no significant differences in the overall Wilkins score between the two groups (8.31±1.2 vs 8.1±1.0, $p=0.33$). No statistically significant difference was noted in the degree of calcification of the leaflets, mobility, sub-valvular apparatus thickening and commissural abnormality ($p>0.05$). Compared to normotensive patients with MR, patients with hypertension were older (51.7±11.1 vs 35.1±14.2 years, $p<0.01$). The majority were in NYHA functional class II or III (71% vs 44%, $p=0.03$), with a greater prevalence of moderate MR, accompanied by a greater degree of impairment of early relaxation in diastole (Table 2.2). Normotensive MR patients had a greater prevalence of dilatation of the left ventricle and severe MR with larger LA volume (Table 2.3). There were no significant differences with regard to the morphology of the mitral valve apparatus or Carpentier classification of leaflet dysfunction between the two groups ($p>0.05$).

A greater proportion of patients with HIV had severe MR compared to HIV negative patients (50% vs 23%, $p=0.015$). However, no significant differences were observed in the echocardiographic parameters relating to dilatation of the LV, LVEF, LV diastolic function or LA volumes ($p>0.05$). Similarly, no significant differences were noted in any morphological parameters or Wilkins score between the two

groups (8.4±1.2 vs 8.0±0.9, p=0.14). All HIV positive patients had type IIIa (restrictive) leaflet dysfunction, compared to HIV negative individuals in whom 15% had mixed lesions (p=0.05). Concomitant organic morphological TV disease was more common than in HIV negative patients (50% vs 21%, p=0.02). A similar degree of TR (p>0.05) was present in both groups. There was no difference in the pulmonary artery systolic pressure between the HIV positive and HIV negative groups (37.2±15.4 mmHg vs 35.2±18.7 mmHg, p=0.64). The degree of RV dilatation (33.5±9.0 mm vs 31.4±5.8 mm, p=0.22) and RV function (11.9±2.9 cm/s vs 13.4±13.2 cm/s, p=0.61) were not statistically different in between the HIV positive and HIV negative groups.

A comparison of clinical characteristics and mitral valve morphology of our cohort with Marcus et al. is depicted in Table 2.4.

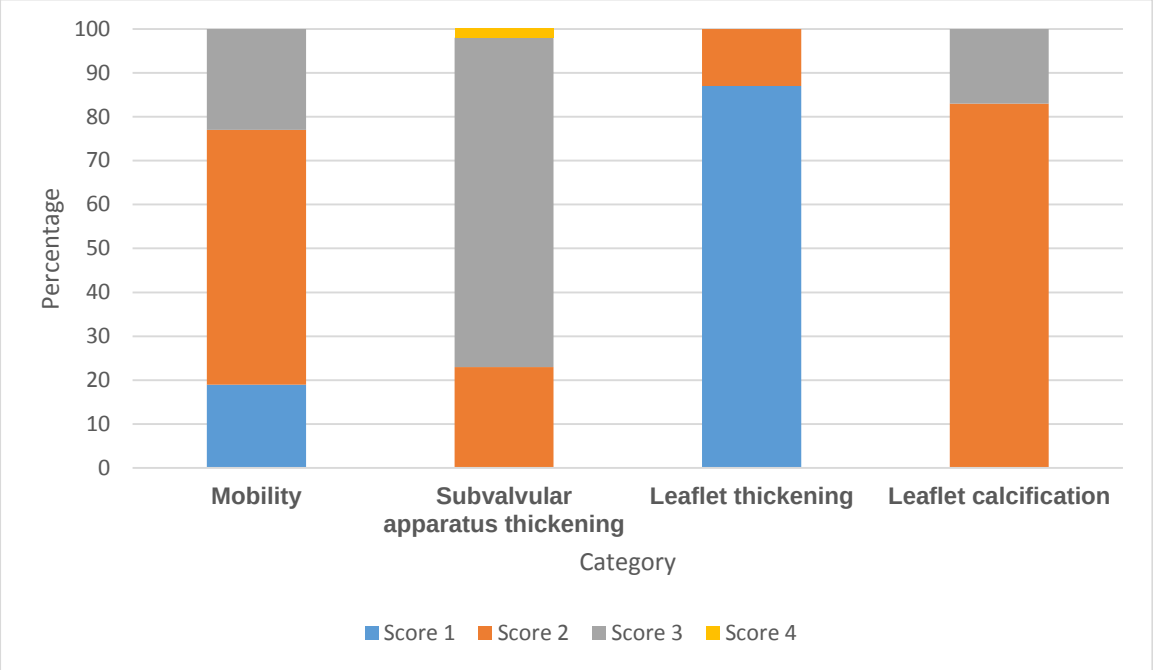


Figure 2.2 Distribution of patient morbidity according to components of the Wilkins score.

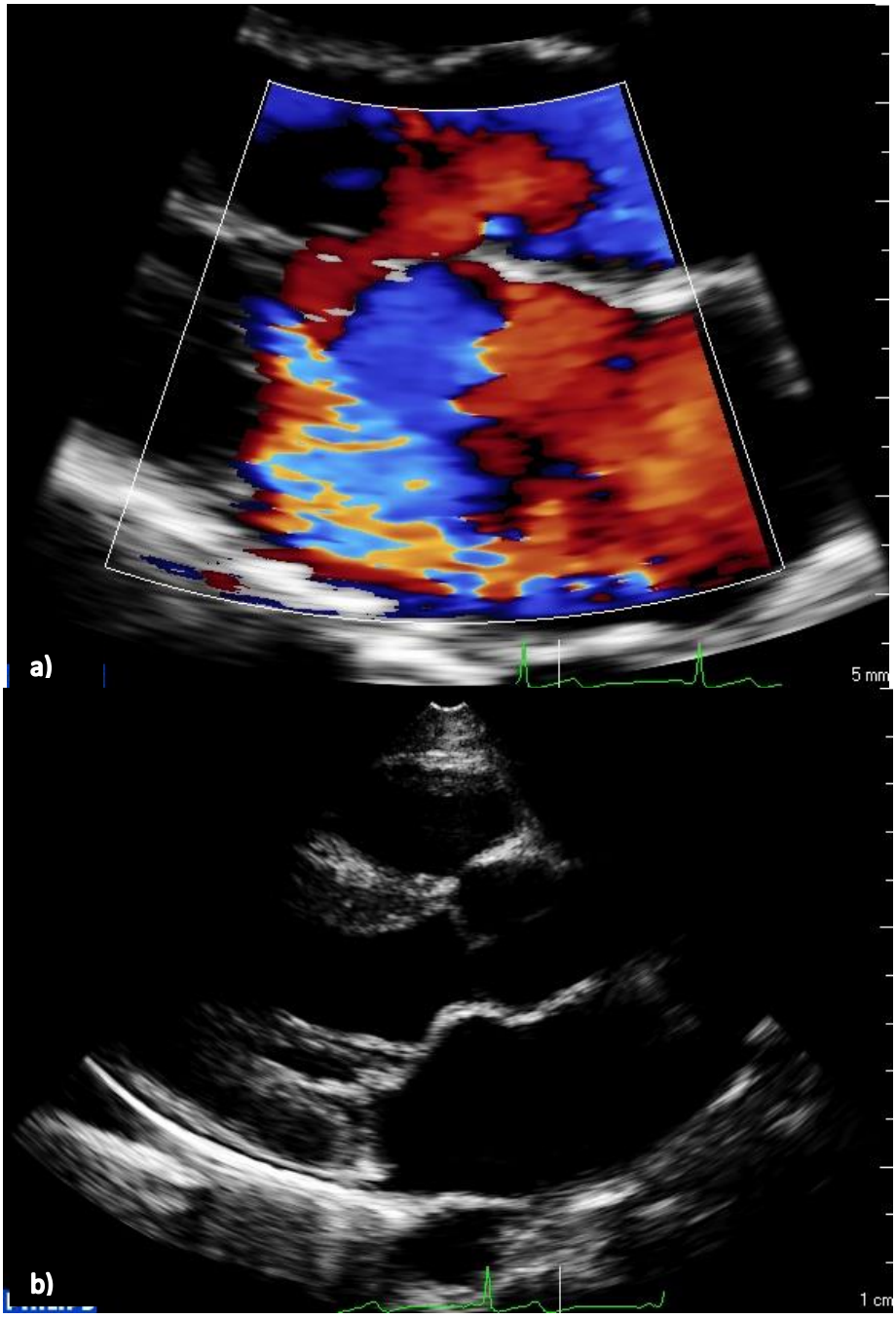


Figure 2.3 a) Parasternal long-axis view depicting an eccentric anteriorly directed mitral regurgitation jet secondary to restricted posterior mitral leaflet motion. b) Parasternal long-axis view depicting a contemporary patient with established rheumatic heart disease: thickened shortened chordae, restricted posterior mitral leaflet.

Table 2.2 Clinical and echocardiographic characteristics according to age.*

Variable	Age<30 (n=22)	Age>30 (n=62)	P Value
Clinical			
Age (Years)	23.3±3.6	51.2±10.1	<0.001
Systolic blood pressure	121.9±11.2	124.9±11.3	0.29
Diastolic blood pressure	77.8±6.83	76.6±9.6	0.60
Body mass index (kg/m^2)	23.84±4.78	28.2±6.23	0.19
Body surface area (m^2)	1.62±0.16	1.72±0.18	0.04
NYHA functional class (I/II and III)	14/8	21/41	0.01
Sex (F/M) (%)	18/4 (81/19)	53/9 (85/15)	0.68
Echocardiographic			
Moderate mitral regurgitation (%)	13 (59)	46 (74)	
Severe mitral regurgitation (%)	9 (41)	16 (26)	0.18
LV end-diastolic diameter (mm)	53.7±9.06	55.7±9.7	<0.0001
LV end-systolic diameter (mm)	38.7±9.31	42.3±10.5	0.15
Interventricular septum diameter (mm)	9.8±5.9	8.6±2.3	0.21
Posterior wall diameter (mm)	7.9±1.1	8.9±1.6	0.01
LV EDV indexed (ml/m^2)†	90.8±22.9	94.8±33.9	0.61
LV ESV indexed (ml/m^2)†	35.5±16.9	42.4±24.7	0.23
LV Mass indexed (g/m2)†	102.2±44.2	105.7±38.5	0.72
Relative wall thickness	0.30±0.1	0.33±0.1	0.24
LV ejection fraction (%)	61.4±12.7	57.1±12.7	0.26
Ejection fraction ≥ 60%	18	30	
Ejection fraction < 60%	4	32	0.006
Average E' (cm/s)	11.4±3.3	7.6±2.3	<0.01
E/E' lateral (cm/s)	13.2±8.2	17.2±9.3	0.04
E/A ratio	1.7±0.34	1.4±0.7	0.05
S' Lateral (cm/s)	8.9±3.3	6.63±1.7	<0.0001
LA volume indexed (ml/m2)†¶	45 (37.1-148.5)	53 (41.2-74.5)	0.53

*Data are presented as mean ± SD, ¶ median (interquartile range) or percentage. † Values are indexed to body surface area. LA – *Left atrium*. LV – Left ventricle. NYHA – New York Heart Association.

Table 2.3 Clinical and echocardiographic features according to the presence or absence of hypertension.*

	Hypertension n=45	**No Hypertension** n=39	**p value**
Age	51.7±11.1	35.1±14.2	<0.0001
Gender			
Female %	86	82	0.62
Clinical parameters			
SBP, mmHg	127.9±8.4	119.5±12.8	0.0008
DBP, mmHg	79.2±8.5	74.2±8.8	0.01
BMI, kg/m^2	28.6±6.1	25.0±5.8	0.01
BSA, m^2	1.7±0.2	1.7±0.2	0.21
NYHA (I/II and III)	29/71	56/44	0.03
Left ventricle			
LV EDD, mm	52.4±8.4	58.3±9.8	0.004
LVESD, mm	39.7±9.5	43.2±10.9	0.12
IVSD, mm	9.0±2.3	8.9±4.6	0.97
PWD, mm	9.1±1.6	8.1±1.3	0.0009
EDV indexed, mL/m^2 †	87.7±29.9	100.9±32.0	0.05
ESV Indexed, mL/m^2 †	35.9±17.7	46.1±27.4	0.046
LV mass indexed, g /m^2 †	100.1±39.4	110.4±40.2	0.24
RWT	0.4±0.1	0.3±0.1	0.0001
LVEF %	58.4±12.6	58.1±13.1	0.91

EF ≥ 60%	24	24	
EF < 60%	20	16	0.61
Average E/E', cm/s	19.2±10.9	17.7±8.9	
E', cm/s	7.4±2.5	9.9±3.4	0.006
E/A ratio	1.3±0.6	1.6±0.6	0.008
Left atrium			
LA volume indexed mL/m^2 †	57.6±24.1	83.37±67.7	0.42
Right Ventricle			
RV S', cm/s	14.6±15.6	11.2±2.5	0.18
PASP, mmHg	33.7±19.2	37.9±16.1	0.28
TR (none/mild/mod to sev) %	38/36/26	33/31/36	0.46
MR severity			
Moderate mitral regurgitation %	82	56	
Severe mitral regurgitation %	18	44	0.009

* Data are presented as mean± SD or %. † Values are indexed to BSA.

BSA – *Body surface area*. BMI – *Body mass index*. DBP - *Diastolic blood pressure*. EDV – *End-diastolic volume*. ESV – *End-systolic volume*. IVSD – *Interventricular septal diameter*. LA – *Left atrium*. LV – *Left ventricle*. LV EDD – *Left ventricular end-diastolic diameter*. LVEF – *Left ventricular ejection fraction*. LVESD – *Left ventricular end-systolic diameter*. NYHA – *New York Heart Association*. RWT- *relative wall thickness* PASP - *Pulmonary artery systolic pressure*. PWD – *Posterior wall diameter.* RV – *Right ventricle*. SBP - *systolic blood pressure*.

Table 2.4 Comparison of Marcus et al study with the current cohort of patients with isolated rheumatic mitral regurgitation.

Variables	Marcus et al (n=219)	Meel et al (n=84)	P value
Clinical			
Age (years)	19±11	44±15.3	<0.001
Females (%)	Not specified	84%	
Race	Black Africans	Black Africans	
NYHA functional class	III (100%)	III (24%)	0.001
Acute Rheumatic fever (%)	14	1.2	<0.001
Co-morbidities (%)	0	78	<0.001
Mitral valve morphology (%)			
Dilated annulus	95	84.5	0.001
Leaflet thickness and pliability			
Thin, pliable	95	5	<0.001
Thickened, non-pliable	59	41	0.0049
Leaflet prolapse	84	20	<0.001
Leaflet calcification (rigid)	5	27	<0.001
Elongated chordae	92	0	<0.001
Ruptured chordae	25	0	<0.001
Commissural fusion	0	30	<0.001

NYHA – New York Heart Association.

2.5 Discussion

The pertinent findings in this contemporary cohort of patients with moderate to severe rheumatic MR include:

(1) A significant increase in the mean age of patients compared to previous studies,

(2) Infrequent occurrence of ARF,

(3) A high incidence of comorbid disease including hypertension and HIV; and,

(4) Advanced morphological changes in the mitral valve including leaflets and sub-valvular apparatus on echocardiography.

These findings are in marked contrast to the detailed evaluation published by Marcus et al. from the same hospital but almost three decades earlier (Marcus et al. 1994). In that study, from the total cohort of 737 patients, 219 had pure MR, 275 pure mitral stenosis and 220 mixed lesions. Further, in Marcus's study, patients with pure MR had thin leaflets, elongated chordae, dilated annuli and anterior leaflet prolapse – findings that were corroborated at the time of surgery (Marcus et al.1994). Pure MR was largely a function of active rheumatic carditis and age – most patients were younger than 20 years of age with clinical carditis documented in 14% and surgical features of acute rheumatic carditis in 47% of the entire MR cohort (Marcus et al. 1994). In contrast, we found only one patient with active carditis. The mean age of our cohort was 44±15.3 years and echocardiography revealed no leaflet prolapse and instead marked leaflet thickening, calcification and retraction accompanied sometimes by abnormality of the chordal structures.

These features are compatible with the proposal that Marcus and ourselves have advanced in which fulminant carditis is thought to lead to pure severe MR and milder or recurrent carditis progressing to pure mitral stenosis or mixed mitral valve

disease (Essop and Nkomo 2005, Essop and Peters 2014, Marcus et al. 1994). Rheumatic MR of patients in the current era results in the predominance of Carpentier type IIIa leaflet dysfunction with Wilkins scores that are similar to patients with MS. We postulate that less fusion of the commissures, predominance of posterior leaflet thickening and immobility, accompanied by sub-valvular abnormalities, predispose patients to develop predominantly regurgitant lesions. The reason some patients develop pure MS is unknown (Essop and Peters 2014). Differences in the interaction of host immunity, initial or recurrent streptococcal infections and chronic exposure of the valve leaflets to abnormalities of haemodynamic flow may account for these difference in morphology and dictate which lesion may predominate.

The current data confirm that there has been a dramatic decline in the incidence of rheumatic carditis in the population of Soweto although the reasons for this are not entirely clear. The striking trend toward a substantial decline in ARF has also been documented in the paediatric section of Baragwanath Hospital with a reduction from 64 cases per year in 1993 to 3 per year in 2010 (Cilliers 2014). This decline was attributed to improved socioeconomic status and better access to health care (Cilliers 2014). Thirty years ago McClaren et al.reported a RHD incidence of 6.9/1000 among school children in Soweto (by auscultation) (Cilliers 2014). Recently, Engel et al. reported a RHD incidence of 20.2/1000 cases among scholars in the Bonteheuwel and Langa communities of Cape Town (by echocardiography), with the prevalence being higher in poorer communities (Engel et al. 2015). The incidence of adults presenting with RHD was reported as high (23.5/100000) at Baragwanath Hospital (Cilliers 2014). The data from other areas of the country are scarce; the REMEDY study did not formally report on the incidence or prevalence of

RHD. However, 25.8% (863/3343) participants were from upper middle income countries (Zuhlke et al. 2015).

Concomitant with the decline in rheumatic fever, diseases associated with western lifestyle and urbanisation have emerged. A considerable number of patients with rheumatic MR currently have comorbidities of hypertension (52%) and HIV (26%). These findings differ considerably from previous studies conducted in our institution. These comorbidities mandate a careful assessment of the patient's clinical presentation since symptoms may not be solely attributed to the MR. It was not the intention of the study to study the impact of blood pressure on MR severity. However, elevated blood pressure may overestimate the echocardiographic severity of MR and should be controlled for, and LV dysfunction may be attributed to concomitant HIV infection in addition to volume overload due to MR.

The morphological abnormalities of the mitral apparatus (thickened and shortened sub-valvular apparatus) and the nature of leaflet dysfunction (Carpentier IIIa) described in the current population has diagnostic implications. MR jets that are eccentric may require careful off-axis imaging to accurately delineate the full extent of the colour jet. Further, an integrated evaluation of MR severity is mandatory due to the limitations of quantitative Doppler in some instances of eccentric jets.

The selection of patients for mitral valve repair maybe more challenging and requires detailed insight into the morphology of the entire valve apparatus. A strategy of exclusively inserting an undersized ring to correct annular dilatation is inadequate in the current context of rheumatic MR. The former strategy was often successful historically in repairing rheumatic MR, since most patients had type II leaflet dysfunction (prolapse), accompanied by annular dilatation (Wisenbauagh et al. 1994a).

An important observation of my study was the high frequency of concurrent TV leaflet abnormality and tricuspid annular dilatation. These abnormalities were not reported by Marcus et al. and no data on surgical repair was given. Our findings suggest that once rheumatic MR is identified careful assessment of the morphology and function of TV is mandatory when selecting patients who will undergo mitral valve surgery. This strategy may reduce the likelihood of the late consequences of unrepaired TR in rheumatic patients which has been previously highlighted (Antunes and Barlow 2007). Late TR causes increased morbidity and mortality despite the presence of successful mitral valve surgery and in addition a second operation to correct the residual TR carries increased mortality (Antunes and Barlow 2007).

There are several limitations to this study. The initial diagnosis of HF was made outside of our clinic with no uniform criteria applied. None of the patients had surgery, so surgical confirmation of the echocardiographic abnormality was not possible. Finally, the population studied may not truly reflect the nature of the disease in rural younger populations, where a greater prevalence of acute rheumatic carditis may be found.

In conclusion the modern cohort of patients with rheumatic mitral regurgitation are older, have less acute rheumatic fever and greater associated comorbidities. The echocardiographic features have evolved to greater leaflet thickening, calcification and reduced motion with little prolapse. These findings may have significant implications for the current management of rheumatic mitral valve disease and contribute to better understanding of the evolution from acute to chronic RHD.

Chapter 3

Left atrial volume and strain parameters using echocardiography in a black population

3.1 Abstract

3.1.1 Background

Left atrial (LA) volume is an important predictor of morbidity and mortality in cardiovascular disease. LA strain is a feasible technique for assessing LA function. The EchoNoRMAL study recently highlighted the possibility that ethnic-based differences may exist in LA size. There is a paucity of data regarding LA parameters in an African population. We sought to establish normative values for LA volumetric and strain parameters in a black population.

3.1.2 Methods and Results

This cross-sectional study comprised 120 individuals from 18 to 70 years of age. LA volumes were measured by biplane Simpson's method and strain parameters were measured using Philips QLAB 9 (Amsterdam, the Netherlands) speckle tracking software. The mean age was 38.7±12.8 years (50% male). Maximum LA volume indexed (LAVi), pre-atrial LAVi and minimum LAVi were 19.7±5.9 mL/m^2, 12.2±4.4 mL/m^2, and 7.7±3.2 mL/m^2, respectively. Females had a higher LAVi compared to males (20.9±6.3 vs 18.6±5.3 mL/m^2, p=0.04). Peak global longitudinal strain in the reservoir phase (ε_R) was 39.0±8.3% and the peak LA strain in the contractile phase (ε_{CT}) was -2.7±2.5%. No gender differences were noted in ε_R. BSA, age, and weight were the main determinants of ε_R on multivariate linear regression analysis.

3.1.3 Conclusion

The data reported in this study establish the normal reference values for phasic LA volumes and strain in a normal black population and serve as a platform for future studies.

3.2 Introduction

The left atrium (LA) has multiple functions. It is a contractile chamber that also acts as a reservoir, conduit, and volume sensor (Bonow et al. 2012). The anatomy and pathophysiology of the LA is complex, and thus, optimal quantification of its function is difficult (Seward et al. 2014, Cameli et al. 2009). Bearing in mind these challenges, LA size and volume are altered in many disease states and are important predictors of morbidity and mortality in many cardiovascular disease states (Vieira et al. 2014, Cameli et al. 2012). Speckle-tracking echocardiography has shown to be a feasible and reproducible technique in the evaluation of longitudinal LA strain (Ɛ), thus providing an additional parameter of LA function (Kowalick et al. 2014, Vianna-Pinton et al. 2009). This may enable earlier identification of subclinical LA dysfunction, which has additional prognostic implications in various disease states (Hoit 2014). However, interpretation of the abnormality does require normal data on vendor-specific software to differentiate normality from pathology. Recent data from the EchoNoRMAL study has highlighted the possibility that echocardiographic measurements of LA size may differ among various ethnic populations, with black Africans having decreased LA diameters than whites (Aune et al. 2015). There are no studies that have documented normative data on LA volume indexed (LAVi) to body surface area (BSA) in black Africans. This is

required to ensure that current levels of abnormality defined in guidelines can be accurately applied to this population. Further, there is no current evidence that ethnicity may affect strain values of the LA since this has not been studied previously. Thus, we sought to establish normal reference ranges of LA volumetric parameters and peak positive LA Ɛ ($Ɛ_{R,}$ LA reservoir function) and peak negative LA Ɛ ($Ɛ_{CT,}$ LA contractile function) in a black African population.

3.3 Methods

3.3.1 Study group

This prospective cross-sectional study was part of an ongoing study being conducted at Chris Hani Baragwanath Academic Hospital to provide normal echocardiographic reference ranges in subjects of African descent. Subjects were recruited from unrelated staff at Baragwanath Hospital and volunteers who presented themselves to the echocardiography laboratory following an advertisement about this study. A total of 190 subjects were screened.

The inclusion criteria were:

1) Absence of symptoms,

2) Normal blood pressure (≤140/90 mm Hg),

3) Absence of diabetes and cardiovascular disease,

4) Absence of chronic medication,

5) Presence of sinus rhythm (heart rate between 50-85 beats/min).

The exclusion criteria were:

1) Abnormal 12-lead electrocardiograms (ECG),

2) Abnormal screening echocardiograms,

3) Suboptimal image quality.

The final sample comprised 120 individuals (60 females) aged 18 to 70 years. The study was approved by the University of the Witwatersrand Ethics Committee (M140114) and was in accordance with the principles outlined in the Declaration of Helsinki. The participants' baseline clinical characteristics were recorded, and the participants subsequently underwent comprehensive echocardiography.

3.3.2 Echocardiographic evaluation

Transthoracic echocardiography was performed on all patients in the left lateral position by experienced sonographers using an S5-1 transducer on a Philips iE33 system (Amsterdam, The Netherlands). The images were obtained according to a standardised protocol. The data were transferred and analysed off-line using the Xcelera workstation (Philips).

3.3.3 Two-dimensional and Doppler quantification

All linear chamber measurements were performed according to the American Society of Echocardiography chamber guidelines (Lang et al. 2015). The biplane

Simpson's method was used for calculation of LA volumes. LA volume was planimetered in the four-chamber and two-chamber views by tracing the endocardial border (pulmonary vein confluence and LA appendage were excluded). Maximum LA volume (LA_{max}) was obtained at left ventricular (LV) end-systole, from the 2-dimensional (2D) frame, just before the mitral valve opened (Vianna-Pinton et al. 2009, Kowalick et al. 2014). Pre-atrial volume (V_{pre-A}) was obtained from the diastolic frame, just before the mitral valve reopened as the result of atrial contraction (Vianna-Pinton et al. 2009). LA minimum volume (LA_{min}) was assessed at LV end-diastole, from the smallest volume seen after LA contraction (Vianna-Pinton et al. 2009, Kowalick et al. 2014).

LA phasic function assessment was done using the following formulae:

1) Reservoir function: LA emptying fraction total = $(LA_{max} - LA_{min})/LA_{max}) \times 100\%$; expansion index = $(LA_{max} - LA_{min})/ LA_{min}) \times 100\%$

2) Conduit function: Passive emptying volume = $(LA_{max} - V_{pre-A})$; passive LA emptying fraction = $(LA_{max} - V_{pre-A}/LA_{max}) \times 100\%$; and conduit volume = LV (stroke volume - $(LA_{max} - LA_{min})$

3) Booster pump function: LA active emptying fraction = $(LA_{pre-A} - LA_{min})/LA_{pre-A}) \times 100\%$; LA active emptying volume = $(V_{pre-A} - LA_{min})$ (Vianna-Pinton et al. 2009, Kowalick et al. 2014, Hoit 2014).

All the LA volumetric parameters were indexed to BSA (Kowalick et al. 2014) (appendix). Measurements relating to LV diastolic function were performed in accordance with the ASE guidelines on diastolic function and included pulsed-wave

Doppler at the mitral tips and tissue Doppler of both medial and lateral mitral annuli (Nagueh et al. 2009).

3.3.4 Speckle-tracking echocardiography

Apical 4- and 2-chamber views were obtained using 2D grayscale echocardiography for speckle-tracking analysis (Cameli et al. 2012, Cameli et al. 2009). This was performed during end-expiratory breath-hold and stable ECG recording (Cameli et al. 2012, Cameli et al. 2009, Vianna-Pinton et al. 2009). An adequate grayscale image that allowed separation of myocardial tissue and surrounding structures was obtained (Cameli et al. 2012). Three consecutive cardiac cycles were recorded and averaged. The frame rate was set between 60 and 80 frames/second. Philips QLAB version 9.0 software allowed off-line semi-automated analysis of speckle-based strain. The endocardial surface of the LA was traced manually in both 4- and 2-chamber views by a 3-point-and-click approach. The system then automatically generates an epicardial surface tracing (*Figure 3.1*). The region of interest was thus created, and this was then manually adjusted as needed to allow for adequate speckle tracking.

The software divides the region of interest into seven segments in the 2-chamber and the 4-chamber views. It then generates the longitudinal Ɛ curves for each segment and a mean curve of all segments (Cameli et al. 2012). From these strain curves the peak left atrial strain in the reservoir phase ($Ɛ_R$) and contractile phase were calculated (Viera et al. 2014). The QRS onset was used as the first reference frame.

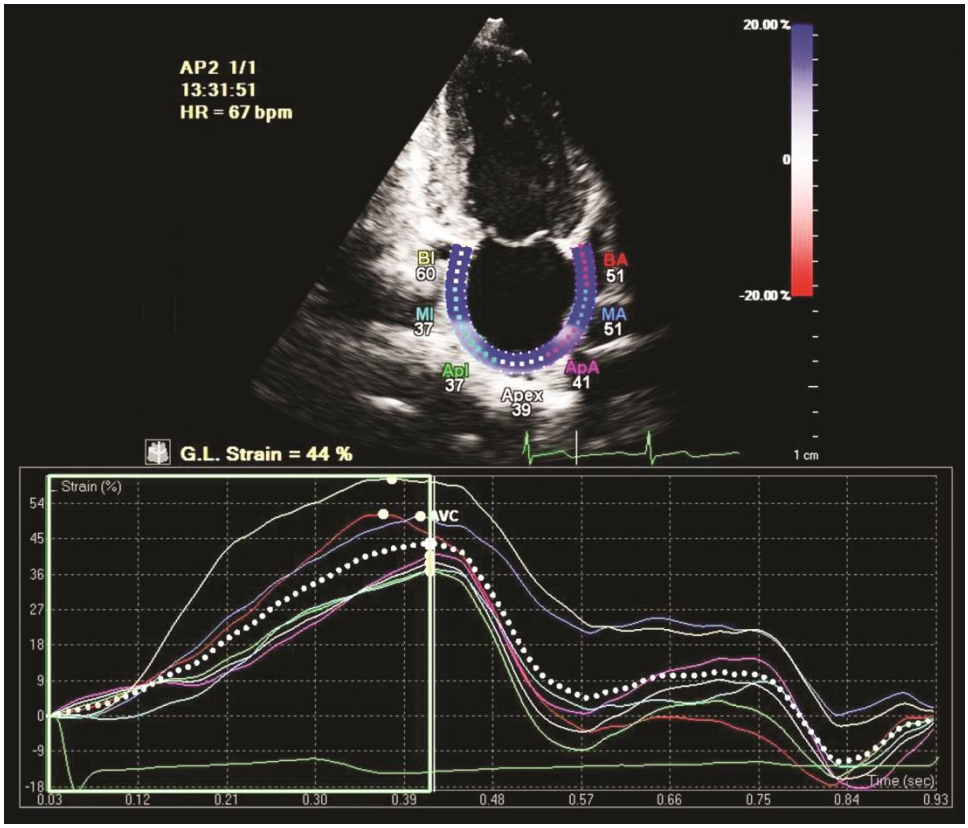


Figure 3.1 Two-chamber view depicting peak systolic strain in the reservoir phase and peak negative strain in the contractile phase in a normal subject.

3.3.5 Statistical analysis

Statistical analysis was performed with Statistica version 12.5, series 0414 for Windows. Continuous variables were expressed as means ± standard deviations (SDs) or medians (interquartile ranges). Univariate and multivariate linear regression analyses were used to identify possible independent determinants of LA $Ɛ_{R,,}$ and maximum LAVi. Multivariate models to predict LA $Ɛ_R$ and for maximum LAVi were selected in a multiple linear regression analysis. Univariate variables with Pearson's correlation coefficient ≥0.8 were not included in the multivariate models. Additionally, only clinically and statistically significant variables (*P <0.05*) were selected for inclusion in multivariate linear regression analysis. The aforementioned models were further analysed using the forward and backward multiple linear

regression methods. The assumptions were verified by performing residual analysis and advanced Durbin-Watson statistics.

The intra-observer and inter-observer variabilities were assessed for peak positive LA ε_R, peak negative LA $\varepsilon_{CT,}$ maximum LAVi, and minimum LAVi. Measurements were done in 20 randomly selected subjects. To assess inter-observer variability two independent observers measured the LA volumetric and strain parameters, whilst intra-observer variability was calculated from the analysis by the same observer after one month of the first measurement. Inter-observer and intra-observer reproducibility was assessed by calculating coefficients of variation (CV). The CV was calculated as the standard deviation of the differences divided by the mean. The T- test for dependent variables was used to compare the mean and SD of the values derived for strain and volumes and to calculate the significance value. A p value<0.05 was considered statistically significant.

3.4 Results

3.4.1 Baseline characteristics and echocardiographic findings

Of the 120 individuals, 60 were male with a mean age of 38.7±12.8 years (Table 1). Females had a higher body mass index (BMI) compared to males (29.8±6.1 kg/m^2 vs 25.9±4.5 kg/m^2, p<0.001) but a lower BSA (1.78±0.17 m^2 vs 1.86±0.19 m^2, p=0.007). There was no difference in weight between the sexes (75.8±15.6 kg vs 75.8±14.1 kg, p=0.9) but males were taller (1.7±0.07 m vs1.58±0.06 m, p<0.001).

3.4.2 LA volumetric parameters for the total sample

The mean maximum LAVi, minimum LAVi, and pre-A LAVi were 19.7±5.9 mL/m^2, 7.7±3.2 mL/m^2, and 12.2±4.4 mL/m^2 respectively (Table 3.2). The maximum LAVi was higher among females than males (20.9±6.3 vs 18.6±5.3 mL/m^2, p=0.04).

Table 3.1 Baseline clinical and echocardiographic characteristics.*

Variable	**Total (n=120)**
Age, years	38.7±12.8
Sex, F:M ratio	60:60
Body mass index, kg/m^2	27.9±5.8
Body surface area, m^2	1.8±0.2
Systolic blood pressure, mmHg	121.9±11.0
Diastolic blood pressure, mmHg	76.3±9.3
Heart rate, bpm	77.2±12.6
End-diastolic diameter, mm	42.7±4.9
End-systolic diameter, mm	27.1±4.6
Interventricular septum end-diastolic diameter, mm	9.3±1.8
LV posterior wall diameter, mm	9.0±1.6
End-diastolic volume index, mL/m^2	49.5±13.6
End-systolic volume index, mL/m^2	18.5±5.9
Ejection fraction, %	62.5±8.1
Relative wall thickness, ratio	0.42 ± 0.1
LV mass index, g/m^2	66.1±18.0
E wave, cm/s	78.5±17.6
A wave, cm/s	58.9±15.5

Deceleration time, ms	140.5±53.4
E/A, ratio	1.4±0.4
E´ medial, cm/s	9.3±2.8
E´ lateral, cm/s	14.1±3.5
E/E` med, ratio	9.1±2.7
E/ E´lat, ratio	5.8±1.5
Average E/E´, ratio	7.4±0.83
S´ med, cm/s	7.4±1.5
S´ lat, cm/s	8.7±2.6

*Data reported as mean ± standard deviation, unless otherwise stated. F:M - female to male. LV - left ventricular.

3.4.3 Determinants of maximum LAVi

On univariate analysis, the main clinical determinants of maximum LAVi were sex (p=0.03), BMI (p=0.009), systolic blood pressure (p=0.03), and heart rate (p=0.0002). On multivariate regression analysis the main predictors of maximum LAVi were male sex, heart rate, and systolic blood pressure after adjustment for age (Table 3.3).

3.4.4 LA strain indices

The mean peak positive LA strain and peak negative LA strain for all subjects were 39.0±8.4% and -2.7±2.5%, respectively (Table 3.2). No gender differences in ε_R were noted (p=0.81).

3.4.4 Factors determining LA reservoir strain

On univariate analysis clinical parameters such as age ($p<0.001$), BSA ($p=0.002$), BMI ($p=0.02$), weight ($p=0.003$), and systolic blood pressure ($p=0.04$) were determinants of ε_R. However, sex was not associated with ε_R. On multivariate linear regression analysis, age, weight, and BSA were independently associated with ε_R after adjustment for sex and systolic blood pressure (Table 3.4).

3.4.5 Reproducibility of LA volumetric and strain parameters

The intra-observer coefficient of variation for maximum LA volume was 3% with a mean difference of 0.23±0.61 ($p=0.10$). The inter-observer variability for maximum LA volume was 0.9% with a mean difference of 2.7±2.6 ($p=0.0001$). The intra-observer coefficient of variation for ε_R was 4.8% with a mean difference (of 3.2±0.67 ($p=0.3$) and for ε_{CT} was 4.6% with a mean difference of 1.43±0.31 ($p=0.3$). The inter-observer variability coefficient was 9% for both ε_R ($p=0.6$) and ε_{CT} ($p=0.6$) with a mean difference of 3.2±0.35 and 1.2±0.13, respectively.

Table 3.2 Left atrial volumetric and strain parameters.*

Variable	Total (n=120)
LA volumes	
Max-LAVi, mL/m^2	19.7±5.9
Min-LAVi, mL/m^2	7.7±3.2
Pre-A LAVi, mL/m^2	12.2±4.4
LA reservoir function	
LA total EV, mL/m^2	12.2±4.8
LAEF total, %	59.9±13.5
LA exp index, %†	152.7 (109.5-228.8)
LA conduit function	
LA PEVi, mL/m^{2†}	6.8 (4.7-9.0)
Conduit vol, mL/m^{2†}	17.8 (12.1-24.5)
LA PEF, %†	36.8 (28-47)
LA pump function	
LA AEVi, mL/m^2	4.6±2.6
LAEF Booster, %	37.7±13.9
LA strain	
ε_R, %	39.0±8.3
ε_{CT}, %	-2.7±2.5

*Data reported as mean ± standard deviation or †median with interquartile ranges. LA - *Left atrial*; LA AEVi - *Left atrial active emptying volume index*; LAEF - *Left atrial emptying fraction*; LA exp index - *Left atrial expansion index;* Max-LAVi - *Maximum left atrial volume index;* Min- LAVi, - *Minimum left atrial volume index*; PEF - *Passive emptying fraction;* PEV - *Passive emptying volume;* Pre - A LAVi - *Pre-atrial contraction left atrial volume index;* ε_R - *Peak left atrial strain in the reservoir phase*; ε_{CT} - *Peak left atrial strain in the contractile phase*.

Table 3.3 Multivariate linear regression analysis for maximum LAVi

Variables	β coefficient ± SE	p value
Model 1 r=0.42 (p<0.0001)		
Age, years	0.01±0.03	0.6
Male sex	-2.7±0.8	0.003
Heart rate, bpm	-0.11±0.01	0.001
Systolic blood pressure, mmHg	0.05±0.02	0.03
Model 2 r=0.32 (p<0.025)		
Age, years	0.006±0.04	0.87
Male sex	-0.82±1.36	0.54
Weight, kg	0.03±0.03	0.29
Height, m	-12.4±7.8	0.11
Systolic blood pressure, mmHg	0.07±0.03	0.02

LAVI - *left atrial volume index*; SE - *standard error.*

Table 3.4 Multivariate Linear Regression Analysis for Left Atrial strain in the Reservoir Phase (ε_R).

Variables	β coefficient ± SE	p value
Model 1 r=0.47 (p<0.0001)		
Age, years	-0.18±0.05	0.001
Male sex	-0.9±1.4	0.50
Systolic blood pressure, mmHg	-0.04±0.04	0.28
Body surface area, m^2	-9.6±2.5	0.01
Model 2 r=0.42 (p<0.0001)		
Age, years	-0.19±0.05	0.001
Male sex	0.14±1.41	0.91
Systolic blood pressure, mmHg	-0.05±0.04	0.23
Weight, kg	-0.09±0.04	0.04

SE - *standard error.*

3.5 Discussion

3.5.1 Main findings

This study provides normative data for LA volumetric parameters and LA strain in a black African population. Females had a higher LAVi compared to males. No difference in peak LA strain was noted between the sexes. Additionally, BSA, weight, and age were important determinants of LA strain.

An increased LAVi is an important marker of chronic pressure overload and is a key measure utilised in clinical practice for the assessment of LV diastolic dysfunction (Nagueh et al. 2009). The recent EchoNoRMAL study indicated that measurements of LA volume may vary considerably among normal individuals in different ethnic populations, implying that certain populations may have lower reference limits for LAVi (Aune et al.2015). In this study, we found that LAVi (19.5±5.9 mL/m^2) in a sub-Saharan African population is within normal defined ranges, albeit on the lower range of defined normality (Figure 3.2) (Lang et al. 2015, Kou et al. 2014, Pritchett et al. 2003 Thomas et al. 2002, Tsang et al. 2002, Wang et al.1984). This is consistent with the findings that ethnicity does influence LAVi measurements, but the mechanism by which this occurs is not understood. Further, when adjusted for 2 standard deviations, the upper limit of this range is 31.3 mL/m^2, which is lower than the value of 34 mL/m^2 utilised in the ASE chamber guidelines (Lang et al. 2015). This implies that consideration of these lower limits should occur when assessing black African patients whose parameters fall within this range of supposed normality. Future studies are required to determine whether this lower level will translate into clinical significance in various disease states.

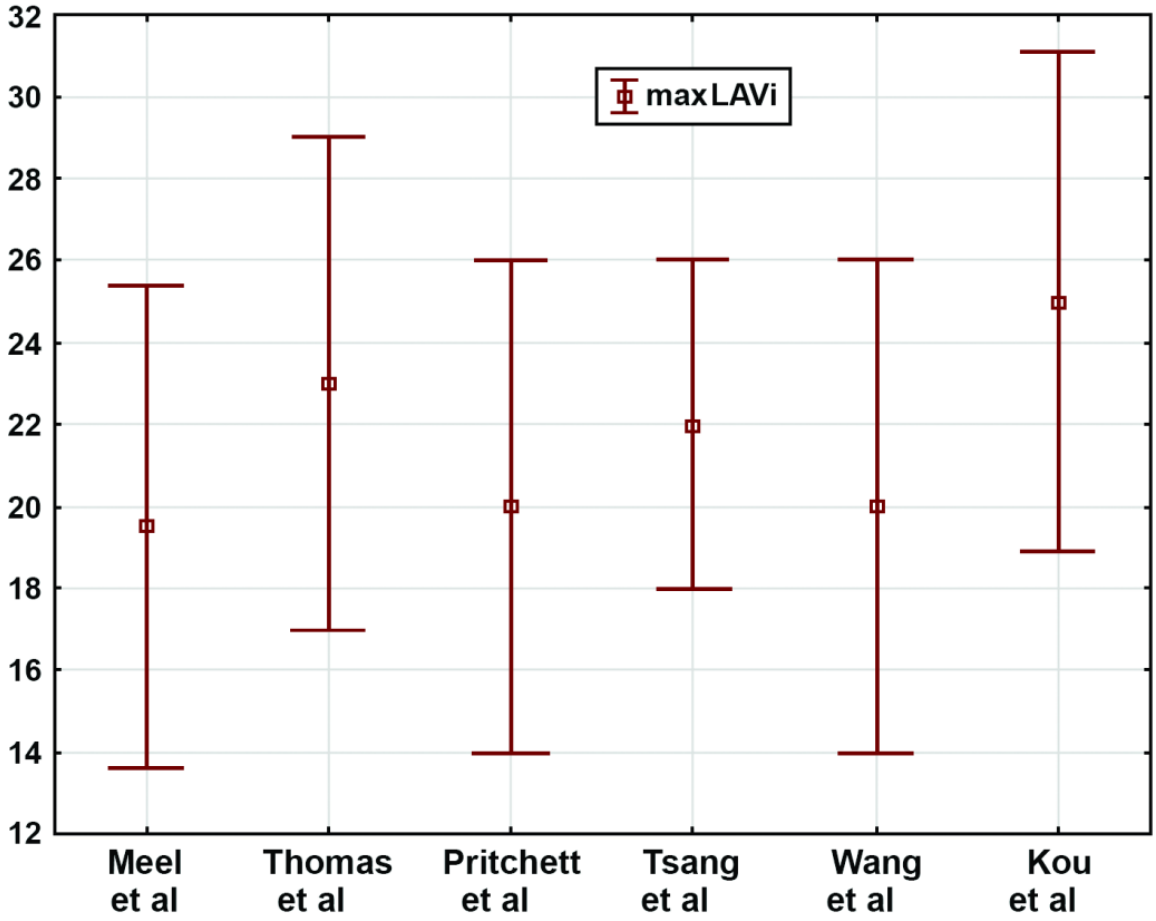


Figure 3.2 Range graph depicting maximum left atrial volume in different studies. The y-axis reflects maximum left atrial volumes in mL/m^2 (mean± standard deviation).

In our study, females had a higher maximum LAVi compared to males. This differs from previous studies in which no difference in maximum LA volume indexed to BSA between sexes was noted (Nikitin et al. 2003, Pritchett et al. 2003, Wang et al. 1984). In this study, females had a higher BMI but a lower BSA compared to males. For a similar weight, females tended to be shorter and this may explain the higher BMI. A higher maximum LAVi in females in this study may be explained by a greater BMI (Caputo et al. 2013, Aurigemma et al. 2009, Leung et al. 2008). Additionally, height may influence LA volumes. Patel et al. showed that prevalence of LA enlargement may be underestimated or overestimated when LA volume is indexed to BSA depending on the individual's obesity status (Patel et al. 2009). Further, in their study it was noted that LA volume indexed to height was not influenced by the level of obesity (Patel et al. 2009). Thus, these anthropometric measurements may need to be taken into account individually instead of simply indexing to BSA or BMI. Our results contrast with older studies of patients with cardiovascular disease in which LA size was influenced mainly by BSA and BMI rather than height (Aurigemma et al. 2009). Aurigemma et al. found weight to be more strongly related to LA size than height (Aurigemma et al. 2009). Due to discrepant findings, the significance of age, sex, and anthropometric parameters as determinants of maximum LAVi remains inconclusive.

There is a lack of data on measurement of strain with Philips QLAB 9 software. Only regional strain data are available from a study done on similar software from the same vendor (Philips QLAB 8.1 software) (Xia et al. 2013). The use of global parameters of LA strain is likely to be more feasible and perhaps more reproducible than regional LA strain analysis in terms of quantitative data and, thus, this study is important to provide some normative values using this vendor's software. The

average values of peak LA strain in the reservoir phase obtained in various studies using GE EchoPAC software are similar to our study (Morris et al. 2015, Sun et al. 2013, Saraiva et al. 2010, Cameli et al. 2009, Kim et al. 2009). However, no direct comparison can be assumed due to current vendor differences in the generation of parameters using speckle tracking. Hence, our study provides reference data for comparison with pathology when using Philips QLAB 9 Software and may offer a useful reference when studying serial evaluation of LA strain in disease states. Our finding of a trend of peak LA strain decreasing with age is similar to findings in studies using other vendors (Sun et al. 2013, Saraiva et al. 2010, Kim et al. 2009). The decline in LA strain had a moderate correlation with aging and implies that, to utilise this parameter to study disease, one must consider the normal age-related decline in peak LA strain.

The impact of biologic variables such as gender, BSA, and BMI on LA peak systolic strain in normal populations has not been extensively studied. In this study as BMI, BSA, and weight increased, LA longitudinal strain decreased. BMI has been found to have an inverse correlation with LA strain, and we found a similar correlation in my study (Caputo et al. 2013, Saraiva et al. 2010). It may be associated with the pro-inflammatory milieu in overweight subjects causing alteration in LV, and subsequently LA, longitudinal strain (Caputo et al. 2013). Sex has been shown to be a factor in determining normal echocardiographic parameters such as right ventricular strain (Chia et al. 2014). However, we found no association between sex and peak LA systolic strain in this population. Finally, it must be highlighted that potential differences in peak global LA reservoir strain may be anticipated among different ethnic groups since variations in LA volumes do occur. However, this has not been systematically studied, and comparisons between

normative data from existing studies is hampered primarily by variations in speckle-tracking software by vendor; and possibly even in different versions of the same software.

Minimal data pertaining to peak negative LA strain in the contractile phase exist. This parameter is a surrogate of LA contraction and would offer important insight into the role of LA contractile function in many disease states in which, a compensatory mechanism for increasing abnormal early relaxation of the LV, necessitates increasing atrial booster function to preserve adequate late LV diastolic filling. Declining LA booster function may be a contributing factor to clinical decompensation in disease states in addition to LV decompensation and perhaps even independently of LV abnormality. Thus, determining normal values and variation with sex and anthropometric measurements on current available vendor software is important to permit further research utilising this parameter in disease states. Currently, there are discrepant data available from a few studies, and this is likely due to different vendors, populations, and techniques being used to measure peak negative strain (Sun et al. 2013, Saravia et al.2010, Kim et al. 2009). The true clinical application of this parameter requires further research.

3.5.2 Study limitations

The study had several limitations:

1) The minority of subjects were older than 60 years of age.

2) LA strain measurement lacks a criterion standard - strain values vary with different software packages.

3) The quantitative values defined for LA strain are vendor-specific.

4) The exercise capacity of the study subjects was not assessed to unmask subclinical diastolic dysfunction and symptoms.

3.6 Conclusion

LAVi measured in a black African population has a reference range that is comparable with guidelines but, importantly, the upper limits of the normal range are lower than guideline definitions. The interpretation of normality requires consideration of sex and anthropometric differences. Measurement of LA strain is feasible and reproducible in this population, and we have provided reference values for this population using QLAB software.

Chapter 4

Effects of age on left atrial volume and strain parameters using echocardiography in a normal black African population

4.1 Abstract

4.1.1 Background

Recent reports have projected an increase in the aging population worldwide. In South Africa where the majority of the population is black, the average life expectancy is on the rise from 52 years in 2005 to 61 years in 2014. Data pertaining to the aging population from the low and middle income countries is scarce. Normal aging amongst other physiological alterations is known to affect cardiovascular structure and function. There are studies in white populations that have evaluated the effects of aging on left atrial (LA) function. No age-related studies pertaining to the LA exist in a black African population.

4.1.2 Objectives

To determine the effects of aging on LA function in a black population.

4.1.3 Methods

This was a prospective cross-sectional study and comprised 120 individuals aged between 18-70 years. The subjects were classified into four age groups: 18-29, 30-39, 40-49, and 50-70 years. LA volumes were measured by biplane Simpson's method, and Philips QLAB 9 (Amsterdam, The Netherlands) speckle-tracking software was used to measure strain parameters (LA peak strain in the reservoir and contractile phase).

4.1.4 Results

The mean age was 38.7 ± 12.8 years (50% men). There was no statistically significant difference in maximum and minimum LA volumes between the four age groups (P>.05). LA pump function increased with age (r = .2, P = .02), and the conduit function decreased with age (r = -0.3, P < .001). There was a significant decrease in the ε_R (P < .0001) with advancing age. Older age was associated with a decrease in diastolic function (r = .4, P < .001). On multivariate linear regression analysis the main predictors of maximum LA volume indexed (LAVi) were male sex, heart rate, E/E´ lateral, and LV mass indexed after adjustment for age. Age was not a significant determinant of ε_R when S´ lateral and E´ medial were added to the model after adjusting for sex and systolic blood pressure.

4.1.5 Conclusions

LA maximum and minimum volumes do not change with age. However, the conduit function decreases with age and the booster function shows a compensatory increase with age as the diastolic function declines with age. ε_R may be a more sensitive marker for assessing LA function than maximum LAVi.

4.2 Introduction

The average life expectancy of South Africans, 80% of whom are blacks, is increasing (Statistics South Africa 2014). Since 2005, life expectancy increased by 8.5 years due to a decline in AIDS related deaths, decreased infant mortality and an improvement in the general health of the populous. Concurrently, the proportion of older black people is increasing. Normal aging results in changes in cardiac structure and physiology (Lakatta and Levy 2003, Gerstenblith et al.1977). For these reasons, age-related reference values in older black individuals are imperative for cardiovascular risk stratification (Lakatta and Levy 2003, Gerstenblith et al.1977).

The LA has been described as a gauge of diastolic burden, and disturbances in its function can result in impairment of overall cardiac performance (D'Andrea et al. 2013, Nikitin et al. 2003). Age-related changes in the LA have been studied extensively in white populations using traditional parameters such as LA size, volumes, and, more recently, 2D strain (Boyd et al. 2011, Aurigemma et al. 2009, Thomas et al. 2002, Spencer et al. 2001). In the Echo-Normal study, the upper reference values for LA diameter were highest for Europeans and American Blacks and lowest for South Asians and Africans (Aune et al. 2015). The change in the upper reference values of LA diameter with increasing age was statistically significant for European, African, and African American men.

Importantly, no age-related reference values for LA volumes or strain exist in black Africans. Additionally, aging populations in the developing world differ from those in developed nations, with respect to limited access to health care, limited social support systems, poverty, rapid urbanisation and adoption of more sedentary lifestyles (Chatterjee et al. 2014). The interplay of these factors coupled with

differences in the ethnicity may cause the two populations to age differently. We suspect that there may be differences in LA structure and function between blacks and Caucasians with normal aging. Thus, we sought to determine the effects of aging on LA function in a black population with the aid of both traditional and newer echocardiographic techniques of 2D strain. We further hypothesised that LA volumetric and strain parameters would demonstrate changes with age in a black population.

4.3 Methods

4.3.1 Study population

From January 2014 to June 2015, 190 normal subjects were screened at our echocardiographic laboratory at Chris Hani Baragwanath Academic Hospital. This cross-sectional sub-study formed part of ongoing research being conducted at our institution to provide normal echocardiographic reference ranges in people of African descent.

The study population was recruited from unrelated staff at Baragwanath Hospital and volunteers who presented themselves to the echocardiographic laboratory following an advertisement about this study. The volunteers were excluded if the image quality was poor or had abnormal 12 - lead electrocardiograms (presence of arrhythmias, chamber enlargement, conduction system abnormalities and evidence of prior infarcts) or screening echocardiogram was abnormal (mitral valve prolapse,

greater than trivial valvular regurgitation, left ventricular hypertrophy and wall motion abnormalities). The subjects were included if they:

1) were asymptomatic,

2) lacked comorbidities (diabetes, cardiovascular disease),

3) were not on chronic medication,

4) were in sinus rhythm.

The final sample comprised 120 individuals (60 women) aged 18 to 70 years. The subjects were classified into four age groups: 18-29, 30-39, 40-49, and 50-70 years. A tolerance of 5 years was allowed for age matching in each subgroup. All the participants gave written informed consent and the study was approved by the local Ethics committee (M140114). A detailed history, clinical examination, electrocardiography and comprehensive echocardiographic exam of the participants were performed.

4.3.2 Echocardiographic examination

Transthoracic echocardiography was performed by an experienced sonographer on a Philips iE33 system (Amsterdam, The Netherlands) using S5-1 transducer. All the echocardiographic measurements were obtained using a standardised protocol, from the standard left parasternal and apical views. An off-line workstation (Xcelera- Philips) was used for data transfer and subsequent analysis.

4.3.3 Two-dimensional and Doppler quantification

Previously described in chapter 3.

4.3.4 2-D Strain imaging

Previously described in chapter 3. The LA stiffness index was calculated non-invasively as the ratio of E/E' lateral and ε_R (Boyd et al. 2011, Kurt et al. 2009).

4.3.5 Statistical analysis

Statistical analysis was performed with Statistica, version 12.5, series 0414 for Windows. Continuous variables are expressed as means ± standard deviations (SDs) or medians (interquartile ranges). Continuous variables according to age categories were compared using one-way ANOVA analysis of variance or Kruskal-Wallis test when the distribution was non-normal. Post-hoc comparisons were performed with the Scheffé test.

Univariate and multivariate linear regression analyses were used to identify possible independent determinants of LA $\varepsilon_{R,}$ and maximum LAVi. Multivariate models to predict LA ε_R and maximum LAVi were selected in a multiple linear regression analysis. Univariate variables with Pearson's correlation coefficient ≥0.8 were not included in the multivariate models. Additionally, only clinically and statistically significant variables (*P <0.05*) were selected for inclusion in multivariate linear regression analysis. The aforementioned models were further analysed using the forward and backward multiple linear regression methods. The assumptions

were verified by performing residual analysis and advanced Durbin-Watson statistics.

The intra-observer and inter-observer variabilities were assessed for peak positive LA ε_R, peak negative LA $\varepsilon_{CT,}$ maximum LAVi, and minimum LAVi. Measurements were done in 20 randomly selected subjects. To assess inter-observer variability two independent observers measured the LA volumetric and strain parameters, whilst intra-observer variability was calculated from the analysis by the same observer after one month of the first measurement. Inter-observer and intra-observer reproducibility was assessed by calculating coefficients of variation (CV). The CV was calculated as the standard deviation of the differences divided by the mean. The T- test for dependent variables was used to compare the mean and SD of the values derived for strain and volumes. A p value<0.05 was considered statistically significant.

4.4 Results

4.4.1 Baseline characteristics and echocardiographic findings

Of the 120 individuals, 60 were men and the mean age of the group was 38.7±12.8 years. Comparisons between the four preselected age groups (Table 4.1) revealed that while all parameters remained within normal defined ranges, there were age related differences. An increment in LV wall thickness ($p< 0.001$), the A wave ($p<0.001$) and E/E' ($p< 0.001$) was noted with aging while a concomitant

decrement in LV volumes (p=0.001) and E wave (p<0.001) was obser*v*ed. No significant changes in LV ejection fraction (p=0.7) and LV mass occurred (p=0.4).

4.4.2 LA volumetric parameters for the total sample

The normative data are presented in Table 4.2. No significant differences were noted between the four age categories in the maximum and minimum LAVi with aging (*P* = 0.1, *P* = 0.2). Furthermore, even though there was a trend of increasing LA_{max} with older age it did not reach statistical significance (*P* = 0.08) (Figure 4.1). No differences were noted in the maximum and minimum LAVi with aging (p=0.1, p=0.2*)*). Further, no correlation was observed between maximum LA volume and age (p=0.08) (Figure 4.1). Analysis of the parameters relating to the various phases of LA function revealed there was no change in reservoir function parameters with age (p>0.05). The conduit function parameters decreased with age while parameters indicative of booster function displayed either a significant increase with age (LA active emptying volume index, p=0.001) or a trend suggestive of increasing function as measured by LA active emptying fraction (Table 4.2, Figure 4.2).

Table 4.1 Baseline clinical and echocardiographic characteristics according to age.*

Variable	Total (18-70) *n*=120	Group 1 (18-29) *n*=34	Group 2 (30-39) *n*=30	Group 3 (40-49) *n*=27	Group 4 (50-70) *n*=29	p value (ANOVA)
Age (y)	38.7±12.8	23.5±3.1	34.5±2.8	43.2±2.7	56.4±6.42	0<.0001
Sex (F:M)	60:60	16:8	13:17	15:12	16:13	0.73
BMI (kg/m^2)	27.9±5.8	25.9±5.8[a,c]	26.2±4.1[b]	31.1 ±5.9	29.2 ± 5.6	0.0003
BSA (m^2)	1.8±0.2	1.8±0.2[a]	1.8±0.2	1.9±0.2	1.8±0.2	0.040
SBP (mmHg)	122±11.0	119.7±10.5	118.9±11.1	126.1±9.9	123.8±11.3	0.04
DBP (mmHg)	76±9.3	72.3±9[a]	76.4±8.7	81.1±7.3	76.5±10.2	0.003
HR	77.2±12.6	78±14	79±13	77±11	75±13	0.468
LV EDD (mm)	42.7±4.9	44±4.3	43.2±5.2	43±5	41±5.3	0.207
LV ESD (mm)	27.1±4.6	27.3±5.4	28±4	27±4.4	26±5	0.20
IV EDD (mm)	9.3±1.8	9.0±2.0[a,c]	9.0±2.0	10±1.4	10±2.3	0.005
LV PWD(mm)	9.0±1.6	8.0±2.0[c]	9.0±1.3	9.3±1.3	10.0±2.0	0.0017
EDV index (mL/m^2)	49.5±13.6	53.0±13.0[c]	54.0±15.0[d]	50.0±12.3	41.0±11.4	0.0010
ESV index (mL/m^2)	18.5±5.9	20.0±5.0[c]	20.0±6.0[d]	19.0±6.3[e]	15.0±5.0	0.0007
LV EF (%)	62.5±8.1	63.1±6.0	63±6.2	61.0±13.0	63.0±7.1	0.731
RWT (ratio)	0.42±0.10	0.37±0.06[a,c]	0.41±0.07	0.44±0.08	0.5±0.12	0.0002
LV mass index (g/m^2)	66.1±18.0	62.2±18.1	67.8±19.3	65.9±17.0	69.0±18.0	0.474
E wave (cm/s)	78.5±17.6	88.0±17.0[c]	76±14.0	82.3±19.0[e]	68.0±15.0	0.0001
A wave (cm/s)	58.9 ± 15.5	53 ± 16.4[c]	54.2±11.4[d]	63 ± 15.2	67.0±15.0	0.0003
DT (m/s)	140.5±53.4	145.0±73.0	129.0±41.0	134.2±45.0	153.4±44.3	0.278
E/A (ratio)	1.4±0.4	1.6±0.5[a,c]	1.4±0.3[d]	1.4±0.3[e]	1.0±0.3	0<.0001
E' medial (cm/s)	9.3±2.8	12.0±2.0[a,c]	10.3±3.0[f,d]	8.1±2.1	7.0±2.0	0<.0001
E' lateral (cm/s)	14.1±3.5	17.1±3.0[a,c]	15.0±3.0[d]	13.0±3.0	11.1±3.0	0<.0001

E/Eˈ medial (ratio)	9.1±2.7	8.0±2.0[a,c]	8.0±2.2[f,d]	11.0±3.0	10.3±3.0	0<.0001
E/Eˈlateral (ratio)	5.8±1.5	5.3±2.0[a]	5.4±1.3[f]	7.0±2.0	6.2±1.3	0.0010
Average E/E´(ratio)	7.4±1.83	6.5±1.4[ac]	6.6±1.4[f,d]	8.5±1.8	8.2±1.7	0<.0001
Sˈmedial (cm/s)	7.4±1.5	8.0±1.2	8.1±2.0[d]	7.3±1.4	7.0 ±1.3	0.005
Sˈlateral (cm/s)	8.7±2.6	9.0±3.0	9.2±3.0	9.0±3.0	8.0±2.0	0.20

*Data reported as mean ± standard deviation or †median (IQR).

[a]Group 1 vs. Group 3 p<0.05, [b]Group 2 vs. Group 3 p<0.05, [c]Group 1 vs. Group 4 p<0.05, [d]Group 2 vs. Group 4 p<0.05, [e]Group 3 vs. Group 4 p<0.05, [f]Group 2 vs. Group 3 p<0.05. BMI - Body mass index. BSA - Body surface area. DBP - Diastolic blood pressure. DT - Deceleration time. EDD - End-diastolic diameter. EDV - End-diastolic volume. EF - Ejection fraction. ESD - End-systolic diameter. ESV - End-systolic volume. F:M - female:male ratio. HR - Heart rate (beats per minute). IV - Interventricular septum. LV - Left ventricular. PWD - posterior wall diameter. RWT - Relative wall thickness. SBP - Systolic blood pressure.

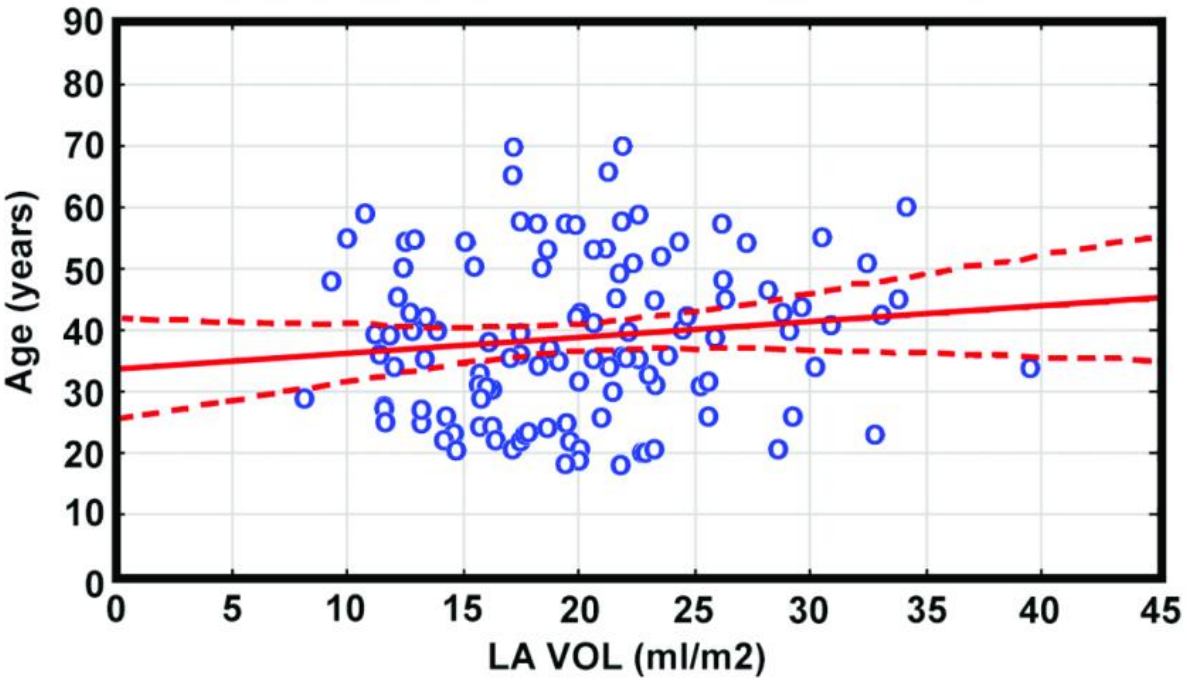


Figure 4.1 Correlation between left atrial volume and age (*r*= 0.14, p=0.08).

Table 4.2 Left atrial volumetric and strain parameters with age.*

Variable	Total (120)	Group 1 (18-29) *n*=34	Group 2 (30-39) *n*=30	Group 3 (40-49) *n*=27	Group 4 (50-70) *n*=29	p value (ANOVA)
LA volumes						
Max-LAVi (mL/m^2)	19.7±5.9	18.4±5.5	19.1±4.7	22.0±7.0	20.2±6.2	0.10
Min-LAVi (mL/m^2)	7.7±3.2	7.3±3.2	7.1±2.6	7.8±3.2	8.5±3.6	0.27
Pre-A LAVi (mL/m^2)	12.2 ±4.4	10.9±4.5[c]	11.1±3.6[d]	12.4±4.4	14.6±4.3	0.003
LA reservoir function						
LA total EV (mL/m^2)	12.2 ± 4.8	11.1±4.2	12.1±4.3	14.2±5.8	11.6±4.6	0.08
LAEF total (%)	59.9±13.5	57.3±13.3	61.9±12.4	63.2±14.1	57.9±13.8	0.25
LA exp index (%)†	152.7 (109.5-228.8)	139 (111.5-218.1)	178.7 (115.4-234)	172.3 (231-114.9)	129.7 (92.4-242)	0.16
LA conduit function						
LA PEVi (mL/m^2)†	6.8 (4.7-9.0)	6.9 (4.7-9.0)	7.4 (6.0-10.2)[d]	8.6 (5.2-11)[e]	4.2(3.1-6.1)	0.0008
Conduit vol (mL/m^2)†	17.8 (12.1-24.5)	19.9 (15.7-28.1)	20.9 (13.9-26.6)	14.6 (11.1-23.2)	15.4 (10.5-18.9)	0.01
LA PEF (%)†	36.8 (28-47)	38.7 (31.6-51)[c]	39.1 (31.4-51)[d]	40.2 (33.6-56)[e]	26 (17.3-35)	0.0001
LA pump function						
LA AEVi (mL/m^2)	4.6±2.6	3.7±2.4[c]	4.0±2.3[d]	4.6±2.7	6.1±2.6	0.001
LAEF Booster (%)	37.7±13.9	32.6±10.6	37.8± 12.5	39.7± 15.4	41.4± 15.8	0.07

LA strain						
ε_R (%)	39.0±8.3	40.7±7.9[c]	42.8±8.5[d]	39.4±7.7[e]	33.2±5.5	<0.0001
ε_{CT} (%)	-2.7±2.5	-3.2±3.0	-2.9±2.5	-2.6±2.2	-1.9±2.1	0.27
Left atrial stiffness index						
E/E' lateral /ε_R	0.2±0.05	0.1± 0.03[a,c]	0.1±0.04[b,d]	0.2±0.06	0.2±0.05	<0.001

*Data reported as mean ± standard deviation or †median (IQR).

[a]Group 1 vs. Group 3 p<0.05, [b]Group 2 vs. Group 3 p<0.05, [c]Group 1 vs. Group 4 p<0.05, [d]Group 2 vs. Group 4 p< 0.05, [e]Group 3 vs. group 4 p<0.05, [f]Group 2 vs. Group 3 p< 0.05. LA AEVi - *Left atrial active emptying volume index;* LAEF - *Left atrial emptying fraction*; *LA exp index - Left atrial expansion index*; Max-LAVi - *Maximum left atrial volume index*; Min- LAVi - Minimum left atrial volume index; PEF - *Passive emptying fraction*; PEV - *Passive emptying volume;* Pre-A LAVi - *Pre- atrial contraction left atrial volume index*; ε_R - *Peak left atrial strain in the reservoir phase*; ε_{CT} -*Peak left atrial strain in the contractile phase.*

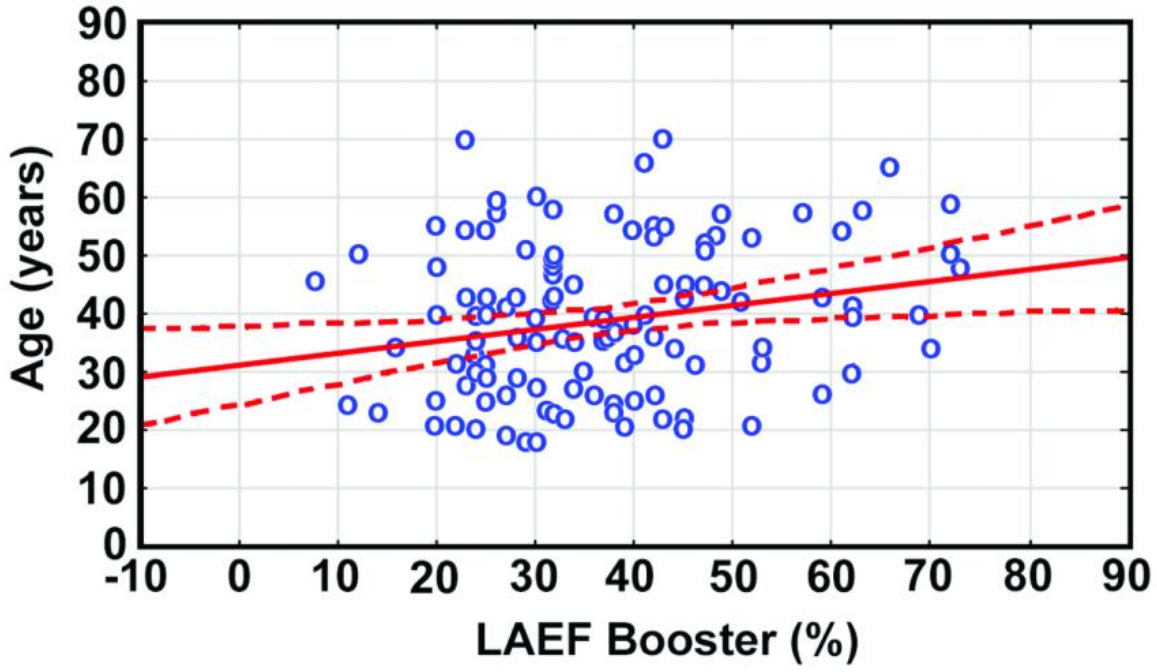


Figure 4.2 Correlation between left atrial emptying fraction and age (*r*=0.2, p=0.02).

4.4.3 Determinants of maximum LAVi

On univariate analysis the main determinants of maximum LAVi were sex (p=0.03), body mass index (p=0.009), systolic blood pressure (p=0.03), heart rate (p=0.0002), end-diastolic volume index (p=0.001), end-systolic volume index (p=0.002), E wave (p=0.01), A wave (p=0.02), E/E' medial (p=0.008), S' lateral (p=0.004), E/E' lateral (p<0.001), average E/E' (p<0.001), minimum LAVi (p<0.001), LA emptying fraction total (p=0.03), pre-A LAVi (p<0.001), and LV mass indexed (LVMi) (p=0.015). Age was not a determinant of maximum LAVi (p=0.2).

On multivariate linear regression analysis, the main predictors of maximum LAVi were male sex, heart rate, E/E' lateral, and LVMi after adjustment for age (Table 4.3).

Table 4.3 Multivariate linear regression analysis for maximum left atrial volume indexed

Variables	β coefficient± standard error	Partial coefficient	R^2	p value
Model 1 *r*=0.54, p< 0.0001				
Age (y)	-0.04±0.04	-0.09	0.11	0.32
Men	-3.2±1.16	-0.25	0.15	0.006
Heart rate (beats/min)	-0.13±0.04	-0.27	0.09	0.003
E/E' lateral (ratio)	1.5±0.39	0.35	0.14	0.0001
LVMi (g/m^2)	0.08±0.03	0.26	0.08	0.004

LVMi - *left ventricular mass index*

4.4.4 LA strain indices

Normative data are presented in Table 4.2. There was a significant decrease in the LA ε_R ($p<0.0001$) with increased age (Figures 4.3 and 4.4). No significant difference was noted in the LA ε_{CT} between the age groups ($p=0.27$). The LA stiffness index increased with age ($p<0.001$) (Table 4.2).

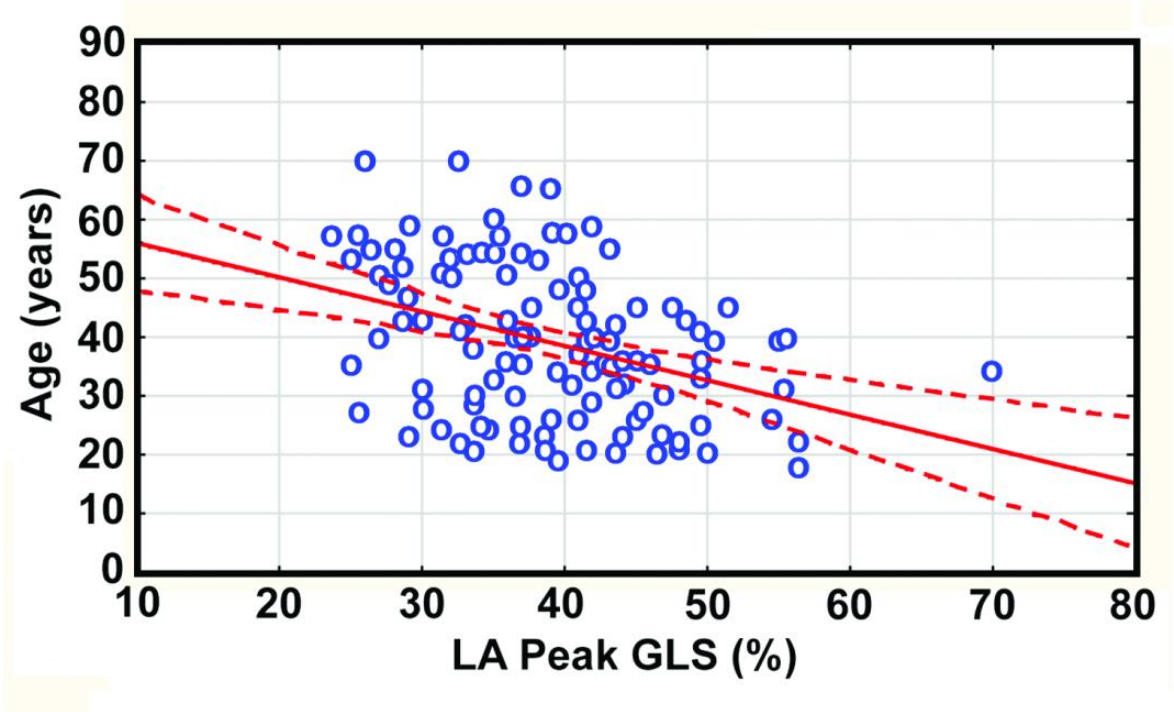


Figure 4.3 Correlation between left atrial peak global longitudinal strain (%) and age (*r*=-0.36, p<0.001).

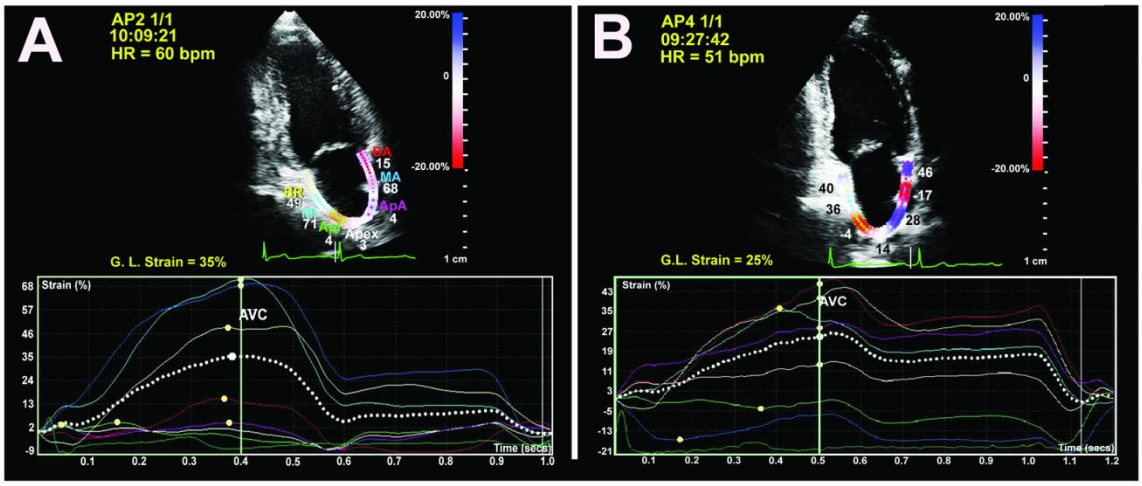


Figure 4.4 Two-chamber view depicting peak left atrial systolic strain in a 21 year-old male (A) compared to a 51-year-old male (B).

4.4.5 Factors determining LA strain

On univariate analysis factors such as age ($p<0.001$), body surface area ($p=0.002$), systolic blood pressure ($p=0.04$), LV mass ($p=0.01$), E wave ($p< 0.001$), E/A ratio ($p=0.04$), E' medial ($p<0.001$), E' lateral ($p<0.001$), E/E' medial ($p=0.002$), S' medial ($p<0.001$), S' lateral ($p<0.001$), average E/E' ($p=0.006$), LA emptying fraction total ($p<0.001$), pre-A LAVi ($p=0.005$), minimum LAVi ($p<0.001$), LA expansion index ($p<0.001$), passive emptying volume ($p=0.003$), and passive emptying fraction ($p<0.001$) were determinants of LA ε_R . On multivariate linear regression analysis, age, E/E' medial, E' medial, and reservoir phase indices (LA expansion index and LA emptying fraction total) were independently associated with LA ε_R after adjustment for sex and systolic blood pressure (Table 4.4). Age was no longer a significant determinant when S' lateral and E' medial were added to the model after adjusting for sex and systolic blood pressure (Table 4.4).

Table 4.4 Multivariate linear regression analysis for left atrial strain in the reservoir phase (ε_R)

Variables	β coefficient ± standard error	Partial coefficient	R^2	p value
Model 1 r=0.57, p< 0.0001				
Age (y)	-0.16±0.05	-0.28	0.19	0.003
Men	-0.6±1.34	-0.05	0.08	0.64
Systolic blood pressure (mmHg)	-0.02±0.04	-0.04	0.14	0.61
Left atrial emptying fraction total (%)	0.23±0.04	0.4	0.03	<0.0001
E/Eˈ medial (ratio)	-0.72±0.27	-0.2	0.25	0.01
Model 2 r=0.57, p<0.0001				
Age (y)	-0.16±0.05	-0.27	0.19	0.003
Men	-0.83±1.33	-0.06	0.08	0.53
Systolic blood pressure (mmHg)	-0.04±0.04	-0.10	0.12	0.26
Left atrial expansion index (%)	0.02±0.004	0.46	0.03	<0.0001
E/Eˈ medial (ratio)	-0.72±0.27	-0.24	0.25	0.009
Model 3 r=0.5, p<0.0001				
Age (y)	-0.09±0.07	-0.12	0.45	0.16
Systolic blood pressure (mmHg)	-0.01±0.04 -0.02	-	0.14	0.071
Men	-0.79±1.37 -0.06	-	0.05	0.56
Sˈ lateral (cm/s)	0.94±0.28	0.30	0.13	0.001
Eˈ medial (cm/s)	0.70±0.33	0.2	0.49	0.03

4.4.6 Reproducibility of LA volumetric and strain parameters

The intra-observer coefficient of variation for maximum LA volume was 3% with a mean difference of 0.23±0.61 (p=0.10). The inter-observer variability for maximum LA volume was 0.9% with a mean difference of 2.7±2.6 (p=0.0001). The intra-observer coefficient of variation for LA ε_R was 4.8% with a mean difference of 3.2±0.67 (p=0.3) and for LA ε_{CT} was 4.6% with mean difference of 1.43±0.31 (p=0.3). The inter-observer variability coefficient was 9% for both LA ε_R (p=0.6) and ε_{CT} (p=0.6) with a mean difference of 3.2±0.35 and 1.2±0.13, respectively.

4.5 Discussion

This study provides normative age-related data for LA volumetric parameters and LA strain in a black African population. Normal aging is associated with key physiological changes such as rising systolic blood pressure and declining LV diastolic function with abnormal relaxation and increased LA stiffness. Volumetric analysis of LA function reveals that global measures of LA function remain normal but conduit function declines with increasing booster function with advancing age. Further, normal aging is associated with an absolute decline in global LA reservoir strain.

A key factor that may influence LA volumetric measurements is aging. Maximum LAVi did not change with aging in our study. Additionally, age was not an independent predictor of maximum LAVi in our study. There are discrepant findings from a number of studies relating to the effect of aging on LA volume (Aune et al. 2015, Lang et al. 2015, D'Andrea et al. 2013, Aurigemma et al. 2009, Okamatsu et

al. 2009, Pritchett et al. 2003, Spencer et al. 2001). This may be attributed to varying sample sizes, racial differences, and different methods and vendors used for assessing maximum LA volumes. However, the impact of aging on LA volumetric measurements that are surrogates of conduit and booster function appears to be more consistent. Our findings suggest that with aging, a decrement in conduit volumes occurs while an increase in booster function volumes occurs simultaneously, which is consistent with other studies (Nikitin et al. 2003, Spencer et al. 2001). This may be explained by an age-associated decrease in early relaxation, thus resulting in relative decrease in the conduit function and greater reliance on booster function for LV filling (Nikitin et al. 2003, Spencer et al. 2001). The evidence for a decline in early relaxation was based on the declining E' on tissue Doppler imaging and E wave on pulsed-wave Doppler in this study. Further, the increase in age-related filling pressures can be attributed to the greater relative increase in the E velocity compared to E' velocity with aging. However, the aforementioned parameters still fall within the normal reference ranges defined in guidelines (Nagueh et al. 2009).

The major factors determining LA ε_R are the initial and final length of the longitudinal fibres. Initial length is determined by atrial contraction and LA minimum volume (Barbier et al.1999). The final length is determined by atrial relaxation, the atrial longitudinal compliance in response to the volume of blood entering the atrium from the pulmonary veins during ventricular systole, and the descent of the mitral annulus during systole (S') (Todaro et al. 2012, Boyd et al. 2011, Barbier et al. 1999). The latter may be affected by factors governing LV systolic function and end-systolic volume (Barbier et al. 1999).

The age-related decline in LA ε_R in our study conforms to earlier studies by Sun et al. and Saraiva et al. (Sun et al. 2013, Saraiva et al. 2010). In this study, factors that may determine initial length, namely LA minimum volume and LA ε_{CT} — a surrogate of LA contraction, do not differ among age groups. The effect of aging on factors determining final length, are more intriguing. There are no validated echocardiographic parameters that can be used as a surrogate of atrial relaxation (Kurt et al. 2009). In this study, LA stiffness increased significantly with aging. The S' decreased with age despite a lack of age dependent change in maximum LA volume. This may infer that with aging in normal individuals, the decrement we observed in peak reservoir strain most likely occurs due to abnormalities determining final length rather than initial length. The S' at both annuli decreases with age while atrial stiffness increases in this study. While age may be a predictor of LA ε_R it appears that S' and indices of diastolic function such as E' are more consistent predictors. The link between decreasing efficient early relaxation and LA strain is difficult to elucidate in normal individuals with normal LA pressures. The decreased LA compliance due to increased pressures would hamper atrial longitudinal function resulting in decreased atrial strain with age. One postulate may be that the same process predisposing to diminishing abnormal early relaxation, may also affect the LA reservoir function, for example, fibrosis of the sub-endocardium and atria with aging or sub-endocardial ischaemia (Boyd et al. 2011). The latter may be associated with decreased longitudinal shortening of the LV during systole, thus causing decreased mitral annular motion and, consequently, diminished atrial longitudinal strain during the reservoir phase.

A final observation from our data is a lack of correlation between volumetric indices, and LA strain with aging. As outlined earlier, with aging there is greater

reliance on booster function for LV filling. However, the LA ε_{CT} does not increase concomitantly. Similarly, LA volume maximum and LA volume minimum do not change with aging implying that volumetric filling during the reservoir phase is maintained despite peak reservoir strain decreasing with age. The above must imply that strain decreases absolutely or relatively to LA volume and is a more sensitive marker of atrial dysfunction with aging (Boyd et al. 2011). The effect of radial compliance or contraction on LA volume was not studied and may represent a compensatory means of maintaining the observed changes in LA volume with age despite the relative or absolute decrement in atrial longitudinal strain.

4.5.1 Study Limitations

This study had several limitations:

1) A minority of subjects were over age 60;

2) LA strain measurement lacks a criterion standard — strain values vary with different software packages;

3) Exercise capacity of the study subjects was not assessed to unmask subclinical diastolic dysfunction and symptoms.

4.6 Conclusion

LA contractility increases with age as the conduit function decreases. These changes reflect the compensatory mechanisms associated with the age-related normal decline in LV diastolic function. There is no change in maximum and

minimum LAVi with healthy aging. There is an age-related decline in LA ε_R before maximum LAVi. This suggests that LA ε_R may be a more sensitive marker for assessing LA function. The aforementioned age-related normative data may serve as a guide for future studies in black African populations.

Chapter 5

Atrioventricular function assessment in chronic rheumatic mitral regurgitation: looking beyond the left ventricle.

5.1 Abstract

5.1.2 Background

Chronic MR has historically been shown to affect the LV function primarily. The impact on morbidity and mortality of increased LA volume in MR has recently been highlighted and yet LA does not feature prominently in the current guidelines compared to the LV. Additionally, LA dysfunction may exist in the absence of LV dysfunction and absence of symptoms; and thus have implications in terms of earlier surgical referral of this patient subgroup. Further, the two chambers function as a unit and thus must be studied as such because the functional abnormality of one impacts the other, especially in diseased states such as MR. Thus, we aimed to study the atrio-ventricular mechanics in CRMR with particular emphasis on the LA, as it may primarily be afflicted by the rheumatic process.

5.1.3 Methods

This cross-sectional study comprised 77 patients with isolated moderate or severe CRMR, and 40 controls. All underwent echocardiographic exam on a Philips iE33 system. The standard LA and LV measurements were performed in accordance with the current ASE guidelines. LA function was assessed in the reservoir, conduit and contractile phase with conventional echocardiography and 2D strain imaging (QLAB 9 speckle tracking software).

5.1.4 Results

The mean age was 44±13.6 with 83% female subject. LA static volumes were higher in CRMR compared to controls ($p<0.05$). LA stiffness index was greater in CRMR than controls (0.95±1.89 vs 0.16±0.13, $p=0.009$). LA dysfunction was noted predominantly in the reservoir and contractile phases compared to controls ($p<0.05$). Conduit function parameters except left atrial passive emptying fraction (LA PEF) were still preserved when compared to controls ($p<0.05$). LA ε_R, LA ε_{CT} and LV peak systolic strain (PSS) were decreased in CRMR compared to controls ($p<0.05$). Eighty-six percent of the patients had decreased LA ε_R, 58% had depressed LV PSS. Decreased ε_R and normal LV PSS was noted in 42%. Thirteen percent had normal ε_R and LV PSS. Only one patient had normal ε_R with decreased LV PSS. On multivariate linear regression analysis, the main determinants of LA ε_R were age, LV PSS and LAVi ($p<0.001$).

5.1.5 **Conclusion**

In CRMR there is predominant LA dysfunction in the reservoir and contractile phases. LA dysfunction likely precedes LV dysfunction. Therefore, abnormalities in LA function may serve as an early indication for surgery. Finally, age irrespective of CRMR may be an important contributor to decline in LA and LV function.

5.2 Introduction

Chronic mitral regurgitation (MR) results in volume overload of the left ventricle (LV) and the left atrium (LA) (Aksakal et al. 2012). The LA compensates by increasing compliance through neuro-hormonal modulation and undergoing structural changes such as cellular hypertrophy and interstitial fibrosis to meet the needs of the new haemodynamic load (Aksakal et al. 2012, Enriquez-Sarano et al. 2005). The LV also undergoes similar adaptation to the increased preload (Gaasch et al. 2008). After a period of compensation, LA and LV dysfunction supervenes, culminating in atrial fibrillation, HF and death if left untreated (Borg et al. 2009). Until now the LV and the LA in MR have been studied in isolation, despite the fact that their interaction is crucial for optimal cardiovascular haemodynamics in both health and disease states (Nishimura et al.1997). Both the LA and the LV undergo phases of compensation before reaching the lower limb of the Frank-Starling curve and irreversible remodelling (Mehrzad et al. 2014, Bonow et al. 2012, Gaasch and Meyer 2008). We suspected that the temporal sequence may differ in an individual patient, where in some LA may transition from a phase of compensation to decompensation prior to LV and the reverse may occur in others, depending on a variable combination of preload, afterload and intrinsic characteristics of the two chambers. Therefore, the alteration in some patients' LA functional indices may serve as an early sign heralding the onset of a decompensated state. This may occur even in the presence of normal LV functional indices and absence of symptoms (Enriquez-Sarano et al. 2005). Further, in RHD, we suspect that the LA haemodynamics will differ, compared to the LA in MR due to other aetiologies, secondary to involvement of the of the LA by the rheumatic process (Edwards and Chisholm 2006, Shriki et al.

2011, Roberts and Vermani 1978, Plaschkes et al. 1971). Additionally, the impact of preoperative dual chamber dysfunction may confer greater postoperative morbidity and mortality than isolated LV or LA dysfunction. Thus, limiting surgical indications to predominantly LV parameters may miss the opportunity to intervene early. Thus, we sought to study the LA and LV function in moderate or severe chronic rheumatic mitral regurgitation (CRMR) with the aid of traditional volumetric parameters and newer echocardiographic techniques of 2D strain. Further, it was hypothesized that in CRMR, LA dysfunction may precede LV dysfunction.

5.3 Methods

This study was part of a prospective cross-sectional study at the Chris Hani Baragwanath Academic Hospital (CHBAH). Patients were enrolled from January 2014 and October 2014. All patients were screened and patients deemed to have moderate or severe CRMR, were referred for possible inclusion in the study. Ninety-one patients with presumed chronic, rheumatic MR underwent clinical evaluation, resting electrocardiogram and detailed echocardiographic assessment according to a pre-determined protocol.

The inclusion criteria were patients aged 18 years or older with echocardiographic features of moderate or severe chronic rheumatic MR. Patients were excluded if:

1) they had significant aortic valve disease;

2) concurrent MS with a valve area of less than 2.0 cm^2;

3) documented ischaemic heart disease;

4) preexisting non-valvular cardiomyopathy;

5) prior cardiac surgery;

6) congenital or pericardial disease;

7) pregnancy;

8) severe systemic disorders such as renal failure;

9) uncontrolled hypertension (systolic blood pressure>140mmHg and diastolic blood pressure>90mmHg) on medication;

9) severe anaemia (haemoglobin <10g/dL).

Fourteen patients were excluded due to the following: AF, anemia, renal dysfunction, mild MR, MR of non-rheumatic etiology and inadequate image quality. The final sample included 77 patients. Forty age and gender-matched controls were also included in the study. A tolerance of 5 years was allowed for age matching.

The study was approved by the University of the Witwatersrand Ethics Committee (M140114).

5.3.1 Echocardiographic evaluation

Transthoracic echocardiography was performed on all patients in the left lateral position by experienced sonographers using a S5-1 transducer on a Philips iE33 system (Amsterdam, The Netherlands). The images were obtained according to a

standardised protocol. The data was transferred and analysed off-line using the Xcelera workstation (Philips).

5.3.2 Two dimensional and Doppler quantification

All linear chamber measurements were performed according to the ASE chamber guidelines (Lang et al. 2005). Maximum LA volume (LA_{max}) was obtained at left ventricular end-systole, from the 2D frame, just before MV opening (Kowallick et al.2014, Vianna-Pinton et al. 2009). Pre-atrial volume (V_{pre-A}) was obtained from the diastolic frame, just before MV reopening as the result of atrial contraction (Vianna-Pinton et al. 2009). LA minimum volume (LA_{min}) was assessed at left ventricular end-diastole, from the smallest volume seen after LA contraction (Kowallick et al. 2014, Vianna-Pinton et al. 2009).

Left atrial (LA) phasic function assessment was done by using the following formulae:

1) Reservoir function: LA emptying fraction (LAEF) total = $(LA_{max} - LA_{min})/LA_{max}) \times 100\%$; Expansion index = $(LA_{max} - LA_{min})/ LA_{min}) \times 100\%$;

2) Conduit function: Passive emptying volume (PEV) = $(LA_{max} - V_{pre-A})$; Passive LA emptying fraction (LAPEF) = $LA_{max} - V_{pre-A}/LA_{max}$ x100%; and conduit volume = LV stroke volume - $(LA_{max} - LA_{min})$

3) Booster pump function: LA active emptying fraction (LAAEF) = $(LA_{pre-A} - LA_{min})/ LA_{pre-A}) \times 100\%$; LA active emptying volume (LA active EV) = $(V_{pre-A} - LA_{min})$ (Vianna-Pinton et al. 2009, Kowallick et al. 2014).

All the LA volumetric parameters were indexed to body surface area (BSA) (Vianna-Pinton et al. 2009).

Left ventricular (LV) end-diastolic- volume (EDV), end-systolic-volume (ESV) and ejection fraction (EF) were assessed using the Simpsons method and indexed to BSA (Lang et al. 2015). Measurements relating to LV diastolic function were performed in accordance with the ASE guidelines on diastolic function and included pulse wave Doppler at the mitral tips and tissue Doppler of both medial and lateral mitral annuli (Nagueh et al. 2009). Measurements relating to the RV were based on the ASE guidelines on the RV (Rudski et al. 2010).

MR was considered rheumatic in aetiology when the morphology of the valve satisfied the World Heart Federation (WHF) criteria for the diagnosis of chronic rheumatic heart disease (RHD) (Reményi et al. 2012), MR severity was assessed using qualitative, semi-quantitative and quantitative methods as per the ASE and ESC valvular regurgitation guidelines (Lancelloti et al. 2013, Zoghbi et al. 2003). In equivocal cases the echocardiographic data was integrated with the clinical evaluation by an experienced cardiologist to distinguish moderate from severe MR.

5.3.3 Speckle tracking echocardiography

5.3.3.1 Left atrial strain

Apical four and two-chamber (4C and 2C) views were obtained using two dimensional grey-scale echocardiography for speckle tracking analysis (Vieira et al. 2014, Vianna- Pinton et al. 2009). This was performed during end-expiratory breath-hold and stable ECG recording (Kowallick et al. 2014, Vieira et al. 2014, Vianna-

Pinton et al. 2009). An adequate grey-scale image that allowed separation of myocardial tissue and surrounding structures was obtained (Vianna-Pinton et al. 2009). Three consecutive cardiac cycles were recorded and averaged (Vianna-Pinton et al. 2009). The frame rate was set between 60 and 80 frames per second (Vianna-Pinton et al. 2009). Philips QLAB version 9.0 software allowed off-line semi-automated analysis of speckle-based strain. The endocardial surface of the LA was traced manually in both 4C and 2C views by a three point and click approach (Vianna-Pinton et al. 2009). The system then automatically generated an epicardial surface tracing (Vianna-Pinton et al. 2009). The region of interest (ROI) was thus created and manually adjusted as needed, to allow for adequate speckle tracking.

The software divides the ROI into seven segments in the 2C and 4C views. It then generates the longitudinal Ɛ curves for each segment and a mean curve of all segments (Vianna-Pinton et al. 2009). The onset of the QRS was used as a reference point for calculation of LA strain.

5.3.3.2 Left ventricular strain

Two dimensional echocardiography images were obtained at end-expiration from LV apical long-axis, 4C, 3C and 2C views with frame rates of 60 and 80 frames per second (Younan 2015). Three consecutive cardiac cycles were recorded and averaged (Marciniak et al. 2007). LV endocardial surface was traced manually in the three views by a point and click approach (Younan 2015, Kocabay et al. 2014). The speckle tracking points were modified to allow for adequate speckle tracking of the LV wall (Younan 2015, Kocabay et al. 2014). The LV was divided into 17 segments. Peak LV longitudinal systolic strain was calculated for apical long-axis 4C, 3C and

2C views, and global LV systolic strain was calculated by averaging the three apical views (Younan 2015, Kocabay et al 2014). The onset of the QRS was used as a reference point for calculation of LV strain.

The LA stiffness index was calculated non-invasively as the ratio of E/E´ lateral and ε_R (Boyd et al. 2011, Kurt et al. 2009).

5.3.4 Statistical analysis

Statistical analysis was performed with Statistica, version 12.5, series 0414 for Windows. Continuous variables are expressed as means ± SDs or medians (IQRs). Student's t test or Mann-Whitney U test were used to compare continuous variables. Categorical variables were evaluated by the chi-square and Fisher's exact test when necessary. Univariate and multivariate linear regression analyses were used to identify possible independent determinants of peak positive LA ε_R. Six separate models to predict peak positive LA ε_R were selected in a multiple linear regression analysis. Univariate variables with Pearson's correlation coefficient ≥0.8 were not included in the multivariate models. Additionally, only clinically and statistically significant variables ($P < 0.05$) were selected for inclusion in multivariate linear regression analysis. The aforementioned models were further analysed using the forward and backward multiple linear regression methods. The assumptions were verified by performing residual analysis and advanced Durbin-Watson statistics.

The intra-observer and inter-observer variabilities were assessed for peak positive LA ε_R, peak negative LA $\varepsilon_{CT,}$ and LV global longitudinal strain. Measurements were done in 20 randomly selected subjects. To assess inter-

observer variability two independent observers measured the LA volumetric and strain parameters (LA and LV), whilst intra-observer variability was calculated from the analysis by the same observer after one month of the first measurement. Inter-observer and intra-observer reproducibility was assessed by calculating coefficients of variation (CV). The CV was calculated as the standard deviation of the differences divided by the mean. The T- test for dependent variables was used to compare the mean and SD of the values derived for strain and volumes and to calculate the significance value. A p value <0.05 was considered statistically significant.

5.4 Results

Baseline characteristics of the study and the control population are shown in Table 5.1. The control and MR groups showed no significant difference with regards to age, gender, BMI, blood pressure and heart rate. Moderate MR was present in 51(66%) and severe MR was present in 26 (34%). The LA and LV diameters and volumes were increased in the study patients compared to controls ($p<0.05$). Surrogates of LV systolic function were worse in CRMR compared to controls (S´ medial: 6.3±1.3 cm/s vs 7.1±1.6 cm/s, $p=0.004$; ESVi: 40.0±22.2 mL/m^2 vs17.8±6.4 mL/m^2, $p<0.0001$). Patients with CRMR had higher E/E' ratio compared to controls (E/E´ medial ratio: 20.1±10.7 vs 9.4±3.0, $p<0.0001$) as a result of higher E wave velocity (133.8±48.1 vs 77.0±17.6, $p<0.0001$). However, there was no difference in the ejection fraction between the group with MR and controls ($p=0.07$).

LA phasic volumes and functional analysis are summarised in Table 5.2. The LA maximum, minimum, and pre-atrial contraction volumes were higher in the study patients compared to controls ($p<0.0001$). However, the indices of reservoir, conduit and contractile function were all depressed in the study patients compared to controls ($p<0.001$). Left atrial stiffness index was greater in MR patients compared to controls (0.95±1.89 vs 0.16±0.13, $p=0.009$).

Maximum-LAVi, minimum LAVi and pre-A LAVi showed no statistical difference between moderate MR and severe MR, despite a trend toward larger volumes in severe MR. There was no difference in the reservoir function parameters between the moderate and severe MR groups ($p>0.05$). Amongst the conduit phase parameters LA PEV was lower in moderate MR (12.0±9.8ml/m^2vs20.4±17.2ml/m^2, $p<0.001$) and is consistent with the greater E wave velocity (114.7±40.4cm/s vs170.5±39.9cm/s, $p<0.001$) in severe MR compared to moderate MR. The active emptying fraction (booster function) was greater in moderate MR compared to severe MR (27.6±13.1%vs17.6±10.7%, $p<0.001$). The LA stiffness index was less in moderate MR compared to severe MR (0.6±1.83vs1.65±1.8, $p=0.01$).

As expected the LV dimensions were less in moderate MR compared to severe MR (LVEDD 52.6±8.4 vs 59.1±9.9, $p<0.001$; 39.1±9.4 vs 45.9±8.2, $p<0.001$). The volumes were greater in severe MR compared to moderate MR (EDVi- 113.3±29.1ml/m^2 vs 82.8±25.1ml/m^2, $p<0.001$; ESVi- 48.1±24.5ml/m^2 vs 35.7±20ml/m^2, $p<0.001$) but there was no difference in the ejection fraction (58.3±17.0%vs 58.5±10.3%, $p=0.19$). There was no difference in systolic function (lateral S' velocity - 7.3±2.1cm/s vs7.3±3.2cm/s, $p=0.2$) between the moderate and severe MR groups. Analysis of diastolic function parameters revealed that there was

no difference in E' but the E wave was higher and consequently E/E' higher in severe MR (13.8±7.4 vs18.4±10.6, p<0.001).

LA peak systolic and contractile strain were decreased in both moderate and severe MR compared to controls (LA peak systolic strain 21.3±9.5 vs 19.5±11.1 vs 39.0±7.3; p<0.001 and Contractile strain -0.48±1.79 vs -0.67±1.46 vs -2.28±2.05; p<0.001) but no difference was noted between moderate and severe MR groups (P>0.05). LV peak global strain was preserved in moderate and severe MR when compared to controls (-15.3±5.0 % versus -16.5±5.5% versus -17.9±2.1%, p=0.06). Thus, there was no difference in LA and LV strain in between moderate and severe MR groups (p>0.05).

LA and LV strain parameters are indicated in Table 5.2 and Figure 5.1. LA peak systolic reservoir strain (ε_R), peak contractile strain (ε_{CT}) and LV peak global systolic strain (LV PSS) were decreased in the MR group compared to the controls (p=0.04) (Table 5.2). Eighty-six percent of MR patients had decreased LA ε_R (Figure 5.1). Fifty-eight percent had depressed LV PSS. Thirteen percent had normal ε_R and LV PSS (category 1). One patient had normal LA ε_R, with decreased LV PSS (category 2). Decreased LA ε_R and LV PSS was present in 44% (category 3). Decreased LA ε_R and normal LV PSS was noted in 42% (category 4).

Table 5.1 Baseline clinical and echocardiographic characteristics of study patients.*

Variable	Study patients (n=77)	Controls (n=40)	p value
Clinical			
Age (years)	44±13.6	42±13.4	0.4
Gender (M:F)	13:64	8:32	0.6
BSA (m^2)	1.7±0.2	1.8±0.2	0.01
BMI (kg/m^2)	27.1±5.9	28.4±6.2	0.3
SBP (mmHg)	124.2±11.4	124±12.5	0.93
DBP (mmHg)	77±9.1	75.7±12.6	0.52
Heart rate (beats/min)	77.1±12.6	76.3±14.1	0.75
NYHA (I/II / III) (%)	42%/ 49%/9%	-	
Hypertension (%)	40	-	
HIV (%)	13	-	
Hypertension and HIV (%)	15	-	
Echocardiographic			
LV EDD (mm)	54.8±9.4	42.5±4.8	<0.0001
LV ESD (mm)	41.4±9.4	27.1±4.2	<0.0001
IVSD (mm)	8.6±2.1	9.5±1.9	0.02
LV PWD (mm)	8.5±1.5	9.2±1.9	0.03
EDVi (mL/m^2) †	93.2±30.1	47.9±13.5	<0.0001

ESVi (mL/m^2) †	40.0±22.2	17.8±6.4	<0.0001
LAVi (mL/m^2) †	64.1±39.9	21.9±4.9	<0.0001
LVEF (%)	58.5±12.9	62.8±11.2	0.07
LVMi (kg/m^2) †	102.7±36.3	65.6±20.3	<0.0001
E wave (cm/s)	133.8±48.1	77.0±17.6	<0.0001
A wave (cm/s)	98.4±33.5	59.6±13.0	<0.0001
Deceleration time (ms)	214.5±62.2	135.4±42.3	<0.0001
E/A ratio	1.5±0.6	1.3±0.4	0.06
E´medial (cm/s)	7.3±2.3	8.8±2.8	0.002
E´ lateral (cm/s)	10.1±4.0	13.4±3.6	<0.0001
E/E´ medial (cm/s)	20.1±10.7	9.4±3.0	<0.0001
E/E´ lateral (cm/s)	15.4±8.8	5.9±1.6	<0.0001
S´ medial (cm/s)	6.3±1.3	7.1±1.6	0.004
S´ lateral (cm/s)	7.3±2.5	8.2±2.6	0.07
PASP (mmHg)	35.1±16.9	21.5±6.4	<0.0001

* Data are presented as mean± SD or %. † Values are indexed to BSA. BSA - *Body surface area*; BMI - *Body mass index*; DBP - *Diastolic blood pressure*; EDVi,- *End-diastolic volume indexed*; ESVi - *End-systolic volume indexed*; HIV - Human Immuno-deficiency Virus; IVSD - *Interventricular septal diameter*; LAVi - *Left atrium volume indexed*; LV - *Left ventricle*; LV EDD - *Left ventricular end-diastolic diameter*; LVEF - *Left ventricular ejection fraction*; LVESD - *Left ventricular end-systolic diameter*; LVMi - *Left ventricular mass indexed*; NYHA - *New York Heart Association*; PASP - *Pulmonary artery systolic pressure*; PWD - *Posterior wall diameter*; SBP - *Systolic blood pressure.*

Table 5.2 Left atrial and ventricular peak systolic strain and left atrial volumetric and phasic functional parameters in chronic rheumatic mitral regurgitation.*

Variable	CRMR (n=77)	Control (n=40)	p value
Volumes			
Maximum LAVi (mL/m^2) †	64.1±39.9	21.9±4.9	<0.0001
Minimum LAVi (mL/m^2) †	39.6±35.5	8.1±3.1	<0.0001
Pre A-LAVi (mL/m^2) †	49.4±39.0	13.6±4.6	<0.0001
Reservoir function			
LA total emptying volume indexed (mL/m^2) †	24.6±13.7	15.6±12	<0.001
LAEF total (%)	45.4±16.5	61.2±12.0	<0.0001
LA exp index (%)	98.6±62.6	194.4±131.8	<0.0001
Conduit function			
LAPEVi (mL/m^2) †	14.9±13.4	8.2±4.4	0.003
LAPEF (%)	26.7±19.4	38.3±14.9	0.001
Conduit volume (mL/m^2) †	28.8±21.6	16.7±9.8	<0.001
Booster function			
LA AEF (%)	24.1±13.1	38.6±13.4	<0.0001
LA AEVi (mL/m^2) †	9.7±6.3	4.9±2.8	<0.0001
Strain parameters			
ε_R (%)	20.7±10.0	39.0±7.3	<0.0001
ε_{CT} (%)	-0.5±1.6	-2.28±2.05	<0.0001

LV global peak systolic strain (%)	-16.1±5.3	-17.9±2.1	0.04
Left atrial stiffness index	0.95±1.89	0.16±0.13	0.009

* Data are presented as mean± SD. † Values are indexed to BSA. LA AEVi - *left atrial active emptying volume index;* LAEF - *left atrial emptying fraction*; LA exp index - *left atrial expansion index*; Max-LAVi - *maximum left atrial volume index*; Min- LAVi - *minimum left atrial volume index*; PEF - *passive emptying fraction*; LA PEVi - *Left atrial passive emptying volume index*; Pre-A LAVi, - *pre- atrial contraction left atrial volume index*; ε_R - *peak left atrial strain in the reservoir phase*; ε_{CT} - *peak left atrial strain in the contractile phase.*

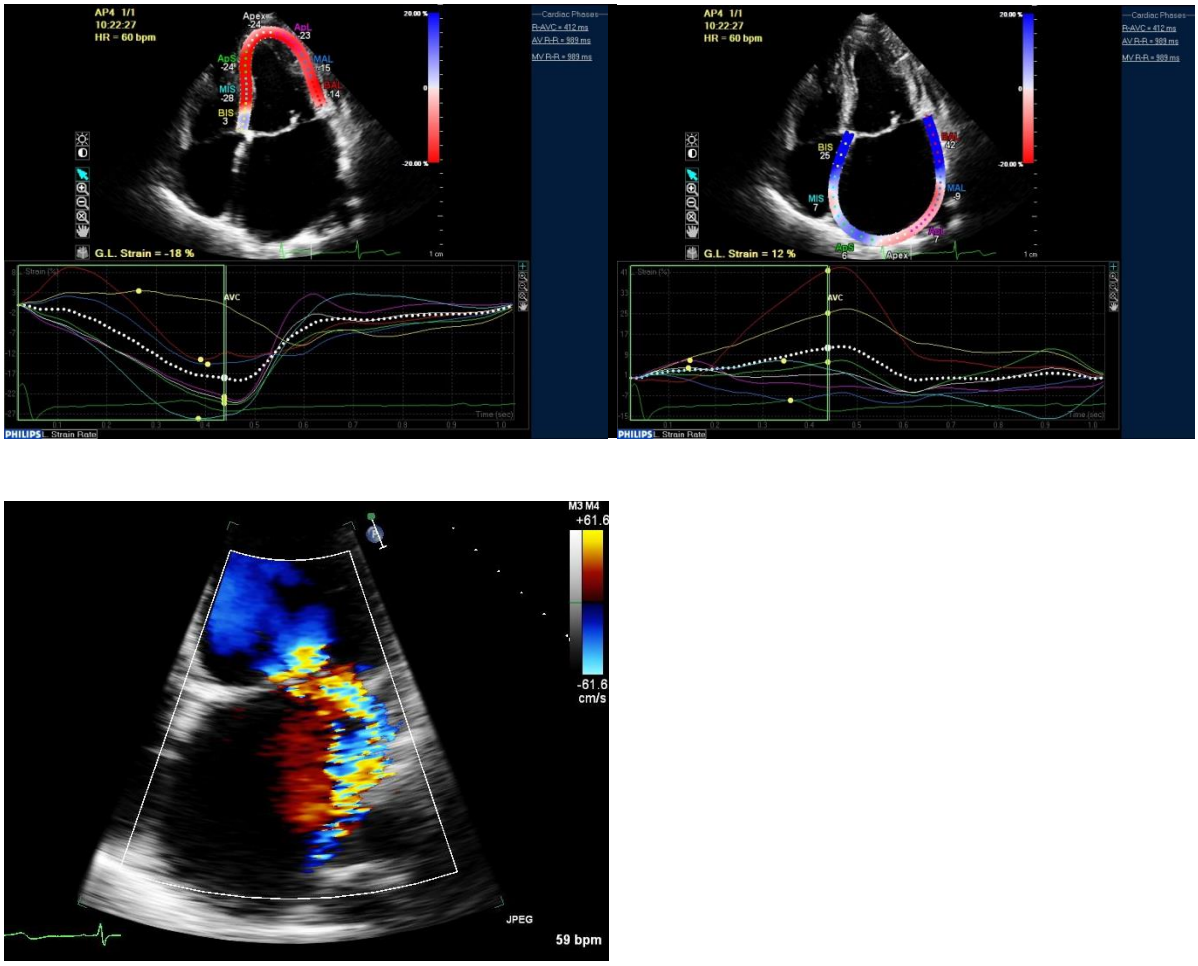


Figure 5.1 Depicting decreased LA peak systolic strain (top right) and preserved LV peak systolic strain (top left) in a patient with severe rheumatic mitral regurgitation (bottom).

5.4.1 Predictors of LA peak systolic strain

On univariate analysis age, gender, LVESD, LVEF, ESVi, S' velocity at medial and lateral mitral annuli, LV PSS, maximum LAVi and hypertension emerged as predictors of peak LA systolic strain in CRMR (Table 5.3).

On multivariate linear regression analysis, the main determinants of LA peak systolic strain were age, LV PSS and maximum LAVi (Table 5.4).

5.4.2 Reproducibility of LA peak systolic strain, LA peak negative strain and LV peak systolic strain

The intra-observer coefficient of variation for LA ε_R was 4.8% with a mean difference of 3.2±0.67 (p=0.3) and for LA ε_{CT} was 4.6% with mean difference of 1.43±0.31 (p=0.3). The inter-observer variability coefficient was 9% for both LA ε_R (p=0.6) and ε_{CT} (p=0.6) with a mean difference of 3.2±0.35 and 1.2±0.13, respectively.

The intra-observer coefficient of variation for LV PSS was 2.4% with mean difference of 1.1±2.7 (p=0.09). The inter-observer variability coefficient for LV PSS was 9.8% with a mean difference of 0.25±2.4 (p=0.6) respectively.

Table 5.3 Univariate analysis for determinants of peak systolic LA strain in chronic rheumatic mitral regurgitation.

Variable	β±SE	R	p value
Age(years)	-0.38±0.07	0.52	<0.001
Gender(M)	6.9±2.9	0.25	0.02
LVESD(mm)	-0.41±0.11	0.39	0.0003
LV ESVi (mL/m^2)	-0.14±0.04	0.32	0.003
LV PSS (%)	-0.89±0.19	0.47	<0.001
LVEF(%)	0.21±0.08	0.27	0.014
Lateral Sˈ(cm/s)	1.49±0.43	0.37	0.0009
Medial Sˈ(cm/s)	3.57±0.76	0.47	<0.001
LAVi (cm/s)	-0.12±0.02	0.48	<0.001
LA stiffness index	-1.2±0.60	0.23	0.04

LAVi - *Left atrial volume indexed*; LVEF - *Left ventriclular ejection fraction*; LVESD - *Left ventricle end-systolic diameter;* LVESVi-*Left ventricular end-systolic volume index*; LV PSS - *Left ventricular peak systolic strain.*

Table 5.4 Multivariate analysis for determinants of peak systolic LA strain in chronic rheumatic mitral regurgitation.

Model 1 R=0.82 p<0.001

Variable	β±SE	p value
Age(years)	-0.31±0.05	<0.001
Gender(M)	2.8±1.96	0.15
Medial Sˈ(cm/s)	1.30±0.63	0.04

LAVi(mL/m^2)	-0.11±0.01	<0.001
LV PSS (%)	-0.48±0.15	0.001
Model 2 R=0.81 p<0.001		
Variable	**β±SE**	**p value**
Age(years)	-0.33±0.05	<0.001
Gender(M)	3.85±1.9	0.05
LV PSS(%)	-0.57±0.15	<0.001
LV ESVi (mL/m^2)	-0.03±0.03	0.37
LAVi (mL/m^2)	-0.10±0.01	<0.001
Model 3 R=0.81 p<0.001		
Variable	**β±SE**	**p value**
Age (years)	-0.33±0.05	<0.001
Gender(M)	3.7±1.9	0.06
LV PSS (%)	-0.60±0.16	0.0003
LVEF(%)	0.02±0.06	0.67
LAVi (mL/m^2)	-0.11±0.01	<0.001
Model 4 R=0.69 p<0.001		
Variable	**β±SE**	**p value**
Age(years)	-0.30±0.06	<0.001
Gender(M)	3.7±2.3	0.11
LV PSS(%)	-0.47±0.21	0.03
LVEF(%)	0.03±0.08	0.62

Medial S' (cm/s)	1.47±0.78	0.06
Model 5 R=0.81 p<0.001		
Variable	**β±SE**	**p value**
Age (years)	-0.33±0.05	<0.001
Gender(M)	3.79±1.97	0.05
LVESD (mm)	-0.01±0.10	0.85
LV PSS (%)	-0.62±0.17	<0.001
LAVi (mL/m^2)	-0.10±0.001	<0.001
Model 6 R=0.81 p<0.001		
Variable	**β±SE**	**p value**
Age(years)	-0.33±0.05	<0.001
Gender(M)	3.8±1.9	0.05
LAVi (mL/m^2)	-0.10±0.01	<0.001
LV PSS (%)	-0.59±0.13	<0.001
LA stiffness index	-0.33±0.38	0.39

LA - *Left atrium*; LAVi - *Left atrial volume indexed*; LVEF - *Left ventriclular ejection fraction*; LVESD - *Left ventricle end-systolic diameter*; LVESVi - *Left ventricular end-systolic volume index;* LV PSS - *Left ventricular peak systolic strain.*

5.5 Discussion

The main findings of this study are:

1) Absolute volumes of the LA increase during the three phases compared to normal whereas the relative percentage change in volume is diminished in all phases.

2) Both reservoir and booster LA strain was decreased in the study group compared to normal individuals.

3) LA reservoir strain was abnormal in the majority of patients (86 %) while concomitant diminished LV strain was found in only half of these patients (44%).

4) Age, maximum LAVi and LV PSS were the most important determinants of peak left atrial reservoir strain.

The LA has three main functions namely: reservoir, conduit and contractile function (Todaro et al. 2012). During the reservoir phase the LA receives blood from pulmonary veins during LV systole; in the conduit phase there is passive emptying of blood into the LV during early diastole; and in the contractile phase the LA actively ejects blood into the LV in late diastole (Todaro et al. 2012). MR is characterised by systolic volume overload of the LA (Moustafa et al. 2011, Borg et al. 2009). In this study volumetric measures of global LA function were increased namely LA maximum, minimum and pre-atrial contraction volume. The increased LA maximum volume would be expected secondary to systolic volume overload as a result of MR which occurs in addition to the normal venous return from the pulmonary veins. An increased pre-A LA and minimum LA volumes similar to prior studies was also noted in the present study (Ren et al. 2014, Aksakal et al. 2012, Moustafa et al. 2011, Borg et al. 2009). However, there appears to be discrepancies in the literature with regard to whether the three phasic LA volumes are increased (Ren et al. 2014, Aksakal et

al. 2012, Moustafa et al. 2011, Borg et al. 2009). Borg et al. and Ren et al. found an increment in the percentage change of reservoir LA volumes with preserved booster function based on volumetric indices (Ren et al. 2014, Yurdakul et al. 2014, Borg et al. 2009). In contrast, both in our study and in those of Aksakal et al. and Moustafa et al., a relative decrement in reservoir and booster function was observed (Aksakal et al. 2012, Moustafa et al. 2011). Of the three phases, the conduit function, was preserved or increased in all the studies (Ren et al. 2014, Yurdakul S et al. 2014, Aksakal et al. 2012, Moustafa et al. 2011, Borg et al. 2009). The possible reasons for similarities and differences in the phasic LA functional parameters in these studies may be attributed to a variable combination of duration and severity of MR, LV compliance, LA compliance and the intrinsic characteristics of the LA and the LV (Gasparovic et al.2014, Ren et al. 2014, Yurdakul S et al. 2014, Cameli et al. 2013, Aksakal et al. 2012, Moustafa et al. 2011, Borg et al. 2009).

It is likely that findings from the present study may relate to altered LA and LV pathophysiology in MR. In the patient exhibiting compensation with significant MR, the LV diastolic function would be expected to be normal or increased to accommodate the increased blood volume that would be required to enter the LV. This ultimately causes an increase in LVEDV, the essential step in the path to LV diastolic overload. Thus, atrial volumetric markers of conduit and booster function would be normal or even potentially relatively increased. Conversely, in the decompensated state, impaired LV systolic function will result in significant diastolic dysfunction and a high LV end-diastolic pressure which would then impair LV diastolic filling and result in higher LA volumes during these phases. The increased pre-A LA and minimum LA volumes observed in this study, implies that atrial filling of the LV during diastole is impaired. This implies that pan-diastolic LV diastolic

dysfunction can occur in patients with normal LVEF and in the absence of overt clinical LV HF. Thus, the atrial volumetric markers in diastole may serve as surrogates for impaired LV diastolic dysfunction of the LV in compensated MR patients. Prior studies and the recent ASE guideline on LV diastolic dysfunction, accentuate the difficulties of utilising conventional mitral inflow Doppler and annular tissue Doppler parameters in MR (Zaid et al. 2013). Identifying this pathophysiological phase may be important as it implies that despite the eccentric remodelling of the LV in MR, the diastolic compliance of the LV may become affected, resulting in suboptimal early filling as reflected by the impairment during the conduit phase. However, with an impairment in LV diastolic early relaxation, atrial booster function would increase resulting in a greater proportion of filling in late diastole as is observed in patients with LV diastolic dysfunction due to other causes e.g. hypertension. This expected increment in booster function does not occur and this must imply the coexistence of intrinsic LA contractile dysfunction. Fibrosis of the LA maybe a key abnormality contributing to this dysfunction which may be attributed to three potential factors: aging, chronic volume overload and the rheumatic process itself (Gasparovic et al. 2014, Cameli et al. 2013, Asakal et al. 2012, Casaclang-Verzosa et al. 2008, Edwards et al.2006, Shriki et al. 2011, Roberts and Vermani 1978, Thiedemann and Ferrans 1977, Plaschkes et al. 1971).

We noted a decrease in LA ε_R and ε_{CT} in the majority of the patients. Similarly, some studies report that strain during the reservoir phase increases with preserved booster strain in MR compared to a normal heart (Borg et al. 2009). These differences relate to all the reasons we proposed above for my volumetric findings. In this study, the decrease in ε_R can be explained by:

1) An increase in initial length maybe expected in this cohort due to increased LA minimum volume.

2) A decrease in the final length maybe due to the decrease in mitral annular systolic descent which we observed.

The latter may reflect LV longitudinal systolic impairment in MR (Zaky et al. 1967, Simonson et al. 1989, Pai et al. 1991, Elnoamany and Abdelhameed 2006).

A second hypothesis is that intrinsic LA compliance is impaired as evidenced by the increased LA stiffness index. Therefore despite an increase in the LA maximum and LA minimum volumes and thus the reservoir volume, the peak ε_R does not increase as expected, due to a limitation in the ability of the atrial wall to stretch in response to volume overload as in the study by Borg et al. (Yurdakul et al. 2014, Borg et al. 2009). This implies that the same pathophysiological process impairing relaxation of the atria (for example fibrosis) may be responsible for intrinsic abnormal atrial contractile function as supported by histopathology and MRI studies (Cameli et al.2013, Gasparovic et al. 2014).

In chronic moderate or severe MR, the two main patterns noted were depressed LA reservoir strain with either normal or depressed LV peak systolic strain. This implies that LA function may decline in some patients before LV longitudinal function. This must relate to different clinical profiles for the same degree of MR e.g. age or intrinsic abnormality of the LA compared to the LV such as degree of fibrosis, abnormal energetics and neuro-hormonal factors. LA contractile performance improves after surgery, suggesting a state of decreased atrial function prior to surgery, even in patients with apparently normal LV function (Dardas et al. 2004).

Based on the aforementioned data from prior studies and the data from this study, I postulate that in chronic MR, five major groups of patients can be identified:

Group 1 - This group comprises patients with normal LA and LV function (category one in this study);

Group 2 **-** is characterised by increased early LV filling (preserved conduit and reservoir function) while atrial contraction is decreased (decreased A') with normal LV function (similar to the findings of Borg et al. 2009);

Group 3 **-** is characterised by decrement in the reservoir, contractile and conduit function of the LA; pan-diastolic decrement of ventricular filling, LV diastolic dysfunction with normal systolic LV function (category 4 in our study and Askakal et al. 2012);

Group 4 **-** decreased LA conduit, contractile and reservoir function; pan-diastolic filling impairment with impairment of LV longitudinal function with normal EF (category 3 in our study, Yurdakul et al. 2014). This correlates to the transitional LV phase of MR and phase where the LA is enlarged with normal or elevated left atrial pressure (Gaasch and Meyer 2008, Braunwald and Awe 1963);

Group 5 – decompensated phase with irreversible abnormalities of the LA and LV structure and function in all phases (Braunwald and Awe 1963, Gaasch and Meyer 2008).

However, from the discussion above and variable findings in different studies it is clear that not all patients with chronic MR can be neatly categorised into these five groups and that numerous grey-zones exist between them. Thus, these five groups may serve as a mere guide to help in risk stratification of patients with MR, who may

or may not benefit from surgical intervention but the decision still needs to be individualised.

In contrast to what we expected, the functional indices of reservoir and conduit function were deranged to a similar extent, in both moderate and severe MR. This may be explained by a combination of factors such as direct involvement of the LA by rheumatic process, volume overload secondary to MR, and age related fibrosis in this cohort of rheumatic MR. Furthermore, it can be speculated that volume overload is not the sole cause of LA dysfunction in rheumatic MR, and that the aforementioned factors contribute to a variable extent, in LA remodelling and impaired function. Additionally, the relatively more compliant LA in moderate MR resulted in a greater booster function and thus active emptying fraction in this group. The greater passive emptying volume in severe MR despite greater LV filling pressures can be explained on the basis of proportionately higher volumes in severe MR compared to moderate MR. As expected there was no difference in the LV ejection fraction between the two groups as this is “preserved” until late stage in the natural history of MR (Bonow et al 2012). LA strain was depressed to a similar degree in both groups, implying abnormalities of strain manifesting even in moderate rheumatic MR, likely due to intrinsic abnormalities of the LA, rather than simply a result of changes induced by volume overload. However, LV strain was preserved in both groups, and this further argues for using LA functional and strain parameters as a guide for clinical follow up and perhaps referral for surgery, rather than LV parameters.

Age, coupled with LV PSS and maximum LAVi were by far the most important predictors of peak LA strain in our study. As the maximum LAVi increased (atrial wall stretch), LV PSS decreased. This was unexpected and can be explained on the basis of decreased LA compliance in the study. Aging was associated with decreased LA peak systolic strain. The decrease in LA reservoir strain can be attributed to a decrease descent of the mitral annulus with age and possibly to intrinsic abnormalities of the LA such as altered energetics and increasing fibrosis as a result of the aging process (Burstein and Nattel 2008, Casaclang –Verzosa et al. 2008, Lakatta and Levy 2003). Thus, identifying abnormal LA strain is important but its causes are likely multifactorial.

5.5.1 Study Limitations

Our study had several limitations:

1) Diagnostic coronary angiogram and right and left heart catheterisation were not performed on all patients unless there was an indication for surgery.

2) MR severity was not confirmed by another modality such as Cardiac MRI or 3D echocardiography.

3) Patients with mild MR and AF were excluded.

5.6 Conclusion

In chronic rheumatic mitral regurgitation there is functional decline of predominantly the reservoir and the contractile atrial phases. Decline in LA function likely precedes the decline in LV function as noted from the predominant decrease in LA longitudinal strain with or without preserved LV strain in this study. Advancing age may be a contributing factor independent of CRMR to changes in LA and LV function.

Chapter 6

Unmasking right ventricular dysfunction in chronic rheumatic mitral regurgitation

6.1 Abstract

6.1.1 Background

In chronic rheumatic mitral regurgitation (CRMR) RV function may be influenced by several mechanisms including interaction with LV mechanics; neuro-hormonal abnormalities; increased afterload associated with secondary pulmonary hypertension; and in RHD, possible direct RV myocardial involvement following rheumatic carditis. No studies have documented abnormalities of RV function by conventional or newer techniques of speckle tracking echocardiography (STE) in CRMR.

The aims of this study were:

1) To test the utility of RV peak systolic strain (PSS) as a tool for assessing RV function in patients with CRMR; and compare STE with traditional RV systolic function indices.

2) To determine predictors of RV PSS.

6.1.2 Methods

We prospectively enrolled 77 patients with moderate or severe CRMR and 40 age and gender matched controls, seen from 2014 and 2015 at the Chris Hani Baragwanath Academic Hospital. All patients underwent transthoracic echocardiography using a Philips iE33 system. The data was transferred and analysed off-line using the Xcelera workstation (Philips). RV PSS and LV PSS were measured using Philips QLAB 9 speckle tracking software.

6.1.3 Results

The mean age was 44±13.6years with 83% females. No difference was noted in the tricuspid annular plane systolic excursion and RV S´ in patients with CRMR and controls (2.1±0.4 cm vs 2.2±3.2 cm, p=0.78; 13.2±11.8 cm/s vs 11.6±2.0 cm/s, p=0.39). There was no difference in RV systolic function in the group with moderate MR compared to the one with severe MR (RV S´11.6 (9.9-14.6) cm/s vs 11.4(9.4-13.4) cm/s, p=0.29). The RV PSS was lower in the CRMR group compared to controls (-16.8±4.5% vs -19.2±3.4%, p=0.003). Patients with severe MR had greater degree of reduction in RV PSS compared to moderate MR group (-14.3±4.23% vs -18±4.18%, p<0.0001). Patients with LV systolic dysfunction had a greater decrement in RV PSS and LV PSS compared to those with preserved LV systolic function (p=0.001). PASP was greater in those with systolic dysfunction compared to those with preserved LV systolic function (p<0.02). However, no difference in the conventional RV systolic function parameters was noted between those with normal LV systolic function and those with poor LV systolic function (p>0.05). On multivariate linear regression analysis after adjusting for covariates, LV PSS was an independent predictor of RV PSS (p=0.01).

6.1.4 Conclusion

In CRMR, RV PSS is a sensitive marker of subclinical RV systolic dysfunction and in addition to LV systolic function, may play an important role with regards to timing of surgical intervention in this patient group.

6.2 Introduction

Systolic function of the RV is a known predictor of mortality after acute myocardial infarction or CABG, in HF and primary PHT (De Groote et al. 2012, Lang et al. 2010, Damy et al. 2009). The limited studies in organic degenerative MR have failed to conclusively define the prognostic role of the RV in MR (Le Torneau et al. 2013). In addition to the LV parameters, RV systolic function provides adjunctive information in the decision-making process regarding surgical intervention in MR (Hyllen et al. 2014, Le Torneau et al. 2013). Preoperative RV function is an important determinant of intraoperative and postoperative outcomes in MR and thus has prognostic implications (Le Torneau et al. 2013, Mafessanti et al. 2012). Additionally, RV dysfunction may have important implications in terms of predicting greater haemodynamic impairment of the LV and secondary PHT due to MR (Grose et al.1983, Polak et al.1983). Yet the RV remains under-studied, partly due to its complex geometry, which presents challenges to its accurate structural and functional assessment by conventional echocardiography (Fukuda et al. 2011, Rudski et al. 2010). Recently, newer imaging techniques such as speckle tracking-derived RV strain have emerged, which offer several advantages over traditional echocardiographic parameters for assessing overt and subclinical RV systolic dysfunction (Morris et al. 2016, Hyllen et al. 2014, Kumar et al. 2014, Fine et al. 2014, Ternacle et al. 2013, Guendouz et al. 2012). There are no studies that have assessed RV function in rheumatic MR.

We thus aimed:

1) To study the RV systolic function using STE and compare RV PSS with conventional echocardiographic parameters.

2) To determine the predictors of RV peak systolic strain in CRMR.

6.3 Methods

We conducted a prospective cross - sectional study at the Chris Hani Baragwanath Academic Hospital (CHBAH). Patients were enrolled from January 2014 and October 2014. All patients were screened and patients deemed to have moderate or severe chronic rheumatic MR were referred for possible inclusion in the study. A total of 91 patients with presumed chronic, rheumatic MR underwent clinical evaluation, resting electrocardiogram and detailed echocardiographic assessment according to a pre-determined protocol.

The inclusion and exclusion criteria were similar to those described in chapter 5. The study was approved by the University of the Witwatersrand Ethics Committee (M140114).

6.3.1 Echocardiographic evaluation

As described in chapter 5.

6.3.2 Two dimensional and Doppler quantification

As described in chapter 5.

6.3.3 Speckle tracking echocardiography

RV free wall peak systolic strain (PSS) was derived from modified apical 4 chamber view (A4C) RV focused view (Kumar et al. 2014). Three consecutive cardiac cycles were recorded and averaged (Todaro et al. 2015). The frame rate was set between 60 and 80 frames per second (Todaro et al. 2015). Once the three points (RV apex, medial and lateral tricuspid annulus) were defined, the software automatically traced the endocardial and epicardial border (Kumar et al. 2014). Philips QLAB version 9.0 software allowed off-line, semi-automated analysis of speckle-based strain. This results in the division of RV into six standard segments in the apical 4-chamber view (Mingo-Santos et al. 2015, Kumar et al. 2014, Konishi et al. 2013). The region of interest (ROI) once created, can be manually adjusted as needed to allow for adequate speckle tracking (Hyllen et al. 2014). The free wall RV PSS was obtained by averaging 3 lateral segments (the basal RV lateral wall, the mid-RV lateral wall, and the apical RV wall) (Todaro et al. 2015). The interventricular septum was excluded from analysis (Nowell et al. 2014, Mingo - Santos et al. 2015, Konishi et al. 2013). The longitudinal Ɛ curves for each segment and a mean curve of all segments was then generated by the software. These curves were used to derive RV free wall PSS.

6.3.3.1 Left ventricular peak systolic strain

As described in chapter 5.

6.3.4 Statistical analysis

Statistical analysis was performed with Statistica version 12.5, series 0414 for Windows. Continuous variables are expressed as means ± SDs or medians (IQRs). Student's t test or Mann-Whitney U test were used to compare continuous variables. Categorical variables were evaluated by the Chi-square and Fisher's exact test when necessary. A p value of<0.05 was recognised as statistically significant.

Univariate and multivariate linear regression analysis was used to identify possible independent determinants of RV PSS. Univariate variables with Pearson's correlation coefficient ≥0.8 were not included in the multivariate models. Additionally, only clinically and statistically significant variables (P <0.05) were selected for inclusion in multivariate linear regression analysis. The aforementioned models were further analysed using the forward and backward multiple linear regression methods. The assumptions were verified by performing residual analysis and advanced Durbin-Watson statistics.

The intra- and inter-observer variabilities were assessed for RV free wall and LV PSS. Measurements were done in 20 randomly selected subjects. To assess inter-observer variability two independent observers measured the strain parameters whilst intra-observer variability was calculated from the analysis by the same observer after one month of the first measurement. Inter-observer and intra-observer reproducibility was assessed by calculating coefficients of variation (CV). The CV was calculated as the standard deviation of the differences divided by the mean. The T- test for dependent variables was used to compare the mean and SD of the values derived for strain and volumes and to calculate the significance value. A p value<0.05 was considered statistically significant.

6.4 Results

6.4.1 Clinical characteristics

There was no statistical significant difference in age, gender, SBP, DBP, BMI and HR between the patients with MR and the controls (p>0.05) (Table 6.1). Hypertension, HIV and combination of the two comorbidities were identified in 41.5%, 12.9% and 15.5%, respectively. Forty-two percent of the patients were in NYHA functional class I, the remainder were in class II (49%) and III (9%), respectively.

Table 6.1 Baseline clinical characteristics of the study population.*

Variable	CRMR n=77	Controls n=40	p value
Age (years)	44±13.6	42±13.4	0.4
Gender (M:F)	13:64	8:32	0.6
Body surface area (m^2)	1.7±0.2	1.8±0.2	0.01
Body mass index (kg/m^2)	27.1±5.9	28.4±6.2	0.3
SBP (mmHg)	124.2±11.4	124±12.5	0.93
DBP (mmHg)	77±9.1	75.7±12.6	0.52
Heart rate (beats/min)	77.1±12.6	76.3±14.1	0.75

* Data are presented as mean± SD or %. DBP - *Diastolic blood pressure.* SBP – *Systolic blood pressure*.

6.4.2 Echocardiographic characteristics

Among the CRMR patients, moderate MR was present in 51(66%) and severe MR in 26 (34%). The LV end-systolic and end-diastolic volumes were higher in the CRMR group compared to controls (p<0.0001) (Table 6.2). The LV systolic and diastolic function parameters were altered in CRMR group compared to controls (p<0.001) (Table 2). Left and right atrial volumes indexed were higher in the MR group compared to controls (LAVi: 64.1±39.9 mL/m^2 vs 21.9±4.9 mL/m^2, p<0.0001; RAVi: 23.1±12.9 mL/m^2 vs 18.6±5.4 mL/m^2, p=0.03) (Table 6.2). Greater degree of PHT was present in the MR group compared to controls (35.1±16.9mmHg vs 22.1±5.6mmHg, p<0.0001). No difference was noted between TAPSE and RV S´ between CRMR and control group; or when moderate and severe MR groups were compared (p>0.05) (Table 6.2).

Table 6.2 Echocardiographic parameters of the study population.*

Variable	CRMR (n=77)	Controls (n=40)	p value
LV parameters			
EDD (mm)	54.8±9.4	42.5±4.8	<0.0001
ESD (mm)	41.4±9.4	27.1±4.2	<0.0001
IVSD (mm)	8.6±2.1	9.5±1.9	0.02
LV PWD (mm)	8.5±1.5	9.2±1.9	0.03
EDVi (mL/m^2) †	93.2±30.1	47.9±13.5	<0.0001
ESVi (mL/m^2) †	40.0±22.2	17.8±6.4	<0.0001

LAVi (mL/m^2) †	64.1±39.9	21.9±4.9	<0.0001
EF (%)	58.5±12.9	62.8±11.2	0.07
LVMi (kg/m^2) †	102.7±36.3	65.6±20.3	<0.0001
E wave (cm/s)	133.8±48.1	77.0±17.6	<0.0001
A wave (cm/s)	98.4±33.5	59.6±13.0	<0.0001
Deceleration time (m/s)	214.5±62.2	135.4±42.3	<0.0001
E/A ratio	1.5±0.6	1.3±0.4	0.06
E´medial (cm/s)	7.3±2.3	8.8±2.8	0.002
E´ lateral (cm/s)	10.1±4.0	13.4±3.6	<0.0001
E/E´ medial (cm/s)	20.1±10.7	9.4±3.0	<0.0001
E/E´ lateral (cm/s)	15.4±8.8	5.9±1.6	<0.0001
S´ medial (cm/s)	6.3±1.3	7.1±1.6	0.004
S´ lateral (cm/s)	7.3±2.5	8.2±2.6	0.07
LV PSS (%)	-16.1±5.3	-17.9±2.1	0.04
RV parameters			
RV base (mm)	32.1±6.9	30.8±4.7	0.28
RV S´ (cm/s)	13.2±11.8	11.6±2.0	0.39
TAPSE (cm)	2.1±0.4	2.2±3.2	0.78
RAVi (mL/m^2) †	23.1±12.9	18.6±5.4	0.03
PASP (mmHg)	35.1±16.9	22.1±5.6	<0.0001
RV Free wall PSS (%)	-16.8±4.5	-19.2±3.4	0.003

* Data are presented as mean± SD or %. † Values are indexed to BSA. EDVi - *End-diastolic volume indexed*; ESVi - *End-systolic volume indexed*; IVSD -

Interventricular septal diameter; LAVi - *Left atrial volume indexed*; LV - *Left ventricle*; EDD - *End-diastolic diameter*; EF - *Ejection fractio*n; ESD - *End-systolic diameter*; LVMi,- *Left ventricular mass indexed*; NYHA - *New York Heart Association*; PASP - *Pulmonary artery systolic pressur*e; PWD - *Posterior wall diameter*; PSS - *Peak systolic strai*n - RAVi,- *Right atrial volume indexed*; RV - *Right ventricle*; TAPSE - *Tricuspid annular plane systolic excursion*.

6.4.3 LV PSS and RV free wall peak systolic strain (RV PSS) in CRMR

LV PSS and RV PSS were lower in patients with CRMR compared to controls (LV PSS: -16.1±5.3% vs -17.9±2.1%, p=0.04; RV PSS: -16.8±4.5% vs -19.2±3.4%, p=0.01) (Table 6.2 and Figure 6.1). When comparing moderate and severe MR groups, patients with severe MR had greater degree of reduction in RV PSS (-15±4.7% vs -17.7±4.2%, p=0.01) (Table 6.3). RV PSS declined as PASP increased (r=0.29, p=0.02) and TAPSE decreased (r=-0.36, p=0.004). RV PSS and LV PSS had a positive correlation (r=0.3, p<0.001) (Figure 6.2). There was no correlation between RV PSS and RV S' (r=-0.16, p=0.17).

Table 6.3 Right ventricular systolic function parameters according to severity of mitral regurgitation.*

Variable	Moderate CRMR (n=51)	Severe CRMR (n=26)	p value
HIV	3(5.8%)	7(26.9%)	0.007
Hypertension	26(50.9%)	6(23.0%)	0.02
Hypertension and HIV	7(13.7%)	5(19.2%)	0.48
RVH(mm)	5.9±1.6	7.2±2.3	0.006

PASP (mmHg)	31.0±12.3	43.9±21.3	0.001
RV S´ (cm/s)	11.6(9.9-14.6)	11.4(9.4-13.4)	0.29
TAPSE (cm)	2.1±0.38	2.0±0.4	0.28
RV free wall PSS (%)	-17.7±4.2	-15±4.7	0.01

* Data are presented as median (IQR), mean± SD or %. HIV - *Human Immunodeficiency virus*; PAS - *Pulmonary artery systolic pressure;* PSS - *Peak systolic strain*; RV - *Right ventricle*; RVH - *Right ventricular hypertrophy;* TAPSE - *Tricuspid annular plane systolic excursion.*

6.4.4 Comparison of RV systolic functional parameters in CRMR according to LV systolic function

RV PSS was diminished in those with EF <60% compared to those with EF≥60% (-14.6±4.1% vs -18.2±4.2%, p=0.0003). LV PSS was higher in those with EF≥60% compared to those with EF<60% (-18.2±3.9% vs -13.1±5.6, p<0.001). Similarly, RVPSS was diminished in those with LV EDD≥55mm compared to those with LV EDD<55mm (-15.1±4.3% vs -18.3±4.2 %, p=0.001). However, no difference in traditional RV systolic function parameter was found between patients with preserved and decreased LV systolic function (p>0.05). PASP was greater in those with depressed systolic function compared to those with preserved LV systolic function (p=0.02) (Table 6.4).

Table 6.4 Comparison of right ventricular systolic function parameters in CRMR according to left ventricular systolic function.*

Variable	**LVEF<60%** **(n=32)**	**LVEF≥60%** **(n=45)**	**p value**
RV S´ (cm/s)	11.3(9.7-13.0)	12.0(9.6-14.7)	0.27
TAPSE (cm)	1.9±0.30	2.1±0.41	0.07
LVPSS (%)	-13.1±5.6	-18.2±3.9	<0.001
RVPSS (%)	-14.6±4.1	-18.2±4.2	0.0003
PASP (mmHg)	39.9±21.5	31.6±11.5	0.03
Variable	**LV EDD≥55mm** **N=37**	**LV EDD<55mm** **N=40**	**p value**
RV S´ (cm/s)	11.7(9.6-13.4)	11.5(9.8-13.9)	0.32
TAPSE (cm)	2.1±0.34	2.1±0.41	0.9
RVPSS (%)	-15.1±4.3	-18.3±4.2	0.001
PASP (mmHg)	39.5±20.4	30.8±11.4	0.02

* Data are presented as median (IQR), mean± SD or %. EDD - *End-diastolic diameter*; LV - *Left ventricle*; PASP - *Pulmonary artery systolic pressure*; PSS - *peak systolic strain*; RV - *Right ventricle*; RVH - *Right ventricular hypertrophy*; TAPSE - *Tricuspid annular plane systolic excursion.*

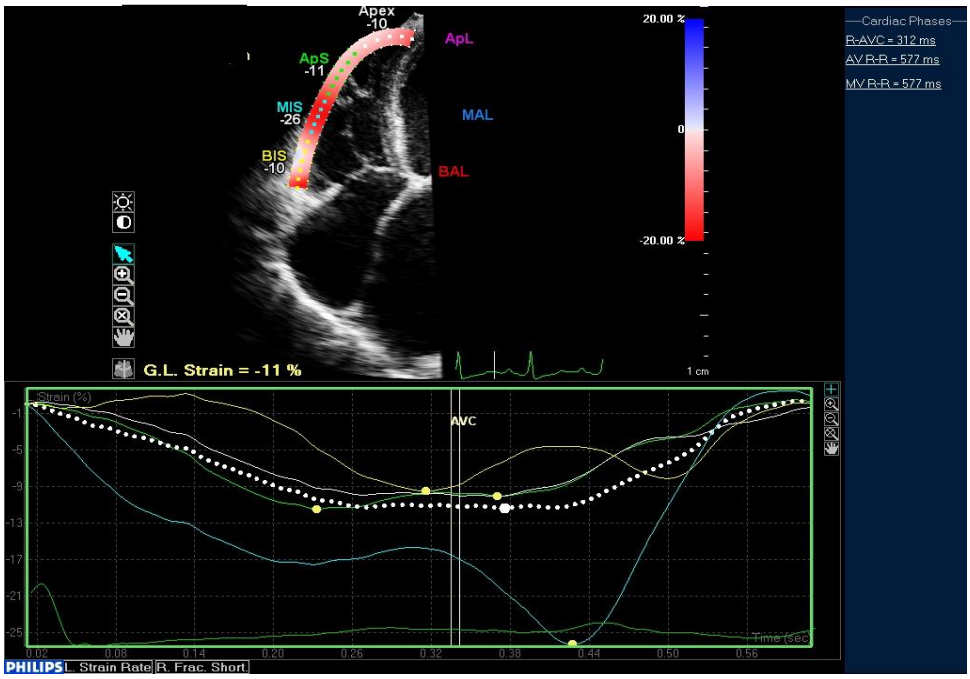


Figure 6.1 Reduced RV free wall peak systolic strain in CRMR.

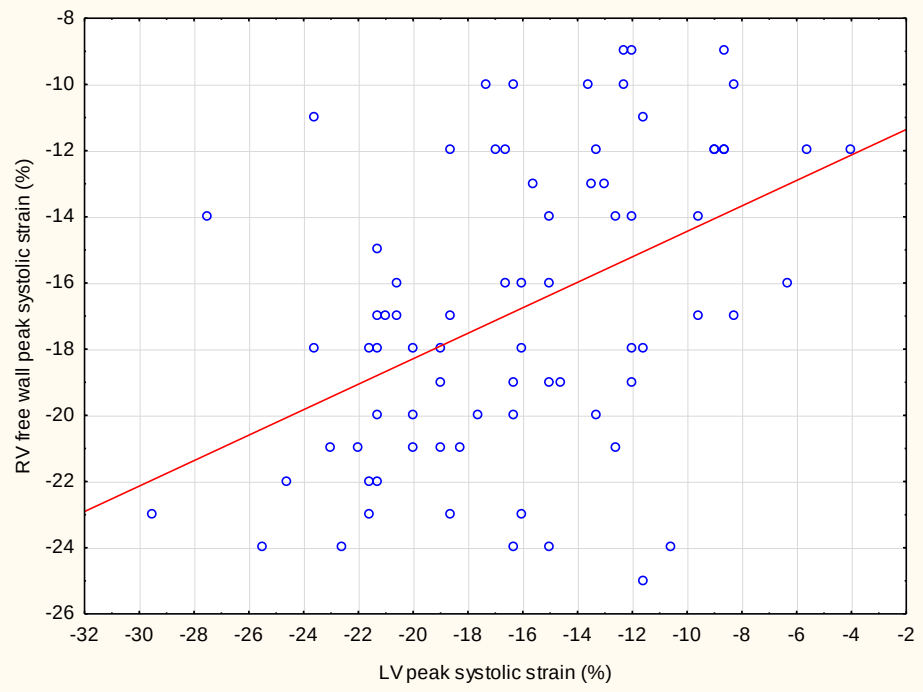


Figure 6.2 Correlation between RV free wall peak systolic strain (Y-axis) and LV peak systolic strain (X-axis) in CRMR.

6.4.5 Predictors of RV PSS

On univariate linear regression analysis severe MR (r=0.38, p<0.0001), TAPSE (r=-0.36, p=0.003), PASP (r=0.31, p=0.006), LVEF (r=0.3, p=0.003), LV EDD (r=0.3, p=0.007), Lateral S´ (r=0.24, p=0.03) and LV PSS (r=0.4, p<0.0001) were determinats of peak RV PSS.

On multivariate linear regression analysis after adjusting for age and gender TAPSE, LV PSS and LV EDD emerged predictors of RV PSS (Table 6.5). LV PSS was the most important determinant of RV PSS (p=0.01) (Table 6.5).

6.4.6 Feasibility and reproducibility of RV free wall PSS and LV PSS

RV and LV PSS measurements were feasible in all 77 patients. The intra-observer coefficient of variation for RV free wall PSS was 7% with a mean difference ± SD of 0.4 ± 2.7 (p=0.5) and for LV PSS was 2.4% with mean difference ± SD of 1.1± 2.7 (p=0.09). The inter-observer variability coefficient was 7.6% for RV free wall PSS with a mean difference ± SD of 0.5 ± 3.8 (p=0.5) and for LV PSS was 9.8% with a mean difference ± SD of 0.25±2.4 (p=0.6), respectively.

Table 6.5 Multivariate linear regression model for RV PSS in chronic rheumatic mitral regurgitation.

R=0.54, p<0.001		
Variable	**β±SE**	**p value**
Age (years)	0.03±0.04	0.41
Gender (M)	-1.29±1.47	0.38
PASP (mmHg)	0.05±0.03	0.13
Severe MR	2.4±1.36	0.07
TAPSE (cm)	-3.7±1.39	0.01
R=0.46, p<0.004		
Variable	**β±SE**	**p value**
Age (years)	-0.01±0.03	0.7
Gender (M)	-1.07±1.28	0.4
LV PSS (%)	0.30±0.12	0.01
Lateral S´ (cm/s)	-0.03±0.24	0.87
LV EF (%)	-0.04±0.04	0.35
R=0.5 p<0.001		
Variable	**β±SE**	**p value**
Age (years)	0.03±0.03	0.36
Gender (M)	-1.5±1.2	0.22
LV EDD (mm)	0.15±0.04	0.003
TAPSE (cm)	-3.9±1.24	0.002
R=0.53 p<0.0001		

Variable	β±SE	P value
Age (years)	0.01±0.03	0.76
Gender (M)	-1.2±1.2	0.31
LV EDD (mm)	0.09±0.05	0.07
TAPSE (cm)	-2.8±1.2	0.02
LV PSS (%)	0.25±0.09	0.01

EDD - *End-diastolic diameter*; Ef - *Ejection fraction*; LV - *Left ventricle*; MR - *Mitral regurgitation*; PASP - *Pulmonary artery systolic pressure*; PSS - *peak systolic strain*; RV - *Right ventricle;* TAPSE - *Tricuspid annular plane systolic excursion.*

6.5 **Discussion**

The pertinent findings of this study are:

1) RV free wall PSS is a more sensitive marker of RV dysfunction than traditional RV systolic function parameters in CRMR.

2) LV PSS was the most important determinant of RV free wall PSS.

RV function impairment and decreased LV ejection fraction are powerful predictors of CVS and overall survival in degenerative MR (Hyllen et al. 2014). The main determinants of RV function are RV load, myocardial function, neuro-hormonal abnormalities and ventricular interaction (Le Torneau et al. 2013a, b, Friedberg and Redington 2014).

Only RV free wall PSS was measured in this study as the interventricular septum contributes minimally to RV function (Fine et al. 2014). RV PSS is known to have prognostic and predictive value in various CV disease states (Lang et al. 2015,

Fine et al. 2014). In this study RV systolic dysfunction was more prevalent by STE than with commonly used conventional markers of systolic function such as TAPSE and RV S'. Speckle tracking echocardiography-derived RV PSS has been shown to be feasible and reproducible for clinical use (Morris et al. 2016, Lang et al. 2015, Ternacle et al. 2013). In this study RV PSS was feasible and reproducible in assessing RV function in CRMR. STE has been shown to be advantageous over conventional echocardiographic parameters used to measure RV systolic function in a variety of CV disorders such as HF, pulmonary hypertension and preoperative and postoperative RV function assessment prior to cardiac surgery (Morris et al. 2016, Hyllen et al. 2014, Ternacle et al. 2013, Guendouz et al. 2012, Fukuda et al. 2011). RV PSS derived by STE was superior in assessment of RV function in this study. The above finding can be explained by technical aspects as STE is not angle-dependent and is less influenced by heart motion compared to TAPSE and RV S' (Lang et al. 2015). Additionally, TAPSE and S' only measure regional RV function, whereas RV free wall strain is able to provide more global assessment of RV function (Lang et al. 2015). Further, Focardi et al. recently showed that among all RV systolic function parameters, RV PSS had the best correlation with RV ejection fraction measured by cardiac MRI (Focardi et al. 2015). Therefore, even though STE is limited by imaging quality and load dependence, unlike traditional echocardiographic parameters, it is able to detect subclinical longitudinal RV dysfunction and thus may help in risk stratification for surgery.

TAPSE emerged as an important determinant of RV PSS in this study. This finding can be explained by the fact that both RV PSS and TAPSE represent longitudinal function of the RV (Konishi et al 2013, Rudski et al 2010). There is still a disprepacy in the literature as to which parameter is the best for measuring RV

systolic function most accurately. There are no studies in MR. Giusca et al and Camelli et al found RV PSS to be a better marker of RV contractility than TAPSE in post endarterectomy patients and for pre-operative assessment of patients for cardiac transplant, respectively. This contrasts with Meris et al where a close correlation between TAPSE and RV PSS was noted in patients with RV systolic dysfunction and in normal controls (Camelli et al 2012, Meris et al 2010, Giusca et al 2009). Focardi et al noted RV PSS to have the best correlation with RV ejection fraction measured by cardiac MRI (Focardi 2015). Therefore, even though TAPSE only measures regional RV function and is subject to limitations as described in prior studies, it may still be utilized as a useful surrogate of RV systolic function in certain groups of patients with poor image quality where RV PSS may not be feasible (Rudski et al 2010). Current right heart function assessment guidelines and chamber guidelines recommend assessment of RV function based on more than one parameter and reserve utility of strain for research purposes only, until more data becomes available (Rudski et al 2010, Lang et al 2015).

The decrease in RV PSS in this study, with preserved traditional markers of RV systolic function would imply presence of subclinical RV dysfunction in these patients. The mechanism of decrement in RV strain may be partially explained by a relatively high PASP in this study - as the RV is extremely sensitive to afterload (Friedberg and Redington 2014, Fukuda et al. 2011). Even small changes in peripheral vascular resistance can markedly decrease RV contractile function. Prior studies have noted a similar relation between RV systolic performance and pulmonary hypertension in degenerative MR (Hyllen et al. 2014, Le Torneau et al. 2013a, b).

Le Torneau et al. have shown that, even though increased RV afterload secondary to PHT was an important cause of RV dysfunction in MR, LV dysfunction also contributed significantly to RV dysfunction, due to their interdependent relationship (Le Torneau et al. 2013a, b). In this study, PASP was only modestly elevated but the markers of LV remodelling and systolic function such as LVPSS, LV EDD and S' velocity were markedly abnormal in CRMR. Therefore, in agreement with Le Torneau et al, we think that LV remodelling and LV dysfunction, in addition to the modest elevation in PASP, may be an important cause of RV function impairment in CRMR. This is supported by the finding of reduced RV PSS in patients with LV EDD≥55 mm, LVEF<60% and reduced LV PSS. However, conventional RV systolic function parameters were still preserved even in presence of LV systolic dysfunction. Hence, once abnormalities in LV systolic function are noted in MR, systematic RV function assessment must be done with not only traditional parameters but also STE, in order to detect subclinical RV dysfunction and avoid mortality associated with biventricular function impairment (Le Torneau et al.2013a, b).

Severe MR was associated with worse RV function impairment, in a study by Le Torneau et al. (Le Torneau et al. 2013a, b). It was found to be a determinant of RV PSS in this study. Volume overload as a result of chronic MR results in LV remodelling as noted in our study, and this in turn, results in abnormalities of RV and LV interaction. RV free wall strain was lower in patients with severe MR compared to moderate MR. This association can be explained by greater chronic volume overload of LV, the left atrium accompanied by increased PASP as a result of backward transmission of increased LV pressure as well as remodelling of the pulmonary vasculature in severe MR compared to moderate MR (Bonow et al.

2012). However, there was no difference in traditional RV systolic function parameters between the moderate and severe MR groups, and thus quantitative RV function assessment in CRMR mandates evaluation by both conventional indices and RV longitudinal strain.

Finally, the decline in RV PSS may be partially attributed to primary RV dysfunction. The intrinsic myocardial function abnormality may be a result of longstanding activation of neuro-hormonal pathways and increased afterload secondary to chronic mitral regurgitation (Friedberg and Redington 2014, Polak et al. 1983). We further speculate that there may be direct involvement of the RV myocardium by the rheumatic process.

6.5.1 Study Limitations

This study had several limitations:

1) A lack of reference standard for RV functional assessment such as additional imaging in the form of cardiac MRI and 3D echocardiography.

2) We did not perform right and left heart catheterisation to measure PASP, pulmonary vascular resistance, and coronary angiogram unless there was clinical indication.

6.6 Conclusion

In CRMR speckle tracking-derived RV PSS is feasible and reproducible. RV PSS is a more sensitive marker for detecting earlier RV systolic dysfunction than traditional RV functional parameters. LV PSS is an important determinant of RV PSS in this study. Therefore, presence of LV systolic dysfunction mandates careful search

for RV systolic dysfunction in MR using STE. These findings may have implications regarding decision for surgical intervention:

1) Presence of significant RV dysfunction may help strategize the preoperative and postoperative management of patients with MR.

2) Earlier referral for surgery before LV dysfunction supervenes in cases where LV function is preserved.

3) Deferring surgery in patients with coexisting LV dysfunction.

Chapter 7

Cardiac magnetic resonance and echocardiographic characteristics of chronic rheumatic mitral regurgitation and relation with biomarkers of collagen metabolism

7.1 Comparison of chronic rheumatic mitral regurgitation severity between cardiac magnetic resonance imaging and echocardiography

7.1.1 Abstract

7.1.1.2 Background

Recently, magnetic resonance imaging (MRI) has emerged as a useful non-invasive tool for assessing valvular lesions, especially where echocardiography is unable to provide complete information. In degenerative mitral regurgitation, MRI has proven useful in accurate assessment of severity of MR, LV structure and function. Assessment of CRMR severity, using cardiac MRI has not been explored. CRMR is largely characterised by eccentric jets and thus accurate quantification is difficult with the guideline recommended PISA method alone. Thus, cardiac magnetic resonance (CMR) may be of added benefit for assessment of lesion severity in CRMR. We sought to study and compare echocardiography with MRI for assessment of CRMR severity.

7.1.1.3 Methods

After application of appropriate inclusion criteria, 22 patients with isolated moderate or severe CRMR underwent cardiac MRI as part of a sub-study at CHBAH. All underwent echocardiography and cardiac MRI on the same day.

7.1.1.4 Results

The mean age was 36.3±13.9 years with 81% females. Overall there was no difference in MR severity (based on qualitative and quantitative parameters) assessment between the two imaging modalities ($p>0.05$). However, six patients were reclassified after MRI to severe MR and one to moderate MR based on quantitative parameters of regurgitant volume (RegV) and RF. EDVi and RegV were higher on MRI compared to echocardiography (98.5(81-111.1) mL/m^2 vs 90.4(71.5-103.8) mL/m^2, $p=0.03$; 47.0±19.9 mL/m^2 vs 34.3 ±15.1mL/m^2, $p=0.003$). There was no difference between ESVi and regurgitant fraction (RF) between echocardiography and MRI ($p>0.05$). Although there was a positive correlation between LV volumes and RegV on the two imaging modalities, there was no agreement between echocardiography and MRI for assessment of MR severity parameters such as RF, RegV and LV volumes.

7.1.1.5 Conclusion

CMR may be a useful adjunctive tool for quantitative assessment of MR severity in equivocal cases where echocardiographic integrated approach of MR assessment is insufficient.

7.1.2 Introduction

Quantification of severity of MR is of utmost importance when considering a patient for surgery, yet the best method for grading MR remains elusive (Enriquez-Sarano et al.1993). Accurate quantification of MR using the current guideline based recommendation such as PISA is appropriate for MR with central jets but poses several limitations in assessment of MR secondary to eccentric jets (Zoghbi et al. 2003, Enriquez-Sarano et al.1993). Further, PISA measurements show poor inter-observer agreement (Biner et al. 2010). CRMR is a disease characterised by predominantly Carpentier IIIa leaflet dysfunction and eccentric jets which make its accurate quantification difficult using the current guideline recommendation. Recently, the utility of CMR has been highlighted in quantification of MR severity in degenerative MR and its role in risk-stratification of patients with MR has been emphasised especially in moderate and severe MR cases where echocardiographic assessment alone may be insufficient (Uretsky et al. 2015, Van De Heyning et al. 2013). The main advantage of CMR as opposed to echocardiographic assessment of MR severity is its ability to quantify LV volumes and flow much more precisely, using semi-automated methods of volume calculation and phase contrast velocity mapping, respectively (Kar and Sharma 2015). To the best of our knowledge this is the first study evaluating severity of CRMR by echocardiography and MRI. We postulate that CMR will be valuable in quantification of CRMR where the jets are predominantly eccentric. Thus, we sought to compare the assessment of MR severity using cardiac MRI quantitative methods of MR severity assessment (RF, RegV and LV volumes) and echocardiography based integrated approach (qualitative, semi-quantitative and quantitative methods).

7.1.3 Methods

This study was part of a prospective cross-sectional study at the Chris Hani Baragwanath Academic Hospital (CHBAH). Patients were enrolled from January and October 2014. All patients were screened, and those deemed to have moderate or severe CRMR were referred for possible inclusion in the study. A final number of 91 patients with presumed chronic, rheumatic MR underwent clinical evaluation, resting electrocardiogram and detailed echocardiographic assessment according to a pre-determined protocol.

The inclusion criteria were patients aged 18 years or older with echocardiographic features of moderate or severe chronic rheumatic MR. Patients were excluded if they had:

1) comorbidities,

2) significant aortic valve disease,

3) concurrent MS with a valve area of less than 2.0 cm^2,

4) documented ischaemic heart disease,

5) preexisting non-valvular cardiomyopathy,

6) prior cardiac surgery ,

7) congenital or pericardial disease,

8) pregnancy,

9) severe anemia (haemoglobin <10g/dL),

10) presence of a pacemaker or defibrillator,

11) claustrophobia,

12) renal dysfunction eGFR<60mL/min,

13) refusal to undergo MRI.

Of the original 91 patients with CRMR, 69 were excluded due to the following:

1) comorbidities (HIV n=22, hypertension n=44, diabetes mellitus n=3),

2) atrial fibrillation (n=4),

3) anaemia (n=3),

4) renal dysfunction (n=3), and

5) inadequate image quality (n=5).

The final sample comprised 22 patients. Fourteen age and gender-matched controls were also enrolled. A tolerance of 5 years was allowed for age matching.

In degenerative MR, varying haemodynamics due to alterations in systolic blood pressure, impact MR assessment (Zoghbi et al. 2003). In rheumatic MR where the orifice tends to be fixed rather than dynamic, the impact of change in afterload is minimal (Uretsky et al. 2015, Zoghbi et al. 2003). Despite this assertion, we performed echocardiography and cardiac MRI on the same day to negate the impact of varying afterload.

The study was approved by the University of the Witwatersrand ethics committee (M140114) and is in accordance with the principles outlined in the Declaration of Helsinki. The baseline clinical characteristics of these individuals were recorded and they subsequently underwent comprehensive echocardiography and CMR imaging.

7.1.3.1 Echocardiographic evaluation

Transthoracic echocardiography was performed on all patients in the left lateral position by experienced sonographers using a S5-1 transducer on a Philips iE33 system (Amsterdam, The Netherlands). The images were obtained according to a standardised protocol. The data was transferred and analysed off-line using the Xcelera workstation (Philips).

7.1.3.2 Two dimensional and Doppler quantification

All linear chamber measurements were performed according to the ASE chamber guidelines (Lang et al. 2015). Measurements relating to LV diastolic function were performed in accordance with the ASE guidelines on diastolic function, and included pulse wave Doppler at the mitral tips and tissue Doppler of both medial and lateral mitral annuli (Nagueh et al. 2009). MR was considered rheumatic in aetiology when the morphology of the valve satisfied the World Heart Federation (WHF) criteria for the diagnosis of chronic rheumatic heart disease (RHD) (Reményi et al. 2012). MR severity was assessed using qualitative, semi-quantitative and quantitative methods as the ASE and ESC valvular regurgitation guidelines (Zoghbi et al. 2003, Lancelloti et al. 2013). MR jet was classified as eccentric if there was contact with the leaflet of the MV posterior to the regurgitant orifice and impingement to the lateral or medial wall of the LA was present. It was deemed central if the MR jet was directed into the centre of the LA (Biner et al. 2010). In equivocal cases the echocardiographic data was integrated with the clinical evaluation by an experienced cardiologist to distinguish moderate from severe MR.

7.1.3.3 Cardiovascular magnetic resonance acquisition and analysis

CMR studies were performed on a 1.5-Tesla whole body scanner (Siemens), using a six-channel phased-array body coil. The images were obtained during patient breath- hold for approximately 8 seconds and were ECG gated (Kim et al. 2000). Left and RV volumes and mass and LA volumes were acquired in line with standard cardiovascular MRI (1.5T magnetom Avanto; Siemens Healthcare, Erlangen, Germany) protocols. Steady-state free-precession imaging (echo times 1.5/3.0 ms, flip angle 60°, temporal resolution 45 ms, slice thickness 7 mm, 3 mm gap, matrix size 256 x 256 mm, field of view 380 x 309 mm) were performed to obtain long axis cines and a contiguous stack of short-axis cines for assessment of LV dimensions, mass and ejection fraction as previously described (Hudsmith et al. 2005). Images were analysed by an independent experienced reader blinded to the echocardiographic results with Argus software version 2002B (Siemens Medical Solutions, Erlangen) as previously described (Karamitsos et al. 2007). The assessment of cardiac function and chamber sizes were performed in standard views in the long-axis (horizontal and vertical) and short axis planes. Ejection fractions for the LV was assessed with the following formula:

Ejection fraction = end-diastolic volume – end-systolic volume/end-diastolic volume.

LV volumes and EF were obtained by semi-automatic tracing of contours on the short-axis images in end-diastole and end-systole, with manual corrections when required (Schulz-Menger et al. 2013, Siemens avanto protocols). From the short-axis LGE images, basal, midventricular, and apical slices were selected based on anatomic landmarks (papillary muscles, LV outflow tract), and endocardial and epicardial borders were traced manually (Schulz-Menger et al. 2013, Siemens

protocols). The anatomy of the MV was assessed in both, the basal short axis and long axis steady-state free-precession cines of the MV, using a standardised approach (Edwards et al. 2014). The severity of MR was based on regurgitant volume (RegV) and fraction. RegV was calculated as the difference between the LV stroke volume and the aortic forward stroke volume. Regurgitant fraction was calculated with the aid of the following formula:

Regurgitant fraction (%) = [mitral regurgitant volume ÷ LV stroke volume] ×100)

(Edwards et al. 2014). Mitral regurgitation was considered severe when RF≥42% (Chan et al. 2008).

7.1.3.4 Statistical analysis

Statistical analysis was performed with Statistica (version 12.5, series 0414 for Windows). Continuous variables are expressed as means ± SDs or medians (IQRs). Categorical data was expressed as percentages. The differences for continuous variables were calculated using Student's t- test or Mann-Whitney U test when the distribution was non-normal. Wilcoxon's matched pairs test was used to compare two dependent samples when distribution was not normal. Chi-square and Fisher's exact test were used to calculate the difference for categorical data for independent samples. McNemar's test was used to compare two dependent samples. Pearson's and Spearman's correlation coefficient were used to calculate correlations depending on whether data was normally or non-normally distributed. Bland- Altman plots were used to display agreement between MRI and echocardiographic variables

used for assessment of MR severity. A p value<0.05 was considered statistically significant.

7.1.4 Results

7.1.4.1 Baseline characteristics

Of the 69 patients excluded, their mean age was 51.7±1.1 years, mean LVEF was 59±13% and LVESD was 43.4±9mm. Fifty eight of these individuals were females. Of the 22 patients included, the mean age was 36.3±13.9 years, 81% were females (Table 7.1.1). All the patients had isolated moderate, or severe chronic rheumatic MR and no comorbidities. Of the 22 patients 10 were in NYHA functional class I, the remainder were NYHA functional class II. Four patients were on medical treatment with diuretics (furosemide) and anti-remodelling therapy (spironolactone, carvedilol, enalapril) for previous HF secondary to MR. Eight patients were on diuretics alone.

Table 7.1.1 Baseline characteristics of the study patients and controls.*

Variable	Study group n=22	Control n=14	p value
Age (years)	36.3±13.9	40.3±14.2	0.40
Gender (F:M)	18:4	10:4	0.36
Systolic blood pressure (mmHg)	123.2±9.5	122.9±5.1	0.91
Diastolic blood pressure (mmHg)	77.2±6.4	74.6±12.3	0.34

Pulse (beats/min)	74.6±13.1	75.5±13.3	0.55
Body mass index (kg/m^2)	24.8±4.7	28±5.7	0.06
Body surface area (m^2)	1.6±0.2	1.7±0.2	0.24

* Data are presented as mean± SD.

7.1.4.2 CMR and Echocardiographic characteristics

The EDVi and ESVi were increased on both echocardiographic exam and on MRI (for normal MRI reference range-see appendix) but when the two modalities were compared there was no difference in ESVi between the two techniques (39.6±19.6 mL/m^2 vs 49.1±36.7 mL/m^2, p=0.1) (Table 7.1.2 and Table 7.1.3). However, there was a difference in EDVi [EDVi-90.4(71.5-103.8) mL/m^2 vs 98.5(81-111.1) mL/m^2, p=0.03)]. On echocardiography, nine patients had LV EDD<55 mm and 13 patients had LV EDD >55 mm. There was no statistically significant difference between EDVi and ESVi between echocardiography and MRI in those with LV EDD<55 mm (EDVi: 84.2±18.4 mL/m^2 vs 91.0±15.7 mL/m^2, p=0.21; ESVi: 32.8±11.7 mL/m^2 vs 31.2±10.3 mL/m^2, p=0.5). In those with LV EDD >55mm (EDVi: 106.8±35.5 mL/m^2 vs 130.5± 49.2 mL/m^2, p=0.08, ESVi: 49.1±24.9 mL/m^2 vs 75.1±45.9 mL/m^2, p=0.050) there was a tendency of volumes to be greater on MRI compared to echocardiography but was not statistically significant. The mitral RegV was higher on MRI than on echocardiography (34.3 ±15.1mL vs 47.0±19.9 mL, p= 0.003). There was no difference in regurgitant fraction (RF) between the two modalities (MRI vs echo: 49.2% (31.7-56.2) vs 33.3% (27.4-47.6), p=0.1). The LV EF measurements were similar on both MRI (58.8±15.1%) and echocardiography (59.8±10.6%). There was a good correlation between EDVi and ESVi

measurements between the two imaging modalities (r=0.69, p<0.001; r=0.7, p<0.001) but the agreement was poor (Figure 7.1.1 and Figure 7.1.2). Similarly, RegV measurements showed modest correlation (r=0.48, p=0.02) and little agreement. RF measurements showed no correlation or agreement between the two modalities (r=0.26, p=0.2) (Figures 7.1.3 and 7.1.4). There was no correlation between echocardiographic effective regurgitant orifice area (EROA), RegV, regurgitant fraction and LV volumes on MRI (p>0.5).

All the MR jets were eccentric (Figure 7.1.5). Echocardiography classified 14 patients as moderate MR and eight as severe MR based on quantitative and qualitative parameters. The EROA and RegV derived using the PISA method were 0.2±0.12 cm^2 and 34.3 ±15.1 mL, respectively. Even though no difference was observed between MR severity assessment in the overall group, we noted discrepant findings in terms of classification of valve lesion severity in seven patients, based on current cut- offs for RegV and fraction, between MRI and echocardiography. Based on RegV and RF, six patients previously classified as moderate MR on echocardiogram were reclassified as severe MR on CMR, and one patient with severe MR on echocardiography was re-categorised as moderate.

Table 7.1.2 Echocardiographic characteristics of the study patients compared to controls.*

Variable	Study group n=22	Control n=14	p value
Echocardiographic parameters			
LV EDD (mm)	56.2±7.4	42.2±6.1	<0.001
LVESD (mm)	41.5±8.6	26.7±4.0	<0.001
LV EDVi (mL/m^2) †	90.4(71.5-103.8)	43.2(35.2-43.2)	<0.001
LV ESVi (mL/m^2) †	39.6±19.6	15.3±4.6	0.001
EF (%)	59.8±10.6	60.6±17.1	0.5
LV mass index (g/m^2) †	100.1±33.8	61.4±18.7	0.004
E wave (cm/s)	147(95.3-197)	81.2(66.6-95.0)	<0.001
E/A ratio	1.7±0.68	1.4±0.38	0.1
Lateral E' (cm/s)	12.8±4.6	13.8±3.9	0.5
Lateral E/E' (cm/s)	13.6±7.5	6.0±1.6	<0.001
Lateral S' (cm/s)	7.6±2.1	7.2±2.2	0.11
PASP (mmHg)	35.0±17.0	20.7±3.8*	0.08
LAVi (mL/m^2) †	44.8(39-62.7)	23.2(17.7-25.4)	<0.001

* Data are presented as median (interquartile range), mean± SD or %. † Values are indexed to BSA. EDVi - *End-diastolic volume indexed*; ESVi - *End-systolic volume indexed*; LAVi - *Left atrial volume indexed*; LV - *Left ventricle*; EDD - *End- diastolic diameter*; EF - *Ejection fraction*; ESD - *End- systolic diameter*; PASP - *Pulmonary artery systolic pressure*.

Table 7.1.3: Comparison between Echocardiographic and CMR characteristics of study patients

Variable	Echocardiographic characteristics n=22	CMR characteristics n=22	p value	Correlation coefficient and p value
Regurgitant volume (mL)	34.3 ±15.1	47.0±19.9	0.003	r=0.48, p=0.02
Regurgitant fraction (%)	33.3(27.4-60.1)	49.2(31.7-56.2)	0.1	r=0.26, p=0.2
Vena contracta (cm)	0.6±0.2	-	-	-
Moderate MR	14(63.6%)	9(41%)	0.14	-
Severe MR	8(36.3%)	13 (55%)	0.3	-
Eccentric jet	22(100%)	22(100%)	-	-
LV EDVi (mL/m^2)	90.4(71.5-103.8)	98.5(81-111.1)	0.03	r=0.69, p<0.001
LV ESVi (mL/m^2)	39.6±19.6	49.1±36.7	0.1	r=0.7, p<0.001
Ejection fraction (%)	59.8±10.6	58.8±15.1	0.7	r=0.3, p=0.08

* Data are presented as median (interquartile range), mean± SD or %. † Values are indexed to BSA. EDVi - *End-diastolic volume indexed*; ESVi - *End-systolic volume indexed*; LV - *Left ventricle;* MR - *Mitral regurgitation*.

Figure 7.1.1 Bland-Altman plot for measuring end-diastolic volume indexed (EDVi)

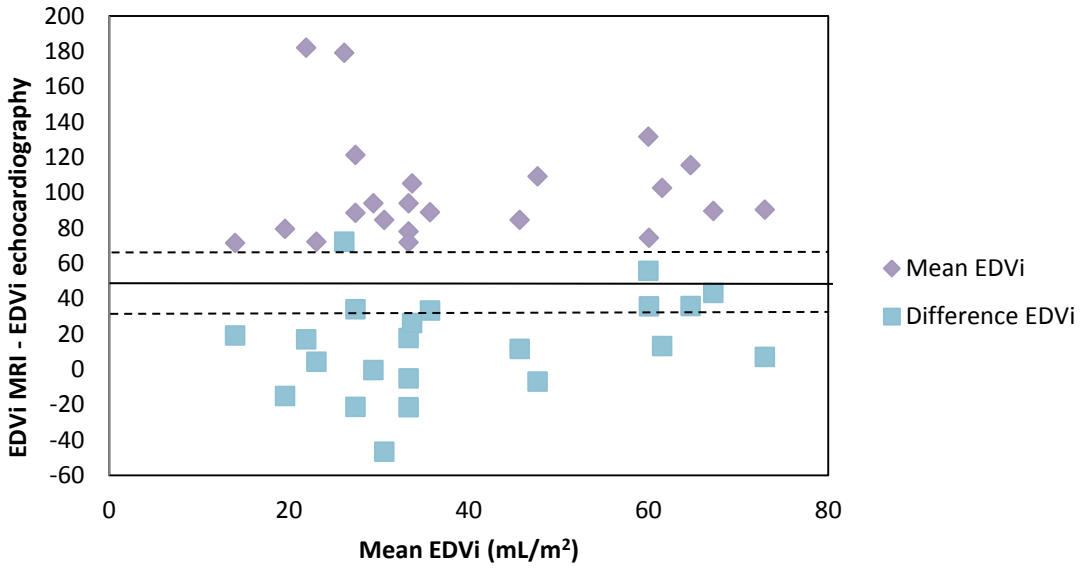


Figure 7.1.2 Bland-Altman plot for measuring end-systolic volume indexed (ESVi)

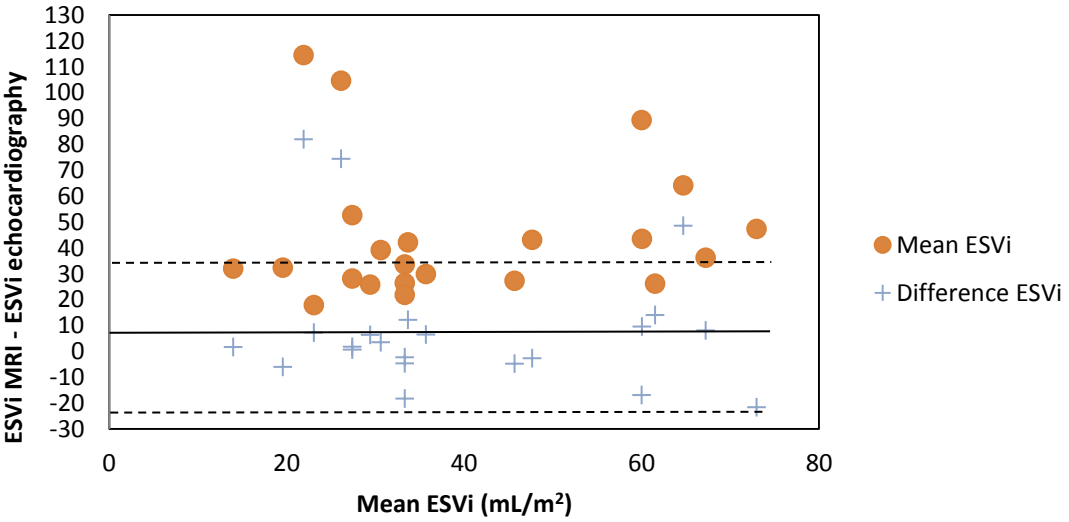


Figure 7.1.3 Bland-Altman plot for measuring regurgitant volume (RV)

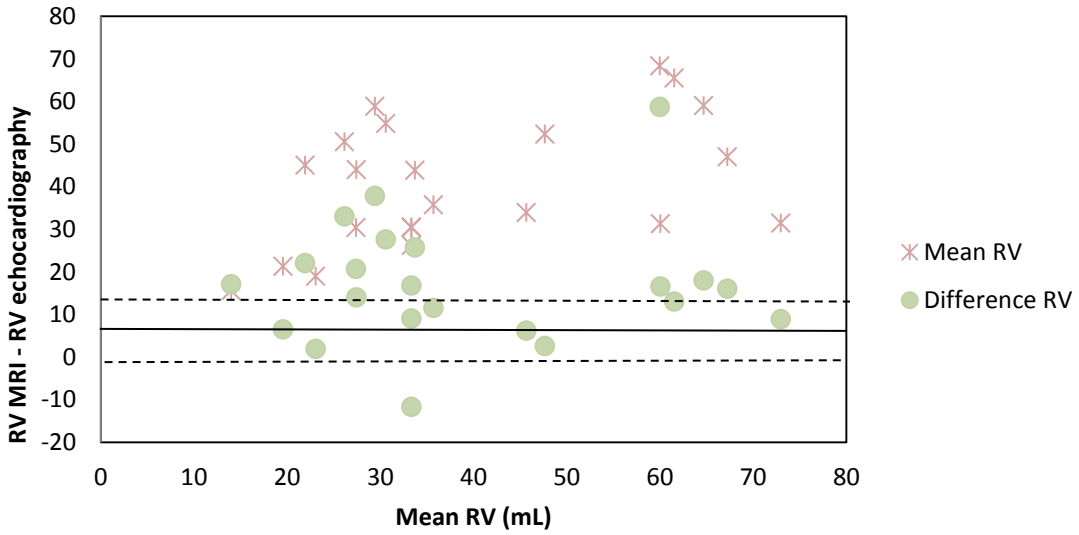
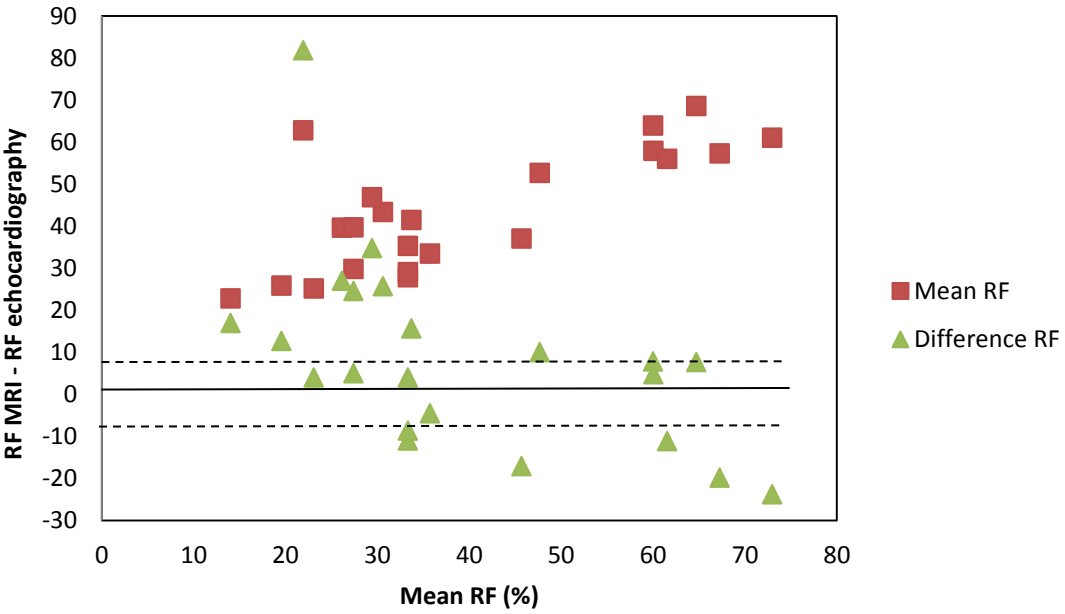


Figure 7.1.4 Bland-Altman plot for measuring regurgitant fraction (RF)



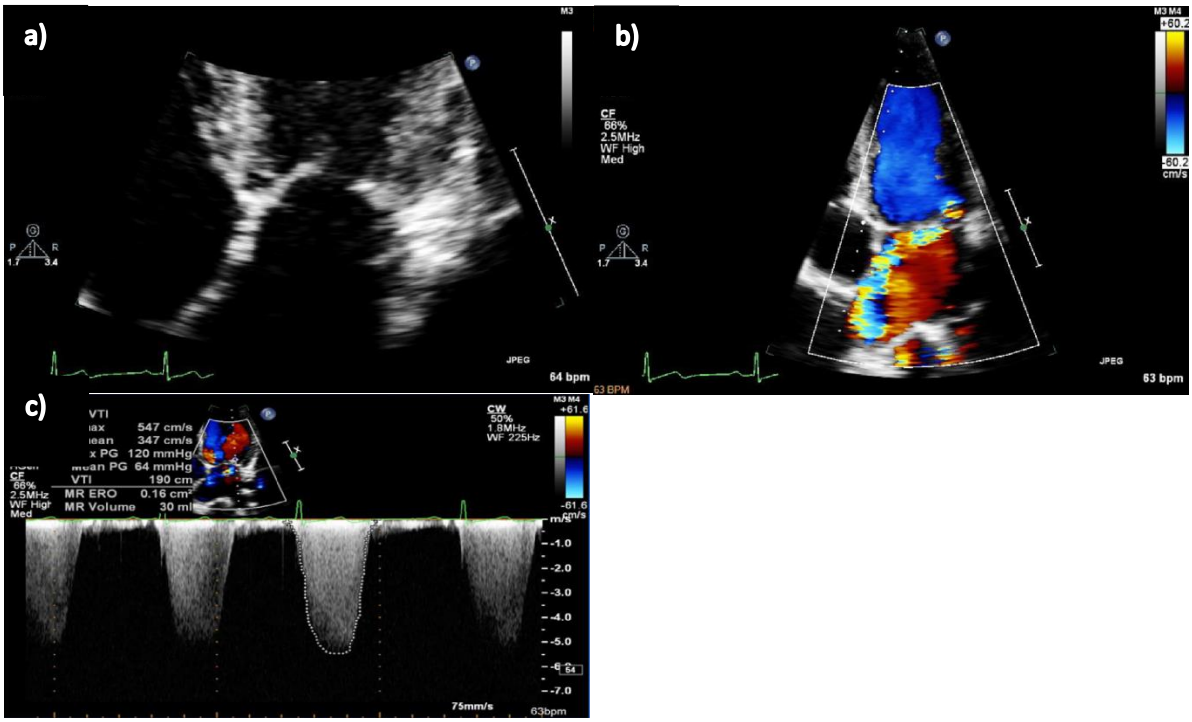


Figure 7.1.5 Two dimensional echocardiographic views depicting: a) Restricted leaflet motion of anterior and posterior mitral leaflet secondary to rheumatic heart disease b) Eccentric mitral regurgitation jet c) Incomplete continuous wave Doppler envelope generated by poor continuous wave Doppler alignment of the jet.

7.1.5 Discussion

The main finding of this study was that echocardiographic and CMR techniques differ with regard to assessment of MR severity based on quantitative parameters in a minority of patients. However, the majority of echocardiography- based integrated approach of severity of MR assessment was concordant with that of MRI quantitative assessment.

There were discrepancies on assessment of MR severity by CMR and echocardiography in seven patients in our study based on quantitative parameters. Various studies have shown superiority or equivalence of MRI over

echocardiography when assessing severity of mitral regurgitation, mostly in the context of degenerative MR (Van De Heyning et al. 2013, Sukpraphute 2012, Uretsky et al. 2010, Cawley and Otto 2009, Hellgren et al. 2008, Gelfand et al. 2006). Our findings concur with a recent study by Uretsky et al. where similar discrepancies in MR quantification, between the two imaging modalities was noted (Uretsky et al. 2015).

The discordance in MR severity assessment between MRI and echocardiography in this study may be as a result of eccentric jets in rheumatic MR due to distorted leaflet morphology. This resulted in errors in quantification of MR severity on echocardiography due to:

1) assumption of sphere when calculating PISA radius,

2) generation of an incomplete continuous Doppler envelope,

3) inaccurate radius measurement and 4) imprecise identification of regurgitant orifice; thus rendering the PISA method suboptimal for MR quantification. (Biner et al. 2010, Cawley and Otto 2009).

The volumes obtained on echocardiography by the biplane Simpson's method tend to be underestimated, especially in large ventricles due to foreshortening of the apex (Uretsky et al. 2015, Van De Heyning et al. 2013, Hellgren et al. 2008). This results in underestimation of the volumes and thus regurgitant fraction. We tried to minimise the aforementioned error by selecting only patients with the best imaging quality for this sub-study and, even then we found overall LV EDVi to be higher on MRI compared to echocardiography. The volumes obtained on MRI may be more reliable, as most post-processing software uses semi-automated algorithms to trace the endocardial border (Kar and Sharma 2015, Hellgren et al. 2008).

RegV measurement was higher on CMR compared to PISA-derived RegV in this study. Studies comparing RegV measurements on MRI and echocardiography in MR have shown variable results with some overestimating RegV on echocardiography, and others underestimating RegV (Van De Heyning et al. 2013). In all studies, these two imaging modalities could not be used interchangeably for measurement of this MR severity parameter. CMR, however, probably allows more accurate quantification of MR based on calculation of RegV using the formulae stated previously (based on phase contrast imaging and planimetry of LV contours at end-systole and diastole) than the PISA method, especially in eccentric jets secondary to rheumatic MR. Additionally, the current cut-offs for RF pertaining to classification of MR severity differ between echocardiography and MRI, with the threshold for severity being lower on MRI compared to echocardiography (Zoghbi et al. 2003, Myerson 2012). Thus, more patients were classified as severe MR on MRI than echocardiography. In this study, CMR added incremental value in accurate quantification of MR, in the moderate and severe MR categories in a minority of patients. In these patients, quantitative and qualitative parameters were not useful in categorising MR severity on echocardiography and thus MRI proved to be a useful adjunctive tool.

The main limitation of this study was the small sample size. None of the controls underwent MRI due to logistical reasons. Patients with mild MR and AF were excluded.

7.1.6 Conclusion

CMR derived quantitative parameters may be useful for accurate classification of moderate or severe rheumatic MR characterised by eccentric jets, especially in equivocal cases, where integrated MR quantification by echocardiographic alone is insufficient.

7.2 Assessment of fibrosis by late gadolinium enhancement imaging and biomarkers of collagen metabolism in chronic rheumatic mitral regurgitation

7.2.1 Abstract

7.2.1.2 Background

Presence of fibrosis by late gadolinium enhancement (LGE) on cardiac MRI has been shown to be of prognostic value in various disease states such as hypertrophic cardiomyopathy, ischaemic heart disease as well as in degenerative MR. In rheumatic mitral regurgitation, the involvement of the myocardium by the rheumatic process has been controversial. Older studies have postulated affliction of predominantly the posterobasal region of the LV by the rheumatic process. Additionally, there are limited studies in humans and animals which have explored the role of biomarkers of collagen metabolism in degenerative MR and rheumatic MR. There are no studies which have explored the prevalence of myocardial fibrosis using LGE and biomarkers in rheumatic MR. Therefore, we sought to study the presence of fibrosis by LGE and biomarkers of collagen turnover in CRMR.

7.2.1.3 Methods

Twenty-two patients with isolated moderate or severe CRMR underwent cardiac MRI as part of a sub-study at CHBAH. All underwent echocardiography and cardiac MRI the same day. Blood tests for biomarkers were drawn at the time of echocardiography.

7.2.1.4 Results

The mean age was 36.3±13.9years with 81% females. Four patients had fibrosis on LGE. PICP and PIIINP were similar to controls except for MMP-1 which was increased compared to controls (log MMP-1 3.5±0.68 vs 2.7±0.9, p=0.02). There was increased MMP-1 activity as the MMP-1 to TIMP-1 ratio was higher in CRMR compared to controls (-1.2±0.6 vs -2.1±0.89, p=0.002). No correlation was noted between biomarkers and CMR parameters (p>0.05).

7.1.2.5 Conclusion

LV myocardial fibrosis in CRMR is rare. CRMR is a state characterised by predominance of collagen degradation rather than synthesis.

7.2.2 Introduction

Myocardial fibrosis can be reliably detected non-invasively using late gadolinium enhancement (LGE) CMR (Doltra et al. 2013). LGE by CMR is a useful non-invasive correlate of myocardial fibrosis on histology (Barone-Rochette et al. 2013). Fibrosis represents an end-stage process in various cardiac conditions, irrespective of aetiology and denotes adverse outcomes (Khan and Sheppard 2006). Limited recent studies have shown the value of cardiac MRI in valvular heart disease such as degenerative MR and aortic stenosis, in predicting prognosis based on presence of fibrosis (Edwards et al. 2014, Hoffman et al. 2014, Barone-Rochette et al. 2013). In CRMR there may be involvement of the LV by the rheumatic process especially in the posterobasal region of the LV (Barlow 1987, Stollerman et al.1975, Choi et al. 2006). Sepulveda et al. reported diffuse, mesocardial and heterogenous enhancement of myocardium by LGE in ARF (Sepulveda et al. 2013). Thus, the possible resultant fibrosis may be studied by LGE and have prognostic value similar to degenerative MR. Further, data concerning biomarkers of collagen degradation and formation in MR are limited and mostly comprise animal studies in degenerative MR (Hezzell et al. 2014, Verheule et al. 2003). In a recent study in rheumatic MR, an increase in biomarkers of collagen synthesis and degradation was reported (Banerjee et al. 2014). Biomarkers of collagen turnover may serve as non-invasive tools for identification of myocardial remodelling and add an incremental value in risk stratification for surgery or institution of aggressive medical treatment at an early stage (Lopez et al. 2010, Braunwald 2008, Spinale et al. 1999).

Thus, we sought to assess:

1) the presence of LV fibrosis in CRMR using cardiac MRI

2) the relation of biomarkers of collagen degradation and synthesis with CMR parameters in CRMR

7.2.3 Methods

This study was part of a prospective cross-sectional study at the Chris Hani Baragwanath Academic Hospital (CHBAH). Patients were enrolled from January 2014 to October 2014. All patients were screened, and patients deemed to have moderate or severe CRMR were referred for possible inclusion in the study. A final number of 91 patients with presumed chronic, rheumatic MR underwent clinical evaluation, resting electrocardiogram and detailed echocardiographic assessments according to a pre-determined protocol. After applying appropriate inclusion and exclusion criteria (detailed in section 7.1), 22 patients were enrolled in this sub-study. Additionally, 14 age and gender-matched controls were enrolled. The study was approved by the University of the Witwatersrand ethics committee (M140114) and was conducted in accordance with the principles outlined in the Declaration of Helsinki. The baseline clinical characteristics of these individuals were recorded and they subsequently underwent comprehensive echocardiography and CMR imaging.

7.2.3.1 Echocardiographic evaluation

Detailed in section 7.1

7.2.3.2 Biomarker analysis / Procollagen III N-terminal propeptide (PIIINP) and procollagen I C-peptide (PIP) analysis

Peripheral venous blood samples were drawn from 14 controls and 22 chronic RHD subjects at the time of echocardiographic examination. Samples were collected in a serum separator tube, and allowed a clotting time of 30 min before centrifuging for 15 min at 1,000 g. The plasma was then separated into aliquots and stored at -80°C before analysis.

7.2.3.3 Procollagen III N-terminal propeptide analysis

Serum concentrations of the procollagen III N-terminal propeptide (PIIINP) was determined by enzyme-linked immunosorbent assay (ELISA) using the USCN Life Science Inc./Cloud-Clone Corp (Wuhan, China) kit according to the manufacturer's instructions. The minimum detectable dose of PIIINP is typically less than 25.9pg/ml.

Briefly, the serum was diluted 1:100 in phosphate buffered saline (PBS-137 mM NaCl-2.7 mM, KCl-8 mM Na_2HPO_4, and 2 mM KH_2PO_4). The standards were prepared immediately before use and were diluted two-fold from 4000pg/mL to 62.5pg/mL. Standards or samples were incubated at 37˚C for 2 hours, aspirated and incubated with anti-PIIINP-streptavidin-conjugated antibody for 1 hour at 37˚C. The wells were washed 3 times, followed by incubation at 37˚C for 30 minutes with biotin-conjugated horse radish peroxidase (HRP). The wells were washed 5 times, followed by the addition of 3,3ˈ,5,5ˈ-Tetramethylbenzidine (TMBZ) substrate solution. The colorimetric reaction between HRP and TMB was stopped by the addition of acid. Absorbance at 450 nm was measured on an ELx800 microplate reader (BioTek(TM)

Instruments, Winooski, VT, USA). Concentrations were determined using a 5PL algorithm (Swart, A).

7.2.3.4 Procollagen Type-I C-peptide (PIP) analysis

Serum concentrations of the procollagen III N-terminal propeptide (PIIINP) was determined by enzyme-linked immunosorbent assay (ELISA) using the TAKARA BIO INC. (Japan) kit according to the manufacturer's instructions. The minimum detectable dose of PIP is typically less than 10ng/ml.

The serum was diluted in a ratio of 1:5, 80mL of PBS (sample diluent) with 20mL of serum. We then transferred 100µl of antibody-POD conjugate solution into the first well and this was followed by addition of 20µl of standard solution prepared beforehand (lyophilised procollagen type-I in one mL distilled water - a dilution series was prepared by mixing the standard solution and the sample diluent with a final concentration of 640ng PIP/mL). The microtitre plate was then allowed to incubate for 3 hours at 37°C. The well contents were discarded and the well was washed 4 times with 400µl of wash buffer [prepared beforehand by diluting 50mL of 10X PBS in wash and stop solution (sulfuric acid) with 450mL of distilled water], carefully emptying the microplate after each wash. This was followed by the addition of 100µl of substrate solution (TMBZ) into each well and incubated at room temperature (20-30°C) for 15 minutes. We then added 100µl of stop solution (1 NH_2SO_4) into each well in the same order as TMBZ. Absorbance at 450nm was measured on an ELx800 microplate reader (BioTek(TM) Instruments, Winooski, VT, USA). Concentrations were determined using a 5PL algorithm (Swart, A).

7.2.3.5 MMP-1 and TIMP-1 analysis

Magnetic luminex screening assay (RnD systems, Minneapolis, USA) was used for the analysis. All the reagents, standards and samples were prepared in accordance to the instructor's manual just prior to the procedure. The minimum detectable dose of MMP-1 is typically less than 2.7pg/ml and for TIMP-1 less than 3.42pg/ml.

The standard cocktails were reconstituted with calibrator diluent RD6-52. The serum was diluted in a 1:10 dilution. The microparticle cocktail was prepared as instructed and were further re-suspended by vortexing. Fifty microlitres of this cocktail was added to each well. After which, 50µL of standard was added. The microplate was sealed and incubated for 2 hours at room temperature on a horizontal microplate shaker set at 800±50 rpm. Prior to the washing, a magnet was applied to the bottom of the microplate. The microplate was washed three times after filling each well with 100µL of wash buffer (PBS). Subsequently 50µL of diluted antibody cocktail was added and the plate resealed and incubated for a further 1 hour at room temperature on the microplate shaker set at 800±50 rpm. This was followed by further washing as mentioned previously. We then added 50µL of Streptavidin-PE into each well followed by incubation on the microplate shaker for 30 minutes. The wells were washed three times before the addition of further 100µl of wash buffer and incubation for 2 minutes on the shaker. Results were obtained using Bioplex manager 5.0 software and checked using a straight line graph and 4Pl method from A Swart.

7.2.3.6 Cardiovascular magnetic resonance acquisition and analysis

CMR studies were performed on a 1.5-Tesla whole body scanner (Siemens), using a six-channel phased-array body coil. The images were obtained during patient breath- hold for approximately eight seconds and were ECG gated (Kim et al. 2000). Left and RV volumes and mass and LA volumes were acquired in line with standard cardiovascular MRI (1.5T magnetom Avanto; Siemens Healthcare, Erlangen, Germany) protocols. Steady-state free-precession imaging (echo times 1.5/3.0 ms, flip angle 60°, temporal resolution 45 ms, slice thickness 7 mm, 3 mm gap, matrix size 256 x 256 mm, field of view 380 x 309 mm) were performed to obtain long axis cines and a contiguous stack of short axis cines for assessment of LV dimensions, mass and ejection fraction as previously described (Hudsmith et al. 2005).

Ten to fifteen minutes after the injection of 0.2 mmol/kg gadolinium-based contrast agent (Magnevist; Schering, Berlin, Germany), 2- or 3-dimensional LGE CMR images were acquired in the same axis and slice thickness used in the cine imaging (Hoffman et al. 2014). Inversion recovery times varying from 200-250 ms were used to null the signal from the intact myocardium (Hoffman et al. 2014).

Images were analysed by an independent experienced reader, blinded to the echocardiographic results, with Argus software version 2002B (Siemens Medical Solutions, Erlangen) as previously described (Karamitsos et al. 2007). The assessment of cardiac function and chamber sizes were performed in standard views in the long-axis (horizontal and vertical) and short axis planes. Ejection fractions for the LV was assessed with the following formula:

Ejection fraction = end-diastolic volume – end-systolic volume/end-diastolic volume
LV volumes and EF were obtained by semi-automatic tracing of contours on the short-axis images in end-diastole and end-systole, with manual corrections when required (Schulz-Menger et al. 2013, Siemens avanto protocols). From the short-axis LGE images, basal, midventricular, and apical slices were selected based on anatomic landmarks (papillary muscles, LV outflow tract), and endocardial and epicardial borders were traced manually (Schulz-Menger et al. 2013, Siemens protocols). Myocardial fibrosis was defined as a region of LGE with signal enhancement greater than the signal intensity of non-enhanced myocardium (as defined by a manually placed region of interest) (Doltra et al. 2013).

7.2.3.7 Statistical analysis

Statistical analysis was performed with Statistica version 12.5, series 0414 for Windows. Continuous variables are expressed as means ± SDs or medians (IQRs). Categorical data are expressed as a percentage. The differences for continuous variables were calculated using Student's t-test or Mann-Whitney U test when the distribution was non-normal. Chi-square and Fisher's exact test were used to calculate the difference for categorical data for independent samples. Pearson's and Spearman's correlation coefficient were used to calculate correlations depending on whether data was normally or non-normally distributed. Biomarker levels (TIMP1, MMP1, and MMP1/TIMP1 ratio) were log transformed before analysis when distribution was not normal. A p value<0.05 was considered statistically significant.

7.2.4 Results

7.2.4.1 Baseline characteristics

The mean age was 36.3±13.9 years, with 81% females (Table 7.2.1). All the patients had isolated moderate or severe chronic rheumatic MR and no comorbidities. Ten patients were in NYHA functional class I, the remainder were NYHA functional class II. Four patients were on medical treatment with diuretics (furosemide) and anti-remodelling therapy (aldactone, carvedilol, enalapril) for previous HF secondary to MR. Eight patients were on diuretics alone.

7.2.4.2 CMR characteristics

In this study LGE was present in four (18%) of patients with CRMR (Table 7.2.2). A varied pattern of LGE of the LV myocardium was noted. These included:

1) transmural LGE in the lateral wall,

2) patchy areas of LGE in the basal septum ,mid-septum and basal inferior wall,

3) transmural fibrosis of the inferior wall and,

4) sub-epicardial LGE in one patient.

The two patients with transmural involvement had normal coronary angiogram (done as part of their surgical workup).

Table 7.2.1 Baseline and echocardiographic characteristics of the study patients and controls.*

Variable	Study group n=22	Control n=14	p value
Clinical parameters			
Age (years)	36.3±13.9	40.3±14.2	0.40
Gender (F:M)	18:4	10:4	0.36
SBP (mmHg)	123.2±9.5	122.9±5.1	0.91
DBP (mmHg)	77.2±6.4	74.6±12.3	0.34
Pulse (beats/min)	74.6±13.1	75.5±13.3	0.55
Body mass index (kg/m^2)	24.8±4.7	28±5.7	0.06
Body surface area (m^2)	1.6±0.2	1.7±0.2	0.24
Echocardiographic parameters			
LV EDD(mm)	56.2±7.4	42.2±6.1	<0.001
LVESD(mm)	41.5±8.6	26.7±4.0	<0.001
EDVi (mL/m^2) †	90.4(71.5-103.8)	43.2(35.2-43.2)	<0.001
ESVi (mL/m^2) †	39.6±19.6	15.3±4.6	0.001
EF (%)	59.8±10.6	60.6±17.1	0.5
LV mass index(g/m^2) †	100.1±33.8	61.4±18.7	0.004

* Data are presented as median (interquartile range), mean± SD or %. † Values are indexed to BSA. DBP - *Diastolic blood pressure.* EDVi - *End-diastolic volume indexed*; ESVi - *End-systolic volume indexed*; LAVi - *Left atrial volume indexed*; EDD - *End- diastolic diameter*; EF - *Ejection fraction;* ESD - *End- systolic diameter*; LV - *Left ventricle*; NYHA - *New York Heart Association functional class.* SBP – *Systolic blood pressure*.

Table 7.2.2 CMR characteristics of the study patients.*

Regurgitant volume(mL)	47.0±19.9
Regurgitant fraction (%)	49.2(31.7-56.2)
EDVi (mL/m^2) †	98.5(81-111.1)
ESVi (mL/m^2) †	49.1±36.7
EF (%)	58.8±15.1
Moderate MR	9 (41%)
Severe MR	13 (55%)
LV mass(g/m^2) †	67 (63-85.8)

* Data are presented as median (interquartile range), mean± SD or %. † Values are indexed to BSA. EDVi - *End-diastolic volume indexed*; ESVi - *End-systolic volume indexed*; EF- *Ejection fraction*, LV - *Left ventricle*; MR - *Mitral regurgitation*.

7.2.4.3 Biomarkers

PIP and PIIINP were not elevated when compared to controls (11.8(6.9-21.6) ng/mL vs 15.7(13.6-18.5) ng/mL, p=0.09; 780.4(727.3-1263.7) vs 1065.1(589.2-1252.0) µg/mL, p=0.13) (Table 7.2.3). Log MMP-1 was elevated in patients with CRMR compared to controls (3.5±0.68 vs 2.7±0.9, p=0.02). There was no difference in Log TIMP-1 between CRMR and controls (4.6±0.39 vs 4.8±0.30, p=0.15). The ratio of Log MMP-1 to TIMP-1 was increased (-1.2±0.6 vs -2.1±0.89, p=0.002).

Table 7.2.3 Biomarkers in the study patients compared to controls.*

Variable	Study group (n=22)	Control (n=14)	p value
Procollagen III NP (ng/mL	11.8(6.9-21.6)	15.7(13.6-18.5)	0.09
Log PIIINP	2.5±0.7	2.7±2.6	0.18
Procollagen I peptide (µg/mL)	780.4(727.3-1263.7)	1065.1(589.2-1252.5)	0.13
Log PIP	6.79±0.57	6.8±0.47	0.29
MMP-1(ng/mL)	37.5(19.9-59.7)	16.2(6.53-37.9)	0.3
Log MMP-1	3.52±0.7	2.7±0.9	0.02
TIMP-1(ng/mL)	95.4(90.4-140.1)	139.2(110.3-155.5)	0.1
Log TIMP-1	4.6±0.4	4.8±0.30	0.15
MMP-1/TIMP-1 ratio	0.26(0.21-0.43)	0.11(0.07-0.26)	0.08
Log MMP-1/TIMP-1 ratio	-1.2±0.6	-2.05±0.89	0.002

*Data are presented as median (interquartile range), mean± SD or %. MMP - *Matrix metalloproteinase*; TIMP - *Tissue inhibitor of matrix metalloproteinase*; PIP - *Procollagen Type IC-Peptide*; PIIINP - *Procollagen III N-Terminal propeptide*.

7.2.4.4 Relationship of biomarkers and MRI parameters

No correlation was noted between biomarkers and CMR parameters of LV volumes, regurgitant fraction and regurgitant volumes (p>0.05).

7.2.5 Discussion

The main findings of this study are:

1) Fibrosis, as assessed by LGE is uncommon in CRMR.

2) Biomarkers suggestive of collagen degradation (MMP-1, MMP1/TIMP-1 ratio) are increased in CRMR, but no change in biomarkers of collagen synthesis (PIP and PIIINP) was noted.

In this study the majority of patients with CRMR did not have fibrosis of LV myocardium on LGE. There are no studies on chronic rheumatic MR to draw comparisons from, but the limited studies done in degenerative MR have shown the presence of fibrosis on LGE in about 30% of patients compared to only 18% in the current study (Edwards et al. 2014, Van De Heyning et al. 2014). In contrast to our study, biological factors such as advanced age, comorbidities such as hypertension and diabetes may have contributed to higher prevalence of fibrosis in these studies (Edwards et al. 2014, Van De Heyning et al. 2014). Further, one study used T1 mapping in addition to LGE, and was able to report on microvascular fibrosis, increasing the detection rate of fibrosis in their study (Edwards et al. 2014). An alternative explanation for a lack of fibrosis in the majority of patients in this study, may be the presence of diffuse fibrosis, which is missed by this technique, as it compares regions of normal myocardium to abnormal myocardium (Doltra et al. 2013). Conversely, fibrosis may indeed be absent, and this is supported by the normal markers of collagen synthesis in this study. The aforementioned hypothesis is further supported on the basis of a study done by Ho et al. in hypertrophic

cardiomyopathy patients, where it was noted that a pro-fibrotic state (as assessed by increased biomarkers of synthesis) preceded the development of fibrosis visible on MRI (Ho et al. 2010). The sample size in our study was too small to draw comparisons based on the presence or absence of LGE, or comment on patterns of enhancement in detail. Interestingly though, LV fibrosis in the four patients was not confined to the posterobasal region, area noted to be affected more commonly by rheumatic fever (Barlow 1987).

A higher prevalence of fibrosis is observed commonly in pressure overload states such as aortic stenosis (Barone-Rochette et al. 2013). The exact mechanism of greater fibrosis in pressure overload states compared to volume overload states remains speculative (Chemaly et al. 2013). The following reasons have been proposed:

1) a greater supply/demand mismatch in pressure overload states resulting in ischaemia and fibrosis.

2) data from animal studies have shown that pro-fibrotic pathways are activated to a larger extent in pressure overload states compared to volume overload states.

3) the predominant pathology in mitral regurgitation may be extracellular volume loss, rather than excessive collagen deposition secondary to activation of Kallikrin-Kinin system, and thereby, of bradykinin which increases MMP activity causing loss of collagen, and LV dysfunction as shown in an animal model (Wei et al. 2012). The predominance of degradation over synthesis results in loss and disruption of the myocardial collagen scaffold and an associated decline in matrix tensile strength, resulting in ventricular dilatation, systolic dysfunction and ultimately death (Lopez et al. 2010).

In our study patients with CRMR had increased collagen degradation as suggested by increase in MMP activity and normal levels of TIMPs and markers of collagen synthesis. This finding supports the lack of myocardial fibrosis observed in our study. These findings differ from the study by Banerjee et al. in 30 patients with CRMR, where they found an increased level of biomarkers of synthesis and degradation. The discrepancy may be explained by:

1) younger patients than this study (mean age 29.6±2 years),

2) possible ongoing rheumatic activity,

3) the inclusion of patients with AF, therefore resulting in increased biomarker levels (Banerjee et al. 2014).

The use of anti-remodelling therapy was similar in the current study to that of Banerjee et al. Thirty to forty percent of their patients were on anti-remodelling therapy with spironolactone and ACEI respectively, and 10% were on beta-blockers. In their study, only biopsies of the leaflets were performed, not the LV to assess the absence or presence of fibrosis. Further, they reported increased thickness of the leaflets and collagen deposition in eight patients that underwent surgery. It is unclear, however, as to whether the primary lesion was MS or MR in this subset of patients. Further, there was increased MMP activity in their MR patients compared to MS, as well as increased MMP to TIMP ratio. They acknowledge that the elevation in PIP was lower than anticipated in their MR cohort, and that markers of collagen degradation, exceeded markers of synthesis in their patients with CRMR.

Previous studies in canine model have proposed that increase in LV mass in MR is not as a result of increased protein synthesis but decrease in collagen

degradation (Carabello 2008). However, we noted an increased LV mass despite increased collagen degradation and normal or decreased protein synthesis in CRMR. Based on our findings we support the concept that the increase in LV mass in MR is likely due to myocyte elongation and changes in collagen cross linkage and collagen weave, and not as a result of decreased collagen degradation (Lorell and Carabello 2000). In this study we noted a lack of relationship between biomarkers of collagen metabolism to LV remodelling and thus biomarker activity is likely not the sole cause of remodelling. Other factors such as wall stress, neuro-hormonal activation and perhaps cytokines such as TGFβ also play an important role (Khan and Sheppard 2006, Tsutsui et al. 1994,).

The main limitation of this study was the small sample size. A larger sample size would have reduced the probability of chance accounting for the absence or presence of fibrosis. A study with a larger sample size with isolated MR, and one with co-morbidites and MR, may be required to account for the finding of fibrosis secondary to isolated MR. Patients with mild MR and AF were excluded. We did not use T1 mapping to exclude presence of microscopic fibrosis and did not perform LV biopsies.

7.2.6 Conclusion

The prevalence of LV fibrosis by LGE imaging is low in rheumatic mitral regurgitation. This finding corroborates with increased level of biomarkers of collagen degradation and normal levels of biomarkers of collagen synthesis.

Chapter 8

Is there a role for Combination anti-Remodelling therapy for Heart Failure secondary to Chronic Rheumatic Mitral Regurgitation?

8.1 Abstract

8.1.1 Background

Chronic mitral regurgitation (MR) is characterised by cardiac volume overload with resultant activation of the neuro-hormonal system. This culminates in cardiac remodelling and eventually heart failure (HF). Few non-randomised studies have looked at the value of beta-blockers and vasodilators in MR. The results from these studies have been equivocal. No study has looked at the value of combination anti-remodelling therapy in heart failure secondary to MR. In developing countries lack of availability of cardiothoracic surgery makes the need to identify successful pharmacologic therapies imperative. We thus aimed to study the effect of anti-remodelling therapy in terms of clinical outcome, and traditional, as well as newer echocardiographic parameters, such as 2D strain, in patients with severe chronic rheumatic mitral regurgitation (CRMR) who presented in HF.

8.1.2 Methods

This sub-study formed part of an ongoing study on CRMR at Chris Hani Baragwanath Academic Hospital (CHBAH). It comprised of 31 patients (29 females). Patients admitted and treated with combination therapy for heart failure (HF) secondary to CRMR with ejection fraction (EF) <60%, NYHA II-III and who refused surgery, were included in this prospective observational study. The patients were followed up at baseline, 3 months and 6 months. They underwent clinical examination, blood tests (urea, creatinine and electrolytes) and their medication was

up-titrated to maximal tolerable doses, as part of their routine management. All patients underwent comprehensive clinical assessment and echocardiography at baseline and at 6 months, once on maximal medical therapy. The echocardiographic data was acquired using the Philips iE33 system. Two dimensional strain imaging was performed using QLAB 9 speckle tracking software.

8.1.3 Results

The mean age was 50.7±8.5 years. There was no change in clinical symptoms and functional status, as assessed by six-minute walk test and Minnesota HF questionnaire at baseline and 6 months of maximal therapy [265.5±103.0 metres vs 275.4±71 meters, p=0.6; 34 (18-61) vs 32.5 (13-48), p=0.3]. None of the patients died or were hospitalised for HF during the study period. Left and right ventricular structural and functional indices remained static (P>0.05). There was no difference in right (RA) and left atrial (LA) volumes before and after maximal therapy [RA - 26.5 (21.7-32) mL/m^2 vs 24.7 (7.4-33.8) mL/m^2 (p=0.6); LA - 60.2 (47.1-89.4) mL/m^2 vs 59.5 (44.2-82.4) mL/m^2 (p=0.8)]. Right (RV) and left ventricular (LV) strain did not show a significant change on treatment [-15.6±5.0% vs -16.4±5.9% (p=0.56); -13.9±4.3% vs -15±4.0% (p=0.28)]. However, the peak LA systolic strain improved at 6 months (18.7±7.7% vs 23.6±8.5%, p=0.02). Furthermore, no difference in CRMR severity was noted at the end of therapy.

8.1.4 Conclusion

This preliminary analysis suggests that combination anti-remodelling therapy may be beneficial for HF secondary to CRMR with no HF related admissions or deaths, and no deterioration in echocardiographic parameters of ventricular size and function.

8.2 Introduction

HF is an end result of various cardiovascular diseases and results from either pressure or volume overload (Hilfiker-Kleiner et al. 2006). The chronic overload of the LV, LA and secondarily RV, results in cardiac remodelling secondary to neuro-hormonal activation with resultant molecular, cellular and interstitial changes (Le Tourneau et al. 2013, Casaclang- Verzosa et al. 2008, Cohn et al. 2000). In chronic MR the persistent volume overload results in myocardial dysfunction through the aforementioned mechanisms. At present surgery is the mainstay of therapy for patients with symptomatic severe MR and markers of LV systolic dysfunction (Nishimura et al. 2014). Surgery is associated with non-negligible morbidity and mortality even in established centres especially in patients with LV dysfunction and high NYHA functional class (Tribuoilloy et al. 1999, Enriquez-Sarano et al. 1995). Use of medical therapy for chronic MR has been largely inconclusive and controversial (Carabello et al. 2008). Most of these were small studies, involving ACEI and beta-blockers in degenerative mitral regurgitation (Ahmed et al. 2012, Carabello et al. 2008, Evangelista et al. 2007). Guidelines on valvular heart disease recommend medical therapy for HF (EF<50%) in chronic MR (class IIa, level of

evidence B) (Nishimura et al. 2014). No study has systematically looked at the effects of combination therapy in HF secondary to MR. There is proven mortality and morbidity benefit of combination anti-remodelling therapy in systolic HF as a result of ischaemia and cardiomyopathies (Yancy et al. 2013, Merlo et al. 2011, Cicoria et al. 2002). Therefore, we hypothesised that a similar benefit may be derived in HF secondary to CRMR. This would potentially offer an alternative option to these patients who are at high risk for surgery or are not inclined to undergo surgical intervention. Further, the benefit of anti-remodelling therapy may extend to asymptomatic or symptomatic patients with significant MR to stabilise the disease process. This might delay the time to surgery or perhaps even obviate the need for surgical intervention in a developing world setting, where surgical delays are inevitable.

We thus aimed to study the effect of anti-remodelling therapy in terms of clinical outcome, and traditional as well as newer echocardiographic parameters such as 2D strain in patients with severe CRMR who presented in HF.

8.3 Methods

This prospective observational sub-study formed part of a larger study on CRMR at the CHBAH. Patients were enrolled from January 2014 and December 2014. All patients were screened and patients deemed to have severe CRMR and presented in HF were referred for possible inclusion in the study. HF was diagnosed as per ACCF/AHA and ESC guideline definition (Yancy et al. 2013, McMurray et al.

2012). The assessment of HF was made based on a combination of the patient's history, clinical signs as well as available clinical records. A total of 66 patients with presumed CRMR underwent clinical evaluation, resting electrocardiogram and detailed echocardiographic assessment according to a pre-determined protocol.

The inclusion criteria were as follows:

1) Patients aged 18 years or older with echocardiographic features of severe CRMR;
2) symptomatic (NYHA II-III);

3) LVEF ≤ 60%;

4) declining surgery or awaiting surgery; and,

5) receiving medical therapy for HF.

Patients were excluded if they had significant aortic valve disease, concurrent MS with a valve area of less than 2.0 cm^2, documented ischaemic heart disease, preexisting non-valvular cardiomyopathy, prior cardiac surgery, congenital or pericardial disease, pregnancy, severe systemic disorders such as renal failure, uncontrolled hypertension (systolic blood pressure >140mmHg and diastolic blood pressure >90mmHg) on medication or severe anemia (haemoglobin<10g/dl).

Thirty-five patients were excluded due to the following: anemia, renal dysfunction, mild or moderate MR, MR of non-rheumatic etiology and inadequate image quality. The final sample included 31 patients. Most HF trials conducted with anti-remodelling agents required a minimum duration of 3 months to demonstrate benefit, and therefore we followed up patients in this study for a period of 6 months (Bangalore et al. 2012).

All patients included in the sub-study were receiving some form of medical therapy for HF. All patients were on the minimum dose of respective HF medication and were up-titrated at 3 months where indicated based on symptoms, blood pressure, and urea and creatinine levels.

All patients enrolled in this study were on a combination of at least one anti-remodelling agent in addition to a diuretic for at least 1 week. Therapy comprised of beta-blockers (atenolol, carvedilol), ACEI/ARBs (Enalapril, perindopril, Telmisartan), and an aldosterone-receptor antagonist (spironolactone), in addition to digitalis and diuretics. The medication was initiated at the discretion of the treating physician. All the aforementioned medication was either down titrated or withdrawn or substituted on follow-up visits if side effects were reported.

The study was approved by the University of the Witwatersrand Ethics Committee (M140114).

8.3.1Clinical follow-up

Patients were followed up at 1 month, 3 months and at 6 months. At 1 month and 6 months a full clinical assessment was done including Minnesota Heart Failure Questionnaire and 6-minute walk test. The dose of the medication was titrated at 1 month and full titration was achieved at 3 months by the treating physician.

8.3.2 Echocardiographic evaluation

Transthoracic echocardiography was performed on all patients in the left lateral position by experienced sonographers using a S5-1 transducer on a Philips iE33 system (Amsterdam, The Netherlands). The images were obtained according to a standardised protocol at baseline and at the 6-month follow-up. The data was transferred and analysed off-line using the Xcelera workstation (Philips). The echocardiographic measurements were done by the researcher at baseline and the follow up measurements were done by an experienced sonographer who was blinded to the initial results.

8.3.3 Two dimensional and Doppler quantification

All linear and volumetric chamber measurements were performed according to the ASE chamber guidelines at baseline and at 6 months (Lang et al. 2015). Measurements relating to LV diastolic function were performed in accordance with the ASE guidelines on diastolic function and included pulse wave Doppler at the mitral tips and tissue Doppler of both medial and lateral mitral annuli at baseline and at 6 months (Nagueh et al. 2009). Measurements relating to the RV were based on the ASE guidelines on the RV (Rudski et al. 2010).

MR was considered rheumatic in aetiology when the morphology of the valve satisfied the World Heart Federation (WHF) criteria for the diagnosis of chronic RHD (Reményi et al. 2012). MR severity was assessed using qualitative, semi-quantitative and quantitative methods (integrated approach) as per the ASE and ESC valvular regurgitation guideline (Lancelloti et al 2013, Zoghbi et al. 2003). In

equivocal cases the echocardiographic data was integrated with the clinical evaluation by an experienced cardiologist to distinguish moderate from severe MR.

8.3.4 Speckle tracking echocardiography

8.3.4.1 Left atrial strain

Left atrial strain was performed at baseline and at 6 months. Apical four and two chamber (4C and 2C) views were obtained using two dimensional grey scale echocardiography for speckle tracking analysis (Cameli et al. 2009, Vianna-Pinton et al. 2009). This was performed during end-expiratory breath-hold and stable ECG recording (Cameli et al. 2009, Vianna-Pinton et al. 2009). An adequate grey-scale image that allowed separation of myocardial tissue and surrounding structures was obtained (Cameli et al. 2009). Three consecutive cardiac cycles were recorded and averaged. The frame rate was set between 60 and 80 frames per second. Philips QLAB version 9.0 software allowed off-line semi-automated analysis of speckle-based strain. The endocardial surface of the LA was traced manually in both 4C and 2C views by a three point and click approach. The system then automatically generates an epicardial surface tracing. The region of interest (ROI) was thus created and manually adjusted as needed to allow for adequate speckle tracking.

The software divides the ROI into seven segments in the 2C and 4C views. It then generates the longitudinal Ɛ curves for each segment and a mean curve of all segments. The onset of the QRS was used as a reference point for calculation of LA strain (Hoit et al. 2014).

8.3.4.2 Left ventricular strain

Left ventricular strain was performed at baseline and at 6 months. Two dimensional echocardiography images were obtained at end-expiration from LV apical long axis, 4C, 3C and 2C views with frame rates of 60–80 frames per second (Younan 2015). Three consecutive cardiac cycles were recorded and averaged (Marciniak et al. 2007). LV endocardial surface was traced manually in the three views by a point and click approach (Younan 2015, Kocabay et al. 2014). The speckle tracking points were modified to allow for adequate speckle tracking of the LV wall. The LV was divided into 17 segments. Peak LV longitudinal systolic strain was calculated for apical long axis 4C, 3C and 2C views, and global LV systolic strain was calculated by averaging the three apical views.

8.3.4.3 Right ventricular strain

Right ventricular strain was performed at baseline and at 6months. RV free wall peak systolic strain (PSS) was derived from modified apical 4 chamber view (A4C) RV focused view (Kumar et al. 2014). Three consecutive cardiac cycles were recorded and averaged (Todaro et al. 2015). The frame rate was set between 60 and 80 frames per second. Once the three points (RV apex, medial and lateral tricuspid annulus) were defined the software automatically traced the endocardial and epicardial border (Kumar et al. 2014). Philips QLAB version 9.0 software allowed off-line semi-automated analysis of speckle-based strain. This results in the division of RV into six standard segments in the apical 4-chamber view (Mingo - Santos et al. 2015, Kumar et al. 2014, Konishi et al. 2013). The region of interest (ROI) once created, can be manually adjusted as needed to allow for adequate

speckle tracking (Hyllen et al. 2014). The free wall RV PSS was obtained by averaging 3 lateral segments (the basal RV lateral wall, the mid-RV lateral wall, and the apical RV wall) (Todaro et al. 2015). The interventricular septum was excluded from analysis (Mingo-santos et al. 2015, Nowell et al. 2014, Konishi et al. 2013). The longitudinal Ɛ curves for each segment and a mean curve of all segments is then generated by the software. These curves were used to derive RV free wall PSS.

8.3.5 Statistical analysis

Statistical analysis was performed with Statistica (version 12.5, series 0414 for Windows). Continuous variables are expressed as mean ± SD or median (IQR). Paired Student's t test or Wilcoxon's matched pairs test were used to compare continuous variables. Categorical variables were expressed as percentage. A p value of < 0.05 was recognised as statistically significant.

8.4 Results

8.4.1 Clinical parameters at baseline and 6 months of treatment

There was no change in systolic blood pressure, diastolic blood pressure and heart rate from baseline to 6 months (125±12.6 mmHg vs 120.1±10.2mmHg, p=0.09); (76.2±12.2 mmHg vs 74.2±11.02 mmHg, p=0.5); 71.5 (70-81) beats/min vs 71.0 (61-80) beats/min, p=0.4)) (Table 8.1). The median Minnesota HF score was 34 (18-61) and 32.5 (13-48) at the start and at the end of treatment at 6 months, respectively (p=0.3). There was no difference in the six-minute walk test at the onset of treatment and at 6 months (265.5±103.0 metres vs 275.4±71 metres, p=0.6). None of the patients were hospitalised for HF and all were alive at 6 months. Baseline and maximum therapeutic doses of respective medication are summarised in Table 8.2.

Table 8.1 Baseline clinical characteristics.*

Variable	n=31
Age (years)	50.7±8.5
Sex (F:M)	29:2
Systolic blood pressure (mmHg)	125±12.6
Diastolic blood pressure (mmHg)	76.2±12.2
Heart rate (beats/min)	71.5(70-81)
Body surface area (m^2)	1.73±0.16
Body mass index (kg/m^2)	28.1±6.1
NYHA II-III	31(100%)
Hypertension (%)	29(93)
HIV (%)	7(23)
Atrial fibrillation (%)	2(6.4)

* Data are presented as median (interquartile range), mean± SD or %. HIV-*Human immunodeficiency virus*; NYHA - *New York heart association functional class*.

Table 8.2 Comparison between baseline and maximum medication dose of the study patients.*

Medication	Number (%)	Baseline dose (mg)	Dose (mg) at 6 months	P-value
Furosemide	30(97)	75±25.9	78.3±34.9	0.67
Nifedipine XL	9(29)	34.4±21.8	47.7±24.3	0.23
Digoxin	7(23)	0.125	0.125	1.0
Enalapril	11(35)	10(2.5-20)	20(10-20)	0.17
Perindopril	11(35)	2.9±1	4±1.7	0.003
Carvedilol	29(94)	12.5(3.125-12.5)	50(37.5-50)	<0.001
Spironolactone	28(90)	25(12.5-25)	50(50-75)	0.001

Data are presented as median (interquartile range), mean± SD or %. *Two patients were on Telmisartan (40mg at baseline and 6 months), and one was on Atenolol (12.5 mg up-titrated to 25 mg at 6 months).

8.4.2 Echocardiographic parameters at baseline and at 6 months of treatment

8.4.2.1 Left and right ventricular indices

There was no change in left ventricular (LV) dimensions in systole or diastole between the two periods (55.5±8.4 mm vs 55.1±8.0 mm, p=0.8); 42.6±9.4 mm vs 40.7±9.5 mm, p=0.43) (Table 8.3). Left ventricular end- systolic indexed and end-diastolic volumes indexed remained unchanged (45.4±17.8 mL/m^2 vs 42.8±15.8 mL/m^2, p=0.5); 81.8(68.9-98.1) mL/m^2 vs 79.1(64.5-99.3) mL/m^2, p=0.6. Hence, there was no difference in the LV ejection fraction at baseline and at the six-month observational period (46.9±8.7% vs 50.9±10.3%, p=0.19). The pulse-wave and tissue Doppler parameters did not show a significant difference from the start to the end of treatment (p>0.05). Left atrial volume indexed remained constant 60.2(47.1-89.4) mL/m^2 vs 59.5(44.2-82.4) mL/m^2, p=0.8. There was no difference noted in the RV dimensions at the start and end of therapy (RV base: 38.3±6.25 mm vs 35.8±8.8 mm, p=0.2). There was no change in RV systolic function parameters at the start and end of treatment (p>0.05). Right atrial volumes indexed to BSA remained constant 26.5(21.7-32) mL/m^2 vs 24.7(7.4-33.8) mL/m^2, p=0.6.

8.4.2.2 Mitral regurgitation severity

Based on the integrated assessment (qualitative and quantitative parameters) MR severity did not change at the end of 6 months. No change in quantitative parameters (which were likely underestimated due to predominantly eccentric MR jets, as previously mentioned in chapter 7.1 of the thesis) of MR assessment was noted at the end of 6 months (VC width: 6.5±1.9 mm vs 6.0±1.6 mm, p=0.2; RF:

31.7% (18.9-57.7) vs 29.2% (15.7-53.5), p=0.2; RV: 29.3±11.2 ml vs 24.3±10.1 ml, p=0.34).

8.4.2.3 Strain parameters

LA peak systolic strain increased at 6 months (18.7±7.7% vs 23.6±8.5%, p=0.02). However, there was no change in right and left ventricular strain at the end of combination therapy (-15.6±5.0% vs -16.4±5.9%, p=0.56; -13.9±4.3% vs -15±4.0%, p=0.28).

Table 8.3 Left and right ventricular echocardiographic parameters before and after 6 months of therapy.*

Variable	Baseline (n=31)	Six months (n=31)	p value
Left ventricular indices			
LV EDD (mm)	55.5±8.4	55.1±8.0	0.8
LV ESD (mm)	42.6±9.4	40.7±9.5	0.43
EDVi (mL/m^2) †	81.8(68.9-98.1)	79.1(64.5-99.3)	0.6
ESVi (mL/m^2) †	45.4±17.8	42.8±15.8	0.5
Ejection fraction (%)	46.9±8.7	50.4±10.1	0.1
E wave (cm/s)	113.2±47.2	112.9±42.1	0.9
A wave (cm/s)	102.0±26.5	99.4±28	0.7
E/A wave (ratio)	1.0±0.4	1.1±0.4	0.3

E´ medial (cm/s)	6.6(4.5-8.2)	5.9(4.7-7.8)	0.2
A´ medial (cm/s)	6.7(5.1-8.2)	7.1(5.9-8.3)	0.5
Medial E/E´(ratio)	18.5±9.5	18.9±9.7	0.8
Medial S´(cm/s)	6.1±1.4	6.1±1.2	1.0
LAVi (mL/m^2) †	60.2(47.1-89.4)	59.5(44.2-82.4)	0.8
Right ventricular indices			
RV base (mm)	38.3±6.25	35.8±8.8	0.2
TAPSE(mm)	20.5±2.9	20.6±2.9	0.9
RV S´(cm/s)	11.1±2.7	11.6±2.5	0.45
RAVi (mL/m^2) †	26.5(21.7-32)	24.7(7.4-33.8)	0.6
PASP(mmHg)	33.2±12.4	31.4±11.5	0.5

*Data are presented as median (interquartile range), mean± SD or %. † Values are indexed to BSA. EDVi - *End-diastolic volume indexed*; ESVi - *End-systolic volume indexe*d; LAVi - *Left atrial volume indexed;* EDD - *End- diastolic diameter*; ESD - *End- systolic diameter*; LV - *Left ventricle*; PASP - *Pulmonary artery systolic pressure*; RAVi, - *Right atrial volume index*; RV - *Right ventricle*; TAPSE - *Tricuspid annular plane systolic excursion.*

8.5 Discussion

The main findings of this study were:

1) There were no HF-related hospitalisation and no deaths were observed at 6 months of maximal medical therapy in CRMR.

2) An improvement in LA peak systolic strain was noted, with no worsening of LV and RV conventional echocardiographic and strain parameters on maximal medical therapy.

Limited older, pre-echocardiographic studies concerning RHD in western populations, demonstrated variable natural histories ranging from CRMR being a benign lesion (with a normal life expectancy), to a severe, progressive and ultimately fatal disease (Ellis et al.1969, Jhaveri et al.1960, Wilson et al.1957). Natural history studies in degenerative MR (with follow-up ranging from 7 months to 10 years), have shown increased risk of sudden cardiac death, and increased postoperative morbidity and mortality in the presence of severe MR, symptoms, arrhythmias, LVESD ≥ 45mm and EF≤60% (Tribuoilloy et al. 2009, Rosenhek et al. 2006, Enriquez-Sarano et al. 2005, Grigioni et al. 1999, Enriquez-Sarano et al. 1995, Kligfield et al. 1987). In a study by Wisenbaugh et al, a LVEDD >52mm in rheumatic MR, was associated with poor postoperative outcomes (Wisenbaugh et al. 1994).

The aforementioned studies primarily pertaining to degenerative, significant MR have evaluated symptomatic and asymptomatic patients. Most of them concluded that with conservative management (medical therapy), outcomes were worse regarding cardiac death, progression to worsening NYHA functional class, LV

dysfunction, HF, atrial fibrillation and pulmonary hypertension (Tribuoilloy et al. 2009, Rosenhek et al. 2006, Enriquez-Sarano et al. 2005, Grigioni et al. 1999, Enriquez-Sarano et al. 1995, Kligfield et al. 1987). Rosenhek et al. showed 55±6% survival free of any indication for surgery in asymptomatic MR at 8 years of follow-up (Rosenhek et al. 2006). Eight deaths were reported at mean follow-up of 69.2 months. In their study 23% of patients were on beta-blockers and 28% were on ACEI therapy. Tribouilloy et al. noted that LV ESD ≥40 mm was associated with increased mortality and patients that were medically treated with ACEI, diuretics and beta-blocker therapy did not show benefit (Tribouilloy et al. 2009). Similarly, Enriquez-Sarano et al. reported that, in the presence of severe asymptomatic MR at 5 years, death resulting from cardiac causes, progression to HF and AF was 22±3%, 14±3% and 33±3%, respectively, in the presence of medical therapy alone. In the study by Kligfield et al., there was increased incidence of arrhythmia-related deaths in patients with MR and poor ejection fraction, but none of the patients that died were on beta-blocker therapy (Kligfield et al. 1987). Muñoz et al compared 29 patients with CRMR on medical therapy alone to 45 patients who underwent mitral valve replacement (Muñoz et al. 1975). They found at 5 year follow-up, a lower survival, faster progression to higher NYHA class and more complications such as HF and atrial fibrillation in the medical therapy group. The main shortcomings of the aforementioned studies are the inclusion of mostly asymptomatic patients with significant MR, and the medication and dosages used, were not systematically documented.

The subset of patients we followed-up, had mostly stage D HF due to organic valvular heart disease. They were on varied combination anti-remodelling therapy as part of their management. This provided us with the opportunity of observing this

subgroup. The lack of change in LV and RV structural and functional indices may be explained by the possible short duration of follow up, disease stabilising effect of anti-remodelling therapy and/or the relatively younger age of our patients (compared to degenerative MR patients). A lack of difference in MR severity even after controlling the SBP in our study may be explained by the small effect of alteration in pressure gradient on regurgitant volume; static LV volumes, and the rheumatic nature of the disease whereby the orifice is fixed and not dynamic as in degenerative MR (Gaasch and Meyer 2008).

There was no change in LV and RV longitudinal strain parameters and this may be attributed to the short duration of follow up. The reason for marked improvement in LA peak systolic strain may be that the LA remodels and recovers earlier than the ventricles, after an injury as shown by Therkelsen et al. (Therkelsen et al. 2006). Additionally, LA reverse remodelling has been known to occur independently of LV reverse remodelling, due to direct effect of drugs that inhibit RAAS (Casaclang-Verzosa et al. 2008). Also, LA strain may be a more sensitive marker for detecting reverse remodelling, than LA volumes, as noted in this study.

There are a number of studies that have evaluated the effects of individual drugs in degenerative MR. Most of these involved beta-blocker or vasodilator therapy (Carabello et al. 2012, Evangelista et al. 2007). The pathophysiologic basis for their use was: 1) to prevent the deleterious effect of sympathetic nervous system in MR (Ahmed et al. 2012, Tsutsui et al.1994); 2) decreasing afterload and LV wall stress thus preventing deleterious remodelling (Ahmed et al. 2012, Evangelista et al. 2007, Carabello 1995, Spinale et al.1994, Wisenbaugh et al.1994). Nevertheless, the results from mostly small, nonrandomised trials were inconclusive (Bore et al. 2013, Carabello et al. 2008). There are no trials that have systematically explored

the effects of combined therapy with or without HF due to organic rheumatic MR. Munoz et al. compared 29 patients with mitral insufficiency on medical therapy alone and those who underwent surgery and found lower survival, faster progression to higher NYHA class and greater degree of complications such as HF and AF in the medical therapy group at 5 years of follow-up (Munoz et al.1975). However, the aforementioned study did not mention the specific drug therapies and dosages involved.

The effect of aldosterone receptor antagonists, has not been evaluated in organic MR in humans. Additionally, no trial has systematically explored the effects of combination therapy (with or without HF), secondary to CRMR. The possible reason for the non-benefit from the aforementioned individual drugs, may be that they block only part of the SNS and RAAS which results in activation of the other arm of this system or alternative pathways. A classic example would be that of aldosterone escape during prolonged ACEI therapy (Opie and Gersh 2013). Other possibilities include, activation of the Kallikrein-kinin system due to an increase in bradykinin, which in turn activates MMPs resulting in collagen loss - a process that may be exacerbated by the inhibition of angiotensin II by ACEI (Wei et al. 2012).

These drugs in combination have synergistic action - for example the combination of an ACEI, beta blocker and aldosterone receptor antagonist, suppresses myocardial fibrosis in systolic heart failure (Bonow et al. 2012). Therefore, combination therapy with drugs that block the SNS and RAAS systems, may be the answer. Most of our patients were on a combination of carvedilol, spironolactone and an ACEI. However, their effect on LV function and rheumatic MR severity remains questionable. Thus, other molecular mechanisms may be at play in heart failure secondary to chronic MR (Hilfiker-Kleiner et al. 2006). Further, no

fibrosis was noted on cardiac MRI in the majority of patients with isolated MR and there was an increase in markers of collagen degradation (Chapter 7.2). Thus, it may partially explain the lack of improvement in LV echocardiographic indices on anti-fibrotic therapy.

Rheumatic disease may primarily result in leaflet fibrosis and distortion, and not directly affect the ventricle, thus resulting in MR with secondary LV volume overload and remodelling (Banerjee et al. 2014, Barlow 1987). Therefore, primary targets should perhaps be leaflet inflammation and abolition of the MR, rather than independently targeting secondary neuro-hormonal and growth-factor pathways (Lorell and Carabello 2000). This hypothesis is partly supported by the regression in LVH observed after aortic valve replacement for aortic stenosis and aortic regurgitation. Similar concepts have been noted in hypertensive heart disease, whereby the effect of anti-remodelling therapy was minimal on fibrosis and LV mass. It was stated that the problem in this disease was primarily high afterload which was the main driver of increased LV mass and fibrosis, and thus one should target the systolic blood pressure rather than downstream signalling cascade.

However, all the patients remained stable on combined medical therapy and none were hospitalised for HF or died during the 6 months of follow up. This finding is relevant as ≥ 50% of patients with systolic HF are re-hospitalised within 6 months of HF assessment (Desai et al. 2012). Further, the lack of sudden cardiac death and HF-related deaths in this study may be attributed to medical treatment, or perhaps it may be a chance finding in a study with small sample size. Therefore, combined medical therapy may serve to stabilise the disease process likely through neuro-hormonal modulation (perhaps the most important compensatory and deleterious mechanism in MR - Tsutsui et al. 1994). Thus, possibly serving as a bridge to

surgery or replacement for surgery in dysfunctional ventricles in a resource limited setting, where most patients present late or have to await surgery.

8.5.1 Study Limitations

There were several limitations to this observational study:

1) The lack of a control arm.

2) A varied combination of medication.

3) The exact duration of therapy at baseline was not clear due to incomplete patient notes.

4) The study subjects and the researcher were not blinded to the treatment.

5) The cardiac MRI to assess MR severity was not performed due to logistical reasons.

6) Not all patients underwent coronary angiogram unless indicated to exclude ischaemic heart disease.

7) The small sample size.

8) The short follow up period.

9) Pre-existing comorbidities.

8.6 Conclusion

We have shown that combination anti-remodelling medical therapy in CRMR may be beneficial to prevent hospitalisation for HF and death. It may have a stabilising effect on HF secondary to chronic rheumatic MR. Further larger studies are needed to test the effect of combination therapy on chronic organic MR.

Chapter 9

Conclusion

9.1 Conclusion

We have observed that the clinical characteristics of contemporary patients with CRMR at CHBAH, is different from that of patients studied with the same disease thirty years ago at this institution (Marcus et al.1994). We specifically chose to examine patients with CRMR, as it is a frequently encountered lesion, and compare my current patients with that of Marcus et al. The relevant demographic and clinical characteristics were documented as part of this thesis and are elaborated in Chapter 1. Our patients were older, suffered from comorbidities and only one patient presented with features suggestive of ARF. This was in stark contrast to the Marcus et al. cohort; where patients were younger with no comorbidities and frequently presented with fulminant rheumatic carditis (Marcus et al. 1994).

Echocardiographic findings contrasted with that of Marcus's patients. In this study, the mitral leaflets were thickened, calcified with restricted leaflet motion secondary to extensive disease of the sub-valvular apparatus as compared to Marcus's patients where the leaflets were pliable and displayed prolapse secondary to elongated chordae (Marcus et al. 1994). The aforementioned change in the clinical profile has important implications in terms of assessment of MR severity. Comorbidities such as uncontrolled hypertension can cause one to overestimate the severity of MR. Further, the more deformed architecture of the MV may result in surgical replacement of the valve rather than repair, with resultant increased morbidity and mortality (Zoghbi et al. 2003, Enriquez-Sarano et al.1995).

In a subsequent chapter, we have presented the atrioventricular mechanics in CRMR. In order to study the former, we first chose to study the LA volumetric and

functional parameters in a normal African population. We found that maximum left atrial volume indexed (LAVi) in a black African population is within the reference range provided in the current chamber guidelines but the upper limits of normal are lower than guideline definitions (Lang et al. 2015). In contrast to other studies, females in this study had a higher maximum LAVi compared to males and this was attributed to a higher BMI. Thus, gender and anthropometric differences must be taken into account when interpreting LA volumetric indices. When we further categorised the study subjects according to age, we noted an increased booster pump function with age, as the conduit function and LV diastolic function declined. The static LA volumes did not change with age.

We found LA strain measurements to be feasible and reproducible using Philips QLAB 9 speckle tracking software. Similar to other studies, LA peak systolic strain declined with age (Sun et al. 2013, Saraiva et al. 2010). There was, however, no change in LA maximum and minimum volumes with increasing age. Therefore, LA peak systolic strain may serve as a more sensitive marker for LA function assessment than volumes. We have thus provided normative data in an African population which can serve as a reference for future studies.

Atrioventricular mechanics in CRMR are altered (Aksakal et al. 2012). We noted LA dysfunction in the reservoir and contractile LA mechanical phases and based on strain parameters, LA dysfunction was more frequent than LV dysfunction. Additionally, these two chambers are dependent on each other for maintenance of optimal function and thus malfunction of one is eventually followed by dysfunction of the other, as noted in this study, where the majority of the patients had LA and LV dysfunction (Nishimura et al. 1997). Further, as most of the patients had LA dysfunction with or without LV dysfunction, we postulate that perhaps in CRMR LA

dysfunction precedes LV dysfunction possibly due to a combination of volume overload and may be direct involvement of the LA by the rheumatic process. However, both chambers cannot be studied in isolation due to the aforementioned relationship and the decision to operate must be individualised. Further, age was found to be an important determinant of LA peak longitudinal systolic strain and thus must be taken into account when interpreting abnormalities of LA function.

We further assessed RV function in rheumatic mitral regurgitation. Traditional RV systolic function parameters such as RV S' and TAPSE were preserved compared to controls. However, RV PSS was depressed in CRMR compared to controls. Thus, we concluded that RV PSS is a sensitive marker of subclinical RV systolic dysfunction. Therefore, in addition to traditional indices of RV function assessment RV PSS must be used to assess RV function. Additionally, LV PSS was the most important determinant of RV PSS. Thus, due to the intimate structural and functional relationship of the left and right ventricles, and the impact of biventricular impairment on postoperative mortality, malfunction of one chamber, usually the LV, requires that the other chamber (RV) must be studied in detail (Le Torneau et al. 2013a,b).

Among the many unexplored issues in CRMR, multimodality imaging and biomarkers form a large gap in the existing knowledge pertaining to this commonly occurring disease entity. Degenerative MR has been fairly well studied with modern imaging but there is still a paucity of data in the field of biomarkers of collagen degradation and synthesis. Interestingly, we noted that CRMR may not be a problem of collagen synthesis but rather a disease, characterised by collagen degradation. This was supported by the increased MMP-1 activity, normal TIMP-1 and markers of collagen synthesis (PIP1 and PIIINP). Further, in comparison to the

previous reports in degenerative MR, the prevalence of fibrosis by LGE on cardiac MRI was low - a finding corroborated by the biomarker results in this study (Edwards et al. 2014, Van De Heyning et al. 2014). Recently, Uretsky et al., reported a discordance in assessment of MR severity between echocardiography and MRI in degenerative MR (Uretsky et al. 2015). We tested this hypothesis in our CRMR patients where all patients had eccentric jets and the PISA method was suboptimal for quantitative MR assessment. We found that there was a difference in MR severity grading between the two techniques in seven patients based on quantitative parameters (Enriquez-Sarano et al.1993). Six of these patients were re-categorised from moderate to severe MR and one from severe to moderate. Overall, when an echocardiographic integrated approach was used, MR severity assessment was concordant with cardiac MRI quantitative assessment in 70% of the patients. Therefore, cardiac MRI was useful for assessment of moderate or severe MR where echocardiography alone was insufficient.

Several human and animal studies, have explored the role of beta-blockers, afterload reducing agents and aldosterone-receptor blockade in degenerative MR, but results have been largely inconclusive (Ahmed et al. 2012, Bernay et al. 2010, Kittleson et al. 2009, Stewart et al. 2008, Evangelista 2007, Tallaj et al. 2003, Tsutsui et al. 1994). Studies have not looked at the effect of combination therapy in HF secondary to MR, even though combination anti-remodelling therapy is used for the management of these patients, and is recommended by the ACC/AHA guidelines (Nishimura et al. 2014). In this study, patients with severe MR on combination HF therapy, were not hospitalised secondary to HF nor were there deaths in this group. An improvement in LA peak systolic strain was noted and the conventional echocardiographic indices did not worsen over a 6-month follow-up period. Thus,

medical therapy may benefit CRMR patients with HF, likely through neuro-hormonal modulation. It may therefore, serve as bridge to surgery in a resource poor setting, and provide an alternative option to patients at high surgical risk and those who decline surgery.

Thus, in conclusion we have shown that the demographic and clinical profile of patients with rheumatic MR has evolved over the last thirty years at CHBAH from young patients with fulminant rheumatic carditis and no comorbidities, to older patients with comorbidities and a low prevalence of ARF. We further explored atrioventricular and RV mechanics in this group of patients after establishing normative data pertaining to LA in an African population. From the former, we have established that, amongst other findings, ethnicity-based differences exist in LA parameters in terms of LAVi albeit still within the reference range provided by ASE chamber guidelines (Lang et al. 2015). There is still a need for further studies on different vendors to standardise normal values pertaining to LA strain, in order to interpret abnormality in various disease states. We have provided age-appropriate values as well, in this population and this would prove useful in an era of an aging population.

We have provided several hypothesis generating conclusions in the context of CRMR which include the following:

1) We suggest that LA dysfunction precedes LV dysfunction based on our finding of predominant LA dysfunction with or without LV dysfunction in CRMR identified on peak systolic strain. Therefore the LA and LV cannot be studied in isolation.

2) RV peak systolic strain is reduced prior to traditional markers of RV systolic function in CRMR, and LV peak systolic strain is an important determinant of RV

PSS. These two chambers should be carefully studied preoperatively to potentially improve postoperative outcomes.

3) CRMR is likely a disease of predominant collagen degradation and not synthesis. This is based on our low observed prevalence of fibrosis in this group of patients. Furthermore, cardiac MRI may serve as an adjunctive tool for assessment of MR severity.

4) Finally, there may be a role for combination anti-remodelling therapy for HF secondary to CRMR.

We hope that these hypotheses may serve as a platform for future larger studies in CRMR and contribute to enhanced clinical care.

Appendix

Calculation of Body Surface Area (BSA)

The body surface area was calculated according to DuBois and DuBois BSA = 0.007184 * $Height^{0.725}$ * $Weight^{0.425}$; M, body weight (kg); H, body height (cm)] (Dubois and Dubois 1916).

Calculation of LV mass on echocardiography

Left ventricular mass and left ventricular mass indexed to body surface area are estimated by LV cavity dimension and wall thickness at end-diastole (Lang et al. 2015). LV Mass (g) =0.8{1.04[([LVEDD + IVSd +PWd]3 - LVEDD3)]} + 0.6

Relative wall thickness (RWT) allows further classification of LV mass increase as either concentric hypertrophy (RWT >0.42) or eccentric hypertrophy (RWT ≤0.42). RWT =2 * PWd/LVEDD.

Assessment Mitral Regurgitation on echocardiography (Lancelloti et al. 2013, Zoghbi et al. 2003)

The mitral valve is assessed in the parasternal long axis (PLAX) view, short axis view, the apical four chamber (A4C) view and the apical three chamber (A3C) view. The severity of mitral regurgitation can be assessed using qualitative and quantitative methods. The assessment of rheumatic mitral valve starts with the

assessment of morphology. The following features are characteristic of the rheumatic mitral valve:

- Thickened mitral valve leaflets,
- Thickening and fusion of the mitral valve commissural edges and chordae,
- The leaflets secondary to commissural fusion open with doming motion,
- Thickening and shortening of chordae.

The qualitative parameters include:

- The left ventricular (LV) size.
    - Mild MR - LV dimensions are within the normal range (i.e. LV end systolic diameter (ESD) < 40mm, LV end diastolic diameter (EDD) < 56mm);
    - Moderate MR - The LV size is between mild and severe;
    - Severe MR - The LVESD is > 40mm and LVEDD is > 56mm.
- The left atrial (LA) size
    - Mild MR - The LA size is normal (i.e. LA diameter < 39mm in PLAX view);
    - Moderate MR – Between mild and severe;
    - Severe MR - The LA diameter is > 39mm.

- Accepted cut-off values for non-significant left-sided chambers enlargement for mitral regurgitation: LA volume 36 mL/m^2, LV end-diastolic volume 82 mL/m^2, LV end-systolic volume, 30 mL/m^2.

- MR jet (as a percentage of the left atrium)
  - Mild MR - The MR jet is less than <20% of the LA size;
  - Moderate MR – variable jet size;
  - Severe MR - The MR jet is > 40% of the LA size or variable size wall impinging jet swirling in LA.
- Spectral Doppler density- MR is mild if the density is faint/parabolic and severe if it is a dense/triangular jet.
- Vena contracta (VC) (the width of the regurgitant jet at its origin
  - Mild MR – The VC is < 3mm;
  - Moderate MR – The VC is 3-7mm;
  - Severe MR – The VC is ≥ 7mm.
- Pulmonary vein flow systolic flow reversal into the pulmonary veins is a marker of severe MR.

Quantitative assessment

The PISA (proximal isovelocity surface area) method is used for assessment of severity for central mitral regurgitation jets. The mitral regurgitation is visualised

from the A4C view. As the blood converges towards an orifice, imaging by Doppler flow reveals concentric shells or hemispheres and these are a representation of isovelocity surfaces. Due to the acceleration of blood in the direction of the orifice aliasing of the velocity occurs and this results in a distinct red blue interface at periphery of the shells. The velocity at this interface is equivalent to the Nyquist limit which is read off the velocity colour scale.

The Nyquist limit can be adjusted to maximise the size of the shell thus the surface area can be calculated using the following formulae:

1) Surface area = $2\pi r^2$.

2) Flow rate = 6.28 x r^2x aliasing velocity.

3) Flow rate = ERO (effective regurgitant orifice) x velocity jet.

The above calculation is based on the fact that the flow through any given shell will equal the flow rate through the orifice.

4) Effective regurgitant orifice (ERO) = flow rate / velocity jet.

The regurgitant volume can be calculated as the product of ERO x TVI (where TVI is the velocity integral of the mitral regurgitation flow as measured by continuous wave Doppler imaging).

From the above calculated parameters mitral regurgitation is considered severe if the EROA is 40mm^2 or more, the regurgitant volume (RegV) is 60ml or above. The mitral regurgitation is mild to moderate if the EROA 20-29mm^2 or a RegV 30-44ml and moderate to severe if the EROA is 30-39mm^2 or RegV of 45-59ml.

Normal values for LV volumes and mass on cardiac MRI (Kawel-Boehm et al. 2015)

Normal LV EDV and ESV for females (20-80 years):76±10ml/m^2 (range: 56-96) and 24±5 ml/m^2 (range: 14-34).

Normal LV ejection fraction for females (20-80 years): 67±5 %(range: 57-77)

Normal LV mass for females (20-80 years): 61±10g/m^2 (range: 41-81).

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