Determining the Optimal Intervention Time for Degenerative Mitral Regurgitation Using Left Ventricle Mechanics

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Abstract

Background: Uncertainty remains about the timing for intervention in primary MR. The incremental and clinical value of newer techniques including LV and LA deformation, 3D LV volumes, myocardial work and cardiac biomarkers are poorly understood. We aimed to examine whether advanced echocardiographic imaging techniques, exercise tests and blood biomarkers may be able to identify the earliest signs of LV dysfunction, predict post-operative outcomes and objectively detect symptoms in patients with primary MR which may help guide the timing of intervention. **Method:** In the asymptomatic cohort, resting and exercise echocardiography combined with CPET were performed prospectively in 97 asymptomatic patients with moderate to severe or severe primary MR. In the surgery cohort, echocardiography was performed at baseline and one year after MV surgery in 98 patients with severe degenerative MR. **Results:** In the asymptomatic cohort, 54% of patients had reduced exercise capacity, i.e. $VO_{2\ peak}$ < 84% of the predicted value. 18% of patients stopped the exercise test because of dyspnoea. Higher rest PASP was a predictor of dyspnoea during exercise testing. LV end-diastolic volume was a better predictor of the subsequent mitral surgery. In the surgery cohort, after mitral surgery, 6 (6%) patients died, and LV dysfunction developed in 12 (12%) patients, i.e. LVEF <50%. Reservoir LA strain and global work index were associated with post-operative LVEF. However, pre-operative GLS and NT-proBNP were independent predictors of post-operative LVEF. LA strain parameters and NT-proBNP were associated with the presence of symptoms However, GWI and PASP were independently associated with the occurrence of symptoms. **Conclusion:** This thesis demonstrated that presence of adverse features markers such as impaired myocardial deformation, reduced myocardial work index, pulmonary hypertension and high NT-proBNP was associated with poor prognosis.

These markers are non-invasive, safe and relatively easy to obtain. The combination of CPET and exercise echocardiography provides unique data in the assessment of symptomatic status and it should be used much more frequently in the assessment of MR and perhaps even incorporated as standard part of clinical practice.

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Appendix

List of Abbreviation

Abbreviation	Definition
2D	Two-dimensional echocardiography
3D	Three-dimensional echocardiography
ACC	American College of Cardiology
AF	Atrial fibrillation
AHA	American Heart Association
BNP	B-type natriuretic peptide
CPET	Cardiopulmonary exercise testing
E wave	Early passive filling of the left ventricle
E' wave	Mitral annular early diastolic velocity
E/E’ ratio	Ratio of early mitral inflow velocity and early mitral annular diastolic velocity
ERO	Effective regurgitant orifice
ESC	European Society of Cardiology
GCW	Global constructive work

GLS	Global longitudinal strain
GWE	Global work efficiency
GWI	Global work index
GWW	Global wasted work
LA	Left atrium
LAV	Left atrial volume
LV	Left ventricle
LVEDV	Left ventricular end-diastolic volume
LVEF	Left ventricle ejection fraction
LVESD	Left ventricular end-systolic dimension
LVESV	Left ventricular end-systolic volume
MR	Mitral regurgitation
MV	Mitral valve
MVP	Mitral valve prolapse
NT-ProBNP	N-terminal pro-type natriuretic peptide
NYHA	New York Heart Association

O_2	Oxygen
O_2 pulse	Oxygen pulse
OUES	Oxygen uptake efficiency slope
PALS	Peak atrial longitudinal strain
PASP	Pulmonary artery systolic pressure
R Vol	Regurgitant volume
RER	Respiratory exchange ratio
RT3D	Real-time three-dimensional echocardiography
S' wave	Systolic longitudinal velocity
sST2	Soluble suppression of tumorigenicity-2
ST2	Suppression of tumorigenicity-2
TEE	Transoesophageal echocardiography
TTE	Transthoracic echocardiography
VCO_2	Carbon dioxide output
VE	Minute ventilation

VE/VCO_2	Minute ventilation–carbon dioxide output relationship (ventilation efficiency)
VO_2	Oxygen uptake
$VO_{2\ peak}$	Highest O_2 volume used in metabolism by the body during CPET
WR	Work rate

Introduction

The appropriate timing of surgery for patients with primary mitral regurgitation (MR) is important, particularly in determining which patients are at high risk and may benefit from early intervention. Symptoms and Left ventricle (LV) dysfunction are risk factors in primary MR. Mitral valve surgery is recommended for symptomatic patients, however, that recognition of symptoms may be tricky, and it may not become noticeable until myocardial dysfunction is advanced. In asymptomatic patients, mitral valve surgery can be considered in the presence of LV dilatation and/or LV dysfunction (1, 2). Despite these recommendations, the optimal timing of mitral valve surgery remains uncertain, given the occurrence of post-operative cardiac dysfunction and heart failure, despite successful surgical intervention. Therefore, it is crucial to identify patients with pre-operative subclinical myocardial dysfunction. The accurate assessment of LV systolic function could be challenging in the presence of MR due to the volume overload compensating mechanism. Various echocardiographic parameters have been investigated in primary MR over several years, however, there is still no reliable alternative to conventional guideline-recommended measures. The incremental and clinical value of newer techniques including LV and LA deformation, 3D LV volumes, myocardial work and cardiac biomarkers are poorly understood. These techniques are straightforward, non-invasive, safe, and painless and can routinely be used in daily clinical practice. In addition, integrated exercise echocardiography with cardiopulmonary exercise testing may offer an objective evaluation of the exercise tolerance and it may improve patient care by supporting clinical decision-making. The overall aim of this thesis is to examine whether advanced echocardiographic imaging techniques and cardiopulmonary exercise tests may be able to identify the earliest signs of LV dysfunction and objectively detect

symptoms in patients with primary degenerative MR. In addition, we aim to identify clinical, blood and echocardiographic biomarkers which predict post-operative outcomes and may help guide the timing of intervention.

Chapter 1

Review of the Literature

1.1 Mitral valve prolapse

1.1.1 Introduction

Mitral regurgitation (MR) is defined as abnormal systolic retrograde blood flow from the left ventricle to the left atrium due to a reduction or elimination of the normal systolic coaptation between anterior and posterior mitral leaflets, which leads to a lack of mitral valve competence. MR is a common valvular disease and is the second most frequent heart valve disease after aortic stenosis (3). Sixty to seventy percent of primary MR cases are degenerative, with mitral valve prolapse (MVP) being the most common etiology (4).

MVP has been recognised for more than 5 decades. Initial reports identified patients with a mid-systolic click and late systolic murmur associated with aneurysmal dilatation of the posterior mitral valve leaflet (5). These findings were thought to be related to a genetically determined defect or weakness of the posterior leaflet. Understanding of this pathology has grown with the advance of diagnostic techniques (histopathology, cardiovascular imaging including echocardiography, biomarkers, and genetics), and management strategies have evolved in conjunction with a better understanding of the natural history of MVP and its physiological effects.

1.1.2 Prevalence

The reported prevalence of MVP has ranged from 0.6% to 15% (6-9). This range corresponds to differences in the demographics (age, gender, ethnicity) of the population examined in the studies and the definition of MVP. In an initial report produced by the Framingham Heart Study, MVP, as diagnosed by M-mode echocardiography, was present in 5% of population (6). However, in a subsequent cohort where diagnosis was made with

an updated definition of MVP based on leaflet displacement (≥2mm) on the parasternal long axis view, 2.4% of the population presented with echocardiographic findings of MVP (7).

1.1.3 Pathology

A spectrum of disease exists, ranging from fibroelastic deficiency and localised prolapse of an isolated scallop to myxomatous Barlow's disease, where an excess tissue and elongated chordae lead to the thickening of valve leaflets and prolapse of multiple scallops (10). Recent histological studies suggest they may be separate disease processes (11). In Barlow-type valves, expansion of the spongiosa layer due to accumulation of proteoglycans, together with intimal thickening on fibrosa and atrialis, leads to diffuse leaflet thickening. In fibroelastic deficiency, focal thickening on the fibrosa of the leaflet near the chordae occurs with increased peri-chordal elastin and diminished collagen content of the chordae, as well as increased myofibroblastic cell proliferation and an increased expression of profibrotic pathways (9). It is hypothesized that these contribute to chordal rupture. Roberts et al. (12) examined the excised posterior leaflet of thirty-seven patients who were undergoing mitral valve repair. Superimposed fibrous tissue was found on both the atrial and ventricular surfaces of the leaflets and chordae, which therefore indicates that fibrous tissue is a major component of leaflet thickening. The researchers found in all thirty-seven patients, the chordae tendineae were "missing" on gross examination. However, histologically the leaflet and chordae tendineae could be easily demarcated. The chordae tendineae were often covered by fibrous tissue on the ventricular aspect of the valve. Therefore, the prevalence of chordal rupture may be higher than previously thought.

Transforming growth factor beta (TGF- β) is thought be a major mediator of valve fibrosis and matrix remodeling in MVP (13-15). Hagler et al. (13) found increased expression of transforming growth factor beta (TGF-β) and increased expression of connective tissue growth factor (CTGF) and matrix metalloproteinase 2 (MMP2) in explanted heart valves in patients with MVP compared to controls. Additionally, TGF- β pathway activation is known to induce valvular interstitial cell differentiation into contractile myofibroblasts (14). Therefore, therapeutic interventions to modulate TGF- β signalling pathway may be beneficial in MVP and are currently being explored (15).

1.1.4 Familial associations, genetics & syndromes

Longstanding reports of familial associations of MVP (16, 17) are common. Delling et al. (17) examined the prevalence of MVP in the offspring of patients with MVP. MVP was present in 5% of the offspring with parental MVP. There was a 4 to 5-fold risk of MVP in offspring where either parent had MVP compared to parents with no MVP. Genetic linkage studies have identified multiple loci for MVP (18-21). Initially, chromosome 16 (Ch16, pp. 11.2-12.1, MMVP1) was identified a genetic locus for MVP with an autosomal dominant pedigree (18). Following this, chromosome 11 (11p15.4, MMVP2) and chromosome 13 (13q31.3-q32, MMVP3) were identified (19, 20). Durst et al. (21), subsequently identified the MMVP2 gene. They found a missense mutation in the DCHS1 gene linked to MVP (21).

An X-linked, recessive form with a locus Xq28 has been identified. Typically, this is associated with multi-valvar defects with myxomatous change (22). Further work using linkage analysis on a family affected by X-linked myxomatous mitral valve disease identified a P637Q mutation in the filamin-A (FLNA) gene in all affected members. Two other missense mutations (G288R and V711D) and a 1944-base pair in-frame deletion

were also identified in 3 additional, smaller, unrelated families (23). Le Tourneau et al. (24) studied 246 subjects from four FLNA mitral valve dystrophy families. The authors identified specific echocardiographic characteristics. In addition to classical features of MVP, they found that mitral leaflet motion was restricted in diastole, and the papillary muscles position was closer to mitral annulus.

In isolated MVP, a genome-wide association study including 1,412 MVP cases and 2,349 controls identified three loci with MVP associations (25). The strongest associations were for 2q35, 17p13 and 22q12. Candidate genes associated with these loci were LMCD1 and TNS1.

An association exists between MVP and a range of syndromes, including Aneuploidy, Marfan syndrome, and Loeys-Dietz syndrome (26). In a range of other syndromes, including Ehlers-Danlos syndrome, Pseudoxanthoma elasticum and Osteogenesis imperfecta, evidence is limited and the link between the syndrome and MVP has not been established clearly (26). Although initially MVP was reported in up to 90% of patients with Marfan syndrome, these data were based on less specific definitions of MVP (27). Contemporary data report a prevalence of MVP between 28 and 40% in patients with Marfan syndrome (27, 28). MVP in these patients predominantly affects both leaflets and is associated with larger aortic root diameters (29). Mitral valve abnormalities are common in hypertrophic cardiomyopathy.

1.1.5 Clinical signs

The clinical features vary greatly depending on the patient. A “mitral valve prolapse syndrome” consisting of a combination of auscultatory and echocardiographic findings, in addition to non-specific symptoms of chest pain, dyspnoea, palpitations, syncope and anxiety, has previously been reported (7). However, whether the symptoms

reported are related to mitral valve prolapse has been challenged. Devereux et al. (30) compared the clinical features of patients with MVP to controls. The findings significantly associated with MVP were a mid-systolic click, late systolic murmur, thoracic bony abnormalities (pectus excavatum, decreased anterior-posterior diameter, scoliosis) low body weight and blood pressure. Eighty-seven percent had mid-systolic click, holo/late systolic murmur or both. The only symptom associated with MVP was palpitation. There was no association with atypical chest pain, dyspnoea, panic attack or anxiety. The Framingham study confirmed these findings, although the prevalence of mid-systolic click (11.1%) and a systolic murmur (22.6%) were lower (31). The click of MVP characteristically varies with dynamic auscultation, with certain manoeuvres changing the timing of the click within systole. Valsalva and standing cause a reduction in end-diastolic left ventricular volumes, resulting in an earlier click. Squatting leads to an increase in end-diastolic volumes and a later click (32, 33).

The mechanism for symptoms is not fully understood but may be related to autonomic nervous system dysfunction (33-35). Boudoulas et al. demonstrated increased adrenergic tone in symptomatic patients with MVP (33). Symptomatic MVP patients had a hypersensitive response to adrenergic stimulation, which reproduced symptoms in the majority of patients (34). This response may be related to polymorphisms of β1 adrenergic receptors (35). Bashore et al. demonstrated that patients with symptomatic MVP and no significant regurgitation had reduced exercise tolerance compared to normal subjects. Furthermore, during upright exercise there is a lack of increment in left ventricular end-diastolic volume, suggesting impaired cardiac filling during upright exercise. This may be explained by reduced venous return and an inappropriate response of the venous capacitance system (36).

1.1.6 Diagnosis

Electrocardiographic abnormalities including repolarisation abnormalities in the inferior leads have been reported. However, the findings are non-specific (30).

The principle diagnostic modality is echocardiography. MVP is defined as displacement of the margin of one or more mitral valve leaflets beyond the annular plane (>2mm) during systole. This is usually identified from the parasternal long axis view. Levine et al. (37) showed the mitral valve annulus is non-planar and saddle shaped and demonstrated that the four-chamber view alone could not be used for diagnosis. Required key diagnostic information includes the location and extent of prolapse, leaflet and chordae morphology (thickening, elongation), severity of valve regurgitation, and haemodynamic effect on the left ventricle (left ventricular end-systolic dimension (LVESD), left ventricular ejection fraction (LVEF) and strain.

Transoesophageal echocardiography (TEE) provides a more accurate localisation of pathology as compared to transthoracic (TTE) studies, particularly if acquired with three-dimensional (3D) imaging. TEE allows for identification of each individual mitral valve scallop and thereby recognition of the complexity of pathology *i.e*. isolated P2 prolapse versus bileaflet involvement or commissural involvement. TEE is therefore recommended if TTE is non-diagnostic and in all cases with complex mitral valve disease, particularly when considering mitral valve intervention (38). When comparing 2D TEE and 3D TEE findings to surgical inspection, 3D TEE had superior accuracy for detection of MVP (96% versus 87%, respectively) (38). Quantitative 3D models allow measurement of mitral annular circumference, diameters and leaflet lengths, which correlate well with surgical findings (39, 40). Calleja et al. found 3D annular circumference correlate with implanted annuloplasty band length and therefore may be useful for perioperative planning for mitral valve repair (40).

The severity of mitral regurgitation depends on integration of a range of parameters (41). Semi-quantitative features consistent with severe mitral regurgitation include vena contracta > 7mm, systolic flow reversal in pulmonary veins, and dominant mitral inflow E wave (>1.2m/s). Quantitative measures include an effective regurgitant orifice (ERO) 40mm² and regurgitant volume 60mls. Consideration should be given to the duration of mitral regurgitation. Mid to late systolic mitral regurgitation may yield a similar effective regurgitant office area to holosystolic mitral regurgitation. However, due to its shorter duration, the regurgitant volume can be as little as half as that of holosystolic mitral regurgitation. This lower regurgitant volume translates to lower event rates (42). The limitations of quantitative measurements include difficulties in measuring the proximal isovelocity surface area, particularly in eccentric jets and where the exact location of the regurgitant orifice is difficult to identify. In addition, poor alignment of continuous wave Doppler with the regurgitant jet in eccentric jets may lead to errors in calculation of the ERO (43).

1.1.7 Progression & risks

The progression and outcomes of MVP are variable. The majority of patients have no clinical sequelae. The main risks relate to the development of severe mitral regurgitation and the requirement for mitral valve intervention (43-45). In a longitudinal follow-up of the Framingham study cohort, Delling et al. (44) found 25% of patients with MVP developed significant mitral regurgitation or required mitral valve intervention during a follow-up period of between 3 and 16 years. Marks et al. (45) defined classical MVP as encompassing patients with leaflet thickening and redundancy, and non-classical MVP as including those without leaflet thickening. Complications of infective endocarditis, moderate to severe mitral regurgitation and the need for mitral valve

replacement were significantly higher in the classic form compared to the non-classic form of MVP.

In addition, a non-diagnostic form of MVP has been described (44). Two sub-types have been recognised: minimal systolic displacement and abnormal anterior coaptation. These share the features with MVP of excessive leaflet motion, bulging of the posterior leaflet relative to the anterior, and coaptation asymmetry, but have <2mm displacement of the leaflet beyond the annulus. During follow-up, 8 (80%) participants with abnormal anterior coaptation progressed to posterior MVP and 17 (34%) subjects with minimal systolic displacement developed posterior MVP or abnormal anterior coaptation. This demonstrates that patients with non-diagnostic MVP morphologies may progress to MVP over time.

In asymptomatic patients, Avierinos et al. (46) identified baseline moderate to severe mitral regurgitation and LVEF < 50% as independent predictors of cardiac mortality (termed primary risk factors) and left atrial diameter >4cm, atrial fibrillation, age > 50 years, mild mitral regurgitation and the presence of a flail leaflet as independent predictors of cardiac morbidity (termed secondary risk factors). The investigators found MVP patients with no risk factors had an excellent 10-year survival rate with only a 2% rate of MVP related events. In contrast, those with at least 1 major risk factor had a 34% 10-year survival with a 78% rate of MVP related events.

1.1.7.1 Sudden death

Mitral valve prolapse has been associated with sudden death, with an incidence of up to 2% per year, and is thought to be associated with ventricular arrhythmia (47, 48). Basso et al. (47) examined the hearts of patients who died from sudden cardiac death with MVP. Bileaflet prolapse was identified in 70% of the cohort. Left ventricular wall fibrosis

at the level of papillary muscles was found in all patients, and in the infero-basal wall in 88% of patients. In a separate comparison of MVP patients with complex ventricular arrhythmia to MVP patients without significant arrhythmia, left ventricular late gadolinium enhancement by cardiac magnetic resonance was identified in 93% and 14%, respectively ($p<0.001$) (47). Therefore, these data suggest papillary muscle fibrosis provides a substrate for arrhythmia in MVP.

Sriram et al. (48) noted patients who suffered from out of hospital cardiac arrest with MVP had an increased burden of ventricular ectopics, bigeminy and non-sustained ventricular tachycardia compared to patients without MVP. Electrophysiology mapping studies have found the ventricular ectopic focus predominately originates from the left ventricular papillary muscles and fascicles and the majority have a Purkinje origin trigger (49). Further studies are required to identify whether routine Holter monitoring for ventricular arrhythmia is an effective strategy to identify patients at risk of sudden death.

Several echocardiographic predictors of sudden death have been established. Grigioni et al. (50) found that patients with a flail leaflet and predominately severe mitral regurgitation had an overall sudden death rate of 1.8% per year. The risk was related to functional class (1% in functional class I and 7.8% in classes III/IV). Nishimura et al. (51) found that the presence of redundant mitral leaflets (defined as thickness of 5mm or more) was the only variable associated with sudden death.

Mitral annulus disjunction is the abnormal atrial displacement of the hinge point of the mitral valve away from the ventricle myocardium. Dejgaard et al. (52) identified 116 patients with mitral annulus disjunction and found a high incidence of palpitations (71%) in the cohort. In addition, there was a high incidence of non-sustained ventricular tachycardia (22%), with 9% suffering aborted cardiac arrest. Seventy-eight percent of the cohort also had MVP; the prevalence of ventricular arrythmia, however, did not differ

between those with or without MVP. This suggests that mitral annulus disjunction itself is arrhythmogenic and may co-exist with MVP.

Most of the data examining the incidence of sudden death in MVP has originated from a series of MVP patients suffering out of hospital cardiac arrest and sudden death victims. Although these studies convincingly demonstrate sudden death occurring in patients with MVP, it is unclear whether the incidence is greater than what would have occurred in an age and sex matched general population. Furthermore, it is unclear whether the degree of mitral regurgitation and left ventricular function is a confounder of sudden death risk in these studies.

1.1.7.2 Stroke

The association between stroke and MVP is controversial. In an early study, Barnett et al. (53) found 40% of young patients (<45 years old) who had a stroke or transient ischaemic attack had MVP compared to just 6.8% of age matched controls. However, this study used M-mode to diagnose MVP, which is less specific for diagnosis. Gilon et al. (54), using a case-control method and updated criteria for MVP, found no difference in the prevalence of MVP between young patients presenting with stroke and controls. In a more contemporary community-based study (55), patients with MVP had a 2-fold excess relative risk of ischaemic cerebral events compared to that expected in an age- and sex-matched population. However, the absolute 10-year risk of cerebral events was low (7%). Age was an important predictor of events, with a 10-year risk of cerebral events where 0.4% events occurred in patients < 50 years old and 16% events in patients > 50 years old. In addition, the development of atrial fibrillation during follow-up was a predictor of ischaemic cerebral events. This, in turn, was related to left atrial size and the severity of mitral regurgitation. Therefore, the risk of stroke in MVP is probably related

to age and the consequences of significant mitral regurgitation, including left atrial dilatation and atrial fibrillation. Currently, no evidence exists for any therapeutic intervention that reduces the risk of stroke in MVP, and there are no guideline recommendations for stroke prevention in MVP.

1.1.7.3 Endocarditis

Several investigators have found the presence of mitral valve prolapse increases the risk of infective endocarditis (56-58). Patients sub-types identified as being at higher risk include those with precordial systolic murmurs, moderate or greater mitral regurgitation and those with flail leaflets (57, 58). Controversy remains surrounding evidence for the use of anti-biotic prophylaxis against infective endocarditis. At present, both European and United States guidelines do not advise anti-biotic prophylaxis for patients with MVP, which is only recommended for patients at higher risk of developing infective endocarditis, including those patients with prosthetic valves, prosthetic implanted for valve repair, previous endocarditis and unrepaired congenital heart disease (59, 60).

1.1.8 Management

1.1.8.1 Symptomatic patients

Both the American Heart Association (AHA) / American College of Cardiology (ACC) and European Society of Cardiology (ESC) recommend (Class I) valve surgery in patients with severe, symptomatic mitral regurgitation due to mitral valve prolapse (59, 60).

1.1.8.2 Asymptomatic patients

In asymptomatic patients, risk stratification is required to decide on optimal management strategy. Enriquez-Sarano et al. (61) demonstrated that the long-term survival after mitral valve surgery in organic mitral regurgitation was impaired when the pre-operative LVEF was <60%. In addition, patients in the same group showed with a pre-operative LVEF> 60% revealed that an LVESD ≥4.5cm predicted impaired post-operative LVEF (62). Tribouilloy et al. (63) showed that an LVESD >4cm in patients with flail leaflets predicted a poor prognosis. Other markers associated with worse prognosis are atrial fibrillation and resting moderate or severe pulmonary hypertension (64, 65).

Some discordance exists between ESC and AHA/ACC guidelines (59, 60). The ESC guidelines recommend (Class I) valve surgery if LVEF < 60% and/or LVESD ≥4.5cm and recommend surgery should be considered (Class IIa) if there is atrial fibrillation, resting pulmonary hypertension (≥50mmHg) or if the LVESD is ≥4cm in the presence of a flail leaflet or left atrial dilatation (≥60ml/m2) and valve repair can be achieved. The AHA/ACC guidelines recommend (Class I) surgery if LVEF ≤ 60% and/or LVESD ≥4.0cm. If valve repair can be achieved, they recommend consideration of surgery (Class IIa) if atrial fibrillation or pulmonary hypertension (>50mmHg) are present. In addition, mitral repair in asymptomatic patients is reasonable (Class IIa) if likelihood of a successful and durable repair without residual mitral regurgitation is >95% with an expected mortality rate of <1%.

In asymptomatic patients without these adverse factors, disagreement exists over whether early surgery or careful follow-up is the best option. Rosenhek et al. (66) showed that with careful follow-up and referral for surgery based on guideline indications

(symptom development, LVEF <60%, LVESD ≥4.5cm, atrial fibrillation or pulmonary artery pressure >50mmHg) patients with asymptomatic, severe degenerative mitral regurgitation had an excellent prognosis, which was no different to that expected of an age- and sex-matched general population. In contrast, Kang et al. (67). performed a study of 207 propensity matched pairs. Early surgery was associated with a lower risk of cardiac mortality than conventional treatment. In the Mitral Regurgitation International Database study (68), 2097 patients with flail mitral regurgitation were followed up for a mean 10 years. Early mitral surgery was associated with a lower risk of heart failure and better long-term survival. However, both of these studies were non-randomised and, therefore, subject to selection bias. Randomised studies of early intervention versus watchful waiting are currently underway (69).

1.1.8.3 Repair versus replacement

Mitral valve repair has been associated with lower operative mortality, increased post-operative LVEF, and better long-term survival compared to valve replacement (70). In addition, from a practical basis repaired valves do not require long-term anti-coagulation. However, there is risk of degeneration of the repair requiring re-operation. Suri et al. (71) examined the outcomes of 1218 patients were followed for a median of 11.5 years. The 15-year incidence of recurrent mitral regurgitation (grade 2 or greater) was 13.3% and the incidence of reoperation was 6.9%. Predictors of recurrent mitral regurgitation were mild intraoperative residual mitral regurgitation, anterior leaflet prolapse, bileaflet prolapse, and lack of annuloplasty ring. David et al. (72) similarly demonstrated that the longevity of mitral valve repair is related to the complexity of mitral valve pathology with myxomatous change and anterior leaflet involvement increasing risk of recurrence of mitral regurgitation.

The ESC guidelines state mitral valve repair should be the preferred technique (Class 1) when the results are expected to be durable (59). The ACC/AHA guidelines state mitral valve repair is recommended (Class 1) in preference to mitral valve replacement when pathology is limited to the posterior leaflet or involves the anterior leaflet or both leaflets when a successful and durable repair can be accomplished (60). In addition to these factors, there are an array of different repair techniques. These can involve a combination of leaflet resection, insertion of annuloplasty ring, and use of artificial chordae (10). Therefore, the outcome of mitral valve repair for an individual patient is likely to be influenced by aetiology of valve dysfunction, anatomical consideration and repair technique. Careful informed consent regarding the likelihood of durable repair is required.

In patients with high peri-operative risk, transcatheter mitral valve technologies are being developed. The EVEREST II study randomised patients with grade 3/4 mitral regurgitation to either percutaneous edge to edge repair or conventional mitral valve surgery in patients with the primary regurgitant jet originating from A2 and P2 scallops (73). Overall, 70.2% of the cohort had mitral valve prolapse. At 5 year follow-up there was no difference in mortality between the two groups. However, the percutaneous valve repair group had a significant increased requirement for mitral valve surgery (27.9% v 9.8%, p-value = 0.003) and grade 3/4 mitral regurgitation (12.3% v 1.8%, p-value = 0.02) compared to the surgical group. Therefore, this technology should be considered for patients at high risk for surgical valve intervention.

1.2 Assessment of subclinical myocardial dysfunction in asymptomatic patient

Because of the controversy over whether early surgical intervention or watchful waiting is the best option in asymptomatic primary mitral regurgitation patients, a debate exists about the current guidelines and the sensitivity of using simple echocardiographic parameters (LVEF, LVESD) as an indication for surgery. In fact, it could be misleading and inaccurate in the presence of mitral regurgitation and its load alteration. Therefore, a need exists for advanced imaging or biomarkers to detect subclinical myocardial dysfunction, which may be present and undetectable by the traditional imaging technique. Furthermore, independent predictors of the outcome of mitral valve intervention in this patient's group is required.

1.2.1 Left ventricle deformation

1.2.1.1 Introduction

LV deformation is a parameter for assessing systolic function. It promises to be a more reliable method for the evaluation of myocardial performance and detecting suboptimal cardiac dysfunction. It is a less load-dependent marker of LV contractility. Strain is a quantitative measurement for myocardial deformation.

Myocardial deformation represents the changes in myocardial muscles, the alternation of myocardial length when it shortens at end of systole compared to its original length during diastole. Basically, it assesses the magnitude of myocardial contraction and relaxation during the cardiac cycle (74).

It can be expressed as $\varepsilon = (L-L0)/ L0$

where ε is strain, L0 is the initial length of the area measured and L is the final length at the time of measurement; it is expressed as a negative percentage.

Initially, strain measurements were derived from tissue Doppler imaging. However, there are a number of disadvantages to this technique. One of the limitations is its inability to differentiate between myocardial movements as a result of tethering effects (passive movement of the non-contractile segments of the myocardial being tugged off by another contracting region) or the movements from true myocardial contraction. Angle dependency and the requirement of a high frame rate are other major limitations to strain analysis by tissue Doppler imaging.

Speckle tracking echocardiography is a newer method to measure strain; it is considered a promising technique to overcome Doppler-derived strain limitation (75). Speckle tracking echocardiography applies a totally different algorithm. It works by computing myocardial deformation from standard two-dimensional echocardiography images to calculate strain directly from speckle motion. Within each myocardial segment, speckles follow the motion of the myocardium, which can be detected and followed by the system frame by frame. Any change in the speckles reflects true myocardial deformation and regional myocardial function for each segment (76).

Moreover, these speckle patterns can be tracked in any direction as speckle tracking echocardiography technology is an angle-independent (77). There are different types of strain: longitudinal, circumferential and radial strain. The apical view can be used to assess myocardial deformation in longitudinal and radial directions. The short axis view can be used to measure radial and circumferential displacement. Left ventricular twists and torsion can be calculated from the rotation movement of the ventricle which is measured by circumferential deformation (78, 79).

Speckle tracking echocardiography has been validated against cardiac magnetic resonance imaging. Amundsen *et al.* (80) found a significant correlation between strain measurement through magnetic resonance imaging and echocardiographic speckle tracking ($r = 0.87$, p-value < 0.001; the 95% limits of agreement were -9.1% to 8.0%). However, excellent image quality is required to accurately track the speckle pattern; also, noise and reverberation artefacts may interfere with and affect the result (78, 81).

1.2.1.2 Global longitudinal strain

Global longitudinal strain (GLS) is defined as the change in longitudinal motion from the base to the apex, and it can be measured from apical views including apical four-, two- and three-chambers views.

Kim et al. (82) studied the predictive value of GLS in 506 patients with severe primary MR who underwent mitral valve surgery, with a median follow-up of 3.5 years. Preoperative GLS was significantly lower (closer to zero) among patients with post-operative adverse cardiac events versus those without. The study showed that a cut-off value of GLS of -18.1% could predict cardiac outcomes and all causes of mortality (with an area under the curve of 0.738, and sensitivity and specificity of 71.4% and 70.7% respectively). Despite the retrospective design of the study and the inclusion of a wide range of cardiovascular morbidity, these findings propose the value of GLS as an independent predictor factor for post-operative LV dysfunction.

In a follow-up prospective study, Mascle et al. (83) examined 88 patients with degenerative MR and demonstrated that a baseline GLS below -18% can predict six-month post-operative LVEF <50%. Witkowski et al. (84) found that < -19% of GLS predicted a lower LVEF < 50% 1- year post-operative in 233 patients (with sensitivity and specificity of 90% and 79%). With a higher pre-operative GLS cut-off value, Mentis

et al. (85) demonstrated that baseline GLS <-21.5% predicted cardiac events after mitral valve surgery. In a conflicting finding, Pandis et al. (86) showed that GLS > -20% preoperatively is associated with lower immediate post-operative LVEF (less than 10%).

Most studies have supported the use of GLS as a predictor of adverse cardiac events in asymptomatic primary MR. Despite the variety of GLS cut-off values, a worse post-operative outcome is associated with lower preoperative GLS (closer to zero).

1.2.2 Left atrial deformation

Originally, speckle tracking echocardiography was adapted to assess left ventricle deformation. Recently, researchers have shown an increased interest in using speckle tracking to evaluate left atrium function and deformation.

As we have mentioned previously, speckle tracking echocardiography enables a non-invasive assessment of cardiac chambers function and deformation with less load dependence and higher reproducibility than other conventional methods. Speckle tracking echocardiography analysis enables assessment of left atrial strain among three phases of LA function: 1. reservoir phase 2. conduit phase 3. booster bump or (contractile) phase.

Reservoir strain reflects the LA peak longitudinal strain. During reservoir phase, LA is stretched and filled with blood from the pulmonary veins. LA strain increases to its positive peak. This phase is affected by the mitral annulus motion toward the apex during LV contraction. As a result, reservoir LA strain reflects both LA compliance and LV longitudinal contraction (87). In the conduit phase, after mitral valve opening left atrium empties blood passively into the LV during ventricular diastole. LA shortens in this phase and strain decreases to a plateau. LA conduit strain is affected by LV diastolic function and age. During the contractile phase or known as the booster pump, left atrium actively

empties the remaining blood into the LV. This action reduces LA strain even further and reflects the LA booster pump function. Many clinical trials have been focused on LA strains during the reservoir phase and booster pump phase for LA function assessment.

In asymptomatic patients with primary MR, significant LA dilatation is considered a predictor of outcome. However, the criteria of surgery indication are still not sufficiently defined and more information on LA systolic function could be helpful in the intervention decision-making (59). Several studies have investigated the efficacy of LA strain derived by speckle tracking echocardiography to assess left atrial performance.

In a single-centre prospective study, Mandoli et al. (88) identified peak left atrial longitudinal strain (PALS) as an independent predictor of functional and prognostic outcomes in 65 patients with primary severe MR. The primary endpoint was the combined events of heart failure and mortality; the secondary endpoint was post-operative functional capacity defined by NYHA and Borg CR10 class). The investigators found patients with peak atrial longitudinal strain ≥21% had 5-year event-free survival: 90 ± 5%. In contrast, those with PALS<21% had 30 ± 9% 5-year event-free survival (p-value < 0.0004). Additionally, the presence of left atrial fibrosis was strongly inversely correlated with PALS <21% (adjusted r^2 0.80, p-value < 0.0001). There was an association between PALS and the functional outcome secondary endpoint with NYHA: $r^2 = 0.11$, p-value = 0.04; Borg CR10: $r^2 = 0.10$, p-value = 0.02). Additionally, an inverse correlation between the value of PALS and the presence of LA fibrosis was found.

These outcomes are in accordance with previous research demonstrating that impaired LA strain was strongly correlated with the grade of LA fibrosis in severe MR patients referred to mitral valve surgery (89).

Cameli et al. (90) demonstrated that the PALS had a prognostic value in asymptomatic patients with moderate primary MR, those with PALS >35% had a 90% incidence of 40-months free of event survival rate.

Yang et al. (91) investigated the role of LA strain in the presence of heart failure symptoms in severe primary MR patients. The study showed that LA strain was independently associated with worse heart failure symptoms (NYHA III). Debonnaire et al. (92) reported that LA strain had better accuracy to identify patients with an indication for mitral valve operation. LA strain ≤24% showed poor survival after mitral surgery, with a median of 6.4 years. In addition to LA volume and dimensions, the assessment of LA mechanical function may provide valuable information regarding postoperative outcomes.

As reported by a systematic review and meta-analysis (93), the normal reference range for LA strain during the reservoir phase was 39.4% (95% CI, 38.0–41%), LA strain during the conduit phase was 23% (95% CI, 21%-25), and for contractile strain or the booster pump phase was 17.4% (95% CI, 16.0–19.0%). With the increased amount of left atrium data and its value in offering supplementary information about cardiac function, further investigations in the emerging imaging may help clinicians in decision-making concerning primary MR.

1.2.3 Myocardial work

Myocardial work is a new non-invasive method to quantify myocardial function. This technique combines the measurement of speckle tracking strain analysis and non-invasive blood pressure to provide a pressure-strain loop of myocardial performance (94). GLS has been considered as an alternative for LVEF, and it was presented as offering a better reflection of LV systolic function in primary MR. However, GLS is sensitive to loading

conditions (preload and afterload) to some extent. It has been demonstrated that myocardial work incorporates dynamic LV pressure (afterload), which could overcome the GLS and LVEF load dependency limitation (95). In addition, incorporating a non-invasive method of blood pressure monitoring that is measured by a simple brachial cuff, makes the method practical and advantageous to use in daily practice Moreover, myocardial work derived from echocardiography has been validated against invasively derived pressure-volume measurements and showed good correlation between them (94, 96).

Myocardial work is presented by the following parameters:

- Global constructive work (GCW; mmHg%), myocardial work performed during shortening (in systole) plus negative myocardial work performed during lengthening (in isovolumetric relaxation).
- Global wasted work (GWW; mmHg%), negative work performed during lengthening (in systole) plus myocardial work performed during shortening (in isovolumetric relaxation).
- Global work index (GWI; mmHg%), a total amount of myocardial work using the area of the pressure-strain loop measured from mitral valve closure to mitral valve opening.
- Global work efficiency (GWE; %), the ratio of global constructive work to the total myocardial work (constructive and wasted work) in all LV segments; GCW/(GCW + GWW).

Reference ranges of myocardial work parameters derived from echocardiography have been reported in the NORRE study (97). In men and women, the lowest value of global constructive work was 1650 mm Hg% and 1544 mm Hg%, while the global work

index was 1270 mm Hg% and 1310 mm Hg%, and global work efficiency was 90% and 91%, respectively. The highest value for global wasted work in men and women was 238 mm Hg% and 239 mm Hg%, respectively. A previous study showed that myocardial work parameters have a good correlation with LVEF and global longitudinal strain (98).

The existing literature on myocardial work has been validated for its prognostic value in different pathologies, such as in heart failure patients in terms of risk factors (99), hypertrophic cardiomyopathy, amyloidosis, and acute coronary syndromes (100). In contrast, limited studies have investigated the utility of myocardial work in valve diseases, particularly in severe primary MR, where it could provide additional information beyond conventional LV systolic performance measurements.

1.2.4 Stress echocardiogram test

Symptoms of exertion is a class I indication for surgery in severe primary MR patients (59, 60). Exercise testing can be a useful tool to objectively assess symptom status. Naji et al. (101) examined the outcomes of 884 consecutive patients with myxomatous mitral regurgitation of ≥ grade III undergoing treadmill exercise echocardiography who reported no or minimal symptoms. Thirty percent of the cohort achieved <100% of age and sex predicted metabolic equivalents. Twelve percent achieved less than 85% of predicted metabolic equivalents. Predictors of the composite endpoint (mortality, myocardial infarction, stroke and heart failure) showed a lower percent of age/sex-predicted metabolic equivalents, lower heart rate recovery, atrial fibrillation, lower LVEF and higher pulmonary artery systolic pressure. This shows impaired exercise capacity can occur in the absence of overt symptoms and this impairment predicts prognosis. In another study, Magne et al. (102) found a lack of

contractile reserve (defined as <2% increase in global longitudinal strain on exercise) predicted mitral valve surgery or death.

1.2.5 Cardiopulmonary exercise test

Cardiopulmonary exercise testing (CPET) using beat-to-beat gas exchange measurement of oxygen uptake (VO_2), carbon dioxide output (VCO_2), and ventilation (VE) is increasingly being linked with stress echocardiogram and particularly measures of the contractile reserve, as this allows a multiparametric assessment (103). The usefulness of CPET lies in its ability to evaluate cardiac output response to exercise (aerobic capacity) by assessing Peak VO_2. CPET allows for the evaluation of pulmonary haemodynamic status (ventilator efficiency), which is commonly assessed by VE/VCO_2 slope (104).

Messika-Zeitoun et al. (105), examined the functional capacity of 134 asymptomatic patients with severe MR by performing CPET exercise stress echocardiography. The study showed that 19% of patients had reduced $VO_{2\ peak} \leq 84\%$. Higher E/E' ratio (p-value < 0.006) and AF (p-value < 0.01) were independent determinants of reduced $VO_{2\ peak}$, whereas effective regurgitant orifice was not. The investigators found patients with $VO_{2\ peak} \leq 84\%$ had a 36% ± 14% three-year rate of clinical events (new AF, heart failure and death). In comparison, those with normal $VO_{2\ peak}$ had 13% ± 4% three-year clinical event rate ($p < 0.02$).

Growing evidence supports the valuable information provided by CPET; however, it has not been fully evaluated in patients with primary MR, and a cardiopulmonary exercise test is infrequently clinically used for MR patients. Thus, additional data are needed to evaluate the exact role of CPET with exercise

echocardiography in clinical practice for asymptomatic severe mitral regurgitation patients.

1.2.6 Cardiac biomarkers

1.2.6.1 Plasma B type natriuretic peptide

Plasma B type natriuretic peptide (BNP) and its inactive amino N-terminal fragment (NT-proBNP) are cardiac hormones. NT-proBNP is synthesised from the hormone pro-BNP and splits into the N-terminal pro-peptide. Both originate mainly from the heart (106). Plasma measurement is accurate for both BNP and NT-ProBNP. However, the plasma level of NT-proBNP is increased five- to ten-fold because of its prolonged half-life compared to BNP. In a comparison study between BNP and NT-ProBNP, Mueller et al. (107) demonstrated that both substances are equally valuable for risk stratification and they have similar receiver operating characteristics and area under the curve. They are widely used as a prognostic tool in patients with heart failure, coronary artery disease or pulmonary embolism. Several studies reported that BNP and NT-proBNP are strong independent prognostic factors for mortality and morbidity in patients with heart failure or symptomatic patients with left ventricle dysfunction (108). It has been found that BNP has value to evaluate symptoms and differentiate cardiac dyspnoea from non-cardiac symptoms (109, 110).

BNP is released from the cardiac myocardium and is elevated in response to diastolic stretch in cardiac entities where volume is overloaded, as in congestive heart failure, mitral regurgitation or severe aortic regurgitation (111). Increased wall stress as a result of pressure overload as in aortic stenosis also raises BNP production (112). Ageing also increases BNP levels in response to cardiac stiffness. Thus, baseline

measurement of BNP is valuable to detect any further increases during close serial monitoring, mostly for asymptomatic valvular disease patients (113).

BNP and prediction of outcome in primary mitral regurgitation

Previous studies have explored the prognostic value of BNP for asymptomatic severe MR patients and have found that it is a powerful predictor of cardiac outcome (114, 115). BNP has also been shown to be a marker of symptom onset and survival in patients with asymptomatic severe MR. Pizarro et al. (116) found a BNP level of ≥105 pg/ml in addition to left ventricular end-systolic diameter indexed to body surface area and effective regurgitant orifice area was an independent predictor of developing heart failure, LV impairment or death. BNP values increase with age and for females, therefore, Clavel et al. (117) investigated the prognostic value of the brain natriuretic peptide ratio (ratio of measured BNP to expected maximal BNP for age and sex of patient) in patients with flail or MVP. The BNP ratio was an independent predictor of survival.

Detaint et al. (118) showed that a high BNP level in primary MR reflects the consequences of MR on cardiac structure and function, rather than MR severity. The research also demonstrated that a median < 31 pg/ml of BNP level was associated with a lower survival rate. The study further indicated that LV end-systolic volume index, symptoms, atrial fibrillation and left atrial volume are independent determinants of high BNP.

Klaar et al. (115) demonstrated the area under the receiver-operating characteristic curve for BNP and NT-proBNP was 0.90 and 0.84 for the prediction of cardiac outcome (LV dysfunction and development of symptoms). Potocki et al. (119) reported a similar receiver operator curve analysis of NT-proBNP and yielded an under the curve value of 0.80 for symptoms prediction, which was significantly higher than for all other

echocardiographic variables. Magne et al. (114) also found that an association exists between BNP level and reduced global longitudinal strain; both are independently associated in patients with primary MR. In a study of moderate to severe MR patients, Kerr et al. (120) found a correlation between elevated plasma BNP and higher pulmonary artery pressure and left atrial area index on rest and on stress echocardiography; even though LV systolic function was preserved on exercise stress echocardiography.

Threshold values

Several studies of MR patients reported BNP and NT-proBNP threshold values, which best predict adverse remodelling or outcomes. For example, Pizarro et al. reported plasma BNP > 105 pg/ml, Detaint et al. demonstrated a cut-off level of BNP > 31 pg/ml, Magne et al. showed a cut-off level of BNP level > 40 pg/ml, Mentias et al. found a cut-off level of BNP > 60 pg/ml. Klaar et al. reported cut-off levels of BNP > 145 pg/mL and NT-proBNP > 407 pg/mL (114-116, 118, 121).

While most of the data is based on an isolated reading of BNP, the best cut-offs for the prediction of outcome have not been established due to heterogeneity in study design and the definition of endpoints. Serial monitoring of BNP and NT-ProBNP levels or measurement of sequential change have not been researched.

1.2.6.2 Soluble ST2

Suppression of tumorigenicity-2 (ST2) is a novel biomarker which has attracted a lot of interest for its utility in heart failure management. ST2 is a member of the interleukin-1 (IL-1) receptor family. ST2 is produced in two isoforms, (sST2) soluble isoform, which is measured in serum, and (ST2L) transmembrane isoform. IL-33 was recognizing as a ligand for ST2L (122). sST2 elevated levels are associated with acute

myocardial infarction and severe chronic heart failure patients (123, 124). Lancellotti et al. (125) reported that sST2 level in the aortic stenosis patient group was associated with an increase in cardiovascular risk. So far, very little attention has been paid to investigating the role of sST2 in primary MR patients.

In summary, cardiac biomarkers express objective laboratory measurements. They are easy to access and can be monitored sequentially. Although biomarkers may not directly influence decisions for intervention at present, adding them to a clinical decision-making algorithm may help detect early MR impact on LV geometry and function and identify patients with a worse prognosis who are more likely to require intervention sooner and, therefore, require closer follow-up.

1.2.7 Three-dimensional transthoracic echocardiography

1.2.7.1 Introduction

LVEF is a load-dependent parameter. Both preload and afterload are altered by regurgitation volume in patients with MR. Thus, LVEF is usually overestimated in the presence of MR because of an increase in preload and reduction in afterload, despite subclinical dysfunction. The left ventricular volume at the end of systole is determined by the afterload not the preload. The current guidelines depend on LVESD and left ventricular end-systolic volume (LVESV); therefore, the accurate determination of LV volume is important.

Three-dimensional echocardiography is one of the major advances in the echocardiography field. The initial attempt to record three-dimensional format of an ultrasound image of human orbita? was in 1960 (126); however, it was not possible to apply it in the clinical field because of significant storage and image quality limitations. Decades later, Dekker et al. (127) demonstrated a 3D image of a cardiac structure by

reconstructing a sequence of two-dimensional echocardiogram images from a traced transducer. However, this methodology has several limitations; time and effort were needed to process offline data for 3D.

Around the early 1990s, the real-time 3D (RT3D) echocardiogram was initially introduced by Ramm et al. (128). This acquisition method offers an effective way to capture cardiac imaging using a matrix-array transducer with an adequate frame rate to reproduce cardiac movement. In recent years, this methodology has been developed to be more efficient and has attracted much interest. Current RT3D technology enables frame-by-frame recognition of endocardial border from a real-time dataset (129).

Recent developments in the field of RT3D with the enhancement of spatial and temporal resolution and with semiautomatic and automatic software analysis have led to novel three-dimensional imaging become more commercialised and applicable to use on different platforms and have thus become more desirable in clinical settings (130).

1.2.7.2 Advantages of real-time three-dimensional echocardiography (RT3D Vs 2D)

RT3D acquisition has a major advantage of better reliability, reproducibility and accuracy for measurement of left ventricular volumes compared to two-dimensional echocardiography. It overcomes a large number of two-dimensional echocardiography limitations (131, 132). The main source of variability of two-dimensional echocardiography data is the absence of the third dimension and that the volume calculation relies on geometric assumptions, whereas the three-dimensional technique represented by RT3D does not depend on geometric modelling of cardiac volume measurement. In addition, when performing two-dimensional echocardiography, where a poor endocardial border exists, specifically in the apical lateral wall segments of the LV,

the operator may try to enhance the endocardial visualisation by tilting the transducer. This movement frequently causes foreshortening and significant variability. RT3D eliminates the errors caused by plane positioning or foreshortened apical views (131).

Several published studies demonstrate the superiority of three-dimensional echocardiography over the two-dimensional approach for the reliability of LV volume measurements. Previous studies have also shown that LV volume and ejection fraction calculated by three-dimensional echocardiography are more comparable to cardiac magnetic resonance volumes, which are the gold standard for the cardiac volume quantification (133, 134). Jenkins et al. (135) showed that cardiac magnetic resonance and three-dimensional echocardiographic volumes have significantly lower intra and intra- observer variability as compared to two-dimensional echocardiographic volumes. Although a high correlation exists between 3D echocardiography and the CMR reference values, data from several studies suggest that LV volumes obtained by three-dimensional method underestimate volumes. Mor-Avi et al. (136) investigated RT3D LV volume underestimation in a multi-centre study and found that the potential source of error is the inability to distinguish between myocardium and endocardial trabeculae of LV. As a result, they suggested the inclusion of LV trabeculae during volume tracing to minimise the error.

More recently, Thavendiranathan et al. (137) used a fully automated trabecular endocardial contouring algorithm to obtain 3D LVEF and volumes of the left ventricle. They showed that automated RT3D echocardiography acquisition of LV function and volume correlates well with LV volumes and LVEF obtained by cardiac magnetic resonance ($r = 0.90, 0.96, 0.98$, for LV end-diastolic, LV end-systolic volumes and LVEF respectively; p-value < 0.001). The usefulness of such an approach has been examined in patient groups with atrial fibrillation where it was found to be highly accurate and

reproducible for left ventricular end-diastolic volume (LVEDV), LVESV r = 0.94, 0.94, respectively and for LVEF r = 0.91; p-value <0.001).

1.2.7.3 Real-time three-dimensional echocardiography in primary mitral regurgitation

RT3D has been shown to provide useful anatomical information in mitral valve evaluation and in helping to understand the interrelationship between valves, especially in degenerative mitral disease. The accuracy of RT3D has been demonstrated in the classification of the aetiology of mitral valve prolapse (137). Direct measure of regurgitant orifice area by RT3D has also shown efficacy in mitral regurgitation quantification (138). However, limited information exists on the clinical value of performing three-dimensional volumes in primary MR.

1.2.7.4 Real-time three-dimensional volume in stress echo

One of the challenges during stress echocardiography evaluation is the narrow time window for each exercise level. To evaluate LV ventricular wall segments and volumetric measurement during stress echocardiography requires acquiring images from different two-dimensional planes on each exercise level. Since each exercise level has a limited time period, this may lead to having some images acquired at different heart rates, or the acquisition may miss the required heart rate level. Image acquisition using a three-dimensional approach is simpler and potentially faster during the examination compared to multiple two-dimensional images. Therefore, the time to complete the stress echo test could be significantly reduced (139-141).

In light of the above, despite the established role of two-dimensional echocardiography for assessing LV function and volume, it has a number of limitations, including angulation, malrotation and foreshortening. RT3D is a major innovation in cardiac ultrasound and has the advantage of being able to overcome these limitations; particularly, the geometric assumption. Direct and automated RT3D provides an accurate and reproducible LV volume.

It would be ideal to use RT3D for LV volume measurement and to assess the LV response to volume overload in a primary MR population. However, no outcomes have been established to use this technique in this population, and the current recommendation for surgery is based on LV dimensions derived from a two-dimensional parasternal long-axis view, Therefore, it is important to determine the value of RT3D in measuring the true LV volume and to incorporate these measurements into clinical decision making.

1.3 Summary

Despite the current guidelines, the optimal timing for intervention in patients with asymptomatic severe mitral regurgitation (early surgery versus watchful waiting) is uncertain. The role of advanced cardiovascular imaging in risk stratification is developing. However, there is still no reliable alternative to conventional guideline-directed measures. Growing evidence exists to support the use of newer techniques including LV and LA deformation, 3D LV volumes, myocardial work and cardiac biomarkers in patients with severe primary mitral regurgitation. The incremental and clinical value of these techniques has been poorly evaluated. Additional data are needed to understand the role of exercise echocardiography and cardiopulmonary exercise tests in clinical decision-making in asymptomatic primary MR patients.

Chapter 2

Methodology

2.1 Study population

Patients with moderate to severe or severe primary mitral regurgitation due to mitral valve prolapse were recruited. The asymptomatic cohort included asymptomatic patients with moderate to severe mitral regurgitation and the surgery cohort included patients with severe mitral regurgitation who were referred to mitral valve surgery. All patients were recruited from St Bartholomew's Hospital and Eastbourne District General Hospital.

2.2 Inclusion and exclusion criteria

Inclusion criteria

- Informed consent
- Age of 18 years or older.
- Mitral valve prolapse
- Mild, moderate or severe degenerative mitral regurgitation was defined by a regurgitant volume of <30, 30 to 59 and ≥ 60 mL respectively, and an effective regurgitant orifice ≥ 20, 20-39 and ≥ 40mm^2 respectively.
- Adequate echocardiography views, including parasternal long axis, short axis, apical two chambers, apical three chambers and four chambers.

Exclusion criteria

- Presence of > mild other left sided concomitant heart valve disease (aortic stenosis, aortic regurgitation and mitral stenosis)
- Symptomatic coronary disease or evidence of irreversible ischaemia.
- Difficult acoustic window with poor image quality during exercise (removed after

enrolment).

- Severe lung disease.
- Pregnancy.
- Inability to consent.
- Inability to complete the study.
- Claustrophobia during exercise test with cardiopulmonary mask, (for asymptomatic cohort).
- Contraindications to exercise testing according to the guidelines (142), (for asymptomatic cohort).

These exclusion criteria were applied to all patients recruited. Other exclusion criteria were different per study and are explained in each chapter separately.

2.3 Study cohorts

A flowchart of the study population according to cohorts' recruitment, inclusion and exclusion criteria is presented in *Figure 2.1*.

Asymptomatic cohort

97 clinically asymptomatic patients with moderate to severe primary mitral regurgitation and preserved left ventricle function underwent comprehensive resting and exercise stress echocardiography combined cardiopulmonary exercise test to evaluate exercise capacity, symptoms, $VO_{2\ peak}$ and left ventricle function. A follow-up resting and exercise stress echocardiography, including cardiopulmonary exercise testing, was performed after 12 months. During follow-up 37 patients, who were referred to valve surgery (due to

development of symptoms or left ventricle function impairment) crossed over to the surgery cohort.

Surgery cohort

98 severe symptomatic patients with primary mitral regurgitation underwent baseline 2D echocardiography and RT3D for left ventricle volumes prior to mitral valve surgery. A follow-up visit for echocardiography was performed 12 months after surgery.

The severity of MR was defined as mild, moderate, or severe, respectively, by a regurgitant volume (R Vol) of < 30, 30 to 59 and ≥ 60 ml/beat, and an effective regurgitant orifice (ERO) ≥ 20, 20-39 and $\geq 40 mm^2$

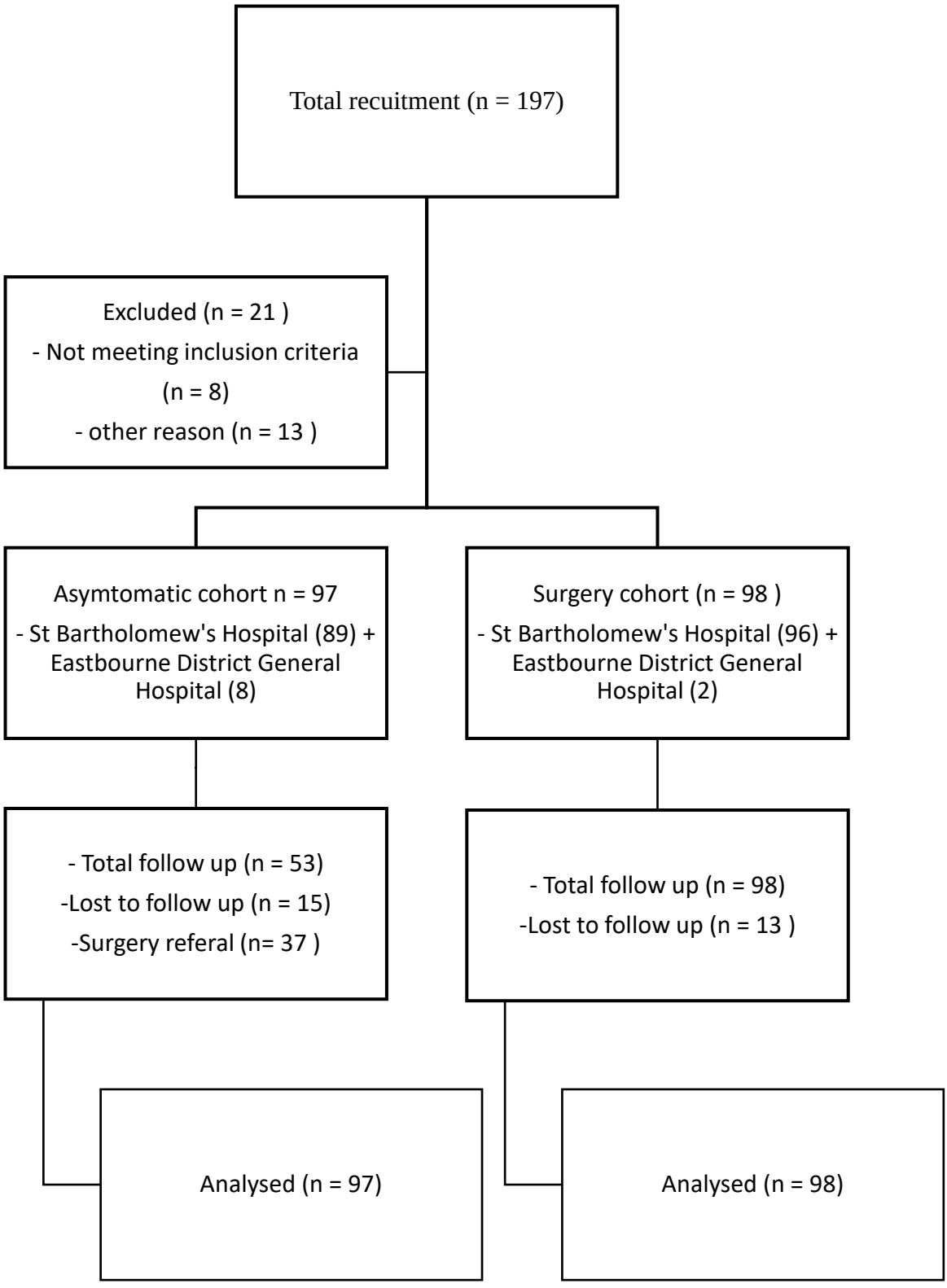


Figure 2.1 A flowchart of the study population according to cohorts' recruitment and inclusion and exclusion criteria.

2.4 Ethical approval

The study was approved by the Central Bristol Research Ethics Committee (REC approval is in appendix A). All participants have given their informed written consent prior to inclusion in the research study, (copy of consent form is in appendix B).

2.5 Study design – participant identification and recruitment

This is a prospective observational study. Patients with primary mitral regurgitation due to mitral valve prolapse were recruited prospectively at St Bartholomew's Hospital and Eastbourne District General Hospital. Patients were recruited from outpatient heart valve clinics.

Potential participants were identified by a consultant cardiologist or a member of their direct clinical team. A participant information sheet was sent to eligible potential participants after investigators verbally approached them. Subsequently, an appointment was arranged with a member of the research team. Adequate time (more than 24 hours) was provided for prospective participants to consider their decision regarding participating in the study and to ask questions. A second appointment was arranged to obtain formal informed consent from qualified participants, who then joined the study.

2.6 Statistical analysis (power calculations)

Power calculations were carried out prior to the beginning of the study on the basis of previous results. For asymptomatic cohort, based on Messika-Zeitoun et al. (105). The overall VO_2 peak was 26 ml/kg/min and VO_2 peak in patients with reduced functional capacity was 22 ml/kg/min, the difference in means was 4 ml/kg/min, with a standard deviation of 5. We estimated that with a sample of 52 patients, the study would have at

least 80% power to detect a difference in VO_2 peak between patients with and without functional limitation.

For the surgery cohort, based on Kim et al. (82), GLS in patients with cardiac events was -16.5% and GLS in patients without a cardiac event was -20%. The difference in means in this study was 3.5%, with a standard deviation of 4%. We estimated that with a sample of 44 patients, the study would have at least 80% power to detect a difference in GLS between patients with and without end-points.

2.7 Baseline clinical assessment

Baseline clinical assessments were obtained for all participants. This assessment included a full medical history, the presence or absence of inclusion and exclusion criteria, an evaluation of cardiovascular symptoms, family history, and a list of medications. Specific attention was paid to cardiovascular problems, as well as smoking history. A physical cardiovascular examination was also performed, including height and weight with calibrated scales and measurement of vital signs (heart rate, blood pressure and oxygen saturation). A twelve-lead electrocardiogram was recorded.

2.8 Symptoms identification

The New York Heart Association (NYHA) functional classification was used for symptom evaluation. MR patients were placed in one of these categories according to how much they are limited during daily physical activity. *Table 2.1* demonstrates the New York Heart Association (NYHA) functional classification of symptoms.

Table 2.1 The New York Heart Association (NYHA) Functional Classification of symptoms

NYHA class	Symptoms
I	No symptoms and no limitations of ordinary physical activity. Such as fatigue, palpitation, or shortness of breath.
II	Mild symptoms and slight limitation of ordinary physical activity (mild fatigue, palpitation, dyspnoea). Comfortable at rest.
III	Marked limitation of physical activity. Comfortable only at rest. Less than ordinary activity causes symptoms (fatigue, palpitation, dyspnoea).
IV	Severe limitation, symptoms occur even at rest or unable to carry on any physical activity without discomfort.

NYHA; The New York Heart Association.

2.9 Baseline echocardiography

A comprehensive two-dimensional transthoracic echocardiogram was performed using commercially available ultrasound imaging machines GE Vivid E9 Vivid E95 (Vingmed-General Electric, Horten, Norway). All echocardiography imaging, including parasternal long axis, parasternal short axis and apical views, was acquired in second harmonic imaging with the patient lying down in the left lateral position. An electrocardiogram lead was attached to the patient during the study, care was taken to ensure good quality tracings to obtain a complete cardiac cycle that ensured a clear representation of the image. After ending the study, all images were transferred to EchoPAC PC Software (version 204, GE Healthcare) for offline analysis. Measurements and calculations of left atrial area and

volume and left ventricle dimensions and volumes were indexed to the body surface area.

2.9.1 Two-dimensional echocardiography acquisition protocol for acquired measurements

Two-dimensional images were obtained with phased-array 3.5 MHz transducer. Echocardiographic views are shown in *Table 2.2.* Views and measurements were obtained in all subjects being scanned for the first time. Sector depth and width were adjusted where necessary to optimize image quality. All measurements were made according to the standard and guidelines recommended by the British Society of Echocardiography (143). Measurements were averaged over three to five cardiac cycles for patients with atrial fibrillation

2.9.1.1 Left ventricle dimension and wall thickness

Loops were acquired in the parasternal long axis view for measurements of LV dimensions and wall thickness. LV wall thickness and left ventricular end-diastolic diameter were measured at the maximum LV dimension before aortic valve opening (at the peak R wave at electrocardiogram). Left ventricular end-systolic diameter was measured at the smallest LV cavity dimension before mitral valve opening. Both LV dimensions were obtained at the level distal to mitral valve leaflet tip. LV wall thickness of interventricular septum and LV posterior wall were calculated at end of diastole in the parasternal long axis view.

2.9.1.2 Left atrial volume and right atrial area

Left atrial anteroposterior diameter was measured at end-systole in parasternal long axis view. This is a linear measurement perpendicular at the level of Sinus of Valsalva of the aortic root to the leading edge of the left atrial posterior wall. For left atrial volumes, the

endocardial left atrial border was traced, and the length was obtained in the apical four- and two-chamber views. Left atrial biplane volume was calculated automatically using the area-length method.

The biplane area-length equation= 8((A1) (A2)/3π)(L) was used.

A focused view of the right atrium using the apical four-chamber view was obtained to measure the right atrium area. The measurement was made by tracing the right atrium border at the end-systole, excluding the right atrial appendage.

2.9.1.3 Left ventricle volume and systolic function

Calculation of ejection fraction from the biplane apical two-dimensional volume measurements is recommended, rather than linear measurements. Thus, the biplane Simpson method was used to calculate ejection fraction by measuring LV volumes in apical four- and two-chamber views. Sector size and depth were reduced for the ventricular view only to optimise the image quality and definition of endocardial borders. LV end-diastolic volume (LVEDV) was obtained by tracing the LV endocardial border at end-diastole, defined as the largest area for the LV in both apical four- and two-chamber views (*Figure 2.2*), where LVESV is defined as the smallest area in each view, EF: (LVEDV-LVESV)/LVEDV x 100. The presence of wall motion abnormalities was assessed by two-dimensional images of the three apical windows.

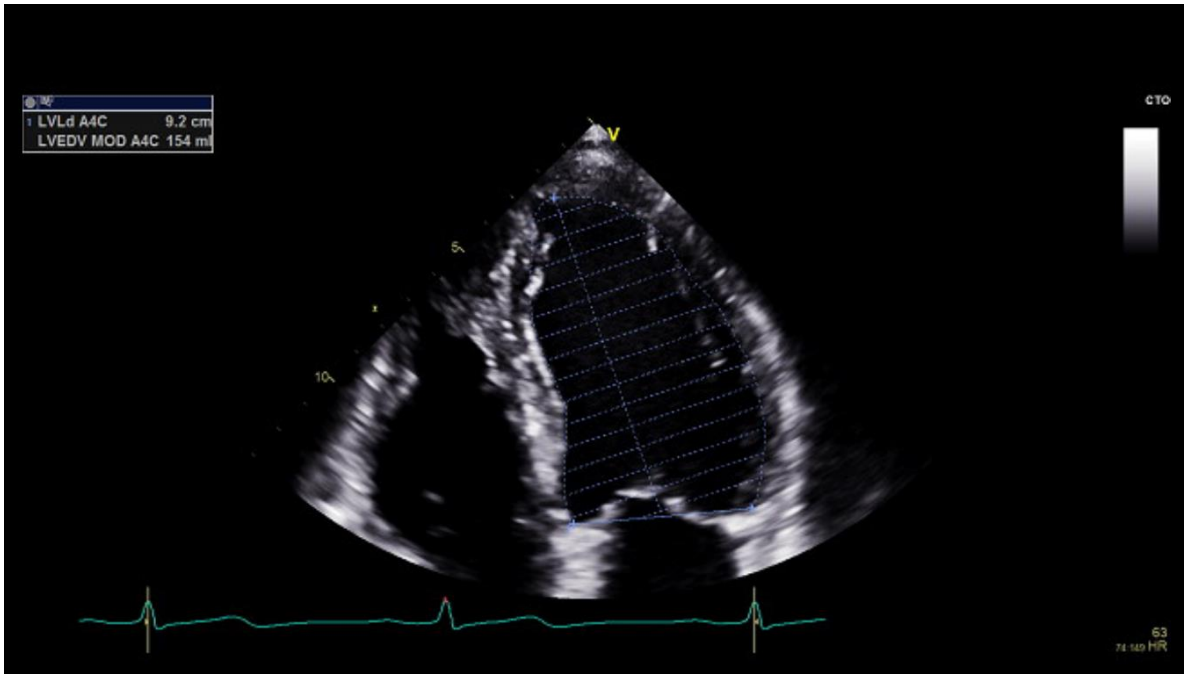


Figure 2.2 left ventricle end-diastolic volume obtained by tracing the left ventricle endocardial border at the end diastole in apical four-chamber view.

2.9.1.4 Tissue Doppler for longitudinal displacement

Tissue Doppler for longitudinal displacement is a method to assess left ventricular systolic function by measuring the mitral valve annulus displacement during the cardiac cycle. The apical four-chamber view was used to obtain velocities of the lateral S' and medial S' mitral annulus longitudinal movement by placing a sample volume on the annulus being examined. Care was taken to minimise the angle between the Doppler cursor and myocardium wall. The velocity scale was adjusted to view the whole envelope of maximum velocity. LV S' average of both lateral and medial values was then calculated.

2.9.1.5 Right ventricle size and function

Right ventricle size was evaluated by measuring the base and mid cavity dimensions.

Basal right ventricle linear dimension was defined as the maximum transverse line of the basal right ventricle. Mid cavity linear dimension was measured at the papillary muscle level, midway between the right ventricle base and apex. Both measurements were obtained at end-diastole.

Right ventricle systolic function was assessed by tricuspid annular plane systolic excursion (TAPSE) in the apical four-chamber view. TAPSE was measured using an M-mode cursor placed perpendicular to the right ventricle free wall and aligned along the direction of the tricuspid lateral annulus. The maximal tricuspid valve annulus movement extending from end-diastole to end-systole toward the apex was measured.

Right ventricular S' wave velocity was also measured to assess global right ventricular systolic function. A pulse wave curser was aligned with the basal segment of the right ventricle free wall and the lateral tricuspid annulus. Measurement was taken by placing the sample volume at the lateral tricuspid annulus in systole. The velocity scale was modified to capture the maximum velocity.

2.9.1.6 Diastolic function

Diastolic function was evaluated by mitral inflow. Velocities of mitral inflow were obtained by placing the sample volume of the pulse wave Doppler cursor at the mitral leaflet tips in the apical four-chamber view. E-wave velocity of early diastolic flow, A-wave velocity of late diastolic flow, deceleration time of E-wave, and E/A ratio were measured. annular velocities (E' and A' wave) were obtained with Doppler tissue imaging by placing the sample volume at the level of the mitral annulus. E'-wave of septal and lateral early diastolic tissue velocity was recorded by placing the sample volume on the

annulus being examined. E/E' ratio was calculated by dividing the E-wave velocity to E'-wave of the mitral annulus to estimate LV filling pressure.

2.9.1.7 Pulmonary artery systolic pressure

Estimated systolic pulmonary arterial pressure was obtained by measuring maximal tricuspid regurgitation velocity. This was measured by aligning a continuous wave Doppler aligned with the direction of tricuspid regurgitation flow. Estimated pulmonary artery systolic pressure was calculated with the modified Bernoulli equation (pulmonary artery pressure = $4v^2$ + estimated right atrial pressure, where v is the maximal tricuspid regurgitant jet velocity in m/s), according to guidelines.

2.9.2 Mitral regurgitation assessment

2.9.2.1 Aetiology

Mitral valve prolapse was identified when the coaptation line was two millimeters or more below the annular plane with the mitral leaflet tip pointed towards the left ventricle (*Figure 2.3, top*). A flail leaflet was observed when the leaflet tip was completely reversed toward the left atrium (*Figure 2.3. bottom*). MVP was diagnosed in the parasternal long

axis or apical long axis view as recommended.

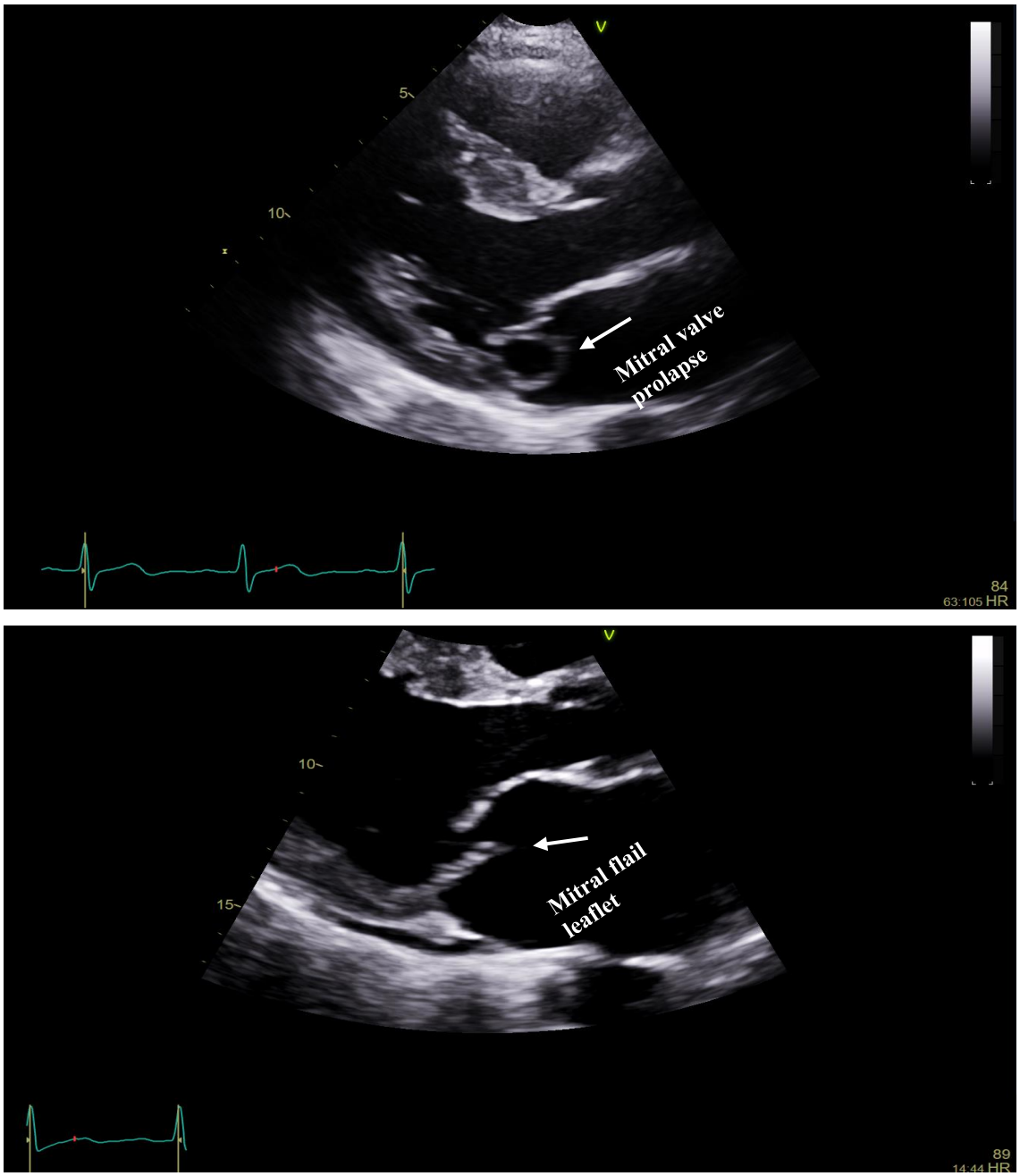


Figure 2.3 Parasternal long axis view showing mitral valve prolapse with coaptation line below the annular plane- top, and flail leaflet with leaflet tip is completely reversed toward the left atrium- bottom.

2.9.2.2 Severity

The degree of mitral regurgitation was quantified according to current recommendations using a multiparametric approach with a combination of semi-quantitative and quantitative parameters. For quantification of severity, effective regurgitant orifice and regurgitant volume were calculated.

2.9.2.3 Colour Doppler imaging

Colour Doppler imaging was performed. The size and extent of the regurgitant jet in the left atrium are proportional to the severity of mitral regurgitation.

Mitral regurgitation is defined as abnormal systolic retrograde blood flow from the left ventricle to the left atrium because of a reduction or elimination of the normal systolic coaptation between anterior and posterior mitral leaflets. Severe mitral regurgitation is a condition where a significant amount of blood leaks backwards into the left atrium.

This method is subject to many errors, however, and there exists a range of variability to take into consideration. Increased left atrial pressure and size may underestimate the colour jet. In addition, technical settings, such as colour gain may also affect colour flow display.

2.9.2.4 Vena contracta

The vena contracta is the narrowest portion of the regurgitant jet as it exits at or just below the level of the regurgitant orifice. The vena contracta was measured in the parasternal long axis or apical four-chamber view. To optimise measurement accuracy, a zoom-on colour Doppler image of the mitral valve was performed to identify the neck where regurgitant flow accelerates as it passes through the orifice. The following quantification

was performed: vena contracta < 0.3cm indicates mild regurgitation; vena contracta > 0.7cm indicates significant MR. Intermediate measurements (0.3 cm - 0.7 cm) require a further quantitative method to confirm its severity.

2.9.2.5 Proximal isovolumic surface area method

The Proximal Isovolumic Surface Area (PISA) method was used for the quantification of MR. PISA reflects the physics of flow acceleration when it passes toward the narrow orifice. The maximum acceleration of the regurgitant flow occurs when the flow from different directions merges at the orifice, which appears as an arch. The hemisphere of the radius (*r* of the PISA) is the distance from the mitral orifice to the colour changing at the top, as blood velocity accelerates and it exceeds the aliasing velocity of colour Doppler scale.

The PISA was visualised in the apical four-chamber view. In case it was not well visualised in the apical four-chamber view (e.g., anterior mitral valve prolapse), parasternal long axis or short axis views were used. The region of interest was zoomed in, and the Nyquist limit was lowered to around 30-40 cm/s. Calculation of the effective regurgitant orifice (ERO) and regurgitant volume (R Vol) were obtained using the standard formula:

ERO= $2\pi r2$ v/ Vmax

R Vol = ERO * VTI MR

(VTI of the mitral regurgitant jet is obtained with continuous wave Doppler sample volume placed on the mitral regurgitant jet guided with colour Doppler image)

Mild, moderate and severe mitral regurgitation correspond to an ERO of $<0.2cm^2$, 0.21 – $0.39cm^2$ and $\geq 0.4cm^2$ respectively, and to a regurgitant volume of <30, 30 to 59 and ≥ 60 mL/beat respectively. In case PISA could not be obtained, the vena contracta was used.

2.9.2.6 Continues wave Doppler of mitral regurgitation jet

The velocity of the regurgitant jet was obtained by placing a sample volume of the continuous Doppler through the regurgitant jet guided by colour Doppler to ensure good alignment of the ultrasound beam with the direction of regurgitant flow to detect maximum velocity signal.

2.9.2.7 Mitral valve inflow velocity

The mitral valve inflow was measured. This measurement was obtained by placing a sample volume of pulse wave Doppler at the mitral valve tips in the apical four-chamber view. Peak E velocities more than 1.5 m/s indicated severe MR.

2.9.3 Echocardiography views

Table 2.2 demonstrates the protocol of the main echocardiography views and the modality imaging and the measurements for each view.

Table 2.2 Echocardiographic views

View	**Modality**	**Measurement**
Parasternal long axis	**2D**	LV cavity Size (LVEDD, LVESD) LV wall thickness (IVSd, LVPWd) LA diameter (end ventricular systole) MV- appearance and function: thickness, calcification, and mobility. Mitral annular disjunction

Parasternal long axis	**Colour Doppler**	Mitral regurgitation Aortic regurgitation
Parasternal long axis RV inflow	**Colour Doppler**	Tricuspid regurgitation (TR)
Parasternal long axis RV inflow	**CW Doppler**	TR velocity (TR Vmax)
Parasternal short axis	**2D**	MV- appearance and function (thickness, mobility, calcification) PSAX -mid at papillary muscles and -at apex for radial function Offline speckle tracking at MV, mid-cavity and apical levels
Parasternal short axis	**Colour Doppler**	Mitral regurgitation Aortic regurgitation Tricuspid regurgitation Pulmonary regurgitation
Parasternal short axis	**CW Doppler**	TR velocity (TR Vmax)
Apical 4-ch	**2D**	LV volume and function: -Simpson's biplane EF (LV end diastolic volume, LV end systolic volume)

		-Offline speckle tracking analysis LV inferoseptum and lateral walls Left atrial area and volume (at end ventricular systole) MV- appearance and function Mitral annular disjunction RV cavity size (RV base diameter, Mid RV diameter) RA size (RA area)
Apical 4-ch	**Colour Doppler**	MV inflow (MR) zoomed for PISA measurement TV inflow (TR)
Apical 4-ch	**CW Doppler**	MR trace and peak velocity (shape, time, and density of signal)
Apical 4-ch	**PW Doppler**	MV inflow E wave, A wave Vmax for LV diastolic function (cursor at MV tips)
Apical 4-ch	**Colour TDI**	E' wave septal (cursor at the septal MV annulus of LV inferoseptum wall) E' wave lateral (cursor at the lateral MV annulus of LV lateral wall) S' wave lateral RV (cursor at the lateral TV annulus)
Apical 4-ch	**M-Mode**	Tricuspid annular plane systolic excursion (TAPSE), cursor at TV annulus for RV systolic function**.**

Apical 2-ch	**2D**	LV volume and function: -Simpson's biplane EF (LV end diastolic volume, LV end systolic volume) -Offline speckle tracking analysis for LV inferior and anterior walls. Left atrial volume (at end ventricular systole)
Apical 2-ch	**Colour Doppler**	Mitral valve inflow (MR)
Apical long axis	**2D**	LV function: -Offline speckle tracking analysis for LV posterior and anteroseptal walls.
Apical long axis	**Colour Doppler**	MV inflow MR jet – zoomed for PISA if possible (MR) AV (AR)
Apical long axis	**CW Doppler**	MR trace and peak velocity if possible

2D; two dimensional, LV; left ventricle, LVEDD; left ventricle end-diastolic dimeter, LVESD; left ventricle end -diastolic diameter, IVSd, interventricular septal end diastole, LVPWd; left ventricle posterior wall end diastole, LA; left atrium, MV; mitral valve. TR; tricuspid regurgitation, RV; right ventricle, CW; continuous wave, EF; ejection fraction, RA; right atrium, PISA; proximal isovelocity surface area, PW; pulse wave, TDI; tissue Doppler imaging, E wave; early mitral inflow velocity, A wave, active filling at late diastole, E' wave; mitral annular early diastolic velocity, S' wave; myocardial systolic excursion velocity, AV; aortic valve, AR; aortic regurgitation.

2.10 Mitral annulus disjunction

Mitral annulus disjunction is a structural malformation of the mitral annulus fibrosus. It is defined by the distinct separation between the mitral annulus at the site of the posterior leaflet insertion and the basal segment of the posterolateral wall of the left ventricular myocardium. Mitral annulus disjunction was identified in the parasternal long axis view or apical four-chamber view at end-systole. The image was zoomed, and gain settings were adjusted for optimal visualization. The degree of mitral annulus displacement was measured as the distance of systolic myocardial absence from the junction of the atrial wall and mitral valve to the basal part of the posterolateral myocardium of left ventricle (*Figure 2.4*).

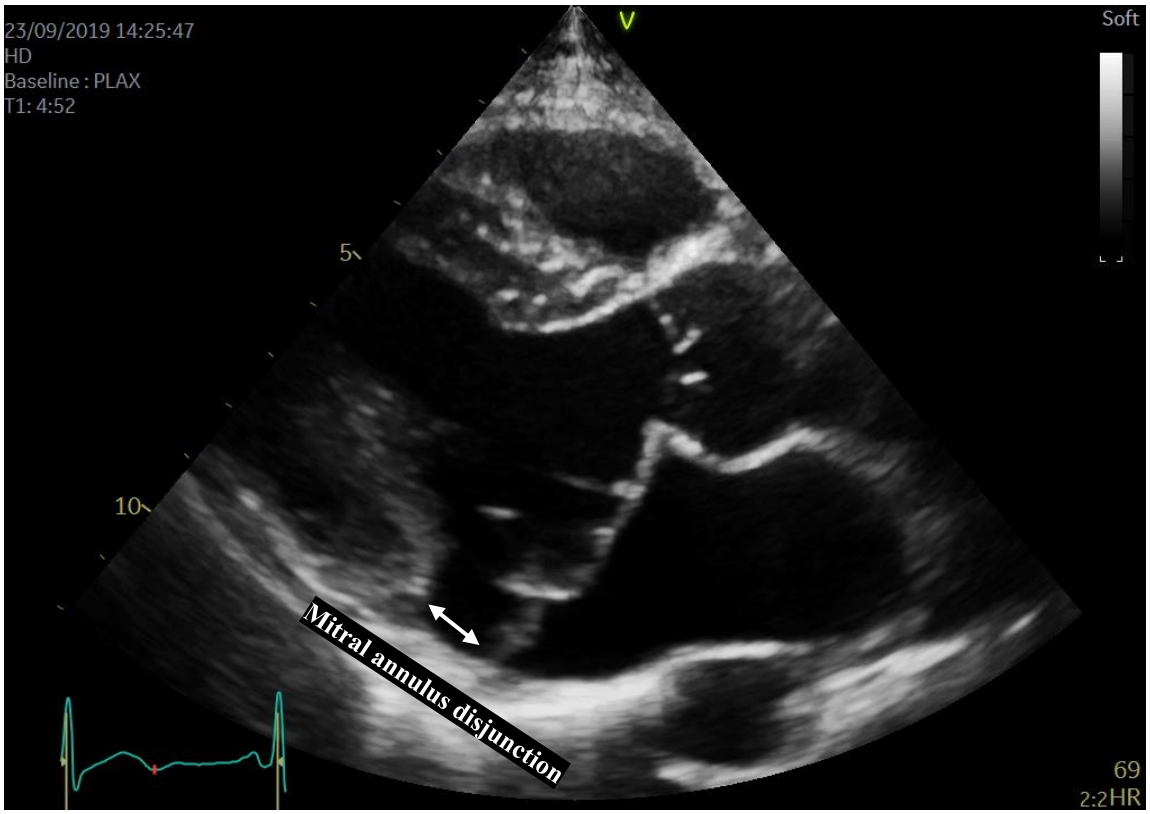


Figure 2.4 Mitral annulus disjunction.

2.11 Speckle tracking echocardiography- global longitudinal strain

Left ventricle deformation was evaluated by speckle tracking analysis of two-dimensional images. speckle tracking is an offline process. It works by analysis of digitally recorded cine loops triggered by an electrocardiogram. The endocardium wall was traced at end of the systolic frame. The algorithm performs automated tracking of the shift of speckle artefacts in the left ventricle wall of two-dimensional images throughout the cardiac cycle. These speckles are randomly generated as a result of reflection, refraction and scattering of the ultrasound beam. The post-processing software works by defining clusters of speckles within the region of interest and following them frame by frame. The left ventricle is automatically divided into six segments and each wall into three myocardial levels, namely basal, mid and apical.

In practice, the AFI (automated function imaging) assessment was activated in EchoPAC software. An analysis was then performed in the following order: apical four-, two- and three-chamber views. After selecting the required image, the software completed an automated tracking of the LV myocardium. Here, it is important to check the quality of tracking of the borders of LV endocardium and epicardium before approving the tracking; any imprecise automated tracking was manually modified to ensure accurate tracking. The width of the region was also adjusted if required, to include the whole of the ventricular myocardium, which allows the system to define accurately the region of interest. Aortic valve closure was identified automatically on spectral Doppler traces. Global longitudinal strain was measured by averaging all 17-segments strain values from apical four-, two- and three-chamber views (*Figure 2.5*). LV segments that could not be adequately tracked were not analysed as they were considered to be inadequate images. The frame rate was between 60 frames per second and 80 frames per second.

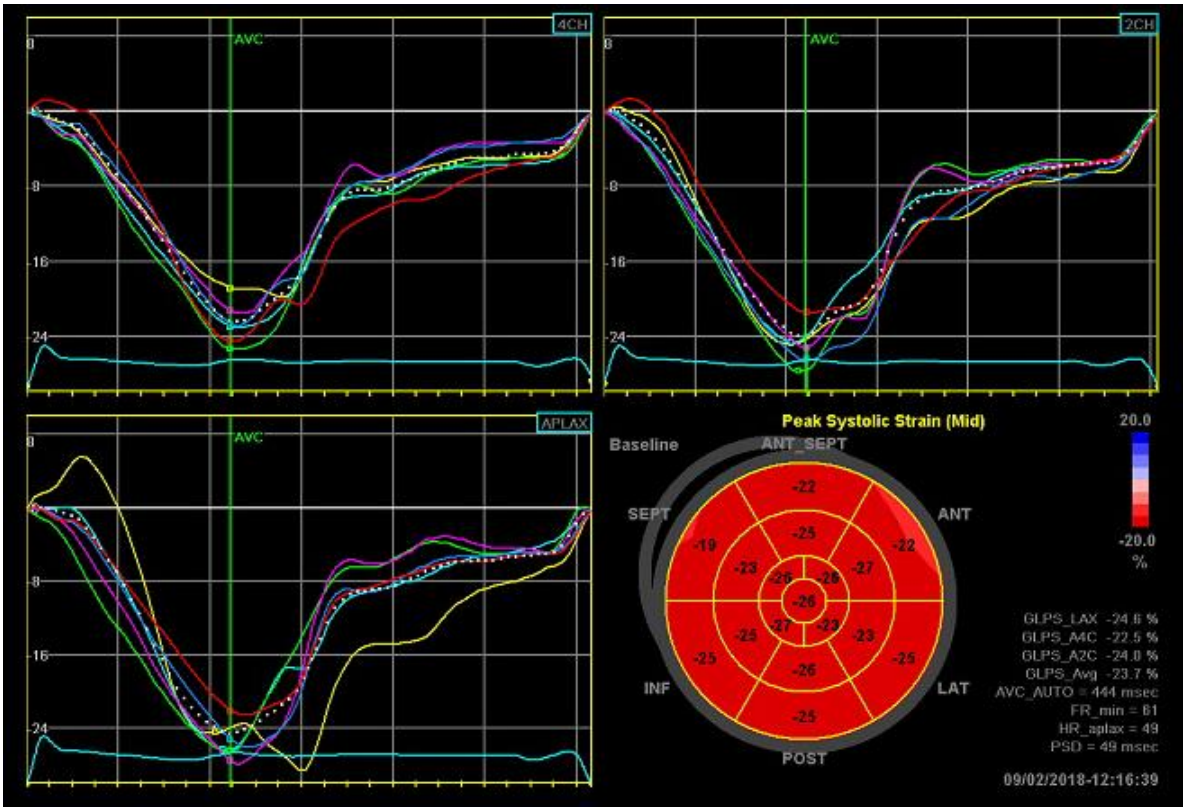


Figure 2.5 Global longitudinal strain in patients with mitral regurgitation.

2.12 Left atrial strain

Left atrial strain by two-dimensional echocardiography was performed in most patients with reasonable acoustic windows and an adequate frame rate. Similar to left atrial volume assessment, the left atrial strain was measured using a biplane algorithm, including apical four- and two- chambers views; thus, two separate images were acquired. dedicated views were acquired for left atrial analysis and care was taken to acquire true apical images to avoid atrial foreshortening and to allow more reliable delineation of the atrial endocardial border. After acquiring the images, Analysis was performed off-line using a commercially available LA strain software package (EchoPAC version 204). Left atrium endocardial border was manually traced in apical four- and two- chambers views. The region of interest (ROI) was delineated, which consists of six segments, defining the

lowest width of ROI, manual adjustment of the ROI was performed when needed. The breath-hold technique was applied as needed, especially if the optimal visualisation of the left atrium was challenging. After the segmental tracking analysis, the longitudinal strain curves for each atrial segment were automatically generated by the software. Peak atrial longitudinal strain was calculated at the end of the reservoir phase for all atrial segments by averaging all strain values of segments in four- and two-chamber views. The frame rate was 60–80 frames per second.

All left atrium strain components were displayed on the screen. These include:

- LA reservoir strain: positive peak left atrial longitudinal strain during left atrial lengthening.
- LA conduit strain: negative atrial strain during ventricular diastole after the opening of the mitral valve.
- LA contractile strain or (booster pump): negative atrial strain during active left atrial contraction.

2.13 Myocardial work

Myocardial work was obtained with global longitudinal strain value, brachial blood pressure measurements and valvular event times. Myocardial work was measured by integrating LV longitudinal strain and arterial blood pressure, as described by Russell et al (94).

First, four-, two- and three-chamber views were acquired, and the global longitudinal strain of the left ventricle was obtained by speckle tracking echocardiography, (Explained in *Speckle Tracking Echocardiography- Global longitudinal strain*). Care was taken when analysing the GLS. The ROI was adjusted to include the entire myocardium. If the

ROI is too wide, myocardial work may be underestimated. In contrast, if the ROI is too small, this may lead to an overestimation of the myocardial work. The timing of the valvular events was determined by placing a pulse-wave Doppler cursor corresponding to the mitral valve and aortic valve opening and closure. The duration of isovolumetric and ejection phases (determined by the opening and closure of the aortic and mitral valves) was applied. The blood pressure of the patient was measured with a simple brachial cuff, and then readings of the systolic blood pressure and diastolic blood pressure were added to the application (peak systolic arterial pressure was assumed to be equal to peak systolic left ventricle pressure in the absence of aortic valve gradient or left ventricular outflow tract gradient).

After completing all the given steps, the software automatically provided myocardial work measurements. Different phases of the cardiac cycle, including isovolumetric contraction, ejection fraction, isovolumetric relaxation, and diastolic filling were separated automatically using the previously determined event timing of the aortic and mitral valve opening and closure on the pressure-strain loop. All myocardial components were then displayed on the screen. These include:

- Global constructive work (GCW): myocardial work during systolic shortening + (-ve) myocardial work during isovolumetric lengthening.

- Global wasted work (GWW): (-ve) myocardial work during lengthening + myocardial work during isovolumetric contraction.

- Global work index (GWI): total myocardial work during mechanical systole including isovolumetric contraction and isovolumetric relaxation calculated using the area of the pressure-strain loop from mitral valve closure to mitral valve opening.

- Global work efficiency (GWE): global constructive work/ (global constructive work+ global wasted work).

The unit of GCW, GWW and GWI is (mmHg%), and GWE is expressed as a percentage (%).

2.14 Three-dimensional transthoracic echocardiography

Real time three-dimensional (RT3D) echocardiography images were acquired from an apical window with the same left lateral position for all participants. This was performed after two-dimensional echocardiographic image acquisition. A 4Vc-D Matrix or X4 matrix array transducer was used for the acquisition of three-dimensional images using a full volume dataset over four consecutive cardiac cycles (*Figure 2.6*). The gain setting was optimised as necessary, and sector width and frame rate were adjusted prior to image acquisition. The image frame rate was set to ≥ 20 frames/s. RT3D volumes were acquired with the patient holding their breath for 5-7 seconds to build up a full single three-dimensional LV volume. The full RT3D left ventricular volume images were stored on EchoPAC. RT3D image was obtained at rest and during exercise at peak stress level for patients in cohort 1. An attempt was made to obtain RT3D images on all patients; however, this was difficult for some patients because of body habitus or a poor window.

RT3D volume analysis was performed offline. The apex and mitral annulus were identified, a semi-automatic border detector method was then used for contour tracing, a pre-configured ellipse was fitted and adjusted to the endocardial border for each frame. The endocardial border was traced at end of diastole (maximum left ventricle cavity, first frame) and at end-systole (smallest left ventricle cavity, prior to the mitral valve closure)

to obtain a RT3D volume. Care was taken to ensure that the papillary muscles and endocardial trabeculae were included in the left ventricular cavity.

Finally, full left ventricular volume was re-constructed automatically by the software frame-by-frame throughout the cardiac cycle. The following measurements were automatically calculated: left ventricle end-diastolic and end-systolic volumes and left ventricle ejection fraction.

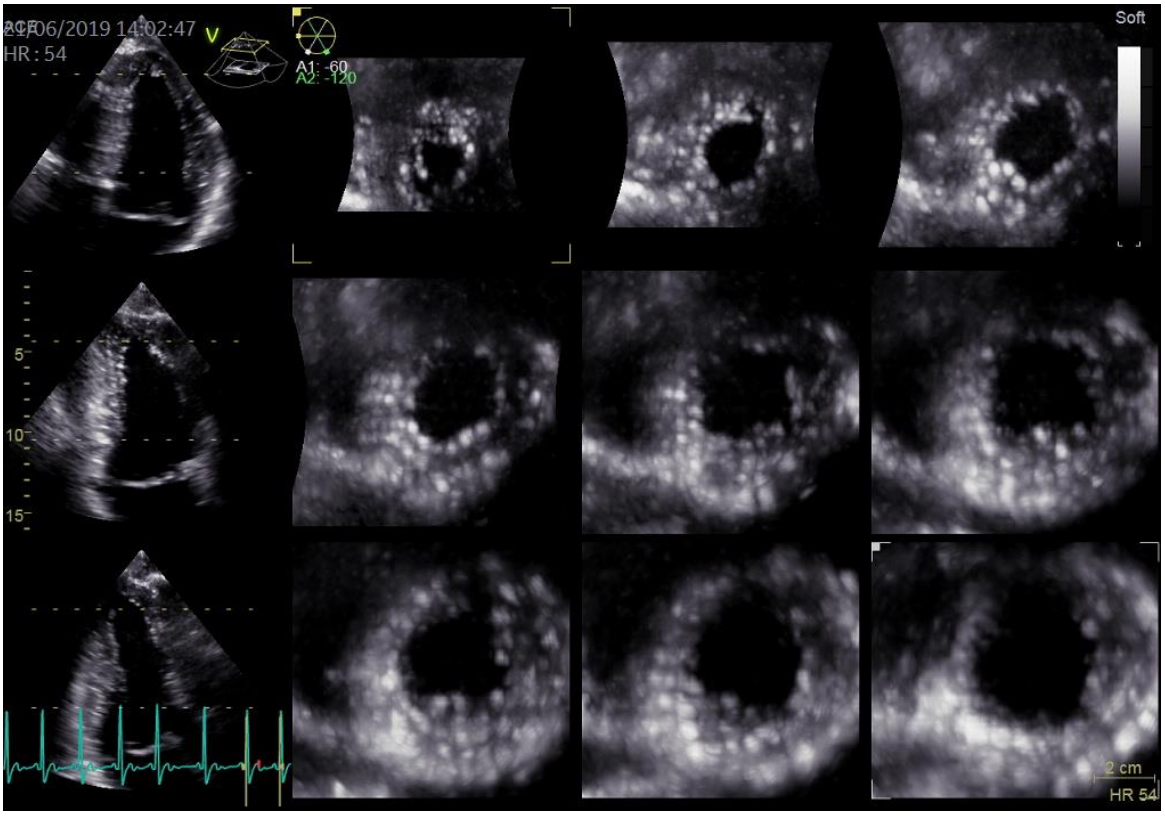


Figure 2.6 Real-time three-dimensional image for left ventricle volume.

2.15 Exercise echocardiography

Patients in the asymptomatic cohort underwent exercise echocardiography and a cardiopulmonary exercise test simultaneously. A symptom-limited bicycle test was performed in a semi-supine position on a tilting exercise bicycle at the exercise testing

room at St. Bartholomew Hospital and at Eastbourne District General Hospital. The room was dedicated and equipped for such testing, emergency equipment including an AED defibrillator, drugs, and an alarm to inform other staff members. The room was spacious, clean and with adequate temperature (20-24 °C, the optimal temperature for a CPET testing (144). Two staff members, a highly skilled exercise physiologist and a cardiologist with advanced life support training, performed all the testing. Prior to the test, patients continued to take their medications as usual. All tests, benefits, and risks involved in the study were properly explained to the participants before providing their written informed consent.

The exercise protocol was performed using a recumbent cycle ergometer (Ergoselect 1200, ergoline GmbH. Lindenstraße 5. D-72475 Bitz, Germany) or (ERG 911 S/L, Schiller, Baar, Switzerland) (*Figure 2.7*). A pre-specified exercise workload protocol was customised according to the patient's functional status. Resting echocardiogram images were acquired before patients started cycling on the semi-recumbent ergometer. Following the acquisition of the baseline imaging, a two- to three-minute rest period was recorded followed by a three-minute warm-up period (unloaded). The work rate (10, 15 or 20 Watt) then gradually increased, aiming for a total exercise test duration of 6 - 12 minutes. Two-dimensional and Doppler echocardiography measurements were made at rest, at low-intensity exercise after roughly three minutes of exercise and at peak exercise when patients were about to finish the test when the respiratory exchange ratio (RER) exceeds 1.0 or when patients reached their maximum effort. Heart rate and oxygen saturation were constantly monitored, and blood pressure was recorded every three minutes. The test was stopped if limiting symptoms including chest pain, and dyspnoea occurred or if significant adverse haemodynamic changes occurred. Exercise image sequences were taken at baseline, at low intensity (approximated at ventilatory threshold

(VT) / heart rate 90 -110 beat/min) if it is feasible, and at peak exertion (RER > 1.0). Patients were verbally encouraged to continue exercising until their maximal exertion.

Figure 2.7 A semi-supine position on a tilting exercise bicycle (ERG 911 S/L).

2.15.1 Protocol of stress echocardiography images

The echocardiographic images were obtained as follows:

- Four-chamber view with colour tissue velocity imaging turned on in the background. Measurement of longitudinal left ventricle function (S' wave velocity) was performed by offline strain analysis by placing the sample volume at the septal and lateral mitral annulus; S' wave was then averaged.

- Zoomed optimised mitral regurgitation with colour Doppler to assess mitral regurgitation severity.
- Continuous Doppler of mitral regurgitation jet.
- Continuous Doppler of tricuspid regurgitation jet and measurement of peak pulmonary artery systolic pressure.
- Grayscale image of apical views, including four-, three- and two-chamber views.

  The apical views were acquired to assess LV contractile reserve. The contractile reserve was defined as $\geq 4\%$ increase in LVEF or $\geq 2\%$ increment in global longitudinal strain during the exercise (102). LVEF was measured by Simpson's biplane, and global longitudinal strain was obtained by analysing strain for each image.
- Gray scale of parasternal views including long axis view, short axis view at basal and apex level.
- Finally, an additional RT3D LV volume was acquired at rest, low and peak intensity. RT3D image for LV volume was recorded at peak stress level with frame rate > 12 Hz.

Images were obtained in real-time and digitally stored offline and analysed after each study with EchoPAC version 204 (GE Medical Systems, Horten, Norway). *Figure 2.8* is an example of stress echocardiography protocol with images acquired at baseline, low-intensity exercise, and peak exercise.

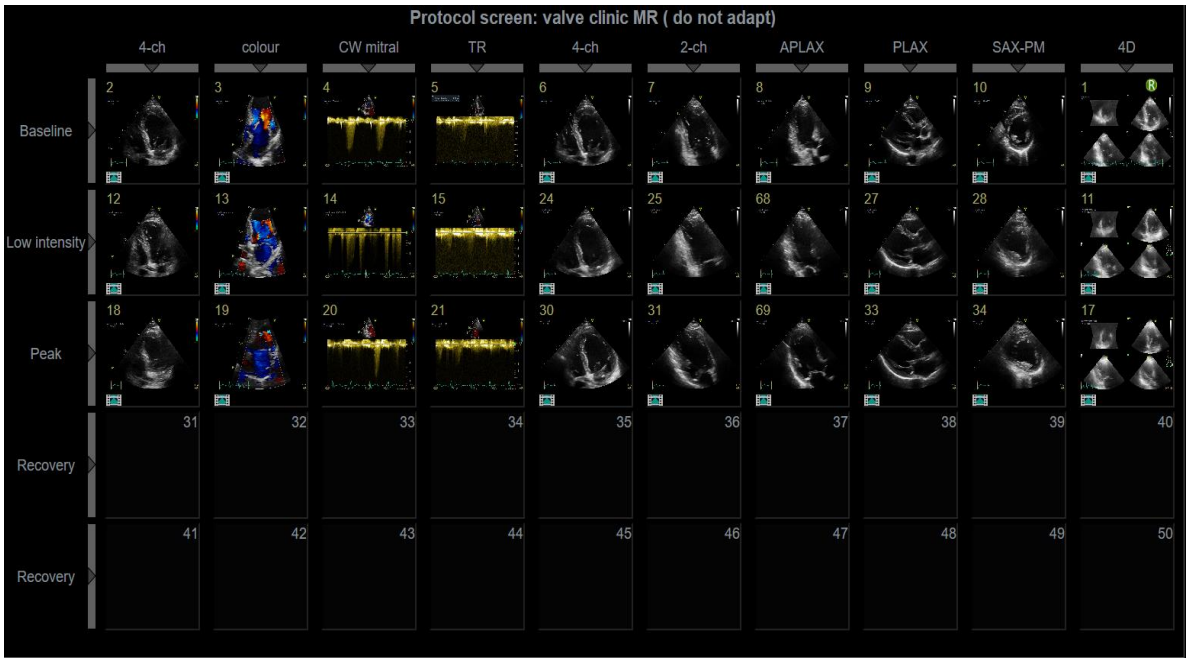


Figure 2.8 Stress exercise protocol with echocardiographic images were obtained at baseline, low-intensity exercise, and peak exercise levels. (Data from patient seen clinically at St. Bartholomew Hospital)

2.15.2 Indication for termination of exercise test

The exercise test was terminated if the participant met guideline criteria for terminating exercise testing (142, 145) as follows:

Absolute indication:

- Systolic blood pressure decreases more than 10 mmHg from baseline during the exercise, especially if associated with evidence of ischaemia.
- Significant angina.
- Dizziness, near-syncope, or ataxia (presence of central nervous system symptoms).
- Sustained ventricular tachycardia.
- Evidence of poor perfusion.

- ST elevation (>1.0 mm) on electrocardiogram without diagnostic Q-waves.
- Failure to monitor electrocardiogram or systolic blood pressure.
- If participant wants to stop.

Relative indication:

- Systolic blood pressure decreases more than 10 mmHg from baseline during the exercise without other evidence of ischaemia.
- Shortness of breath, fatigue, wheezing, or leg cramps.
- Arrhythmias, other than sustained ventricular tachycardia.
- Hypertensive response (systolic blood pressure more than 250 mmHg and/or diastolic blood pressure more than 115 mmHg).
- Development of bundle-branch block during exercise that cannot be differentiated from ventricular tachycardia.
- ST or QRS changes on electrocardiogram.

2.16 Cardiopulmonary stress echocardiography

Cardiopulmonary exercise testing was combined with exercise echocardiography. A breath-by-breath CPET (Quark, Cosmed, Italy) was used to perform a maximal cardiopulmonary exercise test for participants. Volume and gas analyser calibration was performed before every test. Patient characteristics including date of birth, sex, height, and weight were entered into the CPET PC and were used for the calculation of normal predicted values. Exercise protocols were determined based on the participant's functional and fitness status and age. If the chosen protocol is too high, the $VO_{2\ peak}$ value

may be underestimated. If the ramp is too low, the patient could become exhausted before reaching their true maximal exercise tolerance (146). After choosing the desired exercise protocol, the baseline images were acquired while patients lying on the semi-recumbent tilting cycle ergometer (Ergoselect 1200, ergoline GmbH. Lindenstraße 5. D-72475 Bitz, Germany) or (ERG 911 S/L, Schiller, Baar, Switzerland). The CPET face mask was then adjusted for the patient. A two- to three-minute rest period was recorded to establish resting respiratory gas exchange ratio (RER) and haemodynamics measurements test, followed by a three-minute warm-up period with no load. The work rate increased gradually until voluntary exhaustion, aiming for a test duration of 6-12 minutes (147, 148). The participant was verbally encouraged to continue cycling and on maintaining pedal speed at the preferred level, usually ≈60 revolutions per minute. ECG, heart rate and oxygen saturation were constantly monitored, and blood pressure was obtained every three-minutes throughout the test and for at least four minutes into recovery. Symptoms were assessed and quantified during and after exercise.

Oxygen uptake VO_2, breath-by-breath minute ventilation (VE) and carbon dioxide consumption (CO_2) and their ratio (VE/VCO_2 slope) were continuously measured using a breath-by-breath analyser, and these averaged every 10 seconds. RER > 1 was used to indicate maximal effort. Peak oxygen uptake was defined as the highest value recorded during the last 30 seconds of the exercise test, expressed as absolute $VO_{2\ peak}$ ml/ min or adjusted $VO_{2\ peak}$ ml/kg/min and normalised $VO_{2\ peak}$ % (percentage of age, sex and weight predicted). The ventilatory threshold, $VO_{2\ peak}$, VE/VCO_2 slope, Oxygen pulse (O_2 pulse) and the Oxygen Uptake Efficiency Slope (OUES) were calculated.

2.16.1 Standard measurements during cardiopulmonary exercise testing

2.16.1.1 VO_2 peak

$VO_{2\ peak}$ was defined as the highest O_2 volume used in metabolism by the body during exercise expressed as (ml/min) or standardised for the weight (ml kg/min), and percent-predicted value. The predicted $VO_{2\ peak}$ value was measured by Wasserman's formula (149). A cut-off of 84% predicted was used to define the normal $VO_{2\ peak}$. $VO_{2\ peak}$ was measured as the highest value obtained from an average of $VO_{2\ peak}$ values during the last 30 seconds of the exercise test (*Figure 2.9*).

At peak exercise, the following definitions were used:

- VO_2 peak less than 20 (ml kg/min) is mildly impaired
- VO_2 peak less than 15 (ml kg/min) is moderately impaired
- VO_2 peak less than 10 (ml kg/min) is severely impaired

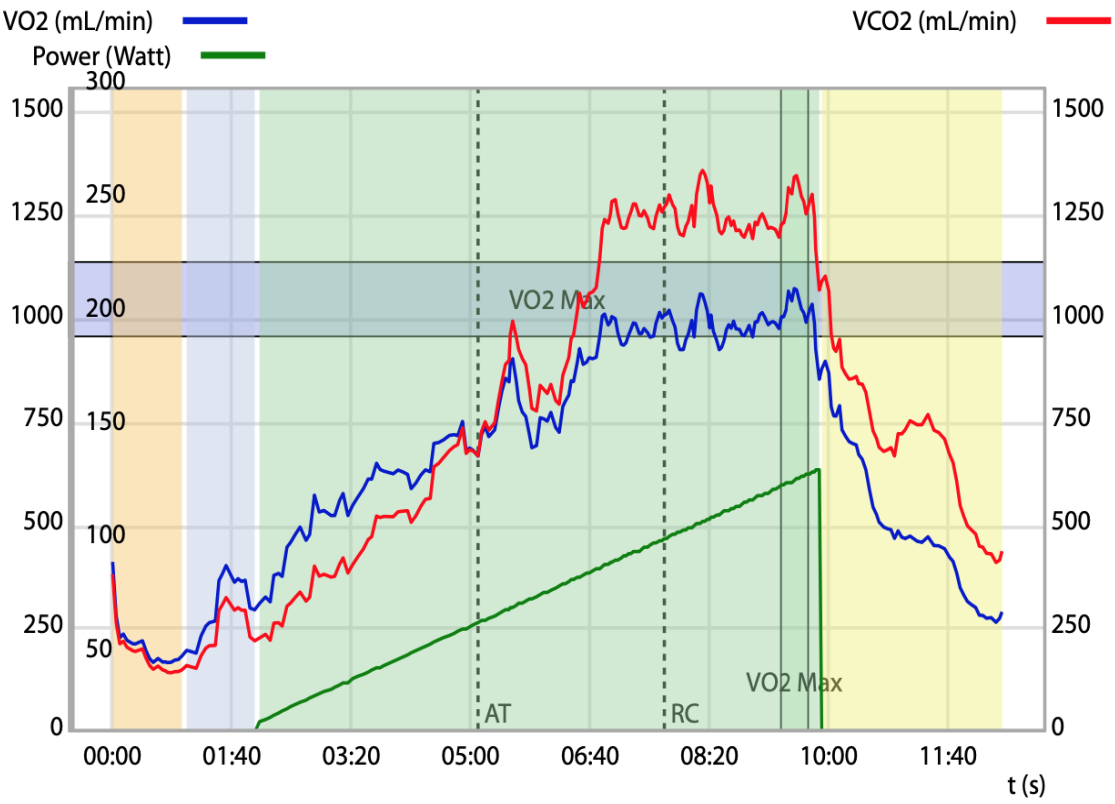


Figure 2.9 Graph demonstrated the VO_2 (blue line), VCO_2 (red line) and workload during the exercise. Determination of the oxygen uptake (VO_2 peak) as the highest value obtained from an average of the last 30 seconds of the exercise test. (Data from patient seen clinically at St. Bartholomew Hospital). VO2 max; maximal oxygen consumption, VCO2; carbon dioxide production, AT; anaerobic threshold, RC; respiratory compensation.

2.16.1.2 Peak respiratory exchange ratio

Respiratory Exchange Ratio (RER) is the ratio of the volume of carbon dioxide production (VCO_2) to oxygen consumption (VO_2).

$RER = VCO_2 / VO_2$

RER helps to determine the anaerobic threshold (AT). At the beginning of the exercise test, VCO_2 is less than VO_2, and RER should be less than 1. During the anaerobic

threshold, VCO_2 and VO_2 are equal; therefore, RER must be 1. Beyond the anaerobic threshold, RER increases to more than 1, reflecting an increase in the production of carbon dioxide from the buffering of lactic acid by HCO_3-, exhale more CO_2 leading to VCO_2 to be greater than VO_2.

2.16.1.3 Minute ventilation–carbon dioxide output relationship (VE/VCO_2 slope)

Minute ventilation (VE) is defined as the measure of ventilation used during the exercise test, which represents the volume of all breaths (inhale or exhale) in one minute.

VE is linked to VCO_2. The more minute ventilation, the higher the VCO_2 value. VE/VCO_2 slope is used to assess the efficiency of ventilation.

- A high VE/VCO_2 slope may suggest poor perfusion in the lung (plenty of ventilation with a little VCO_2).
- A high VE/VCO_2 slope may imply that there is a low $PaCO_2$ (the arterial CO_2 level); low $PaCO_2$ means lower driving pressure and less carbon dioxide is exhaled (low $PaCO_2$ may be found in severe heart failure patients and is associated with very poor prognostic signs in heart failure).

2.16.1.4 Oxygen pulse

Oxygen pulse (O_2 pulse) is defined as the amount of O_2 flowing from the lungs to the blood with each cardiac contraction. It reflects cardiac stroke volume. Normally, O_2 pulse increases during the early the phase of the exercise as a result of stroke volume increases. In pathological states, the stroke volume may not increase, and as a result, the O_2 pulse will reach a plateau and remain at the same value throughout exercise.

O_2 pulse (ml/beat) = VO_2 (ml/min) / HR (bpm).

- O_2 pulse of more than 10 (ml/beat) is the normal achievement at peak exercise.

- O_2 pulse of less than 10 (ml/beat) and plateau suggest limited cardiac output.

2.16.1.5 Heart rate

An increase in the heart rate (HR) is the normal response during exercise. Exercise capacity can be determined by measuring predicted maximum heart rate. Reaching 80% of the predicted maximum HR at the peak exercise is considered normal.

Predicted maximum HR (bpm)= 220 - age. A predicted maximum HR of 80% or more is normal at peak exercise.

2.17 Scheduled follow-up

Scheduled follow-up arrangements were arranged for participants in the asymptomatic and surgery cohorts. In the asymptomatic cohort, follow-up was undertaken 12 months after the baseline assessment. A repeat echocardiogram and exercise stress echocardiogram combined with a cardiopulmonary exercise test was performed. The patients in the surgery cohort were followed up with a repeat echocardiogram 12 months post-mitral valve surgery.

2.18 Blood biomarkers (NT-pro BNP and sST2)

A venous blood sample (5 ml) was drawn from an antecubital vein with the patient resting semi-recumbent and collected into ethylenediaminetetraacetic acid Vacutainer test tubes for both NT-proBNP and sST2 measurements. The sample was transferred to the laboratory facility on the same campus for processing and measurement of NT-proBNP. Roche Modular E170 immunoassay platform was used for The Roche Elecsys NT-

proBNP assay. Samples were centrifuged and standard sampling tubes with separating gel were used to collect serum. Serums can be stable for up to 3 days at 20/25 ^{o}C, 6 days at 2-8 ^{o}C or 24 months > -20 ^{o}C. ELISA technique with a sandwich technique of two monoclonal antibodies and streptavidin-coated microparticles was used for NT- proBNP measurements. The result was determined by the calibration curve. The calibration curve is a device with two-point calibration and a master curve given by the reagent barcode. The range of measurements is 5-35000 pg/ml, the limit of lower detection is 5 pg/ml and the upper limit is up to 300,000 pg/ml.

The blood sample tube for sST2 was taken to the laboratory and centrifuged at 1.300 RCF for 10 minutes for serum separation. The serum was then stored at -80 ^{o}C until further analysis. Measurement of sST2 was performed with Aspect Plus ST2 Rapid Test, with upper linear limit detection of 250 ng/ml and the lower limit of 12.5 ng/ml. To perform the test, the ASPECT-PLUS ST2 test cassette was removed from the refrigerated storage and left at room temperature for 15 minutes. A serum sample (35 uL) was then pipetted into the sample well of the test cassette. After 60 seconds, two drops of test buffer (~110 uL) were added to the test buffer well of the test cassette. The test cassette was then inserted into the reader (inaccurate results may result from a delay longer than 60 seconds after test buffer addition). After approximately 20 minutes the result of sST2 was displayed on the screen.

Chapter 3

Asymptomatic Primary Mitral Regurgitation: Insights from Exercise Echocardiography and Cardiopulmonary Exercise Test

3.1 Abstract

Background and objective: In asymptomatic patients with moderate to severe primary MR, there is limited data regarding the clinical importance of exercise echocardiography and CPET. This study aims to evaluate the role of CPET combined with echocardiography to find which parameter best predicts dyspnoea during exercise, $VO_{2\ peak}$ and the need for mitral valve intervention. **Methods:** Resting and exercise echocardiography combined with CPET were performed prospectively in 97 asymptomatic patients with moderate to severe or severe primary mitral regurgitation. Patients with impaired LV systolic function were excluded. Systolic function assessed by LVEF, S' velocity and LV strain, LV volumes, PASP and main CPET measures were measured during exercise echocardiography. Follow-up was obtained by repeating stress echocardiography and CPET within one year. The clinical management (including referral for mitral valve intervention) was independently decided by the patient's physician. **Results:** Fifty patients (52%) had reduced exercise capacity, i.e. $VO_{2\ peak}$ < 84% of the predicted value. 19% of patients stopped the exercise test because of dyspnoea. The multivariable analysis demonstrated that echocardiography parameters were unable to predict functional capacity ($VO_{2\ peak}$). On multivariate logistic regression analysis, higher rest PASP was the best independent predictor of dyspnoea during exercise testing. LVESV was the only independent predictor associated with mitral valve surgery. **Conclusions**: A proportion of patients whom clinicians classify as asymptomatic MR have reduced exercise capacity or develop symptoms on exertion. Higher resting PASP predicts dyspnoea development during exercise testing.

3.2 Introduction

Mitral valve surgery is recommended in patients with primary mitral regurgitation when patients become symptomatic or when asymptomatic patients develop left ventricle dysfunction or dilatation (1, 2). However, it is not always straightforward to determine when symptoms develop. Patients may not always report symptoms due to the insidious onset of symptoms. LV end-systolic diameter is the guideline-recommended parameter to determine LV dilatation (1, 2). However, other measures of LV dilatation such as LV volumes may recognise dilatation at an earlier stage (150). These observations highlight that it remains challenging to evaluate LV function and detect subclinical LV impairments, and that timing of mitral valve surgery in patients with severe asymptomatic MR remains controversial. Delay of surgery may cause a decline in myocardial function, increasing myocardial fibrosis and remodelling which may lead to an increase in morbidity and mortality (151, 152). Exercise and physical activity play an important role in the management of primary MR patients. CPET can objectively evaluate patients' exercise tolerance, which may be beneficial in the asymptomatic group. Combining CPET with exercise echocardiography may provide additional information on haemodynamic changes during exercise.

The purpose of the study was to identify if patients deemed asymptomatic by clinicians with moderate to severe or severe MR have reduced functional capacity or develop exertional symptoms. In addition, the study aimed to identify which resting echocardiographic parameter was the best predictor of mitral valve surgery during clinical follow-up. It was hypothesised that despite being asymptomatic, a proportion of patients with MR would have reduced $VO_{2\ peak}$ values or develop exertional dyspnoea.

3.3 Methods

3.3.1 Study population

This prospective observational study was conducted at St Bartholomew's Hospital and Eastbourne District General Hospital. A total of 105 participants were recruited. Eight participants were excluded after they were initially recruited because they did not meet the inclusion criteria after further investigation, (four for impaired left ventricular systolic function assessed by biplane ejection fraction, two for inability to perform the exercise test, one for ischaemic heart disease, and one for functional mitral regurgitation). A total of 97 patients were successfully included in the asymptomatic cohort (89 participants were recruited at St Bartholomew's Hospital and 8 participants were recruited at Eastbourne District General Hospital).

All patients were asymptomatic (NYHA I) with moderate to severe or severe mitral regurgitation due to mitral valve prolapse or flail leaflet and preserved left ventricle ejection fraction. All patients underwent supine bicycle exercise echocardiography combined with a cardiopulmonary exercise test. Data are presented in this chapter for the 97 asymptomatic patients who fulfilled the study criteria and completed the baseline assessment.

3.3.2 Clinical assessments

Baseline clinical assessments and cardiac imaging tests including comprehensive transthoracic echocardiography, exercise echocardiography and cardiopulmonary exercise test were performed for all participants. The detailed methodology of each test is explained in the methodology chapter.

3.3.3 Reasons for terminating exercise stress test

1. Shortness of breath (dyspnoea group)

- Patients who claimed they were unable to continue exercising because of severe shortness of breath.
- Patients who experienced prolonged audible and asthmatic lookalike breathing or heavy and rapid breathing that made it difficult for them to continue speaking with the physiologist or cardiologist.

2. General fatigue (exhaustion group)

- Patients who claimed that lower limb tiredness prevented them from pedalling further or when pedalling becomes noticeably difficult for them.
- Those who stopped because of high heart rate as their maximal predicted heart rate (220−age) was achieved.
- Other reasons such as hypertensive or hypotensive response, and arrhythmia without severe shortness of breath.

3.3.4 Follow up

A cardiopulmonary exercise test combined with exercise echocardiography was performed during the two visits. Follow-up appointments occurred 12 months after the baseline visit. The clinical management was determined independently by the patient's cardiologist if the patient should be considered for mitral valve intervention or if the patient should remain under follow-up. Data used for the functional capacity ($VO_{2\ peak}$) predictive model was from the follow-up (second) visit. Data used for cardiac surgery modelling was taken from the first test after referral to the clinic.

3.3.5 Statistical analysis

Data were tested for normality distribution with the Kolmogorov-Smirnov test. Continuous variables are presented as mean ± standard deviation or as median (25th to 75th) percentiles, as appropriate. Categorical variables are presented as absolute values and percentages. Paired t-tests or Wilcoxon tests were used to compare echocardiographic parameters at rest versus during exercise and baseline visit versus follow-up visit. Student t-tests or Mann-Whitney test and X^2 tests were used to determine differences between patients according to exercise-induced dyspnoea, functional capacity, and mitral valve surgery where appropriate. The outcomes were analysed using three endpoints: exercise-induced symptoms, reduced functional capacity ($VO_{2\ peak}$< 84%) during exercise and indication for surgery. Initially, a univariable analysis was performed, testing all the relevant variables potentially associated with outcomes in this population. Subsequently, multivariable analysis was performed on all significant variables of univariate analysis. Multivariable logistic regression analysis was performed to evaluate the association of dyspnoea during exercise test and mitral valve surgery referral with relevant variables at rest and peak exercise (the variables that were significantly associated with dependent variable on univariate analysis). The receiver operator characteristic (ROC) curve was performed to determine which parameter is the best to predict exercise-induced dyspnoea and which one is the best to predict mitral valve surgery. The correlation between $VO_{2\ peak}$ and clinical, demographic, and echocardiographic parameters was investigated using Pearson correlation coefficients or Spearman coefficients, as appropriate. Multivariable linear regression analysis was used to identify determinants of relative VO_2 peak. The data were tested for multicollinearity using a collinearity diagnostic test by using the variance inflation factor (VIF). A VIF cut-off value of 5 was used for the multivariable model, and only variables with a VIF under 5 were included (153). Statistical analysis

was carried out using SPSS version 27.0 (SPSS Inc, Chicago, IL). A value of $P < 0.05$ was considered significant.

3.4 Result

3.4.1 Baseline study data

3.4.1.1 Baseline clinical characteristics

The clinical demographics of the patients investigated are presented in *Table 3.1*. This shows the majority of patients were male (68%) with a median age of 61 years. Twenty-six (27%) of patients were hypertensive and a small proportion of 10 (10%) patients had hyperlipidaemia.

Table 3.1 Baseline clinical characteristics of asymptomatic group

Variables	***Variables***		
Age, years	61 (IQR 49-71)	Heart rate, bpm	73 ± 14
Male, n (%)	66 (68)	AF, n (%)	3 (3)
Height, cm	173± 10	Beta Blocker, n (%)	24 (25)
Weight, kg	74± 15	ACE inhibitors, n (%)	12 (13)
Body mass index, kg/m^2	25 (IQR 22-26)	Diabetes, n (%)	2 (2)
Systolic BP, mmHg	137 (IQR 165-178)	Diuretics, n (%)	7 (7)
Diastolic BP, mmHg	79 ± 9	Warfarin, n (%)	2 (2)

Syncope, n (%)	1 (1)	Antiplatelet agent, n (%)	9 (9)
Hypertension, n (%)	26 (27)	Statin, n (%)	20 (21)
Overweight, n (%)	5 (5)	Amlodipine, n (%)	8 (8)
Smoking, n (%)	12 (13)	Anticoagulant, n (%)	8 (8)
Hyperlipidaemia, n (%)	10 (10)	ARBs, n (%)	3 (3)

IQR; inter-quartile range, AF; Atrial fibrillation, BP; blood pressure; ACE; Angiotensin-converting enzyme, ARBs; Angiotensin receptor blockers.

3.4.1.2 Baseline echocardiography

Baseline echocardiographic parameters are shown in *Table 3.2*. Overall, the left atrium was enlarged, left atrial volume was 89 ml (IQR 71-116). The left ventricle dimensions and volumes were in the upper normal range. Left ventricular volumes by RT3D were bigger than left ventricular volumes measured by 2D (LVEDV 151 ± 42 ml versus 143 ± 41 ml, LVESV 59 ± 18 ml versus 54 ±16 ml, p-value < 0.0001). Echocardiographic measures of systolic function (2D-LVEF, RT3D-LVEF, GLS and S' wave) were in the normal range. Quantification of mitral regurgitation showed an effective regurgitant orifice of 0.47 ± 0.27 cm^2 and regurgitant volume of 64 ± 38 ml.

Table 3.2 Baseline echocardiography parameters in the asymptomatic group

Variables		*Variables*	
LAD, cm	4.2 ± 0.8	RV basal, cm	3.8(IQR3.5-4.1)
LAD indexed, cm/m^2	2.2 ± 0.5	RV mid, cm	3.3 ± 0.6
LAA, cm^2	25 (IQR 20-30)	RA area, cm^2	16.5(IQR14-18)
LAV, ml	89 (IQR 71-116)	PASP, mmHg	17 (IQR 10-24)
LAV index, ml/cm^2	48 (IQR 39-63)	LV S', m/s	10 (IQR 8-12)
LVEDD, cm	5.5 ± 0.6	RV S', m/s	14 (IQR 12-17)
LVEDD index, cm/m^2	3 ± 0.4	TAPSE, mm	24 ± 5
LVESD, cm	3.4 ± 0.6	E/A ratio	1.5(IQR 1.2-1.8)
LVESD index, cm/m^2	1.8 ± 0.3	E wave, m/s	1 ± 0.3
LVEDV, ml	135 (IQR 110-157)	DT, ms	209 (IQR176-256)
LVEDV index, ml/cm^2	70 (IQR 61-85)	E' wave, m/s	11 ± 3
LVESV, ml	50 (IQR 39-63)	E/E' ratio	10 (IQR 8-12)
LVESV index, ml/cm^2	27 ± 8	GLS, %	-20 ± 3

LVEF, %	62 ± 5	Peak SLD	37 (IQR 31-49)
IVS, cm	0.9 ± 0.2	RT3D-LVEDV, ml	151 ± 42
LVPW, cm	1 ± 0.2	RT3D-LVESV, ml	59 ± 18
ERO, cm^2	0.47 ± 0.27	RT3D-LVEF, %	61 ± 5
R Vol, ml	64 ±38		

IQR; inter-quartile range, LA; left atrium, LAV; left atrial volume, LVEDD; left ventricular end-diastolic diameter, LVESD; left ventricular end-systolic diameter, LVEDV; left ventricular end-diastolic volume, LVESV; left ventricular end-systolic volume, LVEF ; left ventricle ejection fraction, IVS; interventricular septum , LVPW; left ventricle posterior wall, ERO; effective regurgitant orifice, R Vol; regurgitant volume, RV basal; right ventricle basal diameter, RV mid, right ventricle mid diameters, RV; right ventricle, PASP; pulmonary artery systolic pressure, S'; systolic longitudinal velocity, TAPSE; tricuspid annular plane systolic excursion, E/A; ratio of the early to late ventricular filling velocities, DT; deceleration time, E' early, passive filling of the left ventricle, E'; mitral annular early diastolic velocity, E/E'- ratio between early mitral inflow velocity and mitral annular early diastolic velocity, GLS; global longitudinal strain, RT3D; real time-three dimensional echo.

3.4.1.3 Cardiopulmonary exercise test measurements

Cardiopulmonary exercise test measurements are shown in *Table 3.3.* Mean RER was 1.2 ± 0.10. Relative $VO_{2\ peak}$ was 22.9 ± 6 ml/kg/min with a wide range (10.0 ml/kg/min to 41.4 ml/kg/min). The median and interquartile range of $VO_{2\ peak}$ was 83% (IQR 76% - 94%). Approximately half (50 (52%)) of the study population had a predicted $VO_{2\ peak}$ of less than 84%. Predicted $VO_{2\ peak}$ varied widely, from 54% to 153%. 18 (19%) of patients stopped exercise because of the development of dyspnoea, and 79 patients terminated the

exercise test due to general fatigue. There was no significant arrhythmia, syncope or death during the exercise test.

Table 3.3 Cardiopulmonary exercise parameters in the asymptomatic group

Variables	*(n=97)*
Workload, watts	145 ± 47
Time exercised, min:sec	9:43 (IQR 8:01 - 10:55)
$VO_{2\ peak}$, ml/kg	1683± 495
Relative $VO_{2\ Peak,}$ ml/kg/min	22.9 ± 6
Predicted $VO_{2\ Peak,}$ %	83 (IQR 76 - 94)
RER	1.2 ± 0.10
O2 pulse, ml/beats	11.8 ± 3
Predicted O2 pulse, %	98 ± 19
OUES, (ml/min O2)/ (L/min VE)	1887 ± 599
VE/VCO2 slope	27 (IQR 24 - 30)
VO2/WR slope	8.7 (IQR 7.6 - 9.7)

IQR; inter-quartile range, VO2; oxygen uptake, RER; raspatory exchange ratio, SBP; systolic blood pressure, VE; ventilation, VCO_2; carbon dioxide, O_2, oxygen, OUES; oxygen uptake efficiency slope, WR; work rate.

3.4.1.4 Rest and exercise echocardiography

The main echocardiographic, heart rate and blood pressure data at rest and during peak exercise (RER>1.1) are reported in *Table 3.4*. Most of the echocardiographic parameters at rest and during exercise were significantly different. However, LV end-diastolic diameter and volume did not change significantly on exercise compared to the rest, whether measured by 2D- or RT3D- echocardiography. Measures of LV systolic function (LVEF, RT3D-LVEF, GLS and S') significantly increased during exercise. Average left ventricle ejection fraction was approximately similar when it was measured by 2D- and RT3D- transthoracic echo. Both 2D- and RT3D- systolic volume significantly decreased (from 54 ± 16 ml, 58 ± 17 ml to 49 ± 17 ml, 51 ± 17 ml, p-value < 0.0001 respectively) during exercise resulting in an increase in exercise LVEF (66 ± 8 %, 66 ± 6%). In general, mean RT3D- LV diastolic volume was higher than mean 2D-LVEDV. Similarly, the observed average of RT3D-LVESV was higher than 2D-LVESV in both rest and during exercise (p-value < 0.0001). Estimated pulmonary artery systolic pressure (PASP) significantly increased during exercise from 18 ± 11 mmHg to 40 ± 19 mmHg, (p-value < 0.0001). 11(11%) patients had resting PASP ≥ 35 mmHg and 15 (16%) patients had a significant increase in PASP ≥60 mmHg during exercise.

Heart rate increased from 72 ± 14 beat/min at rest to 144 ± 22 beat/min at peak exercise, 68 (69%) patients reached ≥ 85% of target heart rate. Systolic blood pressure and diastolic

blood pressure also significantly increased during exercise test from 142 ±17 mmHg and 81 ± 10 mmHg to 196 ± 29 and 96 ±15 mmHg, respectively (p-value < 0.0001)

Table 3.4 Rest and exercise echocardiographic parameters in asymptomatic group

Variables	***Rest***	***Exercise***	***p-value***
LVEDD, cm	5.5 ± .6	5.5 ± .7	.155
LVESD, cm	3.4 ± .6	3.2 ± .6	**.000**
LVEDV, ml	142 ± 40	145 ± 42	.277
LVESV, ml	54 ± 16	49 ± 17	**.000**
LVEF, %	62 ± 5	66 ± 8	**.000**
PASP, mmHg	18 ± 11	40± 19	**.000**
LV S' average, m/s	8 ± 1.9	11 ± 2.4	**.000**
GLS average, %	-20 ± 3	-22 ± 4	**.000**
RT3D- LVEDV, ml	151 ± 42	147 ± 41	.169
RT3D- LVESV, ml	58 ± 17	51 ± 17	**.000**
RT3D-LVEF, %	61 ± 5	66 ± 6	**.000**
Systolic BP, mmHg	142 ±17	196 ± 29	**.000**

Diastolic BP, mmHg	81 ± 10	96 ±15	**.000**
Heart rate, beat/min	72 ± 14	144 ± 22	**.000**

LVEDD; left ventricular end-diastolic diameter, LVESD; left ventricular end-systolic diameter, LVEDV; left ventricular end-diastolic volume, LVESV; left ventricular end-systolic volume, LVEF; left ventricle ejection fraction, PASP; pulmonary artery systolic pressure, S'; systolic longitudinal velocity, GLS; global longitudinal strain, RT3D; real time three-dimensional echo, BP; blood pressure.

3.4.2 Comprehensive analysis of exercise-induced dyspnoea

Asymptomatic patients were stratified into two groups according to the reason for stopping the exercise test (*Table 3.5*):

1. Exhaustion group (General fatigue), 2. Dyspnoea group **(**shortness of breath)

The systolic blood pressure at rest was higher in the dyspnoea group than in the exhaustion group (151 ± 20 mmHg versus 141 ± 16 mmHg, p-value = 0.052). Left atrial volume index was significantly larger in patients who dyspnoea during exercise compared to patients who did not (71 ± 30 ml/m^2 vs 51 ± 23 ml/m^2, p-value = 0.006). Left ventricle dimensions and systolic function (EF, S' velocity and GLS) were comparable in both groups. Left ventricle diastolic and systolic volumes were not significantly different. In addition, the severity of mitral regurgitation was similar in the two groups.

Patients with exercise-induced dyspnoea had significantly higher pulmonary artery systolic pressure at rest and during exercise than the exhaustion group (rest PASP 29 ±14 mmHg versus 16 ±9 mmHg, p-value < 0.0001 and exercise PASP 53 ± 24 mmHg versus 37 ± 16 mmHg, p-value = 0.003) respectively. The proportion of patients with rest PASP ≥ 35 mmHg was significantly higher in the dyspnoea group than in the exhaustion group

(33% versus 6%; p-value = 0.001), in addition, the dyspnoea group had higher exercise PASP ≥ 60 mmHg than the exhaustion group (39% versus 10%; p-value = 0.002). Observed values of the most cardiopulmonary exercise test parameters were comparable in both groups, except VE/VCO_2 slope. Patients who developed symptoms during exercise had higher VE/VCO_2 than patients who stopped the exercise because of general fatigue (30 ± 6 versus 27 ± 5, p-value = 0.037). 10 out of 18 (56%) of patients who developed severe shortness of breath during exercise had reduced predicted $VO_{2\ peak}$, compared to 40 out of 79 (51%) patients who stopped the exercise test because of general fatigue. There was no association between dyspnoea during exercise and reduced functional capacity ($VO_{2\ peak}$ < 80%), (p-value = 0.706).

Table 3.5 Echocardiographic and CPET data according to the reason for stopping the exercise test

Variables	Exhaustion group (General fatigue) (n=79, 81%)	Dyspnoea group (Shortness of breath) (n=18, 19%)	***p-value***
Clinical Characteristics			
Age, years	58±17	62±15	.398
Sex, female, n (%)	26 (32)	5 (28)	.673
BMI, kg/m^2	25±4	24±3	.652
Systolic BP, mmHg	141±16	151±20	**.052**

Diastolic BP, mmHg	80±10	84±12	.561
HR, beat/min	74±13	68±16	.119
Hypertension, n (%)	18 (23)	8 (44)	.066
Hypercholesteremia, n (%)	6 (8)	4 (22)	.066
Beta blocker, n (%)	18 (23)	6 (33)	.349
ACE, n (%)	8 (10)	4 (22)	.160
Rest Echocardiography Parameters			
LAD, cm	4.1 ± 0.7	4.4 ± 0.9	.208
LAV indexed, ml/m^2	51 ± 23	71 ± 30	**.006**
LVEDD, cm	5.4 ± 0.7	5.5 ± 0.7	.994
LVESD, cm	3.4 ± 0.6	3.5 ± 0.5	.700
LVEDV, ml	137 ± 41	151 ± 39	.084
LVESV, ml	51 ± 16	54 ± 19	.492
LVEF (%)	63 ± 5	64 ± 6	.167
RT3D- LVEDV, ml	150 ± 43	157 ± 42	.575
RT3D- LVESV, ml	59 ± 18	62 ± 20	.584

RT3D-LVEF, %	61 ± 5	61 ± 6	.920
GLS, %	-20 ± 3	-21 ± 2	.595
LV S', m/s	10.1 ± 3	9.8 ± 3	.722
PASP, mmHg	17 ± 10	29 ± 14	**.000**
ERO, mm^2	0.47 ± 0.26	0.49 ± 0.36	.963
Exercise Echocardiography Parameters			
$PASP_{peak}$, mmHg	37 ± 16	53 ± 24	**.005**
LV S'_{peak} velocity average	11 ± 2.3	10.9 ± 2.7	**.**691
LV-GLS_{peak}, %	-22 ± 4	-21 ± 4	.698
Systolic BP_{peak}, mmHg	198 ± 28	188 ± 33	.371
Diastolic BP_{peak}, mmHg	96 ± 14	95 ± 17	.931
Predicted HR_{peak}, %	88 ± 11	91 ± 19	.892
Workload, watts	147 ± 46	131 ± 52	.192
Time exercised, min:sec	9:52 ± 2:26	8:39 ± 2:22	.069
$VO_{2\ peak}$, ml/kg/min	23 ± 6	21 ± 5	.114
Predicted $VO_{2\ peak}$, %	87 ± 17	81 ± 14	.503

Peak RER	1.2 ± 0.1	1.2 ± 0.1	**.**150
VE/VCO2 slope	27 ± 5	30 ± 6	**.037**
O_2 pulse, ml/beats	12 ± 3	11 ± 3	.247
Predicted O_2 pulse, %	99 ± 18	96 ± 21	.563
OUES, (ml/min O_2)/ (L/min VE)	1940 ± 601	1647 ± 546	.067
VO_2/WR slope	8.7 ± 1.8	8.2 ± 1.5	.193

Exhaustion group; patients who stopped the exercise test due to general fatigue, Dyspnoea group; patients who stopped the exercise test due to severe shortness of breath, BMI; body mass index, ACE; Angiotensin-converting enzyme, BP; blood pressure, HR; heart rate, LAD; left atrium diameter, LAA; left atrial area, LAV; left atrial volume, LAVI; left atrial volume indexed, LVEDD; left ventricular end-diastolic diameter, LVESD; left ventricular end-systolic diameter, LVEDV; left ventricular end-diastolic volume, LVESV; left ventricular end-systolic volume, LVEF ; left ventricle ejection fraction, RT3D; real time three dimensional echo, GLS; global longitudinal strain, S'; left ventricle systolic longitudinal velocity, PASP; pulmonary artery systolic pressure, TAPSE; tricuspid annular plane systolic excursion, ERO; effective regurgitant orifice, peak; measurement at peak exercise, VO_2; oxygen uptake, RER; raspatory exchange ratio, VE; ventilation, VCO_2; carbon dioxide, O2; oxygen, OUES; oxygen uptake efficiency slope, WR; work rate.

3.4.2.1 Determinants of dyspnoea during exercise

Univariable and multivariable logistic regression analyses were performed to determine the association between dyspnoea during exercise tests and its potential predictors. Univariable logistic regression analysis is shown in *Table 3.6.* LAV index (Wald statistic 6.84, P-value = 0.009), rest PASP (Wald statistic 13.681, P-value < 0.0001), exercise

PASP (Wald statistic 7.52, P-value = 0.006) and VE/VCO_2 (Wald statistic 5.0, P-value = 0.025) were significantly associated with dyspnoea during the exercise test. Other parameters such as index LV dimensions, 2D-LVEF, RT3D-LVEF, GLS and $VO_{2\,peak}$ had no significant association.

In multivariable logistic regression analysis, we included all potential predictor variables from the univariable analysis. Higher rest PASP (Wald statistic 6.170, P-value = 0.013) was the only independent significant parameter associated with dyspnoea during exercise. The logistic regression model was statistically significant, $\chi 2(4) = 21.748$, p-value < 0.0001. The model explained 34% (Nagelkerke R^2) of the variance and correctly classified 86% of cases. The Hosmer and Lemeshow test showed that the model was a good fit to the data as p-value = 0.223 (> 0.05).

Another multivariate model for only the rest predictor parameters including rest PASP and LAV index was done to test the predictive accuracy of the model, confirming that rest PASP was the strongest predictor of dyspnoea during exercise (Wald statistic 11.093, P-value = 0.001). This model was statistically significant, $\chi 2(2) = 20.169$, $p < 0.0001$. explained 32% (Nagelkerke R^2) of the variance and correctly classified 85% of cases. The two models of multivariate regression analysis are shown in *Table 3.7*. The data in the multivariate regression analysis met the assumption that multicollinearity was not a concern, VIF values were less than 2.

Table 3.6 Univariable logistic regression analysis for variables associated with exercise induced dyspnoea

Variable	**Univariable**

	Wald statistic	Odds ratio (95% CI)	P value
Age, years	0.703	1.02 (.98-1.05)	.402
Sex, Female	0.078	0.85 (.27-2.67)	.780
BMI	0.152	0.97 (.83-1.14)	.697
HR	2.20	0.97 (.93-1.01)	.138
Systolic BP	0.750	1.02 (.981-1.050)	.386
Diastolic BP	1.00	1.03 (.97 -1.10)	.318
Hypertension	2.279	0.43 (.143-1.29)	.131
Hypercholesterolaemia	3.44	0.27 (.066-1.08)	.064
Beta blocker	1.145	0.54 (.18-1.67)	.285
ACE	2.166	0.37 (.096-1.40)	.141
LVEDD, cm	0.13	1.16 (.52-2.57)	.716
LVESD, cm	0.85	1.58 (.60-4.21)	.356
2D-LVEF, %	0.67	1.04 (.95-1.15)	.412
RT3D-LVEF, %	0.01	1.01 (.90-1.12)	.919

GLS, %	0.29	0.95 (.79-1.44)	.590
LAV $_{\text{index, ml/cm}^2}$	6.84	1.03 (1.01-1.05)	**.009**
Rest PASP$_{\text{, mmHg}}$	13.681	1.107 (1.05-1.19)	**.000**
TAPSE	2.01	0.915 (.81-1.03)	.157
Peak PASP$_{\text{, mmHg}}$	7.52	1.04 (1.04-1.01)	**.006**
% $VO_{2\ peak}$	2.11	0.97 (.94-1.01)	.146
OUES	3.20	1.00 (.998-1.00)	.074
$VE/VCO_{2\ slope}$	5.03	1.12 (1.02-1.24)	**.025**
% $O_{2\ pulse}$	.332	0.99 (.97-1.02)	.564

BMI; body mass index, ACE; Angiotensin-converting enzyme, BP; blood pressure, LAV index; left atrial volume indexed, LVEDD; left ventricular end-diastolic diameter, LVESD; left ventricular end-systolic diameter, LVEF ; left ventricle ejection fraction, RT3D; real time three dimensional echo, GLS; global longitudinal strain, PASP; pulmonary artery systolic pressure, TAPSE; tricuspid annular plane systolic excursion, VO_2; oxygen uptake, VE; ventilation, VCO_2; carbon dioxide, O_2; oxygen, OUES; oxygen uptake efficiency slope.

Table 3.7 Multivariable logistic regression analysis for variables associated with exercise induced dyspnoea

Variables	**Multivariable**

	Wald statistic	Odds ratio (95% CI)	P value
Model 1			
Rest PASP, mmHg	6.170	1.093 (1.019-1.172)	**.013**
Peak PASP, mmHg	0.055	1.005 (.966-1.045)	.815
LAV index, ml/cm^2	1.547	1.014(.992-1.037)	.214
VE/VCO_2 slope	1.338	1.070 (.954-1.201)	.247
Model 2			
Rest PASP, mmHg	11.093	1.104 (1.041-1.169)	**.001**
LAV index, ml/cm^2	1.437	1.1014 (.991-1.036)	.231

PASP; pulmonary artery systolic pressure, LAV; left atrium volume, VE; ventilation, VCO_2; carbon dioxide.

3.4.2.2 Predication of exercise-induced dyspnoea

The receiver-operator curve analysis was performed for predicting exercise induce dyspnoea on basis of rest and exercise PASP, LAV index and VE/VCO_2 slope, which were significantly associated with developing dyspnoea during exercise. The ROC curves are displayed in *Figure 3.1*. The area under the curve (AUC) for rest PASP; AUC = 0.792, (95% confidence interval (CI): 0.681- 0.903), for exercise PASP, AUC = 0.710, (95% CI:

0.558- 0.863), for LAV index; AUC = 0.695, (95% CI: 0.551- 0.838), for VE/VCO_2 was AUC = 0.660, (95% CI: 0.508 - 0.812), (*Table 3.8).* Rest PASP was superior to the predictive association with exercise-induced dyspnoea, over exercise PASP, LAV index and VE/VCO_2 slope. The optimal cut-off point derived from the ROC curve analysis was 24 mmHg for rest PASP, with a sensitivity of 59 % and specificity of 82%, for exercise PASP was 47 mmHg with a sensitivity of 71 % and specificity of 70%, for LAV index was 53 ml/m^2 with a sensitivity of 65 % and specificity of 68%, and for VE/VCO2 slope was 29 with a sensitivity of 59 % and specificity of 73%.

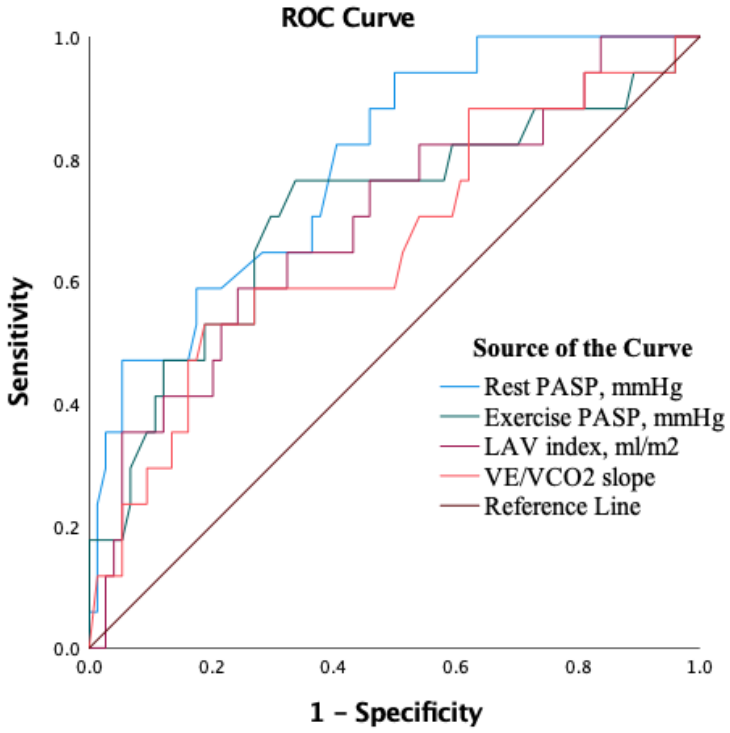


Table 3.8 The area under curve of rest and exercise PASP, LAV index and VE/VCO_2 slope for predicting dyspnoea during exercise.

Figure 3.1 Receiver operating characteristic curves of rest and exercise PASP, LAV index and VE/VCO_2 slope for detecting dyspnoea during exercise.

	AUC	95% CI	p-value
Rest PASP, mmHg	.792	.681-.903	.000
Exercise PASP, mmHg	.710	.558-.863	.007
LAV index, ml/m^2	.695	.551-.838	.013
$VE/VCO_{2\ slope}$	.660	.508-.812	.040

PASP; pulmonary artery systolic pressure, LAV; left atrium volume, VE; ventilation, VCO_2; carbon dioxide.

3.4.3 Follow up

On follow-up, 53 patients completed baseline and follow-up stress echocardiography with cardiopulmonary exercise testing. 44 patients did not have a follow-up stress echocardiogram performed due to undergoing surgery (27 patients), loss to follow-up (4 patients) or withdrawal from the study (13 patients).

Of the 53 patients, eight (15%) patients stopped the exercise test because of dyspnoea (five participants stopped the exercise test because of dyspnoea during the two visits and three patients stopped the exercise test because of dyspnoea at the follow-up visit). No patients suffered from chest pain or syncope during or post-exercise.

Baseline demographics for all follow-up patients are presented in *Table 3.9.* The median age was 61 (IQR 47-71) years, and the majority of the group were male (64%).

Table 3.9 Baseline characteristics of follow-up study sample (visit 2)

Variables	**(n=53)**	**Variables**	**(n=53)**
Age, years	61 (IQR 47-71)	Diabetes, n (%)	1 (2)
Female, n (%)	19 (36)	Smoking, n (%)	5(10)
Height, cm	173± 10	Beta Blocker, n (%)	12 (23)
Weight, kg	74± 15	ACE inhibitors, n (%)	5 (10)

BMI, kg/m2	24.8 ± 4	Diuretics, n (%)	2 (4)
HR, bpm	67 (IQR 61-79)	Warfarin, n (%)	0 (0)
AF, n (%)	1 (2)	Antiplatelet agent, n (%)	6 (12)
Systolic BP, mmHg	132 (IQR 126-146)	Statin, n (%)	11 (21)
Diastolic BP, mmHg	82 ± 12	Amlodipine, n (%)	3 (6)
Hypertension, n (%)	12 (23)	Anticoagulant, n (%)	4 (8)
Overweight, n (%)	2 (4)	ARBs, n (%)	1 (4)
Hypercholesteremia, n (%)	1 (2)		

BMI; body mass index, HR; heart rate, AF; Atrial fibrillation, BP; blood pressure; ACE; Angiotensin-converting enzyme, ARBs; Angiotensin receptor blockers.

3.4.3.1 Rest echocardiography parameters

All echocardiography, exercise and CPET parameters values for baseline visit versus follow-up are presented in *Table 3.10.*

Left ventricle volumes significantly increased during follow up, 2D- LVEDV (136 ± 35 ml at baseline and 146 ± 41 ml at follow up; p-value = 0.002), 2D-LVESV (51 ± 16 ml at baseline and 56 ± 20 ml at follow up visit; p-value = 0.001), RT3D-LVEDV (142 ± 36 ml at baseline and 156 ± 42 ml at follow up; p-value = 0.001) and 3D-LVESV (55 ± 16 ml at baseline and 63 ± 19 ml at follow up visit; p-value < 0.0001). Left ventricle dimensions, LVEF measured by 2D and RT3D, GLS and PASP were similar in all visits.

3.4.3.2 Exercise echocardiography parameters

Exercise LV volumes by RT3D were significantly larger in the follow-up visit compared to the baseline visit. Exercise 2D-LVEDV was also larger at the follow-up visit than at the baseline visit, however, there was no change in 2D-LVESV between the two visits. Exercise LVEF by 2D and RT3D were similar in all visits. Exercise GLS was lower in the follow up visit than baseline visit (-22 ± 3 % versus -21 ± 3 %, p-value = 0.008). In contrast, the mean of S' velocity was higher during the follow-up visit than baseline visit (11.7± 2.3 m/s versus 11 ± 2.5 m/s, p-value = 0.008). Exercise PASP did not differ between the two visits.

3.4.3.3 Cardiopulmonary exercise test parameters

The workload and exercise times were slightly decreased during follow-up visits but not significant (p-value > 0.05). Predicted $VO_{2\ peak}$ was comparable in all visits, $VO_{2\ peak}$ (ml/kg/min) decreased significantly at follow up visit (24 ± 6 ml/kg/min versus 23 ± 6 ml/kg/min; p-value = 0.022). The average VE/VCO_2 slope was higher at the follow-up visit than at the baseline visit (27 ± 4 versus 28 ± 4; p-value = 0.046). Other cardiopulmonary exercise test parameters did not differ between the two visits.

Table 3.10 Echocardiographic parameters of visit one versus visit two of asymptomatic group.

Variable	**Baseline visit**	**Follow up visit**	***p-value***
LVEDD, cm	5.5 ± .6	5.5 ± .7	.915

LVESD, cm	3.4 ± .6	3.3 ± .7	.199
LVEDV, ml	136 ± 35	146± 41	**.002**
LVESV, ml	51 ± 16	56 ± 20	**.001**
LVEF (%)	63 ± 6	62 ± 6	.770
PASP, mmHg	17 ± 9	18 ± 11	.819
LV S' velocity	8 ± 2	8.5 ± 2	**.027**
LV-GLS, %	-20 ± 2	-21 ± 3	.124
RT3D- LVEDV, ml	142 ± 36	156 ± 42	**.001**
RT3D- LVESV, ml	55 ± 16	63 ± 19	**.000**
RT3D-LVEF, %	61 ± 4	60 ± 4	.065
Systolic BP, mmHg	140 ±14	138 ± 23	.416
Diastolic BP, mmHg	80 ± 11	82 ± 12	.246
Heart rate, beat/min	72 ± 13	70 ± 13	.375
Stress echo			
LVEDD $_{peak}$, cm	5.4 ± .8	5.4 ± .6	.862
LVESD $_{peak}$, cm	3.1 ± .7	3.0 ± .7	.363

LVEDV $_{peak}$, ml	142 ± 39	152 ± 41	**.008**
LVESV $_{peak}$, ml	47 ± 17	48 ± 16	.484
LVEF $_{peak}$ (%)	67 ± 7	68 ± 6	.291
PASP $_{peak}$, mmHg	44 ± 18	45± 20	.767
LV S' velocity $_{peak,}$ m/s	11 ± 2.5	11.7± 2.3	**.009**
LV-GLS $_{peak}$, %	-22 ± 3	-21 ± 3	**.003**
RT3D- LVEDV $_{peak}$, ml	147 ± 40	163 ± 40	**.000**
RT3D- LVESV $_{peak}$, ml	52 ± 17	56 ± 16	**.011**
RT3D-LVEF $_{peak}$, %	65 ± 5	65 ± 5	.619
Systolic BP $_{peak}$, mmHg	194± 29	194 ± 23	.931
Diastolic BP $_{peak}$, mmHg	96 ±17	93 ± 14	.308
Heart rate $_{peak}$, beat/min	145 ± 21	141 ± 22	.488
Heart rate max, %	88 ± 11	88 ± 11	.922
CPEX			
Workload	146 ± 46	142 ± 46	.070
Time exercised, min:sec	9:32± 2:11	9:20 ± 1:55	.278

$VO_{2\ peak}$, ml/min	1710 ± 505	1657 ± 492	.067
$VO_{2\ peak}$, ml/kg/min	24 ± 6	23 ± 6	**.022**
predicted $VO_{2\ peak}$/kg, %	88 ± 14	87 ± 15	.568
RER_{peak}	1.2 ± .1	1.4 ± 1.3	.323
VE/VCO_2 slope	27 ± 4	28 ± 4	**.050**
O_2 pulse, ml/beats	12 ± 3	12 ± 3	.484
Predicted O_2 pulse, %	101 ±14	100 ± 17	.663
OUES,	1955 ± 603	1883 ± 527	.069
VO_2/WR slope	8.6 ± 1.6	9 ± 1.5	.205

LAD; left atrium diameter, LAA; left atrial area, LAV; left atrial volume, LAVI; left atrial volume indexed, LVEDD; left ventricular end-diastolic diameter, LVESD; left ventricular end-systolic diameter, LVEDV; left ventricular end-diastolic volume, LVESV; left ventricular end-systolic volume, LVEF ; left ventricle ejection fraction, RT3D; real time three dimensional echo, GLS; global longitudinal strain, S'; left ventricle systolic longitudinal velocity, PASP; pulmonary artery systolic pressure, BP; blood pressure, $_{peak}$; measurement at peak exercise, VO_2; oxygen uptake, RER; raspatory exchange ratio, VE; ventilation, VCO_2; carbon dioxide, O_2; oxygen, OUES; oxygen uptake efficiency slope, WR; work rate,.

3.4.4 Comprehensive analysis of functional capacity

Of the 53 patients undergoing repeat stress echocardiography, 23 (43%) patients had reduced functional capacity (predicted $VO_{2\ peak}$ < 84%). Among the 23, 7 (30%) patients had normal functional capacity at the baseline visit.

The average $VO_{2\ peak}$ significantly reduced from 24 ± 6 ml/kg/min at the baseline visit to 23 ± 6 ml/min/kg at the follow-up visit (p-value = 0.022). During the baseline visit, 22% of the patients with impaired functional exercise stopped the test because of dyspnoea and a similar percentage during the follow-up visit (20%). No association was found between dyspnoea and functional capacity in both visits.

A comparison between patients with normal and reduced functional capacity of the last visit and a correlation to relative peak VO_2 (ml/kg/min) are shown in *Table 3.11*. Baseline visit data were used for the comparison to find a potential predictor of functional capacity.

Clinical characteristics and all echocardiographic primary parameters at rest and during exercise showed no significant difference.

Cardiopulmonary exercise parameters, RER, exercise systolic and diastolic blood pressure and maximum heart rate were not different between patients with normal and reduced functional capacity. Predicted O_2 pulse was higher in patients with normal functional capacity than in patients with reduced functional capacity (105 ±15 % versus 94 ± 12 %; p-value = 0.006). There was a positive $VO_{2\ peak}$ correlation with workload, O_2 pulse, OUES, VO_2/WR slope, maximum heart rate during exercise and systolic blood pressure and negative correlation with VE/VCO_2 slope.

Table 3.11 Clinical characteristics and rest and exercise echocardiography of the follow -up group according to the functional capacity.

Variable	Normal functional capacity (n= 30)	Reduced functional capacity (n= 23)	p-value	Correlation with $VO_{2\ peak,}$ ml/kg/min
Age, year	60±17	55±17	.308	**-.545***
Sex, male, n (%)	18 (60)	16 (69)	.472	.472
BMI, kg/m^2	24±3	25±3	.555	-.240
HTN, n (%)	5(17)	7(30)	.235	-.228
Hypercholesteraemia(%)	0	1(4)	.249	.016
Beta blocker, n (%)	5(17)	7(30)	.235	-.269
ACE inhibitors, n (%)	1(3)	4(17)	.083	-.129
LAA, cm^2	26 ±7	25 ±8	.415	-.087
LAV index, ml/m^2	54±19	48±26	.121	-.096
LVEDD, cm	5.5 ± .7	5.5 ± .7	.353	.254
LVESD, cm	3.3 ± .6	3.4 ± .6	.242	.010
LVEDV, ml	133± 33	133± 37	.648	**.338**§
LVESV, ml	51 ± 15	50 ± 18	.352	**.329**§

LVEF (%)	62 ± 5	63 ± 6	.394	-.179
PASP, mmHg	18 ± 10	16 ± 10	.458	-.525
LV S' velocity, m/s	8.2 ± 2	7.7 ± 2	.610	.381*
LV-GLS, %	-20 ± 2	-20 ± 2	.962	.108
3D- LVEDV, ml	145 ± 35	141 ± 38	.707	.236
3D- LVESV, ml	56 ± 16	56 ± 17	.997	.254
3D-LVEF, %	62 ± 5	61 ± 4	.438	-.150
ERO, mm^2	.43 ± .26	.40 ±.19	.613	-.086
Systolic BP, mmHg	141 ±14	138 ± 13	.401	.055
Diastolic BP, mmHg	78 ± 11	79 ± 12	.845	.104
Heart rate, beat/min	69 ± 11	75 ± 15	.375	.013
Stress echo				
$LVEDD_{peak}$, cm	5.4 ± .7	5.4 ± .8	.913	.176
$LVESD_{peak}$, cm	3.2 ± .6	3.1 ± .8	.242	**.275§**
$LVEDV_{peak}$, ml	144 ± 39	140 ± 40	.756	.255
$LVESV_{peak}$, ml	48 ± 15	46 ± 20	.352	**.413***

LVEF $_{peak}$ (%)	66 ± 7	67 ± 7	.519	-.163
PASP $_{peak}$, mmHg	39 ± 18	39 ± 19	.852	-.117
LV S' velocity $_{peak,}$ m/s	11.3 ± 2	10.5± 3	.923	**.363***
LV-GLS $_{peak}$, %	-22 ± 3	-23 ± 4	.328	.167
3D- LVEDV $_{peak}$, ml	144 ± 41	144 ± 40	.553	.220
3D- LVESV $_{peak}$, ml	48 ± 16	52 ± 20	.968	.148
3D-LVEF $_{peak}$, %	66 ± 5	65 ± 4	.310	.010
CPEX				
Workload	148 ± 49	142 ± 41	.650	**.737***
Time exercised, min:sec	09:30± 2:0	09:38 ± 2:26	.822	.233
Systolic BP $_{peak}$, mmHg	198 ± 33	191 ± 23	.348	**.275**[§]
Diastolic BP $_{peak}$, mmHg	97 ±17	93 ± 16	.398	.159
Heart rate $_{peak}$, beat/min	142 ± 22	146 ± 20	.514	**.513***
% max HR	88 ± 12	88 ± 12	.977	.111
$VO_{2\ peak}$, ml/min	1711± 524	1705 ± 475	.962	**.663***
$VO_{2\ peak}$, ml/kg/min	25 ± 7	23 ± 4	.517	**.870***

predicted $VO_{2\ peak}$/kg, %	93 ± 14	80 ± 8	**.000**	.229
RER_{peak}	1.2 ± .1	1.2 ± .1	.846	-.065
VE/VCO_2 slope	26 ± 4	27 ± 4	.430	**-.547***
O_2 pulse, ml/beats	12 ± 3	12 ± 3	.657	**.456***
Predicted O_2 pulse, %	105 ±15	94 ± 12	**.006**	-.021
OUES,	1957± 591	1964 ± 663	.998	**.507***
VO_2/WR slope	8.7 ± 1.6	8.5 ± 1.6	.646	**.352***

*Correlation with $VO_{2\ peak}$ P<0.01; § correlation with VO2 peak P<0.05; LAD; left atrium diameter, LAA; left atrial area, LAV; left atrial volume, LAVI; left atrial volume indexed, LVEDD; left ventricular end-diastolic diameter, LVESD; left ventricular end-systolic diameter, LVEDV; left ventricular end-diastolic volume, LVESV; left ventricular end-systolic volume, LVEF ; left ventricle ejection fraction, RT3D; real time three dimensional echo, GLS; global longitudinal strain, S'; left ventricle systolic longitudinal velocity, PASP; pulmonary artery systolic pressure, BP; blood pressure, HR; heart rate, $_{peak}$; measurement at peak exercise, VO_2; oxygen uptake, RER; raspatory exchange ratio, VE; ventilation, VCO_2; carbon dioxide, O_2; oxygen, OUES; oxygen uptake efficiency slope, WR; work rate.

3.4.4.1 Determinants of functional capacity

Relative VO_2 peak (ml/kg/min) was negatively correlated with age (rho= -0.545, p-value < 0.0001). The correlation between $VO_{2\ peak}$ and left ventricle S' wave velocity was positively significant at rest and during exercise (r = 0.381; p-value = 0.005 and r = 0.363, p-value = 0.008). Left ventricle end-diastolic and end-systolic volumes were correlated with $VO_{2\ peak}$ (r= 0.319; p-value = 0.021 and r = 0.344, p-value = 0.012). Moreover,

exercise left ventricle end-systolic diameter and volume was correlated with $VO_{2\ peak}$. Other echocardiographic parameters had no correlation with functional capacity.

Univariable and multivariable logistic regression analyses were performed with relative $VO_{2\ peak}$ as the dependent variable to determine the association between functional capacity and echocardiography potential predictors.

On univariable linear regression, reduced $VO_{2\ peak\ (ml/kg/min)}$ was associated with older age, lower rest and exercise S' velocity, and smaller LV systolic and diastolic volume. However, LVESV and LVEDV were highly correlated with each other, (LVEDV, VIF = 6.52; LVESV, VIF = 6.02). after removing the correlated variable from the model, age was the only significant independent predictor for VO_2 peak. Table 3.12 summarises linear regression analyses with $VO_{2\ peak}$ as the dependent variable.

Table 3.12 Linear regression analysis with $VO_{2\ peak\ (ml/min/kg)}$ as the dependent variable

Variables	Univariate			Multivariate		
	B-coefficient	95% CI	P value	B-coefficient	95% CI	P value
Age, years	-0.196	-0.28 to -0.11	**.000**	-0.162	-0.26 to -0.07	**.001**
Rest S' velocity, m/s	1.204	0.38 to 2.03	**.005**	0.123	-0.93 to 1.17	.815
Exercise S' velocity, m/s	0.946	0.26 to 1.64	**.003**	0.421	-0.40 to 1.24	.308

LVDV, ml	0.040	0.01 to 0.07	**.006**	0.012	-0.08 to 0.10	.798
LVSV, ml	0.121	0.02 to 0.23	**.025**	0.049	-0.15 to 0.25	.620

CI; confidence interval, LVEDV; left ventricular end-diastolic volume, LVESV; left ventricular end-systolic volume, S'; left ventricle systolic longitudinal velocity

3.4.5 Cardiac surgery

During follow-up, (38%) 37 patients were referred for mitral valve surgery. Reasons for mitral valve surgery were mitral valve repairable in 8 patients, symptoms in 23 patients, LV dilatation/impairment in 4 patients, and new atrial fibrillation in 2 patients.

Clinical demographics stratified by referral to cardiac surgery from the asymptomatic cohort are presented in *Table 3.13.* Body mass index was higher in patients referred to cardiac surgery than in patients under follow-up (23.9 ± 3 kg/m^2 versus 25.5 ± 3 kg/m^2, p-value = 0.038) respectively. Eight (22%) of the mitral valve surgery patients had hypercholesterolaemia versus one in the follow-up group. Other clinical variables did not differ between the two groups.

Table 3.13 Clinical characteristics in the asymptomatic cohort stratified by referral to cardiac surgery

Variable	(Follow-up group) (n=60, 62%)	(Surgery group) (n=37, 38%)	*p-value*
Age, year	58 ± 18	60 ± 14	ns

Sex, Female, n (%)	23 (38)	8(22)	ns
BMI, kg/m^2	23.9 ± 3	25.5 ± 3	ns
Systolic BP, mmHg	140 ±16	141 ± 15	ns
Diastolic BP, mmHg	79 ± 10	79 ± 9	ns
Heart rate, beat/min	73 ± 14	73 ± 15	ns
Dyspnea during exercise, n (%)	8 (13)	10 (27)	ns
Abnormal functional capacity, n (%)	31(52)	19 (52)	ns
AF, n (%)	0 (0)	3 (8)	ns
Hypertension, n (%)	16 (27)	10 (27)	ns
Hypercholesterolaemia, n (%)	2 (3)	8 (22)	**.004**
Diabetes, n (%)	1 (2)	1 (3)	ns
Smoker, n (%)	6 (10)	6 (16)	ns
Beta blocker, n (%)	15 (25)	9 (24)	ns
ACE inhibitor, n (%)	9 (15)	3 (8)	ns
Warfarin, n (%)	0 (0)	2 (5)	ns
Diuretics, n (%)	3 (5)	4 (11)	ns

Anticoagulants, n (%)	2 (3)	6 (16)	**.025**
ARBs, n (%)	0 (0)	3(8)	**.025**

ns; not significant, BP; blood pressure, AF; Atrial fibrillation, VO2; oxygen uptake, ACE; Angiotensin-converting enzyme, ARBs; Angiotensin receptor blockers.

A comparison of echocardiographic parameters at rest and during exercise and cardiopulmonary exercise test parameters between patients referred to mitral valve surgery versus patients under follow-up is shown in *Table 3.14.*

3.4.5.1 Rest echocardiography parameters

Patients referred to surgery had larger left ventricle volumes. Left ventricular end-diastolic and end-systolic volumes for surgery group versus follow-up group were as follows: 2D-LVEDV (160 ± 41ml versus 126 ± 34 ml, p-value < 0.0001), RT3D-LVEDV (174 ± 40 ml versus 137 ± 38 ml, p-value < 0.0001), 2D-LVESV (57 ± 17 ml versus 48 ± 16 ml, p-value = 0.006), and RT3D-LVESV (68 ± 17 ml versus 54 ± 17 ml, p-value < 0.0001). The surgical group had larger left ventricle end-systolic dimension than the follow-up group (3.5 ± 0.5 cm versus 3.3 ± 0.6 cm, p-value = 0.008). However, left ventricle end-diastolic dimension did not differ between the two groups. Left ventricle ejection fraction by 2D and RT3D at rest were comparable in both groups. Other systolic function measures such as GLS and S' wave velocity did not differ between groups. Left atrial area and volume were significantly higher in the surgery group than in follow-up group (LAV= 121 ± 55 ml vs. 88 ± 37 ml, p-value = 0.001). Observed average value of E wave velocity was higher in the surgery group than in the follow-up group (1.1 ± 0.3 m/s versus 0.9 ± 0.3 m/s, p-value = 0.005). Patients referred to surgery had a higher mean

value of effective regurgitant orifice than the follow-up group (63 ± 29 mm^2 versus 38.3 ± 22 mm^2, p-value < 0.0001).

3.4.5.2 Exercise echocardiography and CPET parameters

During exercise, left ventricle end-diastolic volumes and dimensions were the only echocardiographic variables with a significant difference between the two groups. Exercise 2D left ventricle end-diastolic volume was significantly higher in the surgery group than the follow-up group, 2D left ventricle end-systolic volume, however, did not differ between the two groups during exercise. Exercise left ventricle ejection fraction was slightly higher by 2D and RT3D in patients referred to surgery but without significant difference. Exercise RT3D left ventricle volumes were greater in the surgery group than the follow-up group, however, a significant difference was only in RT3D left ventricle end-diastolic volume not in end-systolic volume.

Left ventricle GLS and S' were similar between the groups during exercise. No difference was found between the two groups regarding blood pressure and heart rate during exercise. The observed average values of all cardiopulmonary exercise test variables were similar for both groups.

Table 3.14 Rest and exercise echocardiography and cardiopulmonary exercise test results stratified by referral to surgery.

Variable	**(Follow-up group) (n=55, 62%)**	**(Surgery group) (n=37, 39%)**	**p-value**
Rest Echocardiography			

LVEDD, cm	5.3 ± 0.7	5.6 ± 0.6	ns
LVESD, cm	3.3 ± 0.6	3.5 ± 0.5	**.008**
LVEDV, ml	126 ± 34	160± 41	**.000**
LVESV, ml	48 ± 16	57 ± 17	**.006**
LVEF (%)	62 ± 5	65 ± 6	ns
LAD, cm	4.0 ± 0.7	4.4 ± 0.8	**.002**
LAA, cm^2	25 ± 7	29 ± 9	**.002**
LAV, ml	88 ± 37	121 ± 55	**.001**
LAV index, ml/m^2	49 ± 20	63 ± 31	**.009**
PASP, mmHg	20± 10	21 ± 11	ns
LV S' velocity, average	10 ± 2.8	10 ± 2.6	ns
LV-GLS, %	-20 ± 3	-20 ± 3	ns
RT3D- LVEDV, ml	137 ± 38	174 ± 40	**.000**
RT3D- LVESV, ml	54 ± 17	68 ± 17	**.000**
RT3D-LVEF, %	61 ± 5	61 ± 6	ns
ERO, mm^2	38.3 ± 22	63 ± 29	**.000**

E wave, m/s	0.9 ± 0.3	1.1± 0.3	**.005**
E/E' ratio	9.9±3	10.2 ± 4	ns
TAPSE, mm	25 ± 4	24 ± 5	ns
Exercise Echocardiography			
LVEDD $_{peak}$, cm	5.3 ± 0.7	5.6 ± 0.6	**.041**
LVESD $_{peak}$, cm	3.2 ± 0.7	3.3 ± 0.6	ns
LVEDV $_{peak}$, ml	132 ± 36	165 ± 44	**.003**
LVESV $_{peak}$, ml	46 ± 16	55 ± 18	ns
LVEF $_{peak}$ (%)	65 ± 9	67 ± 7	ns
PASP $_{peak}$, mmHg	44 ± 16	51 ± 21	ns
LV S' $_{peak}$ velocity, m/s	10.8 ± 2.5	11.4 ± 2	ns
LV-GLS $_{peak}$, %	-22 ± 4	-22 ± 3	ns
RT3D- LVEDV $_{peak}$, ml	137 ± 42	168 ± 32	**.003**
RT3D- LVESV $_{peak}$, ml	48 ± 19	55 ± 13	ns
RT3D-LVEF$_{peak}$, %	66 ± 6	67 ± 5	ns
Systolic BP $_{peak}$, mmHg	195 ± 30	198 ± 28	ns

Diastolic BP $_{peak}$, mmHg	95 ±15	97 ± 14	ns
Heart rate $_{peak}$, beat/min	143 ± 23	146 ± 22	ns
Cardiopulmonary Exercise Test			
Workload	139 ± 46	154 ± 47	ns
Time exercised, min:sec	9:26 ± 2:36	9:59 ± 2:12	ns
VO_{2peak}, ml/min	1620 ± 512	1788 ± 451	ns
$VO_{2\ peak}$, ml/kg/min	23 ± 6	22 ± 5	ns
Predicted $VO_{2\ peak}$/kg, %	86 ± 15	86 ± 19	ns
RER $_{peak}$	1.2 ± 0.1	1.2 ± 0.1	ns
VE/VCO2 slope	28 ± 5	28 ± 6	ns
O_2 pulse, ml/beats	11 ± 3	13 ± 3	ns
Predicted O_2 pulse, %	99 ± 18	98 ± 18	ns
OUES, (ml/min O_2)/ (L/min VE)	1819 ± 621	1986 ± 552	ns
VO_2/WR slope	8.5 ± 2	8.8 ± 1.3	ns

ns; not significant, LAD; left atrium diameter, LAA; left atrial area, LAV; left atrial volume, LAVI; left atrial volume indexed, LVEDD; left ventricular end-diastolic diameter, LVESD; left ventricular end-systolic diameter, LVEDV; left ventricular end-diastolic volume, LVESV; left ventricular end-systolic volume, LVEF ; left ventricle ejection fraction, RT3D; real time

three dimensional echo, GLS; global longitudinal strain, S'; left ventricle systolic longitudinal velocity, PASP; pulmonary artery systolic pressure, ERO; effective regurgitant orifice, E wave; early diastolic trans-mitral flow velocity, E/E', the ratio of early diastolic trans-mitral flow velocity (E) to early diastolic mitral annular velocity(E'), BP; blood pressure, HR; heart rate, $_{peak}$; measurement at peak exercise, VO_2; oxygen uptake, RER; raspatory exchange ratio, VE; ventilation, VCO_2; carbon dioxide, O_2; oxygen, OUES; oxygen uptake efficiency slope, WR; work rate.

3.4.5.3 Determinants of cardiac surgery

The association between echocardiography parameters and mitral valve surgery was identified using univariable and multivariable logistic regression analysis. The data is shown in *Table 3.15*. On univariable logistic regression analysis, higher LVESD (odds ratio 1.03; 95% CI 1.01-1.04, p-value = 0.011), higher LVEDV (odds ratio 1.03; 95% CI 1.01-1.04, p-value < 0.0001), higher LVESV (odds ratio 1.04; 95% CI 1.01-1.06, p-value = 0.012) and higher LAV (Odds ratio 1.02; 95% CI 1.01-1.03, p-value = 0.003) were associated with referral to mitral valve surgery. Whereas systolic function parameters such as LVEF, GLS and functional capacity ($VO_{2\ peak}$) had no significant association with referral to mitral valve surgery.

In multivariable logistic regression analysis, variables that were statistically significant in the univariate analysis were included in the multivariate analysis. Higher LVEDV (Wald statistic 7.648, odds ratio 1.032; 95% CI 0.984 -1.081, p-value = 0.006) was the only significant and independently parameter associated with mitral valve surgery in this model. The logistic regression model was statistically significant, $\chi 2(4) = 24.994$, $p < 0.0001$. The model explained 33% (Nagelkerke R^2) of the variance and correctly classified 73% of cases. This model was a good fit for the data, the Hosmer and Lemeshow test p-value = 0.458 (>.05). However, LVESV and LVEDV were highly

correlated with each other, (LVEDV, VIF = 5.41; LVESV, VIF = 5.44). after removing the LVESV from the model because of the collinearity, Higher LVEDV (Odds ratio 1.020; 95% CI 1.004 -1.037, p-value = 0.017) remained the only significant and independently parameter associated with mitral valve surgery in this model. The logistic regression model was statistically significant, $\chi 2(4) = 21.43$, $p < 0.0001$. The model explained 29% (Nagelkerke R^2) of the variance and correctly classified 73% of cases.

Table 3.15 Univariable and multivariable logistic regression analysis for variables associated with mitral valve surgery

Variable	**Univariable**		
	Wald statistic	Odds ratio (95% CI)	P value
Age, years	0.186	1.01 (0.98 - 1.03)	.667
BMI, kg/m^2	3.76	1.14 (0.99 - 1.29)	.044
LVEDD, cm	2.786	1.75 (0.91 - 3.37)	.095
LVESD, cm	6.525	2.97 (1.28 - 6.83)	**.011**
LVEDV, ml	12.946	1.03 (1.01 - 1.04)	**.000**
LVESV, ml	6.240	1.04 (1.01 - 1.06)	**.012**
LVEF	2.463	1.07 (0.98 - 1.17)	.117
GLS, %	0.099	0.98 (0.84 - 1.133)	.753

LAV, ml	8.218	1.02 (1.01 - 1.03)	**.003**
PASP $_{peak,}$ mmHg	0.898	1.01 (0.99 - 1.03)	.343
$VO_{2\ peak,}$ %	0.002	1.00 (0.98 - 1.03)	.965
OUES	1.293	1.00 (1.00 - 1.00)	.255
$VE/VCO_{2\ slope}$	0.017	1.01 (0.93 - 1.08)	.895
% $O_{2\ pulse}$	.332	1.00 (0.98 - 1.02)	.992
Variable	**Multivariable**		
	Wald statistic	Odds ratio (95% CI)	P value
LVESD, cm	2.280	2.60 (0.75 - 8.98)	.131
LVEDV, ml	7.648	1.03 (0.98 - 1.08)	**.006**
LVESV, ml	3.295	0.93 (0.87 - 1.01)	.070
LAV, ml	0.845	1.01 (0.99 - 1.02)	.358

BMI; body mass index, BP; blood pressure, LAV; left atrial volume, LVEDD; left ventricular end-diastolic diameter, LVESD; left ventricular end-systolic diameter, LVEDV ; left ventricle end diastolic volume, LVESV; left ventricle end systolic volume, RT3D; real time three dimensional echo, GLS; global longitudinal strain, , PASP; pulmonary artery systolic pressure, VO_2; oxygen uptake, VE; ventilation, VCO_2; carbon dioxide, O_2; oxygen, OUES; oxygen uptake efficiency slope.

3.4.5.4 Predication of cardiac surgery

The receiver-operator curve analysis was performed for predicting cardiac surgery on the basis of four parameters significantly associated during univariate anlaysis: Left atrial volume, left ventricle end-systolic diameters, left ventricle end-diastolic volume and LV end-systolic volume. LVEDV was the strongest prognostic model, AUC = 0.771, (95% CI: 0.673 - 0.870). LAV was a strong predictor as well with AUC = 0.722, (95% CI: 0.615 - 0.828). For LVESD AUC = 0.689, (95% CI: 0.580-0.798) (*Table 3.16*). The ROC curves are displayed in *Figure 3.2*. Left ventricle end-diastolic volume had a superior association with cardiac surgery than left ventricle end-systolic dimension. The optimal cut-off point derived from the ROC curve analysis was 91 ml for LAV, with a sensitivity of 74 % and specificity of 70%, and for LVEDV was 149 ml with a sensitivity of 66 % and specificity of 79%.

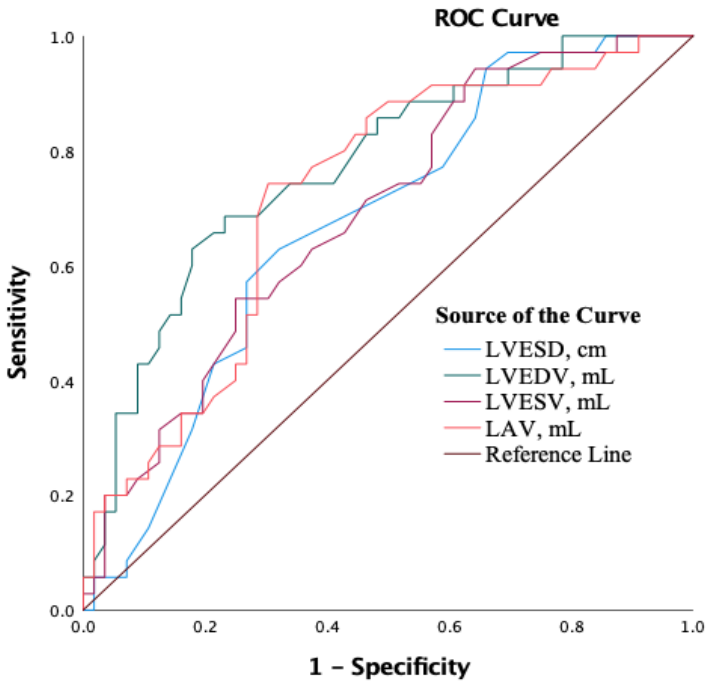


Figure 3.2 Receiver operating characteristic curves of left ventricle end -systolic and -diastolic volume, left ventricle end-systolic dimension, left atrial volume for detecting cardiac surgery.

Table 3.16 The area under curves for left ventricle end -systolic and -diastolic volume, left ventricle end-systolic dimension, left atrial volume for predicting cardiac surgery.

	AUC	**95% CI**	**P-Value**
LVESD	.673	0.563 - 0.784	**.006**
LVEDV	.771	0.673 - 0.870	**.000**
LVESV	.689	0.580 - 0.798	**.003**
LAV	.722	0.615 - 0.828	**.000**

LAV; left atrium volume, LVEDV; left ventricle end-diastolic volume, LVESV; left ventricle end-systolic volume, LVESD; left ventricle end-systolic diameters.

3.5 Discussion

In this study, investigating the utility of a combined exercise echo and CPET in asymptomatic patients with moderate to severe or severe primary mitral regurgitation and preserved ejection fraction, we found. 1) approximately half of the patients (52%) had reduced exercise capacity (predicted $VO_{2\ peak}$ < 84%). 2) 18 (19%) patients developed symptoms (dyspnoea) during exercise testing. 3) Rest estimated pulmonary artery systolic pressure was an independent predictor of dyspnoea development during exercise testing. 4) LV end-diastolic volume was an independent predictor associated with referral for mitral valve surgery.

3.5.1 Exercise-induced dyspnoea

The current (Class 1) recommendation for mitral valve surgery is onset of symptoms in patients with primary severe mitral regurgitation (1, 2). However, waiting for symptoms to develop may be associated with poor long-term outcomes because patients may have irreversible ventricular dysfunction before onset of symptoms. In our study of asymptomatic primary mitral regurgitation patients with preserved ejection fraction, about a fifth of patients who are reportedly symptom-free in their daily life develop exercise-induced dyspnoea. Rest and exercise estimated pulmonary artery systolic pressure, left atrial index and VE/VCO_2 slope were significantly associated with dyspnoea, however, $VO_{2\ peak}$ was not. Rest PASP was superior in predicting symptoms during exercise.

This data suggests the development of symptoms may be insidious and patients may not notice a gradual reduction in exercise tolerance and that this may be unmasked by exercise testing. Exercise testing is readily available and simple to perform. Rest PASP was a predictor of symptoms during exercise. Therefore, it may be reasonable to perform exercise testing in patients with asymptomatic primary MR who have elevated rest PASP as they are the most likely to develop symptoms on exercise. Further, the association between exercise dyspnoea and VE/VCO_2 slope but not with $VO_{2\ peak}$ is interesting, suggesting that ventilatory efficiency perhaps is more important in the generation of symptoms than objective oxygen uptake.

In a previous study, Lancellotti et al (154) reported that rest and exercise PASP were associated with markedly reduced two-year symptoms free survival. Furthermore, exercise PASP >60 mmHg was an independent predictor of the occurrence of symptoms in asymptomatic patients. Toubal et al (155) investigated PASP acquired during the early stage of exercise in asymptomatic MR patients and found that increase in PASP > 15

mmHg was associated with a two-fold increase in the risk of cardiac events (mitral valve surgery, new onset of atrial fibrillation, heart failure, cardiac-related hospitalisation, or cardiac death). Our study was not designed to investigate the long-term outcomes of exercise-induced PASP. However, we found patients with exercise-induced symptoms had a higher proportion of rest PASP ≥35mmHg (33% vs 6%; p-value= 0.001) and were more likely to develop exercise-induced PASP ≥ 60 mmHg (39% versus 10%; p-value = 0.002).

3.5.2 Functional capacity

Evaluation of functional capacity is important in asymptomatic patients with significant mitral regurgitation and preserved left ventricle function. The heart has the ability to compensate before it decompensates. Many patients become unaware of their symptoms in the compensated stage as they limit their activities gradually to avoid symptoms and discomfort, and they are mistakenly identified as asymptomatic. This study demonstrated a high percentage (52%) of asymptomatic MR patients had a reduced exercise capacity confirming that asymptomatic patients may be more limited than what they or their physicians think. Our findings are in agreement with previous studies, functional capacity can be reduced in asymptomatic severe MR even with preserved ejection fraction. Naji et al. (101) have demonstrated that almost one-third of patients failed to achieve 100% of their age-sex predicted METs, despite being considered asymptomatic. Our study shows a higher proportion of abnormal functional capacity than previous studies. Messika-Zeitoun et al. (105) investigated functional capacity in 134 primary MR patients, and predicted $VO_{2\ peak}$ was markedly reduced (≤ 84% of predicted) in 19% of such patients, In another study, Suzuki et al. (156) showed an alteration of functional capacity (predicted $VO_{2\ peak}$ < 80.4%) in 24% of cases. Previous reports have

also demonstrated that predicted $VO_{2\ peak}$ varied widely, from supernormal to severely impaired.

Previous investigations have found conflicting predictors of functional capacity in primary mitral regurgitation patients. Messika et al. (105) reported that LV diastolic dysfunction, atrial fibrillation and forward stroke volume predicted functional capacity, while mitral effective regurgitant orifice did not. Laung et al. (157) found that exercise cardiac output is a determinant of $VO_{2\ peak}$ but not mitral regurgitant volume or fraction. Suzuki et al. (156) found that exercise PASP was independently associated with functional capacity, while Vaturi et al. (158) in a retrospective study, found that left atrium index, age and sex were independent predictors of functional capacity. Functional capacity was determined using treadmill exercise tolerance tests, not cardiopulmonary exercise test.

In our study, we found no relationship between echocardiography and predicted $VO_{2\ peak}$ and therefore no predictive parameters from rest or exercise echocardiography data of $VO_{2\ peak}$. The univariate regression model showed a significant association of rest and exercise left ventricle S' velocity and left ventricle volume with unadjusted $VO_{2\ peak}$, however, the multivariate model showed that age was superior to echocardiographic variables, besides unadjusted $VO_{2\ peak}$ was strongly affected by age, body size and sex.

This demonstrates that echocardiography parameters and predicted $VO_{2\ peak}$ are not related to each other, and echocardiography parameters were unable to predict $VO_{2\ peak}$. Echocardiography and cardiopulmonary exercise test both offer a range of unique parameters in the assessment of patients with MR and provide valuable complementary information about heart function and functional capacity.

3.5.3 Development of symptoms and requirements for cardiac surgery

In this chapter, we explored the association between echocardiography and cardiopulmonary exercise test parameters and mitral valve surgery. In this study, patients had no conventional indications for surgery at entry. Surgery was performed during follow-up if they developed symptoms or if they met the requirements of surgery.

We found that LV end-systolic and -diastolic volume, LV end-systolic diameter and left atrium volume had a significant association with referral to mitral valve surgery in univariate models. However, in a multivariate logistic regression model, the left ventricle end-diastolic volume was the only parameter associated with mitral surgery. In addition, LVEDV and LAV were stronger predictors on ROC curve than LVESD.

Severe primary mitral regurgitation typically leads to left ventricular dilatation followed by left ventricle dysfunction and onset of symptoms. Current guidelines recommend intervention in symptomatic patients or asymptomatic patients if left ventricle ejection fraction $\leq$60% or LVESD is greater or equal to 4cm (1, 2). In this study, at baseline all patients were asymptomatic with no indications for surgery. LVEDV was a better predictor of the development of symptoms and requirement for surgery during follow-up than LVESD.

Linear LV measurements including LVESD are the guideline recommended parameters for surgical intervention in a range of valve diseases. Two-dimensional measurements are simple and rapid to measure. However, linear measurements make geometric assumptions and may underestimate size if not properly aligned to the short axis of the ventricle. In addition, they assess a three-dimensional structure in single plane (159). Therefore, they will only provide useful monitoring of LV size if LV remodelling is symmetrical. There is a good correlation between LV diameters and volumes, however,

the relationship is curvilinear with a wide error in enlarged ventricles (160). Therefore, LV volumes may provide a better quantification of LV size. Our study shows LVESD was a predictor of the development of symptoms leading to surgery, however, LVEDV was better. Further studies with larger sample size and prolonged follow-up are needed to examine this relationship between LV volumes and outcomes in primary MR to determine whether LV volumes could be used to identify the best time to intervene.

3.6 Limitation

The small sample size may be a limitation of this study. The study population was primary MR as a result of mitral valve prolapse or flail leaflet exclusively, other organic causes were not included. Assessment of dyspnoea during exercise test maybe considered subjective. In addition, rest and exercise right atrial pressure were estimated similarly as its difficult to assess right atrial pressure during exercise, this estimation may neglect the exercise potential impact on right atrial pressure. One of the limitations of this study was the short follow-up period (1 year).

3.7 Conclusion

In asymptomatic patients with moderate to severe primary MR and preserved LVEF, clinical evaluation of patients at rest may not always provide a good assessment of patient's symptoms and functional capacity. Functional capacity assessed by $VO_{2\ peak}$ was reduced in approximately half of the study population (52%). Functional capacity range extensively from normal to significantly reduced. Echocardiography parameters were unable to independently predict functional capacity, age was superior during predicting functional capacity. Approximately one-fifth of patients developed exercise-induced symptoms. Resting PASP was an independent predictor for exercise-induced

dyspnoea. LV volumes may provide incremental value in predicting symptom onset and the requirement for surgery compared to LV end-systolic diameters.

Chapter 4

Prognostic Value of Left Ventricle Deformation in a Surgical Population of Primary Mitral Regurgitation

4.1 Abstract

Background and objective: The optimal timing of mitral valve surgery in patients with severe degenerative MR remains controversial. It is conventionally based on the presence of symptoms or determined by LVEF and/or LV dimensions changes. However, these conventional parameters may not reflect reliable LV systolic function in severe primary MR. The aim of this study was to determine whether the assessment of LV deformation by speckle-tracking echocardiography (GLS) is associated with long-term outcomes after mitral valve surgery and whether GLS could help to uncover subclinical pre-operative LV dysfunction for predicting reduction of LVEF postoperatively in degenerative MR. **Methods and results:** A total of 98 patients with severe degenerative MR who underwent MV surgery were included. Echocardiography was performed at baseline and one year after MV surgery. During follow-up period, 6 (6%) patients died, and LV dysfunction developed in 12 (12%) patients, defined as LVEF <50%. In univariate logistic analysis, pre-operative LVEF, AF, age, LVESD, RA area, TAPSE, S' wave and GLS showed significant associations with the composite end-point of all-cause mortality and post-operative LV dysfunction. On multivariate models, age and LVESD were the only independent predictors of the composite endpoint. When investigating post-operative LV dysfunction only, univariate linear regression analysis showed baseline LVEF, LVESD, LVESV, LA volume, TAPSE, RA area and GLS were predictors of long-term post-operative LVEF. By multivariate linear analysis, GLS remained an independent predictor of post-operative LVEF. **Conclusion**: LV end-systolic diameter and age appear to be better predictors of post-operative outcome than GLS. However, this study shows the additive and independent predictive value of pre-operative GLS for predicting post-operative LV dysfunction.

4.2 Introduction

Guidelines recommend mitral valve surgery to be undertaken before LV dysfunction develops (1, 2), mainly because pre-operative LV dysfunction has been associated with adverse outcomes (62, 161, 162). In addition, early mitral valve surgery was reported to be associated with a lower rate of heart failure and a better chance of long-term survival than medical treatment alone (163). A previous study showed that post-operative LV dysfunction is not uncommon and only about one-third of patients who suffer from post-operative LV dysfunction improved their LV function over long-term follow-up (164). Researchers have attempted to identify echocardiographic parameters that are able to predict left ventricle dysfunction postoperatively and found that parameters such as LVEF, LVESD, and PASP are associated with post-operative LV dysfunction (62, 165-167). However, there has been evidence that LV dysfunction can occur postoperatively in patients with normal pre-operative ventricular function (164). Thus, identifying factors that can predict post-operative LV dysfunction is clinically important as it may allow early surgical intervention to reduce the risk of LV dysfunction after mitral valve surgery. LV global longitudinal strain (GLS) has been proposed as a more sensitive and accurate tool than LV ejection fraction (168). Current guidelines mention that GLS could improve risk stratification tools in patients with severe primary MR (1). In spite of emphasising relevant literature on the advantage of the GLS over conventional parameters, there is a conflicting opinion regarding its incremental value (86, 169). In the present study, we assessed the predictive value of GLS derived from speckle tracking strain and the influence of GLS on post-operative events in patients with severe primary MR. We hypothesised that GLS would have a better predictive value for postoperative LV function than conventional parameters including LVEF and LV end-systolic diameters.

4.3 Methods

4.3.1 Study Population

111 patients with severe primary MR, who were referred to St Bartholomew's Hospital for mitral valve surgery were recruited. 13 patients were excluded due to unsuccessful follow-up after mitral valve surgery. Therefore, a total of 98 patients were included in this cohort. All patients had severe MR due to a prolapse or flail leaflet.

4.3.2 Echocardiography and speckle tracking echocardiography

All patients of the study population underwent a transthoracic echocardiographic examination and clinical evaluation before and after mitral valve surgery. Pre-operative echocardiographic data including GLS derived by speckle tracking analysis were undertaken closest to the day of surgery, and post-operative echocardiographic data were undertaken with post-operative period defined as 12 months after MV surgery. The methodology of echocardiographic measurements and LV deformation is explained in detail in the methods chapter (chapter 2).

4.3.3 Follow-up and outcome analysis

Patients were asked to return for follow-up echocardiography 12 months after surgery. All surgical procedures were performed by experienced mitral valve surgeons. The primary endpoint of this study was the composite of post-operative LV dysfunction (defined as an LV ejection fraction less than 50%) and all-cause mortality. The occurrence of death was obtained by medical chart review. The secondary endpoint was post-operative LV dysfunction (defined as an LV ejection fraction < 50%).

4.3.4 Statistical analysis

Distribution of the continuous data was tested with the Komolgorov– Smirnov approach. Normally distributed variables were presented as mean + standard deviation, whereas non-normally distributed variables were presented as median and (25th to 75th) percentiles. Categorical variables were presented as absolute numbers and percentages. Comparisons of variables were performed with Student's t-test or the Mann–Whitney test and X^2 tests where appropriate. The relationship between post-operative events and baseline clinical and echocardiographic characteristics was tested with logistic regression analysis. The study population was divided according to post-operative event occurrence, and post-operative LVEF (< 50 versus ≥50%). To test the value of GLS to predict LV dysfunction after MV surgery, univariable and multivariable linear regression analyses were performed, including other well-established independent predictors. All variables significant in the univariate analysis were entered in the multivariate model. The Hosmer–Lemeshow test was used to assess the multivariate models' fit. Multicollinearity was tested by performing a collinearity diagnostic test. A variance inflation factor (VIF) cut-off value of 5 was used for the multivariable model, and only variables with a VIF under 5 were included(153). All statistical analyses were performed with SPSS version 27.0 (SPSS, Inc., Chicago, IL). A p-value of less than 0.05 was considered significant.

4.4 Results

4.4.1 Baseline clinical characteristics

Baseline clinical characteristics and comparison of characteristics in patients with and without post-operative events are shown in *Table 4.1*. There were 18 (18%) patients with post-operative events. LV systolic dysfunction developed in 12 (12%) patients, and all-

cause death occurred in 6 (6%) patients. The overall mean age of the surgery cohort was 65 ± 14 years, patients with post-operative events were older than patients without events (72 ±12 years versus 62± 13 years, p-value = 0.002). No differences were found in height, weight, body mass index, blood pressure and heart rate between the two groups. A higher prevalence of pre-operative atrial fibrillation was found in the group with post-operative events than in the group without events (50% versus 8%, p-value < 0.0001). The use of ACE inhibitors and anticoagulation was more frequent in patients with post-operative events. The majority of patients were mildly symptomatic, 63 (64%) patients in NYHA class II, and 12 patients (11%) of the patients were in NYHA class III/IV. The proportion of patients with NYHA III/IV was higher in patients with post-operative events than those without events (6 (33%) patients versus 6 (8%) patients, p-value = 0.009). There were no differences between the two groups in other co-morbidities including hypertension, hypercholesterolaemia, smoking, overweight and stroke. There were also no differences in other cardiac medications taken by the two groups at the time of surgery.

All patients had severe mitral regurgitation before mitral valve surgery (effective regurgitant orifice 0.7 ± 0.5 cm^2 and regurgitant volume 95 ± 53 ml) due to either prolapse or flail leaflet. Most patients (52%) had posterior leaflet prolapse, a few (4%) had anterior leaflet prolapse and a flail leaflet was found in 19 (19%) patients. The proportion of mitral valve prolapse locations was comparable in both groups. 75% of the surgery cohort had mitral valve repair, and 26% of patients had mitral valve replacement (bioprosthetic in 13% and mechanical in 12% of patients).

Table 4.1 Baseline characteristics of the patient population according to the occurrence of post-operative events.

Variables	All patients (n=98)	(-) post-operative events n=80 (82%)	(+) Post-operative events n=18 (18)	P-value
Age, years	65 ± 14	62± 13	72 ±12	**.002**
Male, n (%)	56 (57)	47 (59)	9 (50)	.498
Height, cm	171± 11	172± 11	168 ±9	.278
Weight, kg	73 (IQR 63-81)	74 ± 14	68 ± 16	.193
BMI, kg/m^2	25 (IQR 23-27)	26 ±7	24± 5	.335
Heart rate, bpm	73 ± 14	72 ± 13	76 ± 15	.257
Systolic BP, mmHg	132 ± 16	133 ± 15	127 ±18	.170
Diastolic BP, mmHg	79 ± 10	76 ± 9	73 ±12	.314
Risk Factors, n (%)				
AF	15 (15)	6 (8)	9 (50)	**.000**
Hypertension	35 (36)	26 (33)	9 (50)	.162
Hypercholesterolaemia	28 (29)	22 (28)	6 (33)	.621
Syncope	2(2)	2 (3)	0	.498

Smoking	30 (31)	24 (30)	6 (33)	.781
Overweight	10 (10)	9 (11)	1 (6)	.135
Stroke	3(3)	3 (4)	0	.404
Medications n, (%)				
Beta Blocker	32 (33)	23 (29)	9 (50)	.082
ACE inhibitors	22 (22)	14 (18)	8 (44)	**.013**
Diuretics	16 (16)	12 (15)	4 (22)	.454
Warfarin	8 (8)	5 (7)	3 (17)	.145
Antiplatelet agent	7 (7)	6 (8)	1 (6)	.772
Statin	15 (15)	11 (14)	4 (22)	.367
Amlodipine	6 (6)	6 (8)	0	.230
Anticoagulant	15 (15)	9 (11)	6 (33)	**.020**
ARBs	8 (8)	7 (9)	1 (6)	.655
Symptoms, n (%)				**.009**
NYHA I	23 (24)	21 (26)	2 (11)	
NYHA II	63 (64)	53 (66)	10 (56)	

NYHA III or IV	12 (11)	6 (8)	6 (33)	
Mitral Valve Prolapse, n (%)				.421
Posterior	51(52)	42 (53)	9 (50)	
Anterior	4 (4)	2 (3)	2 (11)	
Bi leaflets	24 (25)	20 (25)	4 (22)	
Flail	19 (19)	16 (20)	3 (17)	
Surgery, n (%)				.086
MV replacement (mechanical)	12 (12)	9 (11)	3 (17)	
MV replacement (bioprosthetic)	13 (13)	8 (10)	5 (28)	
MV repair	73 (75)	63 (79)	10 (56)	

IQR; inter-quartile range, BMI; body mass index, AF; Atrial fibrillation, BP; blood pressure; ACE; Angiotensin-converting enzyme, ARBs; Angiotensin receptor blockers, NYHA; New York Heart Association functional classification, MV; mitral valve.

4.4.2 Baseline echocardiography

Post-operative (LVEF)

The mean of preoperative LVEF in patients with post-operative events was 43 ± 9% lower than in those patients without post-operative events 58 ± 4% (p-value < 0.0001).

Pre-operative echocardiographic parameters

Pre-operative echocardiographic parameters according to the occurrence of post-operative events are summarised in *Table 4.2*. The severity of MR assessed by ERO and R Vol were similar in both groups. There were similar results for preoperative left atrial dimension and area. The baseline left atrium volume was higher in patients who had events, however, no significant difference was found between the two groups.

There were no significant differences in preoperative left ventricle volumes between the two groups. However, post-operative events group had lower baseline 2D-LVEF (57 ± 12% versus 63 ± 6%; p-value = 0.002), lower baseline RT3D-LVEF (58 ± 6% versus 62 ± 6%; p-value = 0.023), lower baseline S' wave velocity (8.4 ± 2.3 m/s versus 9.8 ± 2.6 m/s; p-value = 0.044), and greater baseline left ventricle end-systolic dimension (3.8 ± 0.9 cm versus 3.5 ± 0.6 cm; p-value = 0.038).

Patients with post-operative events had greater pre-operative pulmonary artery systolic pressure (36 ±14 mmHg versus 29 ±16 mmHg; p-value = 0.009). Pre-operative right ventricle basal diameter was higher in the post-operative event group whereas pre-operative right ventricle mid diameter was similar in both groups. Pre-operative right atrium area was higher in those with post-operative events than in those without (23 ± 9 cm^2 versus 18 ± 6 cm^2; p-value = 0.013), and baseline TAPSE was lower in the post-operative events group (21 ± 6 mm versus 25 ± 5 mm; p-value = 0.013). Pre-operative diastolic function parameters were comparable in both groups. Baseline GLS in the total Surgery cohort was -20 ± 3.6%. Pre-operative GLS was significantly more impaired among those with post-operative events compared to those without events (-18 ± 5% versus -21 ± 3%; p- value = 0.001).

Table 4.2 Baseline echocardiographic parameters according to the occurrence of post-operative outcome.

Variables	All patients (n=98)	(-) post-operative events (n=80 (82%))	(+) Post-operative events (n=18 (18))	P-value
Pre-operative Echocardiography variables				
LA diameter, cm	4.5 ± 0.9	4.5 ± 0.8	4.7 ± 1	.143
LA diameter index, cm/m^2	2.5 ± 0.6	2.5 ± 0.5	2.7 ±.6	.087
LA area, cm^2	32 ± 12	32 ± 12	33 ±11	.656
LAV, ml	129 ± 53	126 ± 51	145 ± 61	.176
LAV index, ml/cm^2	70 ± 30	68 ± 29	81± 33	.146
LVEDD, cm	5.6 ± 0.8	5.6 ± 0.8	5.7 ± 0.9	.534
LVEDD index, cm/m^2	3.1 ± 0.5	3.0 ± 0.5	3.2 ± 0.6	.069
LVESD, cm	3.6 ± 0.6	3.5 ± 0.6	3.8 ± 0.9	**.038**
LVESD index, cm/m^2	1.9 ± 0.4	1.9 ± 0.3	2.2 ± 0.6	**.002**
LVEDV, ml	156 ± 48	157 ± 45	153 ± 60	.915
LVEDV index, ml/cm^2	84 ± 22	83 ± 20	84 ± 29	.992

LVESV, ml	60 ± 22	59 ± 20	63 ± 28	.560
LVESV index, ml/cm^2	32 ± 10	31 ± 9	35 ± 13	.286
LVEF, %	62 ± 8	63 ± 6	57 ± 12	**.002**
RT3D-LVEDV, ml	160 ± 51	161 ± 49	154 ± 62	.769
RT3D-LVESV, ml	61 ± 21	60 ± 21	64 ± 24	.431
RT3D-LVEF, %	62 ± 6	62 ± 6	58 ± 6	**.023**
LV S' average, m/s	9.6 ± 2.6	9.8 ± 2.6	8.4 ± 2.3	**.044**
IVS, cm	0.9 ± 0.2	0.9 ± 0.2	1.0 ± 0.2	.546
LVPW, cm	0.9 ± 0.2	0.9 ± 0.2	0.8 ± 0.1	.183
ERO, cm^2	0.7 ± 0.5	0.7 ± 0.4	0.9 ± 0.8	.489
R Vol, ml	95 ± 53	95 ± 53	94 ± 55	.826
RV basal-diameter, cm	3.9 ± 0.7	3.8 ± 0.6	4.2 ± .7	**.025**
RV mid-diameter, cm	3.3 ± 0.6	3.2 ± 0.6	3.4 ± .7	.140
RA area, cm^2	19 ± 7	18 ± 6	23 ± 9	**.013**
PASP, mmHg	30 ± 16	29 ±16	36 ± 14	**.009**
RV S', m/s	15 ± 3	15 ±3	13 ± 3	.115

TAPSE, mm	24 ± 6	25 ± 5	21 ± 6	**.013**
E/A ratio	1.7 ± 0.7	1.8 ± 0.7	1.7 ± 0.8	.678
E wave, m/s	1.2 ± 0.3	1.2 ± 0.3	1.2 ± 0.3	.874
DT, ms	205 ± 76	204 ± 63	212 ± 125	.285
E' wave, m/s	10.4 ± 2.7	10.6 ± 2.9	9.5 ± 2	.169
E/E' ratio	11.3 ± 3.7	11.2 ± 3.9	11.8 ± 3.0	.638
GLS, %	- 20 ± 3.6	-21 ± 3	-18 ± 5	**.001**
Peak SL dispersion	39 ± 14	37 ± 12	45 ± 21	.207

LA; left atrium, LAV; left atrial volume, LVEDD; left ventricular end-diastolic diameter, LVESD; left ventricular end-systolic diameter, LVEDV; left ventricular end-diastolic volume, LVESV; left ventricular end-systolic volume, LVEF ; left ventricle ejection fraction, IVS; interventricular septum , LVPW; left ventricle posterior wall, ERO; effective regurgitant orifice, R Vol; regurgitant volume, RV; right ventricle, PASP; pulmonary artery systolic pressure, S'; left ventricle systolic longitudinal velocity, TAPSE; tricuspid annular plane systolic excursion, E/A; ratio of the early to late ventricular filling velocities, DT; deceleration time, E' early, passive filling of the left ventricle, E'; mitral annular early diastolic velocity, E/E'- ratio between early mitral inflow velocity and mitral annular early diastolic velocity, GLS; global longitudinal strain, RT3D; real time-three dimensional echo.

4.4.3 Predictors of outcome after mitral valve surgery

Table 4.3 shows the results for the logistic regression models with post-operative events as a dependent variable. On univariate analysis, age, presence of atrial fibrillation, baseline LVEF, baseline RT3D-LVEF, baseline left ventricle end-systolic dimension, RA

area, TAPSE, S' wave and GLS showed significant associations with events during follow-up, while LA volume and pulmonary artery systolic pressure did not. The result of the multiple logistic regression after sequential inclusion of all parameters from the univariate analysis, revealed that age (odds ratio: 1.1, 95% CI: 1.01 to 1.19; p-value = 0.028) and LVESD index (odds ratio: 33.73, 95% CI: 1.53 to 741.6; p-value = 0.03) were significant determinants for post-operative outcome among the parameters that were significant in univariate analysis. GLS was a predictor of post-operative event (odds ratio: 1.287 95% CI: 1.09 to 1.52; p-value = 0.003), however was not an independent predictor (odds ratio: 1.186, 95% CI: 0.862 to 1.631; p-value = 0.298). Age and LVESD were the only independent predictive variables. The predictor variables were not highly correlated with each other. VIF values were less than 3.

Table 4.3 Univariable and multivariable logistic regression analysis for variables associated with post-operative outcome.

Variable	**Univariable**			**Multivariable**	
	X^2	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value
Age, years	11.6	1.087 (1.03 to 1.15)	**.003**	1.10 (1.01 to 1.19)	**.032**
AF	16.310	12.33 (3.55 to 42.76)	**.000**	4.14 (0.33 to 51.61)	.271
LVEF, %	8.64	.906 (.840 to .977)	**.010**	1.03 (.829 to 1.275)	.802
LA volume, ml	1.690	1.007 (.997 to 1.02)	.192		

LVESD index, cm	8.464	8.21 (1.55 to 43.36)	**.013**	33.73 (1.53 to 741.6)	**.030**
RT3D LVEF, %	5.125	.901 (.820 to .989)	**.028**	.947 (.778 to 1.154)	.591
RAA, cm^2	6.828	1.10 (1.02 to 1.181)	**.011**	.974 (.849 to 1.12)	.720
S' wave, m/s	4.483	.777 (.604 to .999)	**.049**	1.34 (.900 to 2.004)	.156
PASP, mmHg	2.956	1.026 (.997 to 1.06)	.081		
GLS, %	10.252	1.287 (1.09 to 1.52)	**.003**	1.186 (.86 to 1.63)	.298
TAPSE, mm	6.168	0.883 (.796 to .978)	**.017**	.96 (.81 to 1.13)	.586
RV basal diameter, cm	4.901	2.38 (1.09 to 5.19)	**.030**	.99 (0.29 to 3.32)	.977

LVESD; left ventricular end-systolic diameter, LVEDV; left ventricle ends diastolic volume, LVEF; left ventricle ejection fraction, S'; left ventricle systolic longitudina**l** velocity, RT3D; real-time three-dimensional echo, GLS; global longitudinal strain.

4.4.4 Left ventricle dysfunction after mitral valve surgery

A comparison of clinical characteristics and baseline echocardiography parameters according to the occurrence of post-operative LV dysfunction is shown in *Table 4.4*. The mean of post-operative LVEF in patients with post-operative LV dysfunction (LVEF < 50%) was 46 ± 3% and the mean of post-operative LVEF in those patients without post-operative LV dysfunction (LVEF ≥ 50%) was 58 ± 4% (p-value < 0.0001).

Patients with post-operative LV dysfunction were older than patients without LV dysfunction (73 ±11 years versus 62± 13 years, p-value = 0.007). No differences were found in height, weight, body mass index and blood pressure between the two groups. A higher prevalence of baseline atrial fibrillation was found in the group with post-operative LV dysfunction than in the group with normal post-operative LV function (58% versus 8%, p-value < 0.0001).

The severity of mitral regurgitation assessed by ERO and R Vol were similar in both groups. Measures of baseline left atrial size showed that the LV dysfunction group had higher left atrium diameter (5.1 ± 0.7 cm versus 4.5 ± 0.8 cm, p-value = 0.013), higher left atrial area (38 ±9 cm^2 versus 32 ± 9 cm^2, p-value = 0.039), and greater left atrial volume (171 ± 44 ml versus 126 ± 51, p-value = 0.006) than patients who had a normal post-operative left ventricle function.

Patients with post-operative LV dysfunction had lower baseline 2D-LVEF (57 ± 7% versus 63 ± 6%; p-value = 0.002), lower baseline RT3D-LVEF (58 ± 6% versus 62 ± 6%; p-value = 0.026) than normal post-operative LV function group, but similar S' wave velocity in both groups. Baseline left ventricle end-systolic dimension was higher in the LV dysfunction group (3.9 ± 0.7 cm versus 3.5 ± 0.6 cm, p-value = 0.021). Indexed left ventricle end-diastolic dimension was significantly higher in the LV dysfunction group (3.3 ± 0.7 cm/m^2 versus 3.0 ± 0.4 cm/m^2, p-value = 0.037), however, there were no significant differences in unindexed left ventricle end-diastolic dimension between the two groups. Patients with post-operative LV dysfunction had higher 2D LVESV (75 ± 24 ml versus 59 ± 20 ml, p-value = 0.030) and higher RT3D LVESV (73 ± 21 ml versus 60 ± 21 ml, p-value = 0.037). However, no significant differences were found in 2D/RT3D left ventricle end-diastolic volume.

Patients with post-operative LV dysfunction had greater pulmonary artery systolic pressure (40 ± 12 mmHg versus 29 ±17 mmHg, p-value = 0.002). Right ventricle size assessed by basal and mid diameter were higher in the LV dysfunction group. The right atrium area was higher in those with post-operative LV dysfunction than in those without (26 ± 8 cm^2 versus 18 ± 6 cm^2; p-value = 0.001), TAPSE was lower in the LV dysfunction group (20 ± 6 mm versus 25 ± 5 mm; p-value = 0.007), but right ventricular S' wave was comparable between the two groups. Diastolic function parameters were comparable in both groups. GLS was significantly more impaired among those with post-operative LV dysfunction compared to those with normal LVEF (-17 ± 5 % versus -21 ± 3%; p-value = 0.001). *Figure 4.1.* shows that patients with post-operative left ventricle dysfunction had a lower baseline LVEF and GLS than those without LV dysfunction

Table 4.4 Clinical characteristics and baseline echocardiographic parameters according to the occurrence of post-operative left ventricle dysfunction

Variables	Post-operative LVEF≥ 50% n=80 (87%)	Post-operative LVEF<50% n=12 (12)	P- value
Post-operative LVEF, %	58 ± 4	46 ± 3	
Clinical Characteristics			
Age, years	62 ± 13	73 ±11	**.007**
Male, n (%)	47 (59)	6(50)	.567

Height, cm	172 ± 11	168 ± 7	.326
Weight, kg	74 ± 14	71± 16	.476
Body mass index, kg/m^2	26 ± 7	25 ± 5	.894
Heart rate, bpm	72 ± 13	80 ± 16	.095
Systolic BP, mmHg	133 ± 15	124 ± 16	.056
Diastolic BP, mmHg	76 ± 10	75 ± 11	.805
AF, n (%)	6(8)	7(58)	**.000**
Pre-operative Echocardiography variables			
LA diameter, cm	4.5 ± 0.8	51 ± 0.7	**.013**
LA diameter index, cm/m^2	2.5 ± 0.5	2.9 ±.6	**.027**
LA area, cm^2	32 ± 9	38 ±9	**.039**
LAV, ml	126 ± 51	171 ± 44	**.006**
LAV index, ml/cm^2	68 ± 29	94± 26	**.006**
LVEDD, cm	5.6 ± 0.7	5.9 ± 1.0	.153
LVEDD index, cm/m^2	3.0 ± 0.4	3.3 ± 0.7	**.037**
LVESD, cm	3.5 ± 0.6	3.9 ± 0.7	**.021**

LVESD index, cm/m^2	1.9 ± 0.3	2.2 ± 0.5	**.005**
LVEDV, ml	157 ± 45	176 ± 57	.127
LVEDV index, ml/cm^2	83 ± 20	95 ± 28	.065
LVESV, ml	59 ± 20	75 ± 24	**.030**
LVESV index, ml/cm^2	31 ± 9	40 ± 11	**.006**
LVEF, %	63 ± 6	57 ± 7	**.002**
RT3D-LVEDV, ml	161 ± 49	175 ± 61	.281
RT3D-LVESV, ml	60 ± 21	73 ± 21	**.037**
RT3D-LVEF, %	62 ± 6	58 ± 6	**.026**
LV S' average, m/s	9.9 ± 2.6	9.0 ± 2.4	.294
IVS, cm	1.0 ± 0.2	1.0 ± 0.2	.842
LVPW, cm	0.9 ± 0.2	0.1 ± 0.1	.504
ERO, cm^2	0.7 ± 0.4	1.2 ± 0.9	.079
MR-RV, ml	95 ± 53	120 ± 57	.313
RV basal-diameter, cm	3.9 ± 0.6	4.4 ± .7	**.010**
RV mid-diameter, cm	3.2 ± 0.6	3.7 ± .5	**.023**

RA area, cm^2	18 ± 6	26 ± 8	**.001**
PASP, mmHg	29 ±17	40 ± 12	**.002**
RV S', m/s	15 ±3	13 ± 3	.059
TAPSE, mm	25 ± 5	20 ± 6	**.007**
E/A ratio	1.8 ± 0.7	2.2 ± 0.7	.152
E wave, m/s	1.2 ± 0.3	1.3 ± 0.3	.111
DT, ms	204 ± 63	166 ± 29	.081
E' wave, m/s	10.6 ± 2.8	10.1 ± 2	.560
E/E' ratio	11.2 ± 3.9	12.4 ± 3.2	.374
GLS, %	-21 ± 3	-17 ± 5	**.001**
Peak SL dispersion	37 ± 12	46 ± 23	.357

LA; left atrium, LAV; left atrial volume, LVEDD; left ventricular end-diastolic diameter, LVESD; left ventricular end-systolic diameter, LVEDV; left ventricular end-diastolic volume, LVESV; left ventricular end-systolic volume, LVEF ; left ventricle ejection fraction, IVS; interventricular septum , LVPW; left ventricle posterior wall, ERO; effective regurgitant orifice, MR-RV; regurgitant volume, RV; right ventricle, PASP; pulmonary artery systolic pressure, S'; left ventricle systolic longitudina**l** velocity, TAPSE; tricuspid annular plane systolic excursion, E/A; ratio of the early to late ventricular filling velocities, DT; deceleration time, E' early, passive filling of the left ventricle, E'; mitral annular early diastolic velocity, E/E'- ratio between early mitral inflow velocity and mitral annular early diastolic velocity, GLS; global longitudinal strain, RT3D; real time-three dimensional echo.

4.4.5 Predictors of left ventricle function after mitral valve surgery

In this analysis, we investigated the baseline predictors of post-operative LV dysfunction. Pre-operative parameters including LVEF, GLS, LVESD, LVESV, LA volume, RA area and TAPSE showed weak but significant correlations with post-operative LVEF (*Figure 4.2, 4.3 and 4.4.* GLS had a negative correlation and baseline LVEF had a positive one, the correlation coefficients of pre-operative LVEF and GLS tended to be higher than the other correlated variables (r = .336; p-value = 0.001, r = -.326; p-value = 0.002) respectively. GLS had better correlation with post-operative LVEF than other parameters LVESD index (r = -256; p-value = 0.014), LVESV index (r = -.248 p-value= 0.019), LA volume (r = -.219; p-value = 0.039), RA area (r = -.268; p-value = 0.010) and TAPSE (r = .206 p-value 0.048). Whereas pre-operative pulmonary artery systolic pressure did not correlate with post-operative LVEF.

The results of univariate and multivariate linear regression analysis are shown in *Table 4.5.* Predictors of post-operative LVEF by univariate linear regression analysis were pre-operative LVEF, LVESD index, LVESV index, GLS, left atrial volume index, RA area and TAPSE. Multivariate linear analysis was performed to evaluate the independent predictors of post-operative LVEF from variables that were statistically significant in the univariate analysis. The result of the multiple linear regression revealed that pre-operative GLS (B-coefficient -.447, 95% CI -.884 to -.011; p-value = 0.045) was an independent determinant for the dependent variable. The value for VIF was less than 3 for all predictor variables, indicating that multicollinearity was not a problem in the regression model. The model explained 20.7% (R^2 0.207) of the variance of LVEF after surgical corrections. The receiver-operator curve analysis was performed for post-operative LV dysfunction on the basis of global longitudinal strain. The area under the curve for GLS; AUC = 0.712,

(95% CI: 0.521- 0.903), p-value < 0.0001. The optimal cut-off point derived from the ROC curve analysis was -17.8% for GLS with a sensitivity of 55 % and specificity of 87%.

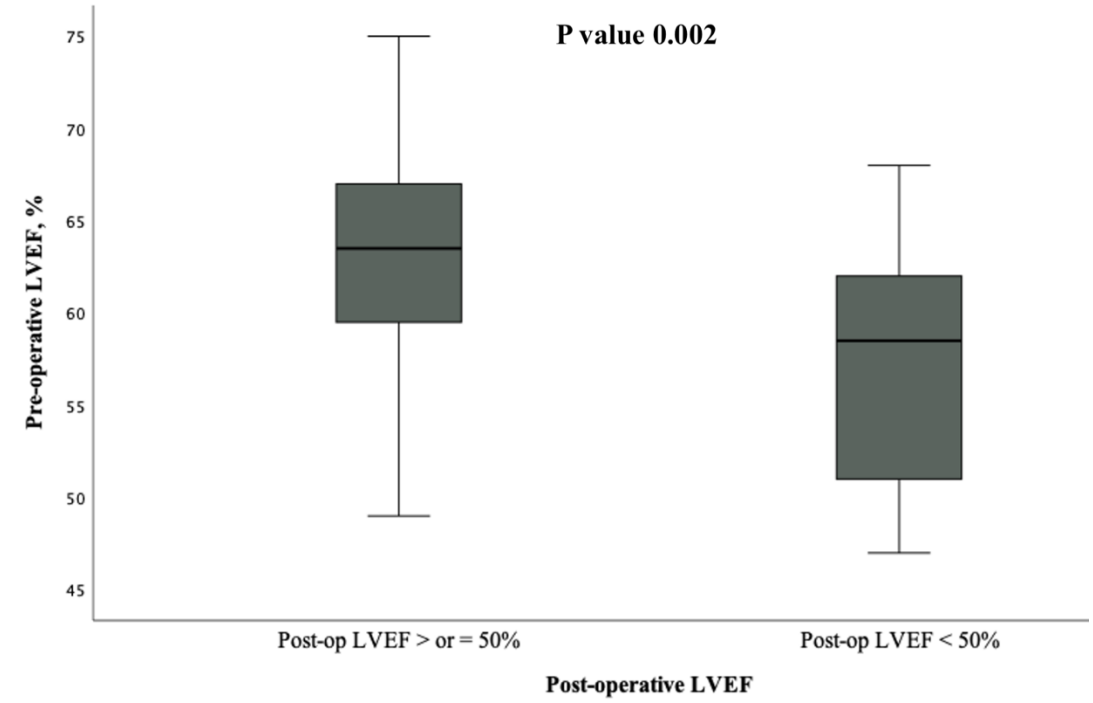
Table 4.5 Univariate and multivariate linear regression analysis with post-operative left ventricle ejection fraction as the dependent variable

Variable	**Univariate**		
	B-coefficient	**95% CI**	P value
Age, years	-.067	-.158 to .023	.142
BMI, kg/m^2	.084	-.128 to .224	.591
LVEDD index, cm/m^2	-1.862	-4.48 to .757	.161
LVESD index, cm/m^2	-4.514	-8.09 to -.937	**.014**
LVEDV index, ml/m^2	-.047	-.102 to .009	.098
LVESV index, ml/m^2	-.176	-.294 to -.059	**.004**
2D-LVEF, %	.320	.132 to .508	**.001**
GLS, %	-.520	-.841 to -.199	**.002**
LAV index, ml/cm^2	-.042	-.081 to -.002	**.039**

PASP, mmHg	-.041	-.14 to .033	.277
TAPSE, cm	.215	.002 to .428	**.048**
RAA, cm2	-.240	-.421 to -.058	**.010**

Variable	**Multivariate**		
	B-coefficient	**95% CI**	P value
LVESD index, cm/m^2	.479	-4.08 to 5.04	.835
LVESV index, ml/m^2	-.107	-.272 to .059	.204
2D-LVEF, %	-.031	-.335 to .273	.839
GLS, %	-.447	-.884 to -.011	**.045**
LAV index, ml/cm^2	-.042	-.092 to .009	.103
TAPSE, cm	.091	-.175 to .340	.467
RAA, cm2	-.050	-.241 to .192	.663

BMI; body mass index, LAV index; left atrial volume indexed, LVEDD; left ventricular end-diastolic diameter, LVESD; left ventricular end-systolic diameter, LVEF; left ventricle ejection fraction, GLS; global longitudinal strain, PASP; pulmonary artery systolic pressure.



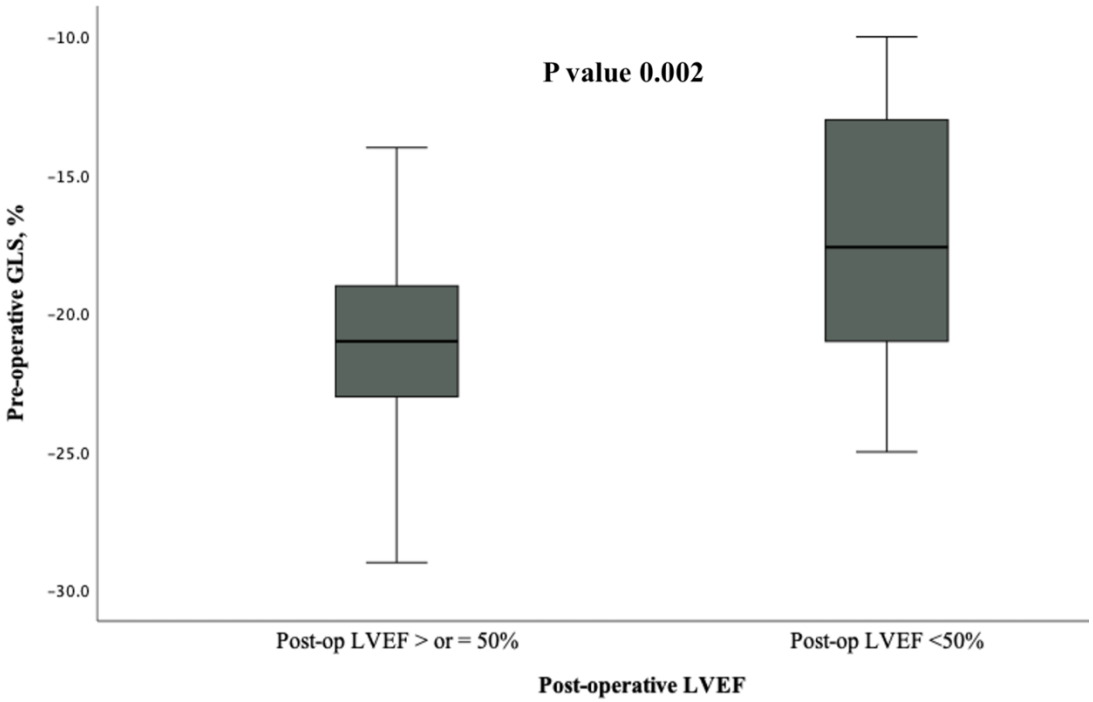


Figure 4.1 Comparison of pre-operative LVEF- top, and pre-operative GLS- bottom, between normal post-operative left ventricle function and post-operative left ventricle dysfunction

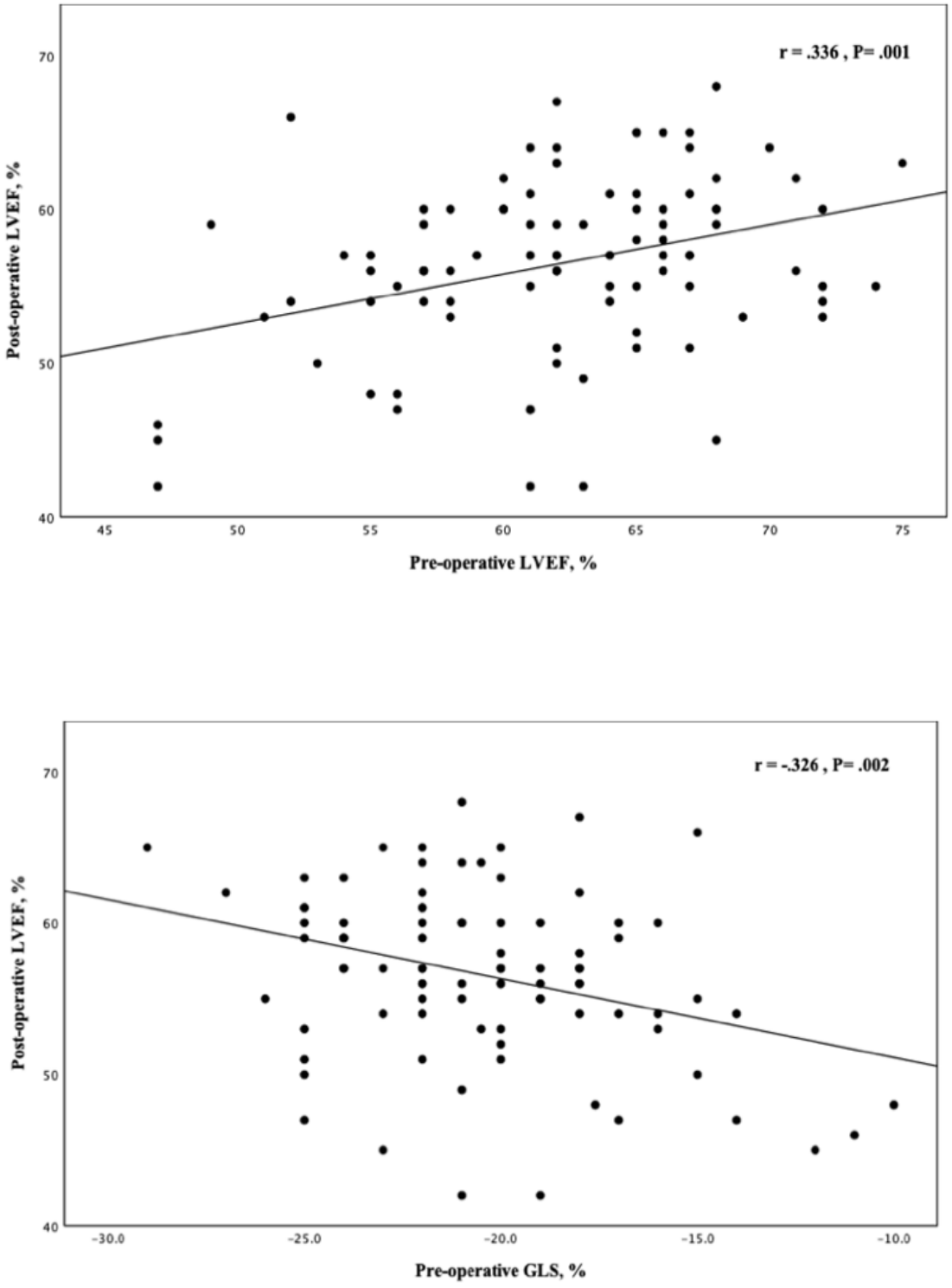
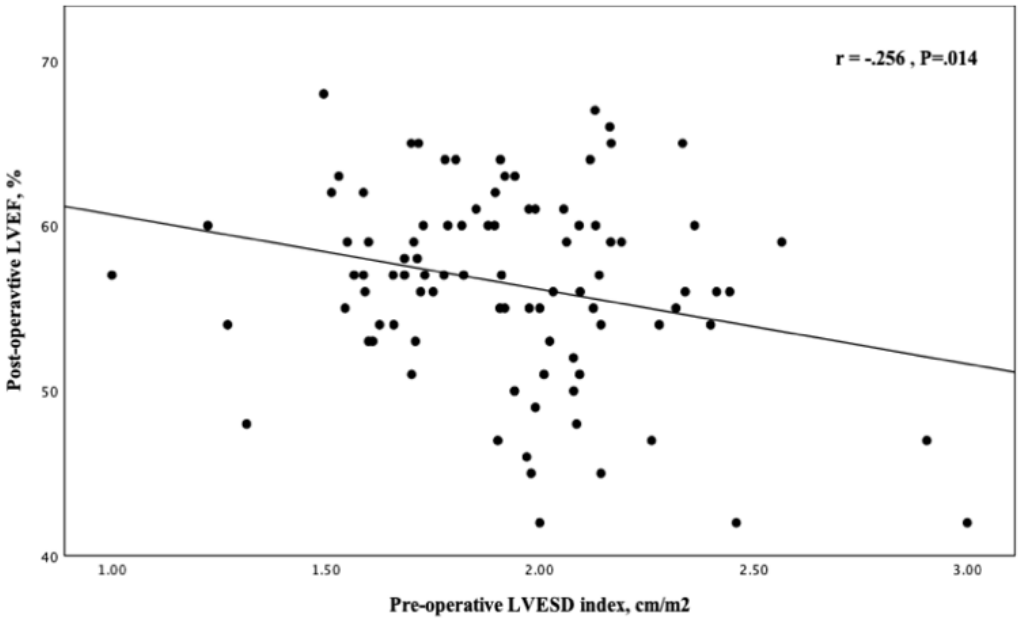


Figure 4.2 Scatterplots for the relationship between post-operative left ventricle ejection fraction and (baseline left ventricle ejection fraction - top and baseline global longitudinal strain - bottom)



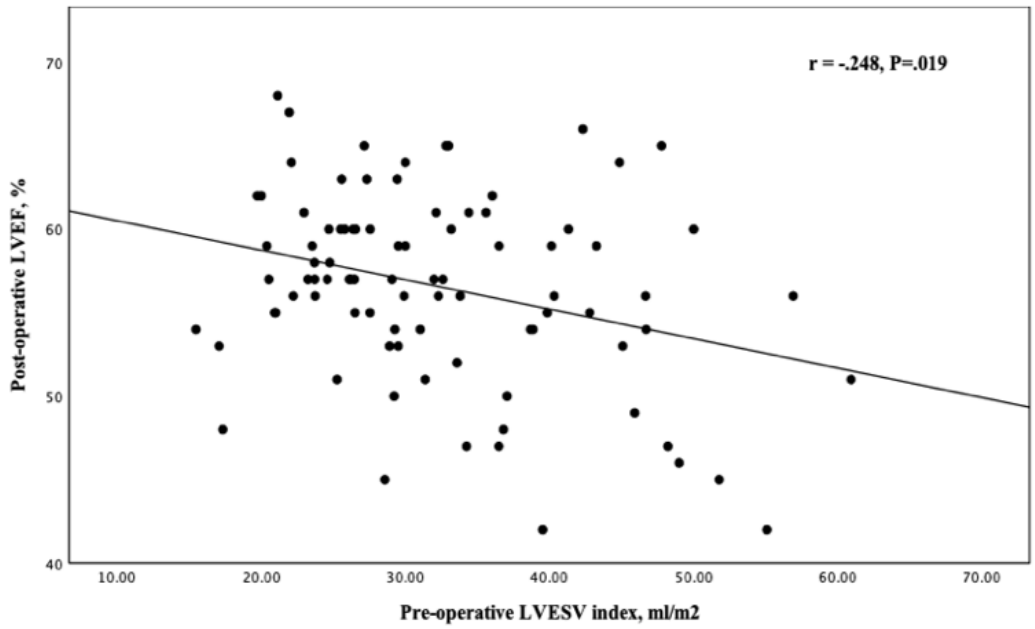


Figure 4.3 Scatterplots for the relationship between post-operative left ventricle ejection fraction and (baseline left ventricle end-systolic diameters- top and left ventricle end-systolic volume – bottom).

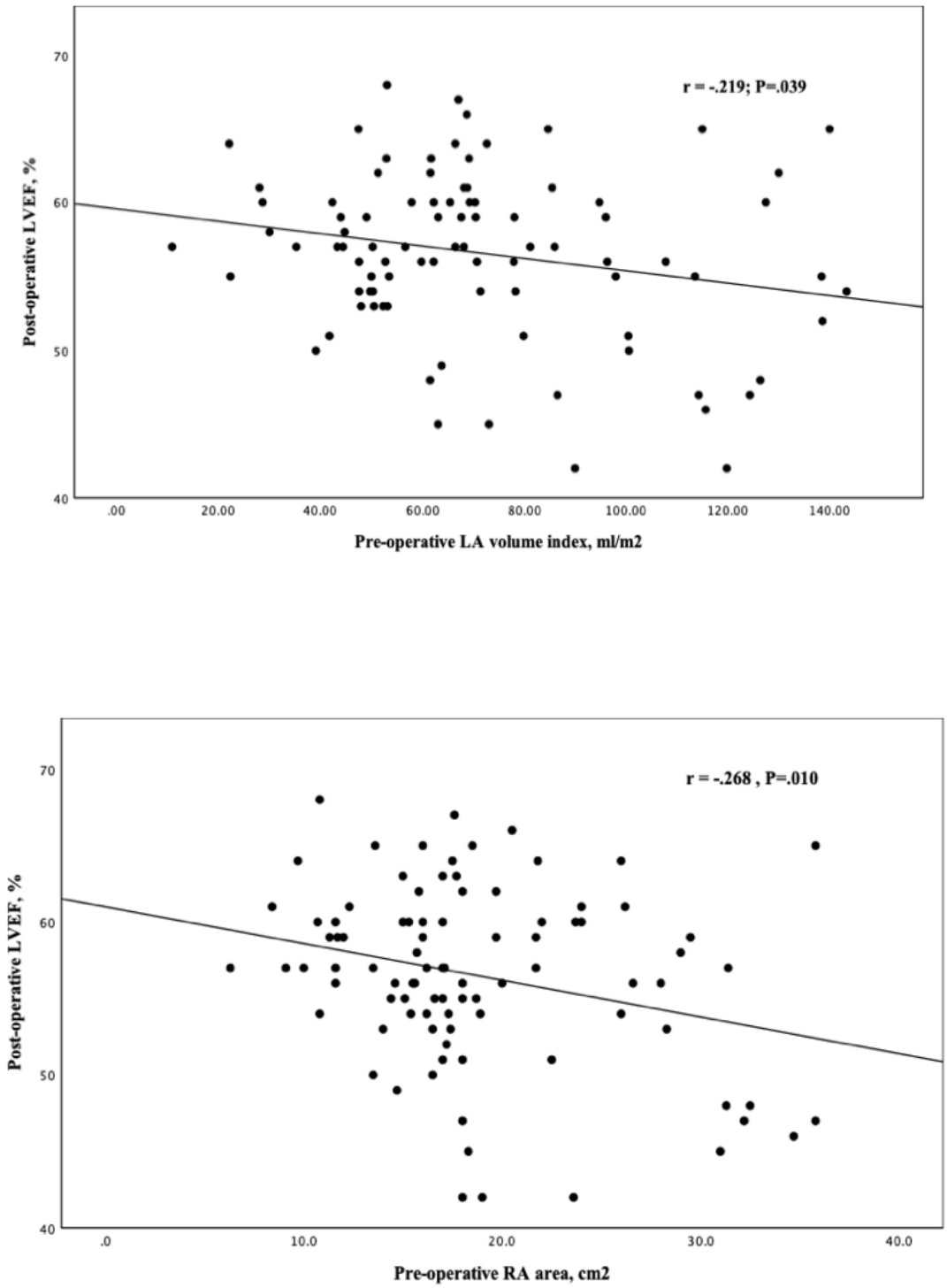


Figure 4.4 Scatterplots for the relationship between post-operative left ventricle ejection fraction and (baseline left atrial volume index- top and right atrial volume- bottom).

4.5 Discussion

In this study in patients with severe primary MR who underwent mitral valve surgical correction, we have shown that 1. Twelve % of patients had a post-operative myocardial dysfunction with LVEF of less than 50%. 2. Pre-operative GLS was associated with all-cause mortality and post-operative LV dysfunction, however, GLS was not an independent predictor. Only age and LVESD were independently associated with post-operative events. 3. GLS was an independent prognostic factor for the prediction of left ventricle dysfunction after mitral valve surgery.

The appropriate timing of mitral valve surgery in mitral valve prolapse remains controversial. Current guidelines recommended mitral valve surgery for symptomatic patients with severe primary MR. In asymptomatic patients with severe MR, mitral valve surgery can be considered in the presence of LV dilatation and/or LV dysfunction, LA dilatation, high systolic pulmonary arterial pressure or in case of new onset atrial fibrillation, specifically when the likelihood of repair is high, and the surgical risk is low. European guidelines recommend MV surgical correction, regardless of symptomatic status, when a decrease in LVEF $\leq$ 60% and/or increase in LVESD $\geq$40 mm is observed, in reference to the increasing evidence of the impact of pre-operative parameters on post-operative outcomes (1). American guidelines support MV surgery if there is a reduction in LVEF or increase in LVESD during follow-up in serial echocardiographic exams, based on the growing evidence that patients profit from surgery mostly when patients still have preserved LV function (2).

Despite these recommendations, optimal timing of mitral valve surgery remains a clinical challenge, since assessment of LV systolic function accurately remains challenging as LVEF and left ventricle dimension may not reflect the true ventricular

systolic function because LVEF is often overestimated by the compensated mechanism of left ventricular volume overload due to severe mitral regurgitation. Myocardial impairment may occur before a subclinical left ventricle systolic dysfunction can be detected (170). Therefore, more attention has focused on determining other parameters which are able to better detect subclinical left ventricular systolic dysfunction and predict post-operative outcomes.

4.5.1 Global longitudinal strain as a prognostic marker for outcomes after mitral valve surgery

Left ventricle global longitudinal strain has been found to be more sensitive and accurate in assessing left ventricle function and current guidelines refer to the potential incremental value of GLS over LVEF for risk stratification in patients with severe primary mitral regurgitation.

The prognostic value of GLS was investigated in previous studies which showed that a more impaired GLS was associated with long-term mortality. Kim et al. (82) retrospectively studied the prognostic value of pre-operative GLS in primary MR patients who underwent mitral valve surgery and reported that GLS was a powerful independent predictor of cardiac events and of all-cause mortality, and appears to be a better predictor than conventional measures. However, among their study population, degenerative mitral regurgitation was not the only group included. Approximately 10% of the patient cohort had rheumatic or congenital mitral regurgitation. In another study, Mentias et al (85) showed that abnormal baseline GLS and reduced exercise capacity were independently associated with higher mortality in patients with asymptomatic significant mitral regurgitation, and GLS offered additive prognostic utility to previously known predictors such as left ventricle dimension and preserved LVEF. However, GLS was measured using

Velocity Vector Imaging. There are inter-vendor differences in the measurement and reporting of GLS and therefore require validation with other vendors. Hiemstra et al (171) studied GLS in patients with primary mitral regurgitation who underwent solely mitral valve repair and reported that GLS is independently associated with cardiovascular events and all-cause mortality.

Our result was in line with the previously mentioned studies showing GLS was associated with post-operative events (mortality and LV dysfunction) alongside conventional parameters. However, in a multivariant logistic regression model, age and LV end-systolic diameter were independently associated with post-operative events. LV end-systolic diameter which is a well-recognised prognostic marker was superior to global longitudinal strain in predicting the outcome after mitral valve surgery.

4.5.2 Global longitudinal strain as predictor of LVEF after mitral valve surgery

Left ventricle dysfunction is not uncommon after mitral valve surgery. We found that approximately 12% of patients developed LV dysfunction (EF<50%). Our proportion is in line with previous studies, Witkowski et al (84) found that the incidence of long-term postoperative LV dysfunction was 12% of 233 patients with organic mitral regurgitation undergoing mitral valve repair.

Several studies have attempted to find pre-operative echocardiographic parameters that are associated with post-operative left ventricle dysfunction. Previous research has found that pre-operative LVEF, LVESD, PASP and GLS were associated with immediately post-operative LVEF (62, 86, 164-166). Florescue (172) et al. studied

28 asymptomatic patients with primary MR and reported that pre-operative GLS predicted a reduction of LVEF <10% at 14 days after mitral valve repair. In a similar study, Pandis et al (86) in a retrospective study of 130 patients found that GLS was an independent predictor of immediate reduction of LVEF >10% (measurements were performed 3 to 4 days after mitral valve surgery). Pandis and colleagues' findings were similer to the Florescue et al study. Patients with post-operative LVEF reductions > 10% had higher baseline GLS compared with patients with LVEF reductions ≤ 10% ($P < .001$). However, these studies investigated post-operative change in LVEF rather than the absolute post-operative value of LVEF as an outcome and they were interested in the immediate post-operative LV function. Our study investigates post-operative LV dysfunction after a longer follow-up period.

Our finding confirms the work of other studies in this area. Muscles et al. (83) in an observational study found that LV GLS added value to LVESD as independent predictors of LV dysfunction <50% after 6 months of mitral valve surgery, however, their study was limited to investigating determinants of post-operative LV dysfunction at 6 months. Our study was obtained with extended follow-up. With longer follow-up, Witkowski et al (84) reported that impaired GLS <19.9% was a strong and independent predictor of long-term post-operative LV dysfunction < 50% together with LVESD ≥40 mm. However, we found that in the multivariate linear regression GLS was the only independent predictor for post-operative reduction <50%.

4.6 Limitation

The relatively small sample size is one of the limitations of this study. Patients with atrial fibrillation were included in the study population. Some previous studies of GLS excluded atrial fibrillation patients because of the variability of the cardiac cycle from beat to beat. However, measurements averaged over several beats in patients with atrial fibrillation is recommended. The end-point of post-operative LV function is important. However, a longer follow-up would allow investigation of the impact of this end-point on heart failure hospitalisations and mortality. The COVID-19 pandemic limited the recruitment of patients due to the temporary cessation of elective cardiac surgery, out-patient and research during the three main COVID-19 waves.

4.7 Conclusion

In patients with severe degenerative MR who underwent mitral valve surgery, pre-operative LVESD and LVEF were predictors of post-operative LV function. However, pre-operative GLS was the only independent predictor of post-operative LV function. Our study confirms the usefulness of LV mechanics assessed by global longitudinal strain and measuring pre-operative GLS may be helpful to determine optimal timing for surgery in patients with severe primary MR.

Chapter 5

Left Atrial Deformation by Two-Dimensional Speckle-Tracking Echocardiography in Patients with Primary Mitral Regurgitation: Association with Symptoms, Functional Capacity and Left Ventricular Remodelling

5.1 Abstract

Background: Left ventricle remodelling is well known as associated with outcomes in primary MR patients. However, chronic MR may induce significant LA changes before LV changes occur. LA strain derived by speckle tracking echocardiography is a novel technique that allows an accurate assessment of all phases of LA function. The aims of this study are to examine the role of LA strain on functional capacity in primary MR patients and to explore its association with post-operative LV function after mitral valve surgery. **Methods and results:** A total of 160 patients with chronic severe primary MR were recruited. LA strain including reservoir, conduit and contractile phases were measured. The primary outcome was the presence of symptoms. Secondary outcomes were 1. reduced functional capacity (VO_2 < 84%) for asymptomatic cohort, and 2. post-operative LV dysfunction (LVEF< 50%) for surgery cohort. LA strain parameters were associated with the presence of symptoms in univariate logistic analysis. However, on multivariate regression analysis, higher PASP was the best independent predictor of symptoms (p-value= 0.001). The multivariate linear analysis demonstrated that reservoir LA strain and E' were independent echocardiographic determinants of $VO_{2\ peak}$ and VE/VCO2 slope. In a univariate model, reservoir LA strain was associated with post-operative LVEF. However, in multivariate analysis, pre-operative LA volume and GLS were the only independent predictors of post-operative LVEF. **Conclusion:** LA strain was associated with heart failure symptoms, however, higher PASP was the best independent predictor of symptoms. LA strain could be valuable in evaluating the functional capacity quantified by CPET. In addition, LA strain demonstrated an association with post-operative LV dysfunction, but LA volume and GLS were better predictors. Assessment of LA strain may offer additional information about cardiac performance, which could help in the prognosis of primary MR patients.

5.2 Introduction

Severe LA dilatation is a pathological response to left atrial volume overload in severe chronic mitral regurgitation, aimed to maintain left atrial pressure and prevent pulmonary congestion (173). An increased left atrial volume is considered to be a powerful predictor of poor outcomes in severe organic mitral regurgitation, even in patients without symptoms or with preserved left ventricle ejection fraction (174). Left ventricle remodelling is well known to be associated with cardiac outcomes (82, 84), However, chronic MR may induce significant left atrial changes, potentially affecting left atrial myocardial contractility and relaxation before left ventricle changes occur. The assessment of left atrial size and function may offer additional information about cardiac performance, which could help in identifying the subclinical myocardial dysfunction. Speckle tracking echocardiographic deformation analysis of left atrial strain is a unique tool which allows an accurate assessment of all phases of atrial function including reservoir, conduit and contractile phases.

Therefore, the aims of this study were (1) to characterise left atrial reservoir, conduit, and contractile function using speckle-tracking deformation imaging in patients with chronic moderate to severe or severe primary MR; (2) to determine its clinical relation to the other conventional LV and LA parameters for the prediction of cardiac outcomes; (3) to examine the role of LA strain on functional capacity; and (4) to explore its association with post-operative left ventricle function after mitral valve surgery.

5.3 Method

5.3.1 Study population

In this chapter, 177 patients with severe primary mitral regurgitation were initially recruited. Seventeen participants were excluded from data analyses due to the insufficient quality of data. Therefore, the remaining 160 patients were included in this analysis. All patients had moderate to severe or severe mitral regurgitation due to a prolapse or flail leaflet.

5.3.2 Clinical assessments

A comprehensive baseline transthoracic echocardiography and offline left atrial strain analysis measured using speckle tracking analysis were performed for all patients in this study population. The two cohorts were included in the study population, 1. Asymptomatic cohort of 87 patients with moderate to severe or severe MR who underwent exercise echocardiography combined with cardiopulmonary exercise test and 2. Surgery cohort of 89 patients with severe primary MR who had mitral valve surgery and underwent pre- and post-operative echocardiographic evaluation. Echocardiographic measurements including left atrial deformation, exercise stress echocardiography and cardiopulmonary exercise test are described in detail in the methods chapter (chapter 2).

5.3.3 Follow-up and outcome analysis

Patients in the surgery cohort were asked to return for follow-up echocardiography 12 months after surgery. Experienced mitral valve surgeons performed all surgical procedures. The primary outcome of this study was the presence of symptoms according to NYHA functional classification (NHYHA > I). The secondary outcomes were 1. reduced functional capacity assessed by CPET (defined as a predicted $VO_{2\ peak}$ was less

than 84%) for the asymptomatic patient cohort, 2. post-operative left ventricle dysfunction (defined as an LVEF less than 50%) for the surgery cohort.

5.3.4 Statistical analysis

Statistical analysis was performed using SPSS version 27.0 (SPSS, Inc, Chicago, IL). All data are expressed as mean ± SD unless otherwise stated. Left atrial strain phasic functions (reservoir strain, conduit strain and contractile strain) were approximately normally distributed. X_2 test for categorical variables and student t-test or Mann-Whitney test for continuous variables was used for the difference of clinical and echocardiographic variables between 1. symptomatic versus asymptomatic patients, 2. patient with normal versus reduced functional capacity (Appendix C), and 3. patients with normal versus impaired LVEF, as appropriate. Univariate logistic analysis was used to identify variables with significant association with symptoms and were entered into multivariate logistic regression analysis to determine whether atrial deformation parameters could predict symptoms. The correlation between $VO_{2\ peak}$ and $VE/VCO_{2\ slope}$ and relevant parameters was investigated using Pearson correlation coefficients or Spearman coefficients, where appropriate. Univariate and multivariate linear regression analysis was used to identify determinants of $VO_{2\ peak}$ and $VE/VCO_{2\ slope}$. Univariate logistic regression was used to test the association between LA strain and subsequent need of surgery (Appendix C). To test LA deformation parameters in predicting post-operative left ventricle dysfunction, univariable and multivariable linear regression analyses were performed, introducing other well-established independent predictors. All variables significant in the univariate analysis were entered into the multivariate model. Multivariate models' fit was assessed by the Hosmer–Lemeshow approach. To determine if multicollinearity was not a concern, a collinearity diagnostic test was performed on the data. A variance inflation factor (VIF)

cut-off value of 5 was used for the multivariable model, and only variables with a VIF under 5 were included(153). P-values < 0.05 was considered statistically significant.

5.4 Results

5.4.1 Baseline study data

We divided the patients into two groups: Symptomatic and Asymptomatic, 71 (44%) patients had symptoms **(**≥NYHA II), and 89 (56%) patients were asymptomatic (NYHA I). The clinical demographics of the patients according to the presence of symptoms are presented in *Table 5.1*. The overall age of the study population was 61 ±15 years. Patients with symptoms were older than asymptomatic patients (65 ±14 years versus 56 ± 16 years, p-value = 0.003). Heart rate was similar in the two groups. The systolic blood pressure was higher in asymptomatic patients than in symptomatic patients and diastolic pressure was comparable between the groups. A higher prevalence of atrial fibrillation was found in the group with symptoms than in the group without symptoms (20% versus 2%, p-value < 0.0001). The use of ACE inhibitors, diuretics and anticoagulation were more frequent in the symptomatic group.

Table 5.1 Baseline characteristics of the patient population according to the occurrence of symptoms.

Variables	All patients (n= 160)	Asymptomatic n=89 (56%)	Symptomatic n=71 (44%)	P-value
Age, years	61 ± 15	56± 16	65 ±14	**.003**

Male, n (%)	96 (60)	60 (67)	36 (51)	**.032**
Height, cm	171 ± 10	173± 10	169 ± 11	**.024**
Weight, kg	73 ± 14	73 ± 14	72 ± 15	.596
Body mass index, kg/m^2	25 ± 3.5	25 ± 3	25± 4	.247
Heart rate, bpm	73 ± 14	73 ± 13	73 ± 15	.585
Systolic BP, mmHg	136 ± 17	138 ± 17	132 ±16	**.011**
Diastolic BP, mmHg	77 ± 10	78 ± 9	76 ±11	.180
Risk Factors, n (%)				
AF	16 (10)	2 (2)	14 (20)	**.000**
Hypertension	49 (31)	19 (21)	30 (42)	**.004**
Hypercholesterolaemia	33 (21)	9 (10)	24 (34)	**.000**
Smoking	36 (23)	11 (12)	25 (35)	**.001**
Medications n, (%)				
Beta Blocker	44 (28)	21 (24)	23 (32)	.202
ACE inhibitors	31 (19)	9 (10)	22 (31)	**.001**
Diuretics	19 (12)	6 (7)	13 (18)	**.025**

Warfarin	6 (4)	2 (2)	4 (6)	.269
Antiplatelet agent	16 (10)	11 (12)	5 (7)	.473
Statin	30 (19)	19 (21)	11 (16)	.346
Amlodipine	12 (8)	8 (9)	4 (6)	.703
Anticoagulant	19 (12)	6 (7)	13 (18)	**.025**
ARBs	10 (6)	4 (5)	6 (9)	.304

AF; Atrial fibrillation, BP; blood pressure; ACE; Angiotensin-converting enzyme, ARBs; Angiotensin receptor blockers.

5.4.2 Echocardiography data

Table 5.2 shows the difference in baseline echocardiographic parameters between symptomatic and asymptomatic patients. Measures of left atrial size showed that left atrial diameter, area and volume were significantly larger in patients with symptoms compared to patients without symptoms. Systolic function assessed by LVEF, S' velocity and GLS were comparable in both groups. Left ventricle dimensions and volumes were not significantly different.

Patients with symptoms had significantly higher pulmonary artery systolic pressure than patients without (PASP 33 ± 17 mmHg versus 16 ±9 mmHg, p-value < 0.0001). Measures of diastolic function showed that patients with symptoms had a higher E wave, lower deceleration time, lower E' wave and higher E/E' ratio (12.2 ± 3.8 versus 9.8 ± 3.4 p-value < 0.0001), E/A ratio did not differ between the two groups.

Left atrial strain parameters

Reservoir left atrial strain ranged from 6 % to 43 % with a mean of 23 ± 8 %. The overall mean value of conduit left atrial strain was -14 ± 6 % and contractile left atrial strain mean was -8 ± 5 %. Left atrial strain was significantly more impaired among those with symptoms compared to those without symptoms: Reservoir left atrial strain (21 ± 8 % versus 25 ± 8 %; p-value = 0.001), conduit left atrial strain (-13 ± 6% versus -15 ± 5% p-value = 0.026) and contractile left atrial strain (-7 ± 5% versus -9 ± 5%, p-value = 0.034).

Table 5.2 Baseline echocardiographic parameters according to the occurrence of symptoms

Variables	All patients (n=160)	Asymptomatic n=89 (56%)	Symptomatic n=71 (44%)	P-value
LA diameter, cm	4.3 ± 0.9	4.2 ± 0.8	4.6 ± 0.8	**.003**
LAD indexed, cm/m^2	2.4 ± 0.5	2.3 ± 0.5	2.5 ± 0.5	**.000**
LA area, cm^2	30 ± 10	27 ± 8	35 ±13	**.000**
LAV, ml	116 ± 53	103 ± 45	133 ± 57	**.000**
LAV indexed, ml/cm^2	64 ± 29	56 ± 25	74 ± 32	**.000**
LVEDD, cm	5.5 ± 0.7	5.6 ± 0.6	5.5 ± 0.8	.373
LVEDD indexed, cm/m^2	3.0 ± 0.4	3.0 ± 0.4	3.0 ± 0.6	.440

LVESD, cm	3.4 ± 0.6	3.4 ± 0.5	3.5 ± 0.6	.176
LVESD indexed, cm/m^2	1.9 ± 0.3	1.9 ± 0.3	1.9 ± 0.4	.273
LVEDV, ml	147 ± 47	145 ± 41	150 ± 53	.895
LVEDV indexed, ml/cm^2	79 ± 22	77 ± 20	81 ± 23	.373
LVESV, ml	51 ± 20	54 ± 17	58 ± 23	.712
LVESV indexed, ml/cm^2	30 ± 9	29 ± 8	31 ± 10	.242
LVEF, %	62 ± 6	63 ± 5	62 ± 6	.658
LV S' average, m/s	9.8 ± 2.6	10.2 ± 2.7	9.4 ± 2.5	.097
PASP, mmHg	26 ± 15	20 ± 11	33 ± 17	**.000**
RV S', m/s	15 ± 3	15 ± 3	15 ± 3	.792
TAPSE, mm	24 ± 5	25 ± 5	24 ± 6	.360
E/A ratio	1.7 ± 0.7	1.7 ± 0.6	1.8 ± 0.7	.593
E wave, m/s	1.1 ± 0.3	1.0 ± 0.3	1.2 ± 0.3	**.031**
DT, ms	210 ± 64	219 ± 68	198 ± 58	**.027**
E' wave, m/s	10.4 ± 2.8	11 ± 2.7	9.8 ± 2.7	**.003**
E/E' ratio	10.8 ± 3.8	9.8 ± 3.4	12.2 ± 3.8	**.000**

GLS, %	- 20 ± 3	-20 ± 3	-20 ± 4	.714
Reservoir LAS, %	23 ± 8	25 ± 8	21 ± 8	**.001**
Conduit LAS, %	-14 ± 6	-15 ± 5	-13 ± 6	**.026**
Contractile LAS, %	-8 ± 5	-9 ± 5	-7 ± 5	**.034**

LA; left atrium, LAD; left atrial diameter, LAV; left atrial volume, LVEDD; left ventricular end-diastolic diameter, LVESD; left ventricular end-systolic diameter, LVEDV; left ventricular end-diastolic volume, LVESV; left ventricular end-systolic volume, LVEF ; left ventricle ejection fraction, RV; right ventricle, PASP; pulmonary artery systolic pressure, S'; systolic longitudinal velocity, TAPSE; tricuspid annular plane systolic excursion, E/A; ratio of the early to late ventricular filling velocities, DT; deceleration time, E; early passive filling of the left ventricle, E'; mitral annular early diastolic velocity, E/E'- ratio between early mitral inflow velocity and mitral annular early diastolic velocity, GLS; global longitudinal strain, LAS; left atrial strain.

5.4.3 The association between the presence of symptoms and left atrial strain

Table 5.3 shows the result for the logistic regression models with symptoms as the dependent variable. On univariate analysis, LA strain showed a significant association with symptoms. Reservoir LA strain (Wald statistic 8.522, odds ratio: 0.937, 95% CI: 0.897 to 0.98; p-value = 0.004), conduit LA strain (Wald statistic 4.826, odds ratio: 1.070, 95% CI: 1.007 to 1.14; p-value = 0.028) and contractile LA strain (Wald statistic 5.972, odds ratio: 1.088, 95% CI: 1.01 to 1.163; p-value = 0.015). The other variables that had an association with symptoms were age, left atrial volume, PASP, and E' wave. Other parameters for ventricular remodelling including left ventricle size, LVEF and GLS were not associated with symptoms.

The result of the multiple logistic regression after sequential inclusion of all parameters from the univariant analysis revealed that only pulmonary artery systolic pressure (Wald statistic 11.374, odds ratio: 1.075, 95% CI: 1.031 to 1.120; p-value = 0.001) was an independent predictor of symptoms. The predictor variables were not highly correlated with each other. VIF values were less than 2. The model explained 35% (Nagelkerke R^2) of the variance and correctly classified 72% of cases. The Hosmer and Lemeshow test showed that the model was a good fit to the data as p-value = 0.954 (>.05). The association of left atrial strain parameters and symptoms was not independent when they were included in the multivariate logistic regression model, reservoir LA strain (p-value = 0.069), conduit LA strain (p-value = 0.239) and contractile LA strain (p-value = 0.295). *Figure 5.1* shows a comparison of pulmonary artery systolic pressure and left atrial strain between symptomatic and asymptomatic groups.

Table 5.3 Univariable and multivariable logistic regression analysis for variables associated with symptoms

Variable	**Univariable**		
	Wald statistic	Odds ratio (95% CI)	P-value
Age, years	8.819	1.04 (1.012 to 1.059)	**.003**
LAVI, ml/m^2	11.96	1.012 (1.005 to 1.02)	**.001**
PASP, mmHg	23.54	1.084 (1.05 to 1.112)	**.000**

E’ wave, m/s	6.976	0.842 (0.740 to 0.97)	**.008**
LVESDI, cm	1.807	1.961 (0.735 to 5.235)	.179
LVEDV, ml	1.267	1.008 (0.994 to 1.023)	.260
LVEF, %	1.147	.970 (0.918 to 1.025)	.284
GLS, %	.058	1.012 (0.918 to 1.116)	.809
Reservoir LAS, %	8.522	0.937 (0.897 to 0.98)	**.004**
Conduit LAS, %	4.826	1.070 (1.007 to 1.14)	**.028**
Contractile LAS, %	5.972	1.088 (1.01 to 1.163)	**.015**

Variables	**Multivariable**		
	Wald statistic	Odds ratio (95% CI)	P-value
Age, years	.644	0.985 (.950 to 1.022)	.422
LAVI, ml/m^2	1.814	1.011 (.995 to 1.027)	.178
PASP, mmHg	11.374	1.075 (1.031 to 1.120)	**.001**
E’ wave, m/s	3.112	0.860 (.728 to 1.017)	.078
Reservoir LAS, %	2.612	0.954 (.954 to 1.010)	.106

CI; confidence interval, LAVI; left atrial volume indexed, PASP; pulmonary artery systolic pressure. E'; mitral annular early diastolic velocity, LAS; left atrial strain.

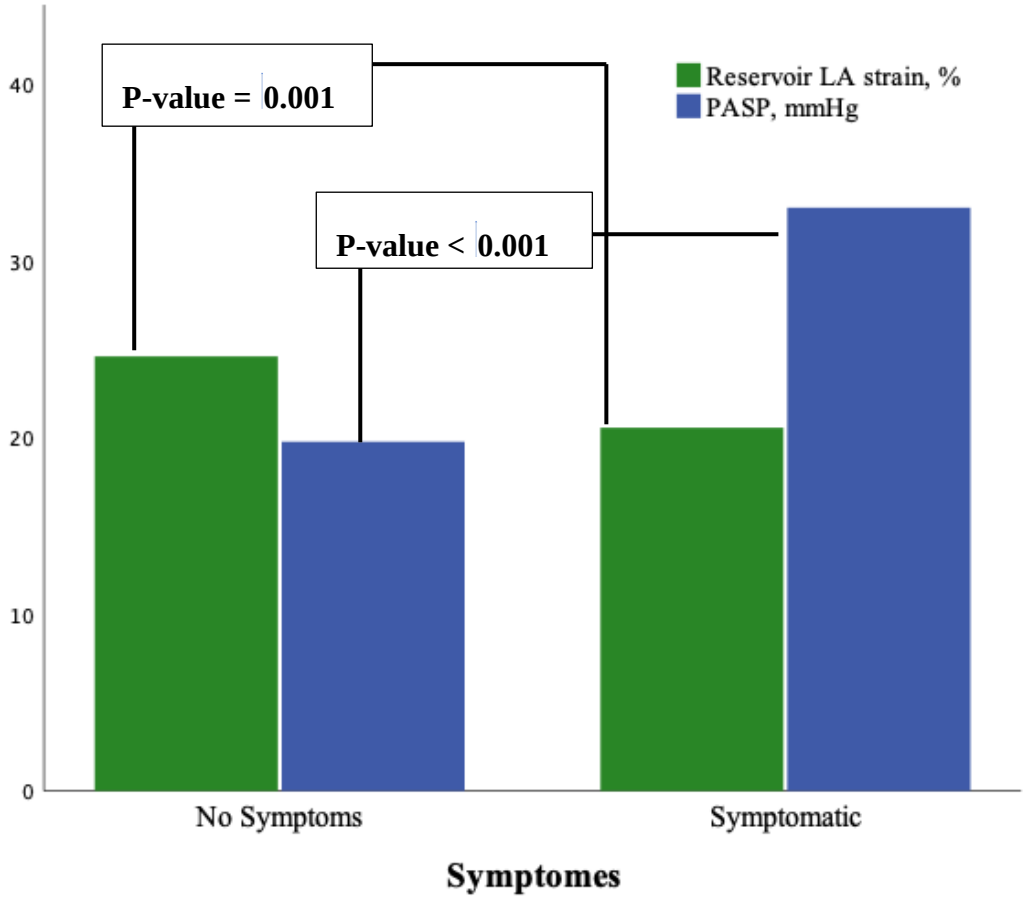


Figure 5.1 Pulmonary artery systolic pressure and reservoir left atrial strain in symptomatic patients and in asymptomatic patients

5.4.4 Determinants of left atrial strain

5.4.4.1 The Association between left atrial strain and echocardiographic parameters

Table 5.4 shows the relationship of the reservoir and the conduit LA strain with echocardiographic parameters. Reservoir LA strain was negatively correlated with age, LA diameters, LA volume and GLS and positively correlated with longitudinal systolic function (LVEF and S' wave) (*Figure 5.2, 5.3 and 5.4*). All showed significant but weak correlation. The best correlation with LA strain was found with age (r = -.480, p-value < 0.0001) and S' wave (r = .437, p-value < 0.0001).

Conduit LA strain was positively correlated with age (r = .482, p-value < 0.0001), and there was a significant but weak correlation with left ventricular systolic function parameters (LVEF, GLS and S' wave).

LA strain was not related to the severity of mitral regurgitation (ERO and R Vol) nor pulmonary artery systolic pressure. LA strain showed no correlation with left ventricle dimensions nor volumes (p-value > 0.05).

Table 5.4 Correlation of reservoir LA strain with echocardiographic parameters.

Variables	Reservoir LA		Conduit LA strain	
	r	p-value	r	p-value

Age	-.480	**.000**	.482	**.000**
LADI, cm/m2	-.255	**.001**	.147	.964
LAVI, ml/m2	-.202	**.011**	.038	.631
LVDDI, cm/m2	-.007	.934	-.114	.149
LVSDI, cm/m2	-.097	.222	-.060	.451
LVDVI, ml/m2	.170	.032	-.305	**.000**
LVSVI, ml/m2	-.001	.992	-.156	**.049**
PASP, mmHg	-.265	.130	.130	.103
S’ wave, m/s	.437	**.000**	-.324	**.000**
LVEF	.302	**.000**	-.203	**.010**
GLS	-.363	**.000**	.316	**.000**
ERO	-.004	.962	-.064	.472
R Vol	.108	.223	.014	.912
E wave, m/s	.060	.472	-.260	.002
E/E’	-.269	**.001**	.162	.058

LAS; left atrial strain. LADI; left atrium diameter indexed, LAVI; left atrial volume indexed, LVEDDI; left ventricular end-diastolic diameter indexed, LVESDI; left ventricular end-

systolic diameter indexed, LVEDVI; left ventricular end-diastolic volume indexed, LVESVI; left ventricular end-systolic volume indexed, LVEF ; left ventricle ejection fraction, PASP; pulmonary artery systolic pressure, S'; left ventricle systolic longitudinal velocity, E'; mitral annular early diastolic velocity, E/E'- ratio between early mitral inflow velocity and mitral annular early diastolic velocity, GLS; global longitudinal strain.

5.4.4.2 Linear regression analysis to predict reservoir left atrial strain

Table 5.5 shows a linear regression analysis with reservoir left atrial strain as the dependent variable. In univariate regression analysis: there was a positive association between reservoir left atrial strain and age, LA volume, LVEF, S' wave, GLS and diastolic function assessed by E/E' ratio.

Multivariable analysis was performed for the identification of the independent association of left atrial strain. Age (β -coefficient -0.159, 95% CI: -0.245 to -0.072, p-value < 0.0001) and GLS (β -coefficient -0.557, 95% CI: -0.995 to -0.119, p-value = 0.013) remained independently associated with reservoir LA strain. The data in the multivariate regression analysis (table 5.5) met the assumption that multicollinearity was not a problem, VIF values were less than 2. The overall model fit was R^2 = .370.

Table 5.5 Univariate and multivariate regression analysis with reservoir LA strain as the dependent variable.

Variables	**Univariate analysis**		
	β -coefficient	**95% CI**	**P value**

Age, years	-.245	-.315 to -.175	**.000**
LAVI, ml/m^2	-.053	-.094 to -.013	**.011**
LVEF	.408	.206 to .611	**.000**
S' wave	1.294	.871 to 1.718	**.000**
GLS	-.873	-1.228 to -.518	**.000**
E/E'	-.526	-.847 to -.206	**.001**
Variables	**Multivariate analysis**		
	β -coefficient	**95% CI**	**P value**
Age, years	-.159	-.245 to -.072	**.000**
LAVI, ml/m^2	-.028	-.069 to .014	.187
LVEF	.124	-.112 to .360	.302
S'	.432	-.077 to .940	.095
GLS	-.557	-.995 to -.119	**.013**
E/E'	-.175	-.501 to 152	.292

CI; confidence interval, LAVI; left atrial volume indexed, LVEF; left ventricle ejection fraction, S'; left ventricle systolic longitudina**l** velocity, GLS; global longitudinal strain, E/E'; ratio of the early to late ventricular filling velocities.

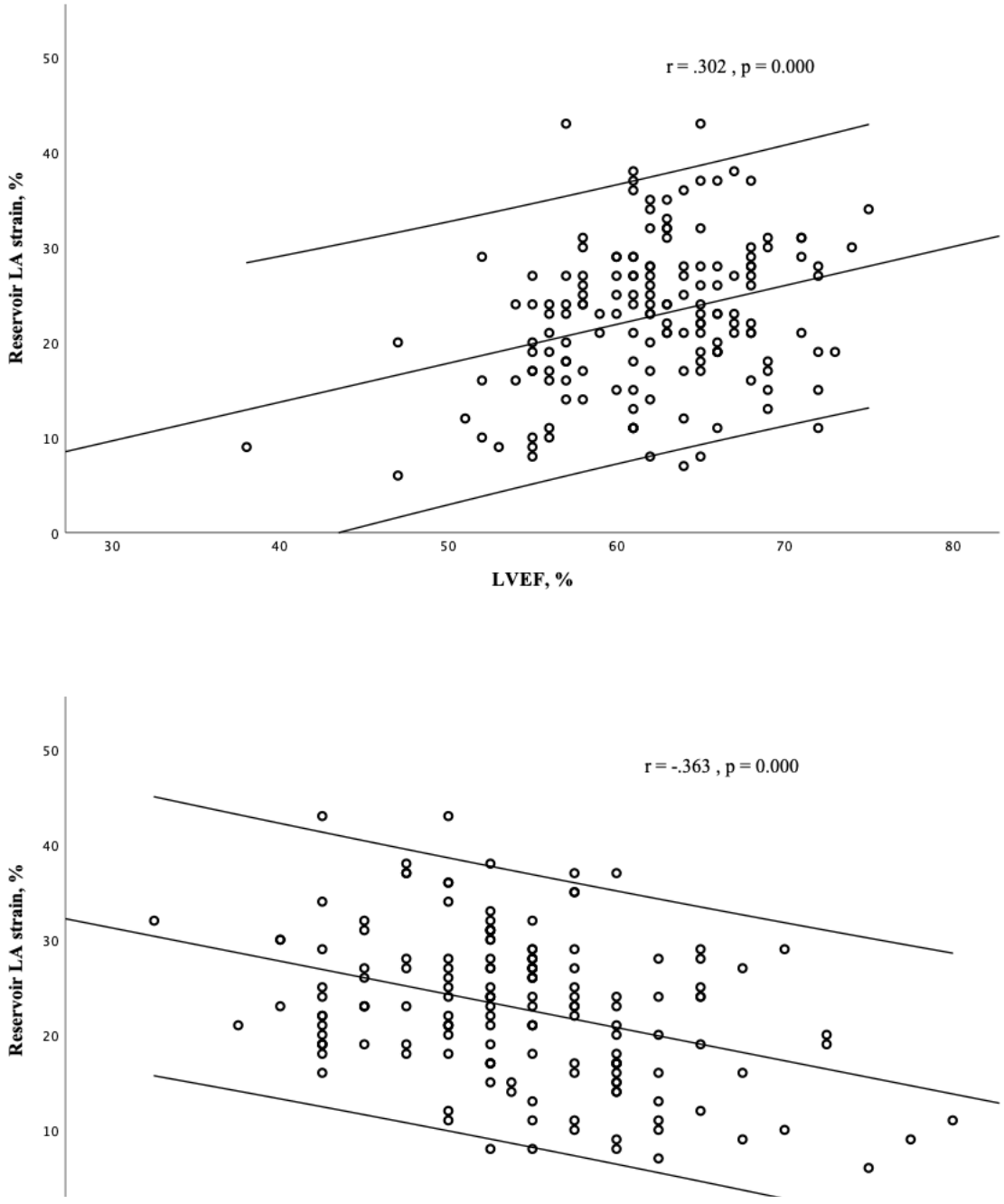


Figure 5.2 Scatterplots for the relationship between reservoir left atrial strain and (left ventricle ejection fraction - top and global longitudinal strain - bottom)

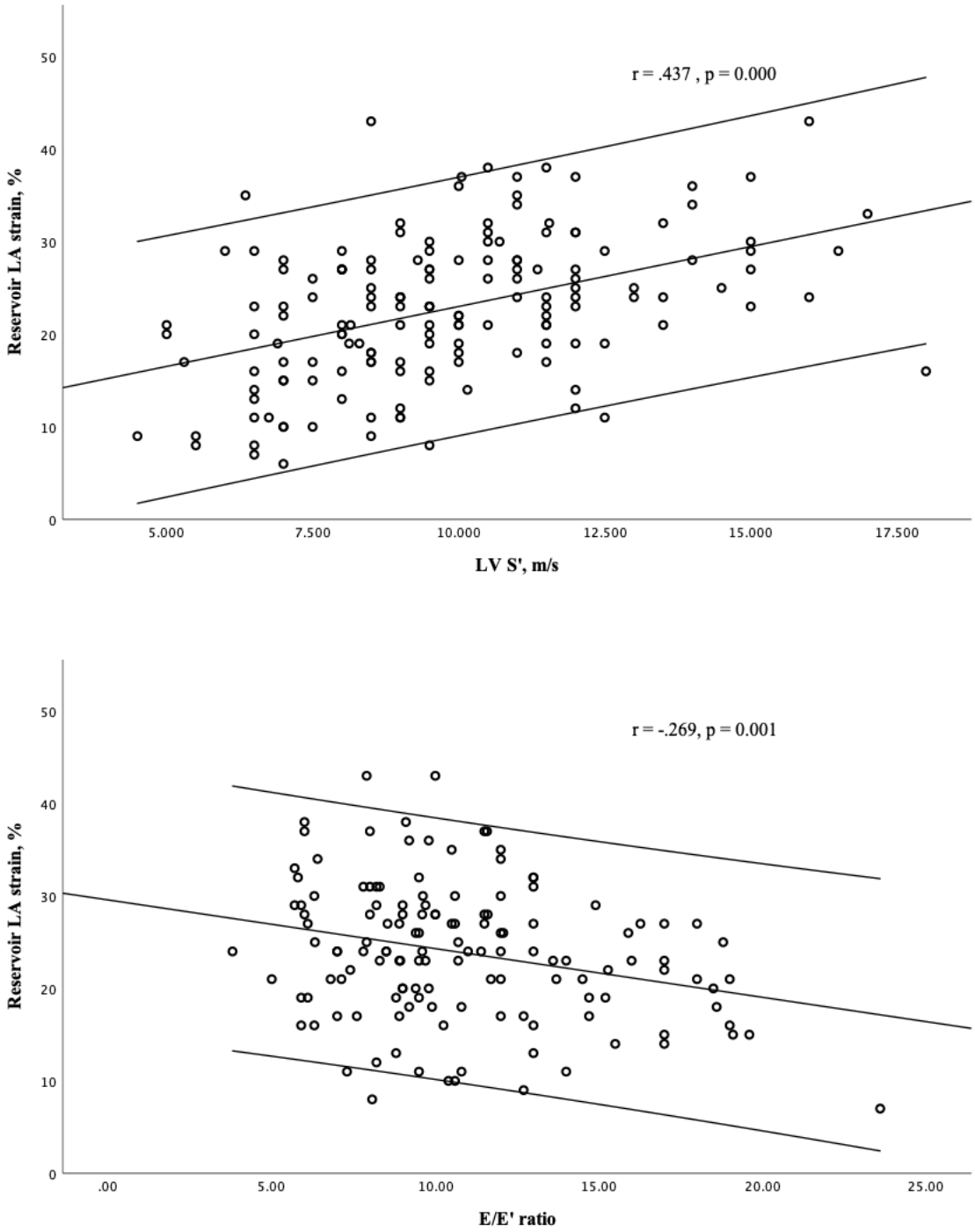
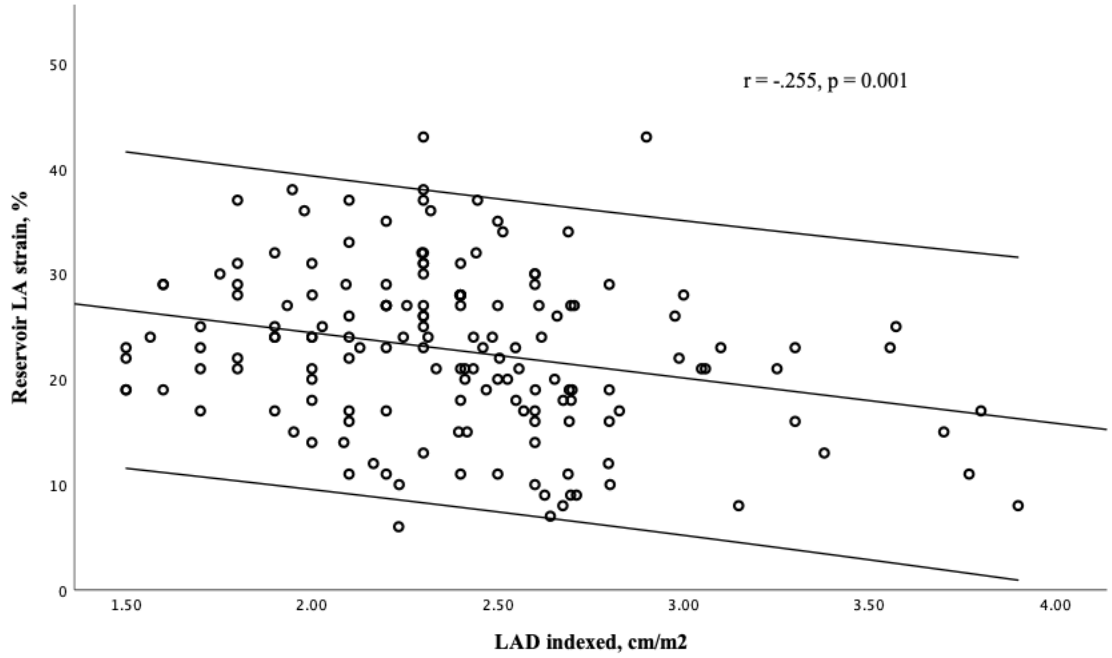


Figure 5.3 Scatterplots for the relationship between reservoir left atrial strain and (S' wave - top and E/E' ratio - bottom)



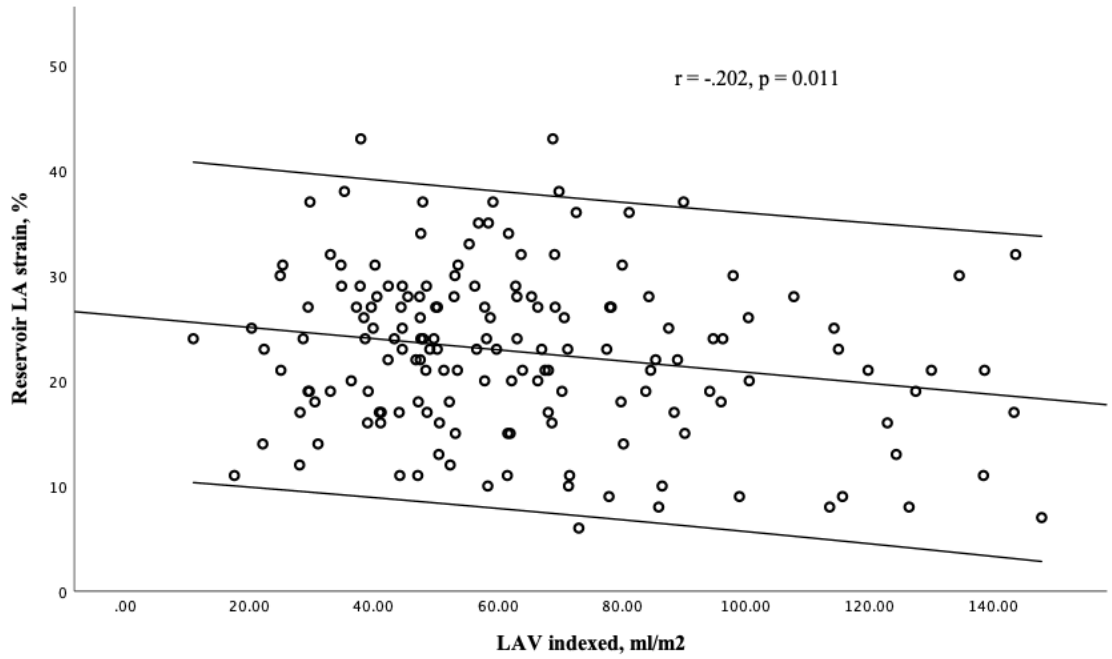


Figure 5.4 Scatterplots for the relationship between reservoir left atrial strain and (left atrial diameter - top and left atrial volume - bottom)

5.4.5 The association between the functional capacity and left atrial strain

In this sub-analysis, we included the cohort of asymptomatic patients who underwent stress echocardiography and cardiopulmonary exercise testing. 44 (51%) patients had reduced functional capacity ($VO_{2\ peak}$ < 84% predicted) and 43 (49%) patients had a normal functional capacity. Age, sex, body mass index, blood pressure and heart rate did not differ between the two groups. in addition, left atrial strain measures and all echocardiographic parameters were comparable between the two groups. *Table 5.6* shows left atrial strain parameters of the asymptomatic population according to the functional capacity.

Table 5.6 Left atrial strain parameters of the population according to the functional capacity.

Variable	**Normal functional capacity (n= 43 (49%))**	**Reduce functional capacity (n= 44(51%))**	***p-value***
Reservoir LAS, %	25 ± 7	23 ± 8	.272
Conduit LAS, %	-16 ± 6	-14 ± 5	.355
Contractile LAS, %	-10 ± 4	-9 ± 6	.110

LAS; Left atrial strain.

5.4.5.1 Relationship of left atrial strain with $VO_{2\ peak}$ and $VE/VCO_{2\ slope}$

Table 5.7 demonstrates the correlation between echocardiographic parameters with relative $VO_{2\ peak}$ and VE/VCO_2 slope. Age was more strongly correlated with $VO_{2\ peak}$ and VE/VCO_2 slope than any echo parameter. Eight echo parameters correlated with relative $VO_{2\ peak}$, however, all the correlation coefficients were low. Left ventricle volume, diastolic function and left atrial strain were correlated with relative $VO_{2\ peak.}$ Whereas, left ventricle end-diastolic volume, LVEF, S' wave, diastolic function and left atrial strain were correlated with VE/VCO2 slope.

LA strain was linked with exercise capacity. Reservoir LA strain was positively correlated with $VO_{2\ peak}$ (r = 0.327, p-value < 0.0001) and negatively correlated with VE/VCO_2 slope (r = - 0.325, p-value = 0.002), conduit LA strain was negatively correlated with $VO_{2\ peak}$ (r = - 0.367, p-value < 0.0001) and positively correlated with VE/VCO_2 slope (r = 0.357, p-value = 0.001). Contractile LA strain was not associated with both $VO_{2\ peak}$ and VE/VCO_2 slope.

Table 5.7 Correlation of relative $VO_{2\ peak}$ and VE/VCO_2 slope with echocardiographic parameters.

variables	Correlation with relative $VO_{2\ peak}$ (ml/kg/min)		Correlation VE/VCO_2 slope	
	r	p-value	r	p-value
Age, years	-.503	**.000**	.483	**.000**
Heart rate, bpm	.070	.517	-.098	.100

LVEDV, ml	.233	**.030**	-.220	**.040**
LVESV, ml	.219	**.042**	-.255	**.017**
LVEF, %	.056	.608	.098	.364
S’ wave, m/s	.252	**.018**	-.283	**.008**
E/A	.222	**.048**	-.201	.074
E’	.388	**.000**	-.325	**.004**
E/E’	-.256	**.024**	.211	.066
LAV, ml	.147	.175	.078	.464
ERO, mm2	.030	.801	-.006	.958
MR-RV	.018	.881	.126	.265
PASP, mmHg	-.101	.353	.257	**.016**
GLS, %	-.077	.488	-.005	.962
Reservoir LAS, %	.327	**.000**	-.325	**.002**
Conduit LAS, %	-.367	**.000**	.357	**.001**
Contractile LAS, %	-.135	.212	.164	.128

LAV; left atrial volume, LVEDV; left ventricular end-diastolic volume, LVESV; left ventricular end-systolic volume, LVEF; left ventricle ejection fraction, GLS; global

longitudinal strain, E' wave; mitral annular early diastolic velocity, S'; left ventricle systolic velocity, PASP; pulmonary artery systolic pressure, LAS; left atrial strain.

5.4.5.2 Univariate linear regression analysis

Left atrial strain variables were entered into a simple regression model. $VO_{2\ peak}$ as the dependent variable and reservoir and conduit LA strain as the independent variable. This demonstrated linearity between variables. Against relative $VO_{2\ peak}$, a simple regression model was significant for both reservoir LA strain (β coefficient 0.260; p-value = 0.002) and for conduit LA strain (β coefficient -0.405; p-value < 0.0001) (*Table 5.8*). Against VE/VCO_2 slope, simple regression analysis showed significant association for both reservoir LA strain (β coefficient -0.216; p-value = 0.001) and for conduit LA strain (β coefficient 0.276; p-value = 0.003) (*Table 5.9*). The other echocardiographic parameters entered into a univariate linear model and were significantly associated with $VO_{2\ peak}$ were LV volume indexed, E' wave. Whereas, LV volume indexed, PASP, E' wave and LV S' wave associated with VE/VCO_2 slope.

Table 5.8 Univariate regression analysis with $VO_{2\ peak}$ (ml/kg/min) as the dependent variable.

Variables	**Univariate**		
	β coefficient	**95% CI**	**P value**
LVEDVI, ml/m^2	.106	0.042 to 0.171	**.002**

LVESVI, ml/m^2	.248	0.087 to 0.408	**.003**
E' wave, m/s	.763	0.340 to 1.086	**.001**
LV S' wave, m/s	.450	- .016 to 0.916	.058
Reservoir LAS, %	.260	0.098 to 0.422	**.002**
Conduit LAS, %	-.405	-0.626 to -0.184	**.000**
Contractile LAS, %	-.121	-0.378 to 0.136	.351

CI; confidence interval, LVEDV; left ventricular end-diastolic volume indexed, LVESV; left ventricular end-systolic volume indexed, S'; left ventricle systolic velocity, E' wave; mitral annular early diastolic velocity, LAS; left atrial strain.

Table 5.9 Univariate regression analysis with VE/VCO_2 slope as the dependent variable.

Variables	**Univariate**		
	β -coefficient	**95% CI**	**P value**
LVEDVI, ml/m^2	-.048	-.101 to .006	.079
LVESVI, ml.m^2	-.143	-.274 to .012	**.033**
PASP, mmHg	.106	.001 to .210	**.048**
E' wave, m/s	-.613	-.979 to -.247	**.001**

LV S' wave, m/s	-.463	-.845 to -.081	**.018**
Reservoir LAS, %	-.216	-.344 to -.088	**.001**
Conduit LAS, %	.276	.097 to .456	**.003**
Contractile LAS, %	.160	.042 to .372	.136

CI; confidence interval, LVEDVI; left ventricular end-diastolic volume indexed, LVESVI; left ventricular end-systolic volume indexed, S'; left ventricle systolic velocity, E' wave; mitral annular early diastolic velocity, LAS; left atrial strain.

5.4.5.3 Multivariate linear regression analysis

A multivariate regression model was established to determine which of the main echocardiographic parameter was able to predict $VO_{2\ peak}$ and $VE/VCO_{2\ slope}$. In *Table 5.10*, the multivariate regression model showed that reservoir LA strain (β coefficient 0.22, 95% CI 0.054 to 0.390, p-value = 0.010) and E' wave (β coefficient .694, 95% CI 0.252 to 1.036, p-value = 0.003) were significant predictors for $VO_{2\ peak}$. The overall model fit was R^2 = 0.28, p-value = 0.001. *Table 5.11* shows that the independent significant predictors of the VE/VCO_2 slope were reservoir LA strain (β coefficient -0.152, 95% CI -0.292 to -0.012, p-value = 0.034) and E' wave (β coefficient -0.457, 95% CI -0.822 to 0.093, p-value = 0.015). The predictor variables in the multivariate regression model were not highly correlated with each other. VIF values were less than 2. The overall model fit was R^2 =0.24, p-value = 0.001. Reservoir left atrial strain (*Figure* 5.5), conduit left atrial (*Figure* 5.6) and E' wave (*Figure* 5.7) were plotted against $VO_{2\ peak}$ and VE/VCO_2 slope.

Table 5.10 Multivariate regression analysis with $VO_{2\ peak}$ as the dependent variable.

Variables	Multivariate		
	β -coefficient	**95% CI**	**P value**
LVEDVI, ml/m^2	-.029	-.150 to .091	.630
LVESVI, ml/m^2	.241	-.041 to .523	.093
E' wave, m/s	.626	.201 to 1.050	**.004**
Reservoir LAS, %	.215	.054 to .390	**.010**

CI; confidence interval, LVEDVI; left ventricular end-diastolic volume indexed, LVESVI; left ventricular end-systolic volume indexed, E' wave; mitral annular early diastolic velocity, LAS; left atrial strain.

Table 5.11 Multivariate regression analysis with VE/VCO_2 slope as the dependent variable.

Variables	Multivariate		
	B-coefficient	**95% CI**	**P value**
LVESVI, ml/m^2	-.086	-.212 to .040	.179
PASP, mmHg	.076	-.020 to .172	.120
E' wave, m/s	-.457	-.822 to .093	**.015**

LV S’ wave, m/s	.006	-.393 to .406	.975
Reservoir LAS, %	-.152	-.292 to -.012	**.034**

CI; confidence interval, LVEDV; left ventricular end-diastolic volume, LVESV; left ventricular end-systolic volume, S’; left ventricle systolic velocity, E’ wave; mitral annular early diastolic velocity, LAS; left atrial strain.

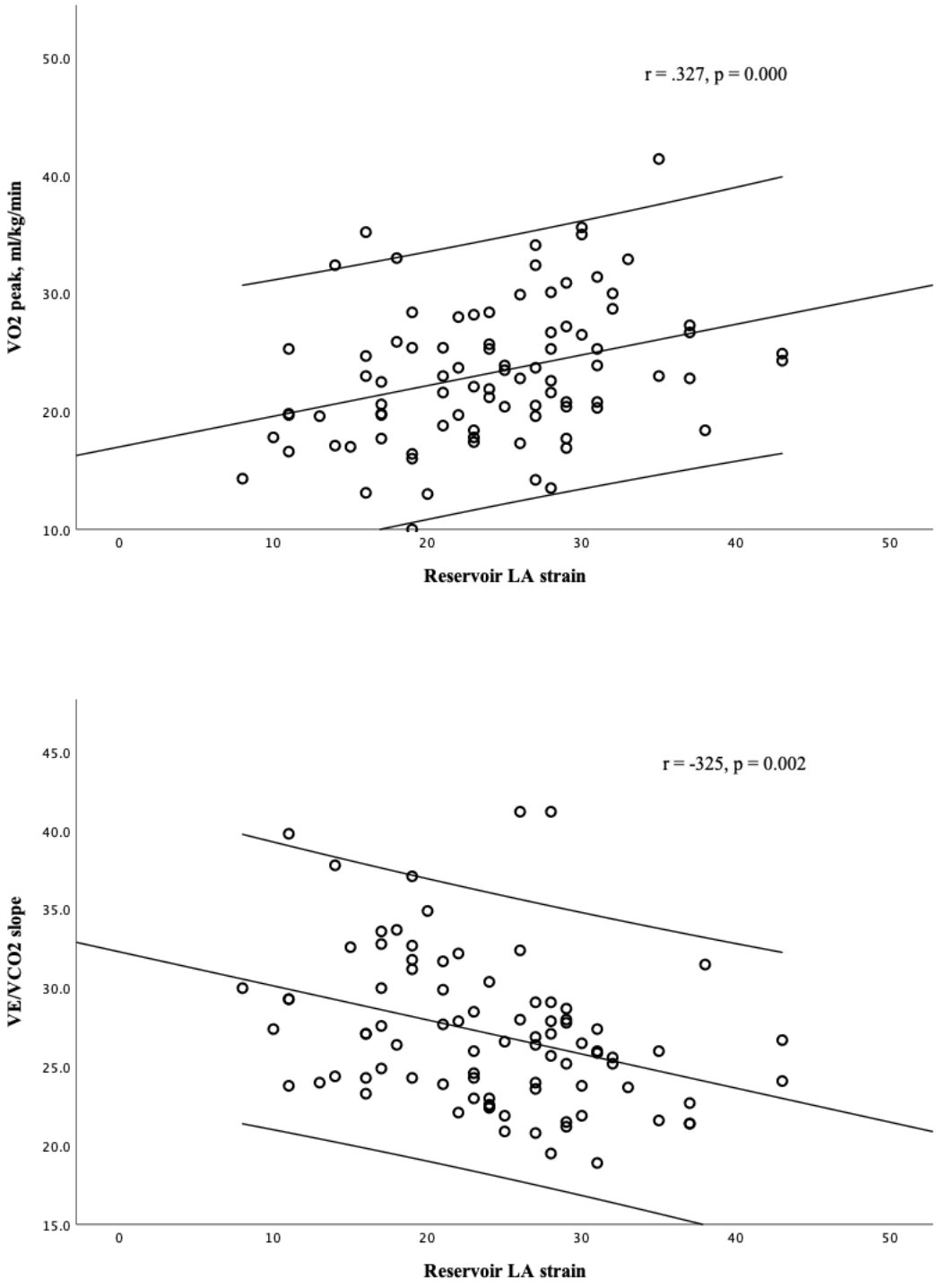


Figure 5.5 Scatterplots for the relationship between reservoir left atrial strain and relative $VO_{2\ peak}$ - top and VE/VCO_2 slope - bottom)

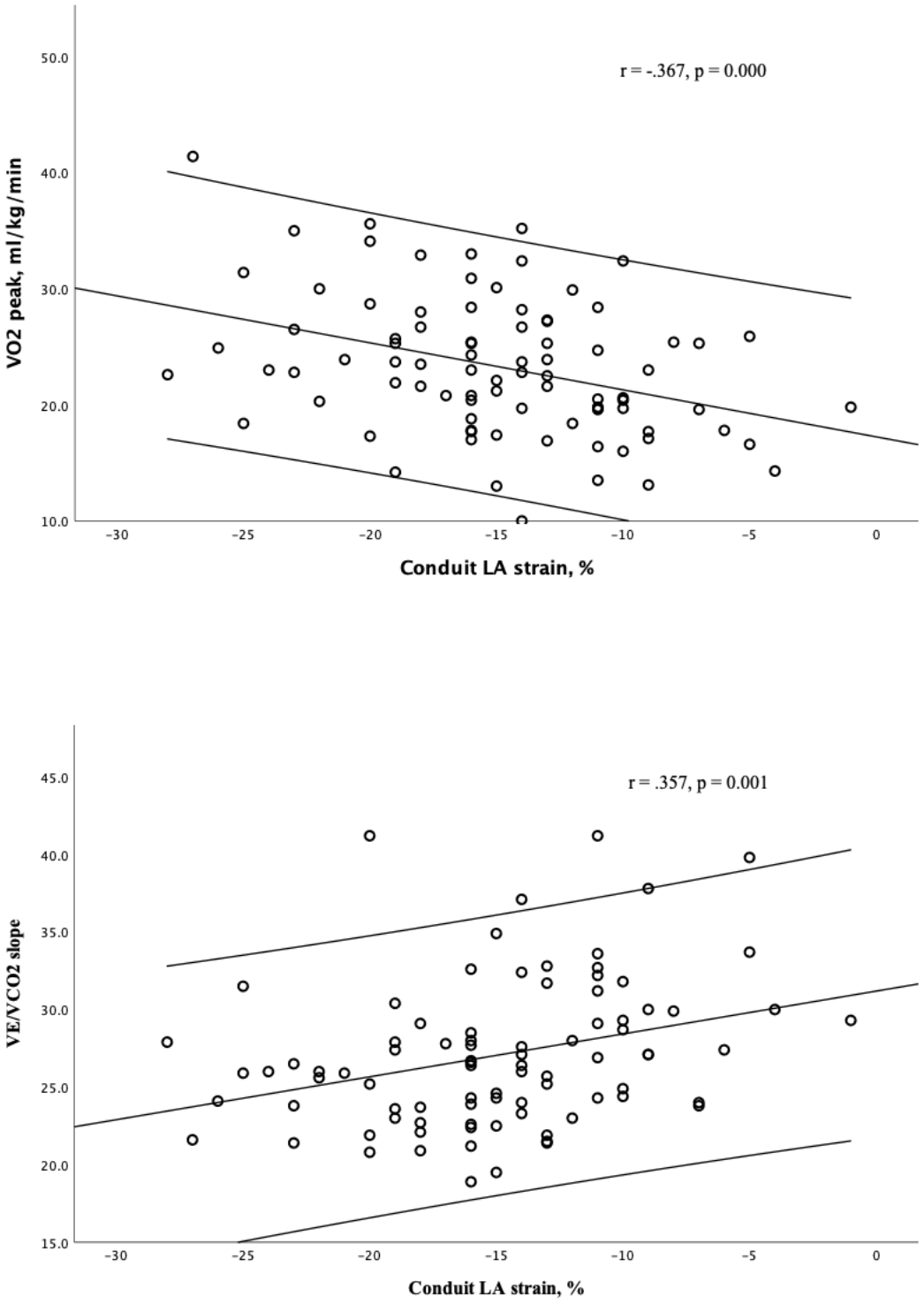


Figure 5.6 Scatterplots for the relationship between conduit left atrial strain and relative $VO_{2\ peak}$ - top and VE/VCO_2 slope - bottom)

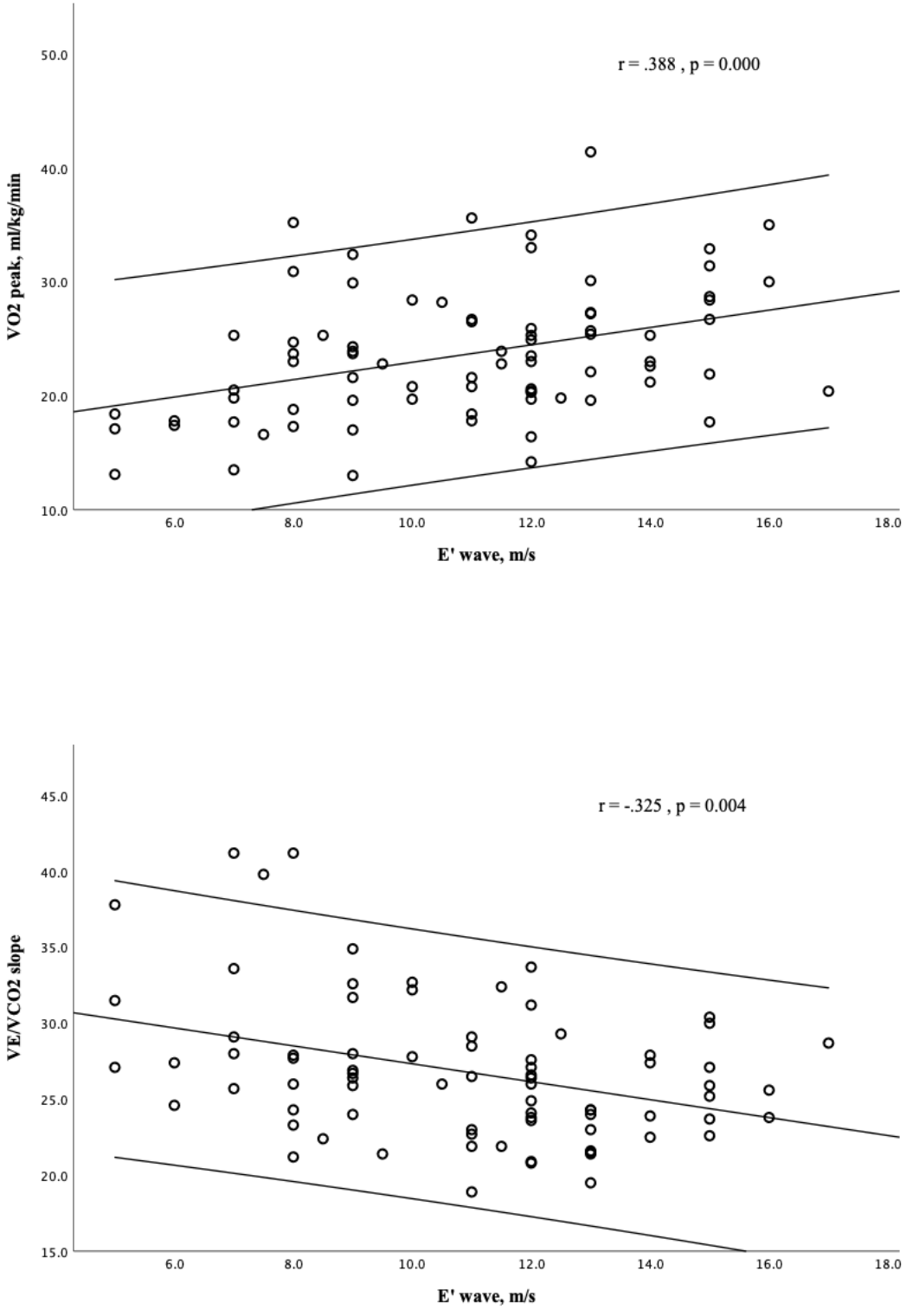


Figure 5.7 Scatterplots for the relationship between E' wave and relative $VO_{2\ peak}$- top and VE/VCO_2 slope - bottom)

5.4.6 Requirement for mitral valve surgery

During follow-up of the asymptomatic cohort, (38%) 37 patients were referred for mitral valve surgery and 59 (62%) patients remained under medical follow-up.

Left atrial strain parameters according to referral status to cardiac surgery for the asymptomatic cohort are presented in *Table 5.12.* Left atrial strain parameters did not differ between patients who were referred to cardiac surgery and patients who were under follow-up.

Table 5.12 Left atrial strain parameters according to referral status to cardiac surgery

Variable	**(Surgery -) (n=59, 62%)**	**(Surgery +) (n=37, 39%)**	***p-value***
Rest Echocardiography			
Reservoir LAS, %	24 ± 7	25 ± 9	.422
Conduit LAS, %	-15 ± 5	- 16 ± 5	.449
Contractile LAS, %	-9 ± 4	-9 ± 6	.956

LAS; left atrial strain.

5.4.7 LA strain and post-operative LV dysfunction

We looked into the post-operative LV dysfunction and left atrial strain relationship in the surgery cohort. A total of 89 patients with severe MR who underwent MR surgery were included.

12 (14%) patients had post-operative LV dysfunction (post-operative LVEF< 50%) and 77 (87%) patients had normal post-operative left ventricle function (LVEF ≥ 50%). *Table 5.13* shows a comparison of the main clinical characteristics and baseline echocardiography parameters between the post-operative LV dysfunction group and normal post-operative LV function group.

Patients with impaired post-operative LV function were older than patients with normal post-operative LV function (71 ±12 years versus 61 ± 13 years, p-value = 0.015). The post-operative LV dysfunction group had higher left atrial, bigger left ventricle end-systolic dimension and lower baseline LVEF (58 ± 9% versus 63 ± 5%, p-value = 0.010). Pulmonary artery systolic pressure was higher in patients with impaired LVEF. Reservoir left atrial strain was significantly lower in patients with post-operative LV dysfunction compared to patients with normal post-operative LVEF (18 ± 11% versus 23 ± 7%, p-value = 0.048). The observed mean values of conduit and contractile LA strain were lower in the impaired left ventricle group, however, no significant difference was found between the two groups (p-value > 0.05).

Table 5.13 Clinical characteristics and baseline echocardiographic parameters according to the occurrence of post-operative left ventricle dysfunction

Variables	post-operative LVEF≥ 50% (n=77, 87%)	Post-operative LVEF<50% (n=12, 14%)	P- value
Clinical Characteristics			
Age, years	61 ± 13	71 ±12	**.015**
Male, n (%)	46	6(50)	.524
Body mass index, kg/m^2	25 ± 3	25 ± 5	.928
Heart rate, bpm	72 ± 13	79 ± 15	.159
Systolic BP, mmHg	133 ± 15	128 ± 17	.239
Diastolic BP, mmHg	77 ± 9	76 ± 11	.700
Pre-operative Echocardiography variables			
LAVI, ml/m^2	69 ± 29	91 ± 29	**.022**
LVEDDI, cm/m^2	3 ± 0.4	3.2 ± 0.6	.175
LVESDI, cm/m^2	1.9 ± 0.3	2.1 ± 0.4	**.034**
LVEDV, ml	158 ± 47	168 ± 47	.352
LVESV, ml	59 ± 21	70 ± 27	.111

LVEF, %	63 ± 5	58 ± 9	**.010**
LV S' average, m/s	9.9 ± 2.6	8.7 ± 1.7	.294
PASP, mmHg	29 ±16	36 ± 13	**.037**
E/A ratio	1.8 ± 0.7	2.0 ± 0.8	.360
E' wave, m/s	10.7 ± 2.8	10.0 ± 2.8	.391
Reservoir LAS, %	23 ± 7	18 ± 11	**.048**
Conduit LAS, %	-15 ± 5	-12 ± 6	.067
Contractile LAS, %	-8 ± 5	-6 ± 6	.289

LVEF; left ventricle ejection fraction, BP; blood pressure, LAV; left atrium volume, LVEDDI; left ventricle end-diastolic diameter indexed, LVESDI; left ventricle end-systolic diameter indexed, LVEDV; left ventricle end-diastolic volume, LVESV; left ventricle end-systolic volume, S'; left ventricle systolic velocity, PASP; pulmonary artery systolic pressure, E/A; ratio of the early to late ventricular filling velocities, E' wave; mitral annular early diastolic velocity, LAS; left atrial strain.

5.4.7.1 The association between LA strain and post-operative LVEF

After performing a simple regression analysis, reservoir left atrial strain was a predictor for LVEF after surgery (β -coefficient .176, 95% CI 0.026 to 0.326, p-value = 0.022). In addition, left atrial volume indexed, LVESD indexed and LVEF were associated with post-operative LVEF. A multivariate regression analysis was performed including parameters that had a significant association in the univariate analysis. Independent

predictors of post-operative LVEF were index left atrial volume (β -coefficient -0.048, 95% CI -0.094 to -0.003, p-value = 0.037) and GLS (β -coefficient -0.470, 95% CI -0.932 to -0.007, p-value = 0.047). The data in the multivariate regression analysis met the assumption that multicollinearity was not a concern, VIF values were less than 3. The overall model fit was $R^2 = 0.20$, p-value= 0.005 (*Table 5.14*). Index left atrial volume was a stronger predictor of LVEF after surgery than left atrial strain.

Table 5.14 Univariate and multivariate regression analysis with post-operative LVEF as the dependent variable.

Variables	**Univariate analysis**		
	β -coefficient	**95% CI**	**P value**
Univariate analysis			
Age, years	-.068	-.158 to .023	.140
LAVI, ml/m^2	-.041	-.081 to -.001	**.045**
LVESDI, cm/m^2	-2.240	-4.342 to -.137	**.037**
LVEF, %	.300	.110 to .491	**.002**
PASP, mmHg	-.014	-.089 to .062	.719
GLS, %	-.542	-.872 to -.212	**.002**

Reservoir LAS, %	.176	.026 to .326	**.022**

Variables	**Multivariate analysis**		
	β -coefficient	**95% CI**	**P value**
LAVI, ml/m^2	-0.048	-0.094 to -0.003	**.037**
LVESDI, cm/m^2	-0.716	-4.837 to 3.406	.731
LVEF, %	0.129	0.123 to 0.380	.312
GLS, %	-0.470	-0.932 to -0.007	**.047**
Reservoir LAS, %	0.001	-0.168 to -0.170	.988

CI; confidence interval, LAVI; left atrial volume indexed, LVESDI; left ventricular end-systolic diameter indexed, LVEF; left ventricle ejection fraction, PASP; pulmonary artery systolic pressure, GLS; global longitudinal strain, LAS; left atrial strain.

5.5 Discussion

We studied the left atrial strain in patients with primary mitral regurgitation. The main findings of the study were: 1. Left atrial strain was significantly lower in symptomatic patients 2. Left atrial strain was associated with symptoms, however, PASP was a better independent echocardiographic predictor of symptoms. 3. Reservoir left atrial strain was an independent predictor of relative $VO_{2\ peak}$ and VE/VCO_2 slope. 4. Reservoir LA strain

was a predictor of post-operative LVEF but not an independent one, pre-operative left atrial volume and GLS had a better predictive value.

Severe left atrial dilatation (LAVI ≥ 60 mL/m^2) in patients with primary mitral regurgitation is an independent predictor of poor outcome, even in those with preserved LVEF and those without symptoms (174). Progressive left atrial dilatation is a compensatory adaptation to volume overload in chronic primary mitral regurgitation, which enables left atrial pressure homeostasis (173). Chronic mitral regurgitation causes LA remodelling that affects the compliance and the elastic properties of LA with subsequent increase of LA pressure (175). Left atrial deformation measured using speckle tracking echocardiography has been proposed for early detection of subtle changes of myocardial function and for risk stratification of patients with primary mitral regurgitation. Most of the previous studies have focused their attention on the analysis of ventricular remodelling rather than atrial remodelling (82, 84). However, a reduction of LA strain may appear earlier than changes in left ventricle myocardial function, possibly because it is the first chamber to be affected by the volume overload of MR. In addition, the LA has a thinner wall, which could make it less capable of maintaining wall stress caused by volume overload.

Phasic atrial activity including reservoir, conduit and contractile (booster pump) functions are important for left ventricle filling and are affected by atrial compliance and contraction, and the LV mitral annulus movement during systole (176, 177). In the present study, LA reservoir function reflected LV longitudinal systolic function (LV S' wave, apical systolic motion of the LV base). Although it has been reported that LA reservoir strain is significantly influenced by the degree of mitral regurgitation, LA strain increased in mild MR and decreased in severe MR (178). However, the present study showed that

MR severity is not associated with left atrial reservoir function, this may be because that we only included patients with significant regurgitation and no mild MR was included.

5.5.1 Left atrial strain and the occurrence of symptoms

Our study confirms the previous observations that LA strain was significantly lower in patients with symptoms, while LV remodelling parameters including LV GLS, LVEF did not show any relevance among symptoms states, probably due to LV hypercontractility in response to volume overload. Yang et al. (91) demonstrated that peak LA strain was related to the occurrence of the worse heart failure symptoms corresponding to NYHA class III in patients with chronic severe primary MR. In our study, reservoir LA strain was significantly associated with heart failure symptoms (≥NYHA II), however, PASP was the only independent parameter for predicting the occurrence of the symptoms. This finding supports the result in chapter 3 in this thesis that rest PASP was an independent predictor for dyspnoea during the exercise test in asymptomatic patients with moderate to severe MR. LA strain can help risk stratify asymptomatic patients with moderate and severe mitral regurgitation (90). Ring et al. (179) investigated patients with moderate to severe MR with no guideline-based indications for surgery and found that reservoir and contractile LA strain were independently associated with surgery-free survival time and that LA strain helps identify patients who more likely require mitral surgical intervention. However, in our study, we examined the association between left atrial strain parameters and the subsequent need for mitral valve surgery in asymptomatic MR patients who had no conventional guideline indications for surgery at entry into the study. We found that LA strain measurements were not associated with mitral valve surgery.

5.5.2 Left atrial strain and CPET parameters

The determinants of the reduced functional capacity in MR are uncertain. Previous investigations have found conflicting predictors of $VO_{2\ peak}$ in primary MR patients (105, 156). The impact of reservoir LA strain on functional capacity is supported by the independent association of $VO_{2\ peak}$ and reservoir LA strain. In the present study, we found that diastolic function parameters were independently associated with $VO_{2\ peak}$. In the previous studies, diastolic function is an important determinant of exercise capacity (180, 181).

VE/VCO_2 slope represents exercise ventilatory efficiency. The VE/VCO_2 slope is related to the severity of heart failure and is a useful index of symptoms during exercise (182). A previous study demonstrated that VE/VCO2 slope is a powerful predictor of mortality of chronic heart failure (183). VE/VCO_2 slope is independent of the patient's effort, in contrast to $VO_{2\ peak}$ which may be confounded by the exercise effort. In patients with primary MR, the value of the VE/VCO_2 slope has not been fully evaluated. In our study, we found that reservoir and conduit LA strain were correlated with VE/VCO_2 slope and reservoir LA strain was an independent determinant of VE/VCO_2 slope alongside the diastolic function. LA strain by speckle tracking echocardiography has the advantage of angle independency which can overcome the Doppler limitations of diastolic function parameters.

5.5.3 Left atrial strain and post-operative LV dysfunction

LA strain has been found to offer incremental prognostic value over standard echocardiography parameters in patients with primary MR. Debonnaire et al. (92) reported that reservoir LA strain was related to long-term post-operative survival and it was an accurate predictor for patients with mitral valve surgery indications. Yang et al

(184) found that impaired peak LA strain was a predictor of worse prognosis (death or mitral valve surgery induced by heart failure development) in patients with chronic severe primary MR. In our study, we investigated whether baseline LA strain predicted post-operative ventricular dysfunction. We found that reservoir LA strain was impaired in patients with post-operative LV dysfunction (LVEF< 50%) and was significantly associated with post-operative LVEF. However, on multi-variate analysis, pre-operative LA volume and GLS were the only independent predictors of post-operative LV dysfunction.

5.6 Limitation

The relatively small sample size of this study. LA strain by speckle tracking echocardiography has some technical limitations and requires the presence of optimal 4- and 2- chamber apical views to allow an easy delineation of the endocardial border and to avoid left atrial foreshortening to ensure adequate measurement of strain. The end-point of post-operative LV function is important. However, a longer follow-up would allow investigation of the impact of this end-point on heart failure hospitalisations and mortality.

5.7 Conclusion

LA strain assessed by speckle tracking echocardiography was associated with heart failure symptoms, however, PASP was a better and independent predictor for symptoms. LA strain could be valuable in evaluating the functional capacity quantified and assessed by CPET as LA strain was an independent predictor of $VO_{2\ peak}$ and VE/VCO_2 slope. In

addition, LA strain demonstrated an association with post-operative LV dysfunction, but LA volume and GLS were better predictors of post-operative LVEF.

Chapter 6

Prognostic Role of Myocardial Work in Primary Mitral Regurgitation Patients

6.1 Abstract

Background: LV pressure-strain loops offers a non-invasive method of measuring myocardial work. It is a new echocardiographic method with potential advantage over GLS by incorporating measurements of LV deformation and LV pressure. In patients with primary MR, the optimal timing for intervention is challenging. We investigated the role of myocardial work parameters and their prognostic value in primary MR. **Methods:** Echocardiography was performed in 157 patients with primary moderate to severe or severe MR. Myocardial work measures were estimated by non-invasive LV pressure-strain loop analysis. The following myocardial work indices were included: global work index (GWI), global constructive work, global wasted work, and global work efficiency. The study population was divided into 2 cohorts. Asymptomatic cohort: 85 patients with asymptomatic MR underwent exercise echocardiography combined with CPET. Surgery cohort: 87 patients who had MV surgery underwent follow-up echocardiography 12 months after surgery. **Results:** GWI and PASP were independently associated with the occurrence of symptoms even after multivariable adjustment for other predictors of the outcome, GWI (p-value = 0.035) and PASP (p-value = 0.011). In asymptomatic cohort, MW parameters did not differ between groups of normal and reduced functional capacity. In surgery cohort, GWI was associated with post-operative LVEF. However, on multivariable regression analysis GLS was superior to GWI (p-value= 0.023). **Conclusion:** In primary MR, impaired GWI was associated with the occurrence of symptoms. Patients with post-operative LV dysfunction are characterised by reduced GWI. However, GLS was superior to GWI in predicting post-operative LVEF. Myocardial work may offer additive prognostic information in addition to established echocardiographic parameters. Further large studies are required to investigate the role of these parameters in MR.

6.2 Introduction

Left ventricle ejection fraction is a standard echocardiographic parameter for the assessment of LV systolic function (185). In daily clinical practice, LVEF is widely recognised and recommended to help decide the timing of surgery (186). However, in patients with primary MR, LVEF may not reflect the true LV systolic contractility because of haemodynamic changes and volume overload (187). Global longitudinal strain is suggested as an alternative for LVEF, to improve the ability to capture the true LV systolic function (188). However, it has also been shown that GLS is influenced by LV geometry and loading condition (preload and afterload) (189). Recently, a novel method to evaluate myocardial performance has been introduced as a non-invasive technique of myocardial work estimation (94). Myocardial work considers both myocardial deformation and myocardial shortening (afterload) and combines non-invasive arterial blood pressure (measured noninvasively) with global longitudinal strain (quantified by speckle tracking echocardiography analysis) (190). The role of myocardial work in primary MR has not been investigated. The aims of this study were 1. To describe global myocardial work parameters in patients with primary MR, 2. to assess the relationships of myocardial work with other echocardiographic parameters, and 3. to evaluate the association of myocardial work with functional capacity and post-operative LV dysfunction.

6.3 Method

6.3.1 Study population

In this chapter, 177 patients with significant degenerative MR were recruited. However, we excluded twenty patients because the quality of their data was inadequate. All 157 patients who were included in the data analysis underwent baseline clinical assessment and echocardiography and including non-invasive arterial blood pressure measurements. All patients had primary moderate to severe or severe MR due to a prolapse or flail leaflet, 85 patients from the asymptomatic cohort and 87 patients from the surgery cohort.

6.3.2 Clinical assessment

Asymptomatic patients with moderate and severe MR underwent stress echocardiography test and cardiopulmonary exercise test. Patients with severe primary MR who had mitral valve surgery underwent pre-operative echocardiography and 12-month follow-up post-operative echocardiography. Myocardial work of LV was measured by integrating LV longitudinal strain and arterial blood pressure, as described by Russell et al (94). Myocardial work analysis was performed offline for all patients. The methodology of the echocardiography, myocardial work and exercise test is described in detail in chapter two (methods chapter).

6.3.3 Follow-up and outcome analysis

Patients who had mitral valve surgery were asked to return for an echocardiography follow-up visit 12 months after surgery. Patients were stratified according to the symptoms. The primary outcome was the presence of symptoms (defined as $\geq$ NYHA II), symptoms were classified according to NYHA functional classification. The

secondary outcomes were: 1. reduced functional capacity (defined as a predicted $VO_{2\ peak}$ less than 84%) for the asymptomatic cohort. 2. post-operative LV dysfunction (defined as an LV ejection fraction less than 50%) for the surgery cohort.

6.3.4 Statistical analysis

Continuous data are presented as mean ± standard deviation or median (25th percentile-75th percentile) as appropriate. Distrbuation of myocardia work parameters was presented in histogram graph (Appendix D). Categorical data are presented as absolute numbers and percentages. Student t-tests were used for parametric data, the Mann-Whitney U test was used for non-parametric data and the X_2 test was used for categorical data to analyse the differences in clinical and echocardiographic characteristics between 1. Symptomatic patients versus asymptomatic patients, 2. Patients with reduced functional capacity during CPET versus patients with normal functional capacity, and 3. Patients with impaired post-operative LVEF versus patients with normal post-operative LVEF. Correlation analyses were performed using either Pearson's or Spearman's correlation coefficient to assess the correlations of myocardial work with VO2 peak, VE/VCO2 slope and other echocardiographic parameters. Univariate and multivariate logistic regression analyses were used to determine whether myocardial work parameters could predict symptoms. Univariate and multivariate linear regression analysis was used to identify determinants of $VO_{2\ peak}$ and $VE/VCO_{2\ slope}$ and to examine the association between myocardial work parameters and post-operative. The Hosmer–Lemeshow test was used to evaluate the multivariate models' fit. A collinearity diagnostic test was performed on the data to ensure that multicollinearity was not a concern. A variance inflation factor (VIF) cut-off value of 5 was used for the multivariable model, and only variables with a VIF under 5 were included (153). Statistical analyses were performed

using the SPSS version 27.0 (SPSS inc., Chicago, USA). A p-value of <0.05 was considered significant.

6.4 Results

6.4.1 Baseline study data

Patients were stratified according to the occurrence of symptoms: 65 (41%) patients with symptoms **(**≥NYHA II), and 92 (56%) patients without symptoms (NYHA= I).

Clinical characteristics of both groups are presented in *Table 6.1*. The overall mean age of the study population was 61 ± 15 years. The majority of the study population were male (60%). Patients with symptoms were older than asymptomatic patients. Weight, body mass index and heart rate were comparable in the two groups, however, height was lower in the symptomatic group compared to the asymptomatic group (p-value= 0.050). Diastolic blood pressure was similar between the groups. Asymptomatic patients had higher systolic blood pressure than symptomatic patients (p-value = 0.045). Patients with symptoms had a higher prevalence of atrial fibrillation compared to the group without symptoms (20% versus 2%, p-value < 0.0001). A higher prevalence of hypertension and hypercholesterolaemia was found in symptomatic patients. In addition, smoking was more frequent in patients with symptoms (p-value = 0.020). The use of ACE inhibitors, diuretics and anticoagulation were more frequent in the symptomatic group.

Table 6.1 Baseline characteristics of the patient population according to the occurrence of symptoms

Variables	All patients (n= 157)	(-) Asymptomatic n= 92 (56%)	(+) Symptomatic n= 65 (44%)	P-value
Age, years	61 ± 15	58± 16	65 ±14	**.006**
Male, n (%)	94 (60)	61 (66)	33 (51)	**.050**
Height, cm	171 ± 10	172 ± 10	169 ± 11	**.045**
Weight, kg	72 ± 14	73 ± 13	72 ± 16	.682
Body mass index, kg/m^2	25 ± 3	25 ± 3	25± 4	.769
Heart rate, bpm	73 ± 14	73 ± 13	73 ± 14	.836
Systolic BP, mmHg	135 ± 17	138 ± 17	131 ±17	**.016**
Diastolic BP, mmHg	77 ± 10	78 ± 9	76 ±11	.087
Risk Factors, n (%)				
AF	15 (10)	2 (2)	13 (20)	**.000**
Hypertension	48 (33)	22 (24)	26 (40)	**.031**
Hypercholesterolaemia	32 (19)	10 (11)	22 (34)	**.000**

Smoking	34 (23)	14 (15)	20 (31)	**.020**
Medications n, (%)				
Beta Blocker	43 (29)	22 (24)	21 (32)	.245
ACE inhibitors	30 (19)	10 (11)	20 (31)	**.002**
Diuretics	19 (16)	6 (7)	13 (20)	**.011**
Warfarin	6 (5)	1 (1)	5 (8)	.035
Antiplatelet agent	15 (10)	10 (11)	5 (8)	.505
Statin	29 (19)	17 (19)	12 (19)	.998
Amlodipine	12 (7)	9 (10)	3 (5)	.230
Anticoagulant	18 (16)	6 (7)	12 (19)	**.021**
ARBs	10 (7)	4 (4)	6 (9)	.217

AF; Atrial fibrillation, BP; blood pressure; ACE; Angiotensin-converting enzyme, ARBs; Angiotensin receptor blockers.

6.4.2 Echocardiography data

In *Table 6.2,* baseline echocardiographic parameters are compared between symptomatic and asymptomatic patients. Patients with symptoms had larger left atrial dimensions, left atrial area, and volumes (LAV indexed: 74 ± 31 ml/m^2 versus 56 ± 25 ml/m^2, p-valve <

0.000) than patients without symptoms. No differences were observed between the two groups regarding left ventricle dimensions and volumes. LVEF was also similar in both groups. Symptomatic patients had a higher S' wave (9.4 ± 2.5 m/s versus 10.2 ± 2.7 m/s, p-value = 0.047). Estimated pulmonary artery systolic pressure was higher in patients with symptoms (33 ± 17 mmHg versus 21 ± 10 mmHg, p-value < 0.0001). Right ventricle function assessed by RV S' wave and TAPSE was comparable between the groups. Measures of diastolic function showed that patients with symptoms had a higher E wave (1.2 ± 0.3 m/s versus 1.0 ± 0.3 m/s, p-value = 0.014) , lower deceleration time (197 ± 59 ms versus 218 ± 67 ms, p-value = 0.051) , lower E' wave (9.9 ± 2.8 m/s versus 10.9 ± 2.7 m/s, p-value = 0.009) and higher E/E' ratio (12.1 ± 3.9 versus 9.9 ± 3.4 p-value < 0.0001), whereas the E/A ratio did not differ between the groups. LV GLS was similar in both symptomatic and asymptomatic patients.

Myocardial work

Global work index (GWI) varied from 862 to 3234 mmHg % with a mean of 2054 ± 433 mmHg %. Global constructive work (GCW) ranged from 1365 to 3928 mmHg % and a mean of 2609± 503 mmHg %. Global wasted work (GWW) varied from 31 to 383 mmHg with a mean of 143 ± 77 mmHg %. The overall mean value of global work efficiency (GWE) was 94 ± 3 % and ranged from 77 % to 98 %. Patients with symptoms showed significantly lower values of GWI (1918 ± 415 mmHg % versus 2150 ± 422 mm Hg %, p-value = 0.001) and lower value of GCW compared with asymptomatic patients (2508 ± 453 mmHg % versus 2679 ± 527 mmHg %, p-value = 0.036). GWW and GWE mean values were similar in both groups (134 ± 70 mmHg % versus 149 ± 81 mmHg %; p-value = 0.225 and 94 ± 4 % versus 94 ± 2 %; p-value = 0.520) respectively.

Table 6.2 Baseline echocardiographic parameters according to the occurrence of symptoms.

Variables	All patients (n=157)	(-) No Symptoms n=92 (56%)	(+) Symptoms n=65 (44%)	P-value
LAD, cm	4.3 ± 0.8	4.2 ± 0.8	4.5 ± 0.9	**.005**
LAD indexed, cm/m^2	2.4 ± 0.5	2.3 ± 0.4	2.5 ± 0.5	**.001**
LAA, cm^2	29 ± 9	27 ± 8	33 ± 10	**.000**
LAV, ml	116 ± 52	104 ± 48	134 ± 54	**.000**
LAV indexed, ml/cm^2	64 ± 29	56 ± 25	74 ± 31	**.000**
LVEDD, cm	5.5 ± 0.7	5.5 ± 0.6	5.5 ± 0.9	.373
LVEDD indexed, cm/m^2	3.0 ± 0.4	3.0 ± 0.4	3.1 ± 0.5	.857
LVESD, cm	3.4 ± 0.6	3.4 ± 0.5	3.5 ± 0.6	.728
LVESD indexed, cm/m^2	1.9 ± 0.3	1.9 ± 0.3	1.9 ± 0.4	.273
LVEDV, ml	147 ± 47	145 ± 42	150 ± 54	.790
LVEDV indexed, ml/cm^2	80 ± 22	78 ± 20	82 ± 24	.379
LVESV, ml	56 ± 20	54 ± 17	58 ± 24	.549

LVESV indexed, ml/cm^2	30 ± 9	29 ± 8	32 ± 11	.222
LVEF, %	62 ± 6	63 ± 5	62 ± 6	.471
LV S' average, m/s	9.8 ± 2.7	10.2 ± 2.7	9.4 ± 2.5	**.047**
PASP, mmHg	26 ± 15	21 ± 10	33 ± 17	**.000**
RV S', m/s	15 ± 3	15 ± 3	15 ± 3	.861
TAPSE, mm	24 ± 5	25 ± 5	24 ± 5	.360
E/A ratio	1.7 ± 0.7	1.6 ± 0.6	1.8 ± 0.7	.289
E wave, m/s	1.1 ± 0.3	1.0 ± 0.3	1.2 ± 0.3	**.014**
DT, ms	210 ± 65	218 ± 67	197 ± 59	**.051**
E' wave, m/s	10.5 ± 2.8	10.9 ± 2.7	9.9 ± 2.8	**.009**
E/E' ratio	10.8 ± 3.8	9.9 ± 3.4	12.1 ± 3.9	**.000**
GLS, %	- 20 ± 3	-20 ± 3	-20 ± 3	.911
Peak SL dispersion	41 ± 17	41 ± 18	40 ± 16	.855
GWI, mmHg %	2054 ± 433	2150 ± 422	1918 ± 415	**.001**
GCW, mmHg %	2609 ± 503	2679 ± 527	2508 ± 453	**.036**
GWW, mmHg %	143 ± 77	149 ± 81	134 ± 70	.225

GWE, %	94 ± 3	94 ± 2	94 ± 4	.520

LAD; left atrium diameter, LAA; left atrium area, LAV; left atrial volume, LVEDD; left ventricular end-diastolic diameter, LVESD; left ventricular end-systolic diameter, LVEDV; left ventricular end-diastolic volume, LVESV; left ventricular end-systolic volume, LVEF ; left ventricle ejection fraction, RV; right ventricle, PASP; pulmonary artery systolic pressure, S'; systolic velocity, TAPSE; tricuspid annular plane systolic excursion, E/A; ratio of the early to late ventricular filling velocities, DT; deceleration time, E; early passive filling of the left ventricle, E'; mitral annular early diastolic velocity, E/E'- ratio between early mitral inflow velocity and mitral annular early diastolic velocity, GLS; global longitudinal strain, GWI; global work index, GCW; global constructive work, GWW; global wasted work, GWE; global work efficiency.

6.4.3 The association between myocardial work and occurrence of symptoms

Logistic regression analysis is presented in *Table 6.3* with symptoms as a dependent variable. Global work index was significantly associated with symptoms (Wald statistic 10.198, odds ratio: 0.999, 95% CI: 0.998 to 0.999; p-value = 0.001). Global constructive work showed significant association with symptoms (Wald statistic 4.182, odds ratio: 0.999, 95% CI: 0.999 to 1.000; p-value = 0.041). In addition, age, LA volume indexed, PASP and E/E' ratio were significantly associated with the occurrence of symptoms on univariate regression analysis. LV systolic function parameters such as LVEF, S' wave and GLS were not associated with symptoms. Furthermore, there was no association between GWW and GWE and symptoms.

On multivariate logistic regression, GWI (Wald statistic 4.438, odds ratio: 0.999, 95% CI: 0.998 to 1.000; p-value = 0.035) and PASP (Wald statistic 6.481, odds ratio: 1.055, 95% CI: 1.012 to 1.100; p-value = 0.011) were the only independent predictors of symptoms. None of the predictor variables in this model was correlated with each other

and the VIF values were less than 2, which indicates that multicollinearity will not be a concern. The model explained 31% (Nagelkerke R^2) of the variance and correctly classified 73% of cases. The Hosmer and Lemeshow test showed that the model was a good fit to the data as p-value = 0.129 (>.05).

Table 6.3 Univariable and multivariable logistic regression analysis for associations with symptoms

Variable	**Univariable**		
	Wald statistic	Odds ratio (95% CI)	P value
Age, years	7.832	1.033 (1.010 to 1.057)	**.005**
LAVI, ml/m^2	13.343	1.023 (1.011 to 1.036)	**.000**
PASP, mmHg	21.378	1.076 (1.043 to 1.110)	**.000**
E/E' ratio	10.505	1.183 (1.069 to 1.309)	**.001**
GWI, mmHg %	10.198	0.999 (0.998 to 0.999)	**.001**
GCW, mmHg %	4.182	.999 (.999 to 1.000)	**.041**
GWW, mmHg %	1.461	.997 (.993 to 1.002)	.227
GWE, %	.417	.966 (0.869 to 1.074)	.518
Variables	**Multivariable**		

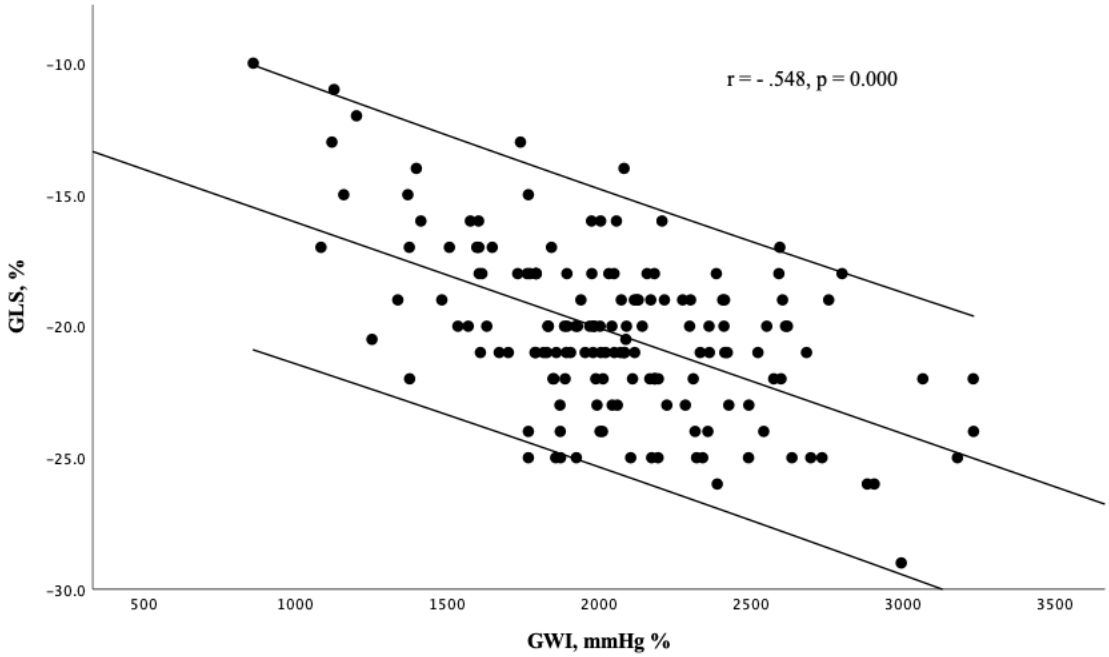
	Wald statistic	Odds ratio (95% CI)	P value
Age, years	.016	1.002 (.972 to 1.033)	.899
LAVI, ml/m^2	.834	1.007 (.992 to 1.022)	.361
PASP, mmHg	6.481	1.055 (1.012 to 1.100)	**.011**
E/E' ratio	.992	1.067 (.939 to 1.213)	.319
GWI, mmHg %	4.438	0.999 (.998 to 1.000)	**.035**

CI; confidence interval, LAVI; left atrial volume indexed, PASP; pulmonary artery systolic pressure. E'; mitral annular early diastolic velocity, GWI; global work index, GCW; global constructive work, GWW; global wasted work, GWE; global work efficiency

6.4.4 Correlations of myocardial work with other echocardiographic parameters

GWI and GCW were not related to age. However, GWW and GWE showed weak correlation with age (rho= 0.209, p-value = 0.009 and rho= -.299, p-value < 0.0001) respectively. GWI showed a positive correlation with LVEF (r = 0.390, p-value < 0.0001), negative correlation with LV GLS (r = -0.548, p-value < 0.0001), PASP (r = -0.23, p-value = 0.004) and LV end-systolic volume (r = -0.22, P-value = 0.005). GCW also showed a significant correlation with LV GLS (rho = -0.526, p-value < 0.0001) and with LVEF (rho = .349, p-value < 0.0001). GWI and GCW and their relationship with LV systolic function parameters (LVEF and GLS) are presented in *Figure 6.1* and *Figure 6.2.* GWW was only related to the GLS (rho = .216, p-value = 0.007) (*Figure* 6.3). GWE

had a correlation with GLS (rho = -.401, p-value < 0.0001) and weak correlation with S' wave (rho= .225, p-value = 0.005) and LVEF (rho = .173, p-value = 0.030) (*Figure* 6.4). Myocardial work parameters were not related to MR severity, LA size or LV diastolic function.



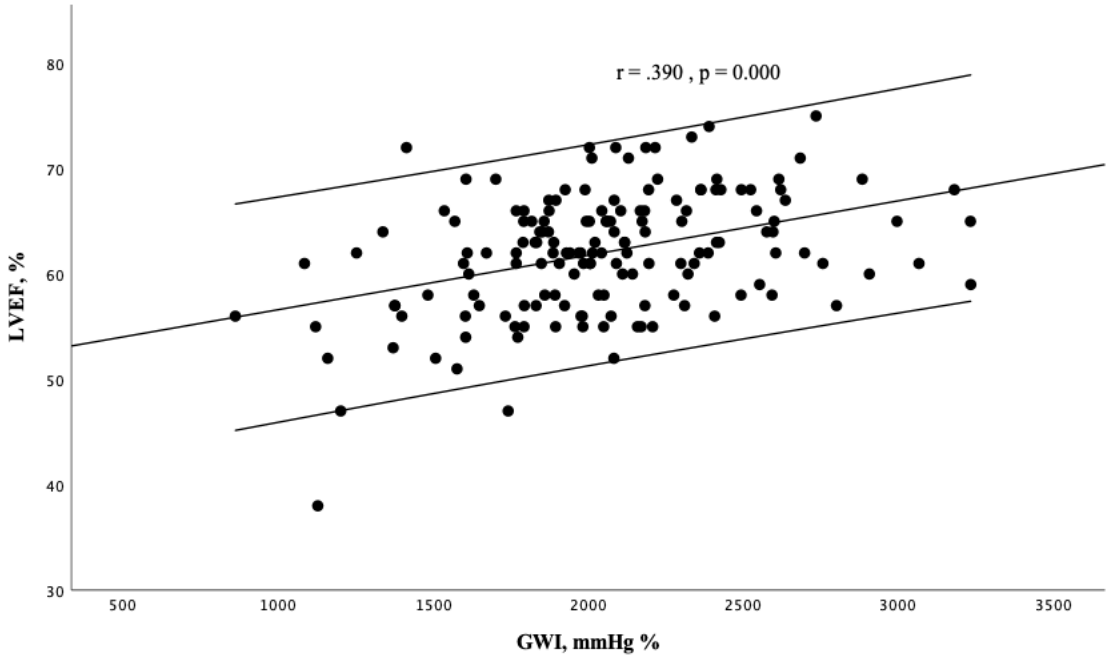


Figure 6.1 Scatterplots for the relationship between global work index and (global longitudinal strain - top and left ventricle ejection fraction – bottom)

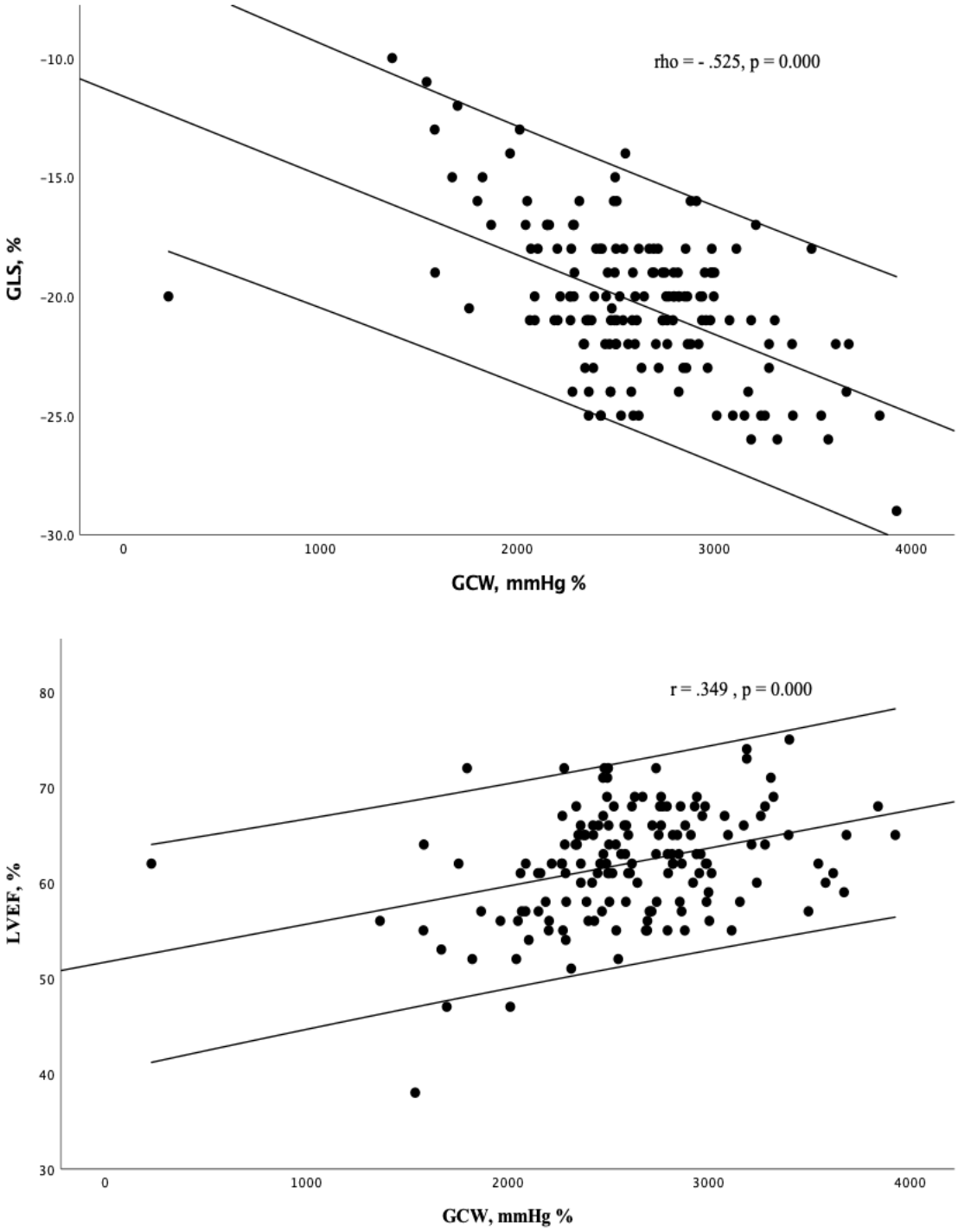


Figure 6.2 Scatterplots for the relationship between global constructive work and (global longitudinal strain - top and left ventricle ejection fraction - bottom)

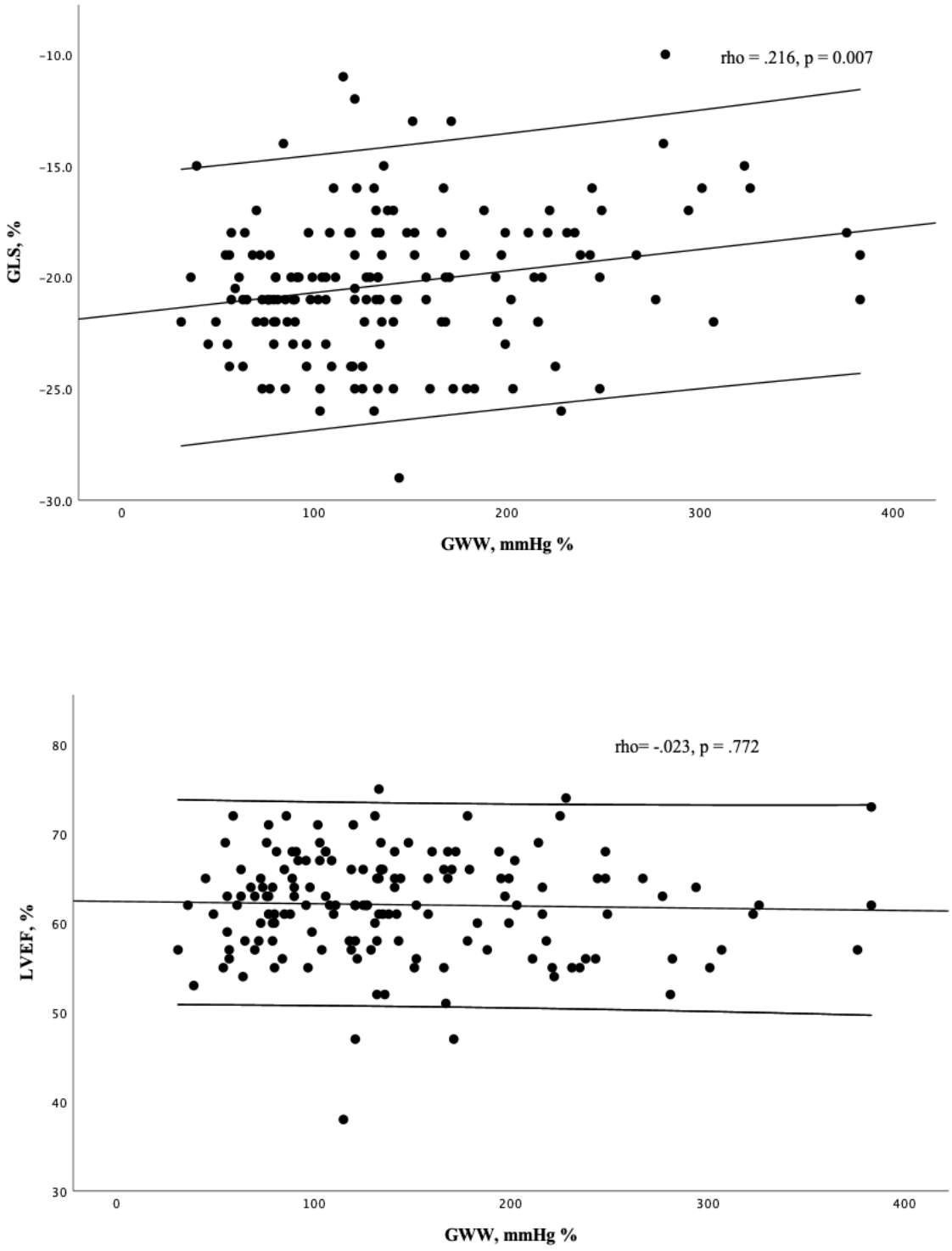
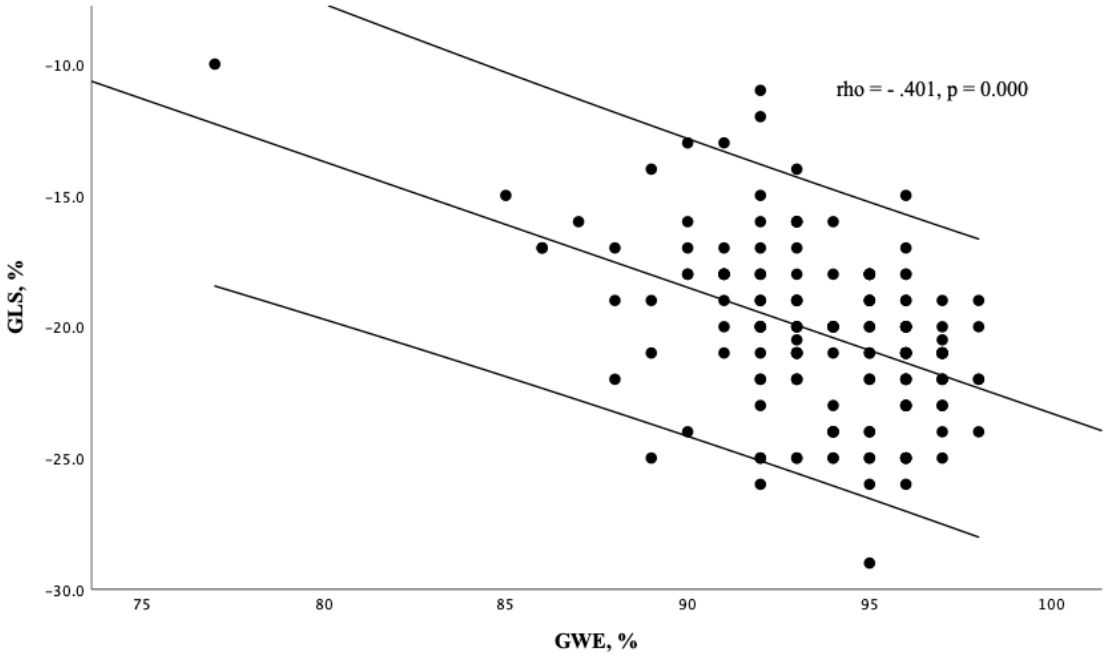


Figure 6.3 Scatterplots for the relationship between global wasted work and (global longitudinal strain - top and left ventricle ejection fraction - bottom)



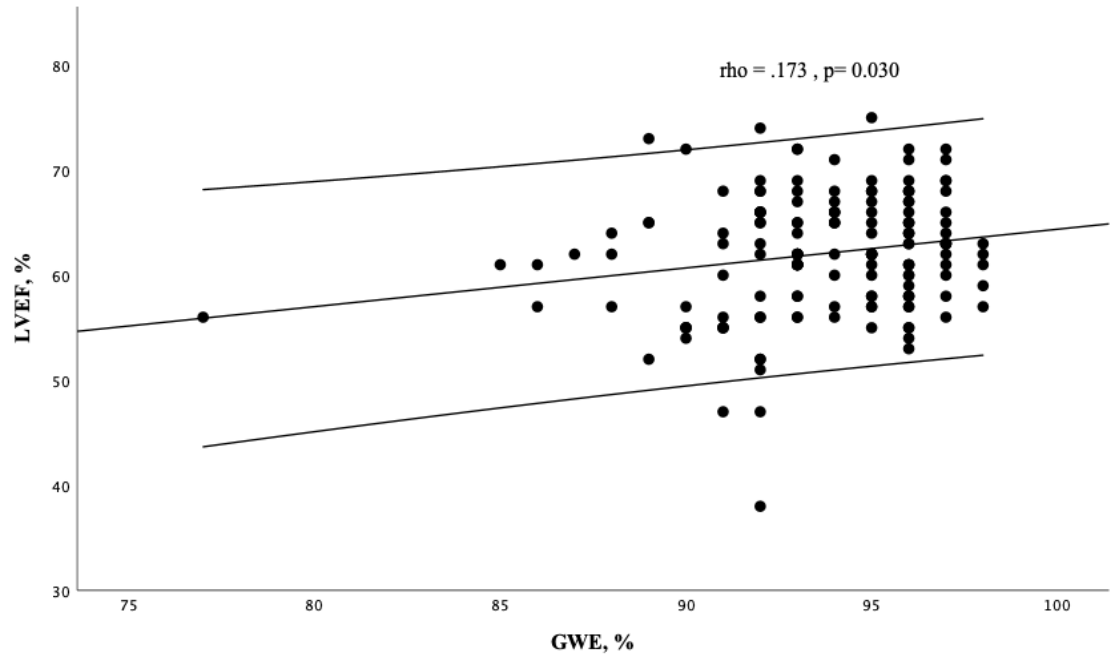


Figure 6.4 Scatterplots for the relationship between global work efficacy and (global longitudinal strain - top and left ventricle ejection fraction – bottom).

6.4.5 Myocardial work and functional capacity

We examined the relationship of myocardial work with functional capacity assessed by cardiopulmonary exercise test and their relationship with relative $VO_{2\ peak}$ and $VE/VCO_{2\ slope}$. A total of 85 patients who underwent stress echocardiography combined with CPET were included in this analysis. 43 (51%) patients had reduced functional capacity (VO2 peak < 84% predicted) and 42 (49%) patients had a normal functional capacity *Table 6.4* showed that the observed mean values of myocardial work components including GWI, GCW, GWW and GWE were similar between the two groups, patients with reduced functional capacity and patients with normal functional capacity (with p-value > 0.05).

Table 6.4 Myocardial work parameters according to the functional capacity.

Variable	$VO_{2\ peak}$,% ≥84%) (n= 42 (49%))	$VO_{2\ peak}$,% < 84%) (n= 43(51%))	*p-value*
GWI, mmHg %	2204 ± 394	2122 ± 437	.376
GCW, mmHg%	2713 ± 590	2707 ± 447	.960
GWW, mmHg%	156 ± 92	157 ± 80	.970
GWE, %	94 ± 3	94 ± 3	.599

GWI; global work index, GCW; global constructive work, GWW; global wasted work, GWE; global work efficiency.

Correlations of myocardial work with CPET parameters

Table 6.5 demonstrates the correlation between the relative $VO_{2\ peak}$ and VE/VCO_2 slope with myocardial work parameters. There was no relationship found between myocardial work components including (GWI, GCW, GWW and GWE) and relative $VO_{2\ peak}$ and VE/VCO_2 Slope (p-value > 0.05).

Table 6.5 Correlation of relative $VO_{2\ peak}$ and VE/VCO_2 Slope with myocardial work parameters

Variables	Correlation with relative $VO_{2\ peak}$ (ml/kg/min)		Correlation VE/VCO_2 slope	
	r	p-value	r	p-value
GWI, mmHg %	.084	.448	.012	.910
GCW, mmHg%	.087	.427	-.040	.716
GWW, mmHg%	-.175	.109	.129	.241
GWE, %	.193	.077	-.116	.289

GWI; global work index, GCW; global constructive work, GWW; global wasted work, GWE; global work efficiency.

6.4.6 Requirement for mitral valve surgery

During follow-up of the asymptomatic cohort (asymptomatic patients with moderate to severe MR), (38%) 37 patients were referred for mitral valve surgery and 59 (62%) patients remained under follow-up.

Myocardial work parameters according to referral status to cardiac surgery are presented in *Table 6.6.* There was no difference in myocardial work parameters between patients who were referred to cardiac surgery and patients who were under follow-up.

Table 6.6 Myocardial work according to referral status to cardiac surgery

Variable	**(Surgery -) (n=59, 62%)**	**(Surgery +) (n=37, 39%)**	***p-value***
GWI, mmHg %	2120 ± 400	2230 ± 438	.233
GCW, mmHg %	2645 ± 551	2813 ± 455	.149
GWW. mmHg %	156 ± 94	158 ± 72	.916
GWE, %	94 ± 3	94 ± 3	.659

GWI; global work index, GCW; global constructive work, GWW; global wasted work, GWE; global work efficiency.

6.4.7 Myocardial work and post-operative LV dysfunction

In the surgery cohort of 87 patients with severe primary MR who underwent mitral valve surgery, 11 (13%) patients had post-operative LV dysfunction (post-operative LVEF<

50%) and 77 (87%) patients had normal post-operative LV function (LVEF ≥ 50%). *Table 6.7* shows a comparison between the post-operative LV dysfunction group and the normal post-operative LV function group for the main clinical characteristics and baseline echocardiography parameters.

Patients with post-operative LV dysfunction were older than patients with normal post-operative LV function (72 ±12 years versus 61 ± 13 years, p-value = 0.008). Sex, body mass index, heart rate and blood pressure were similar between the two groups. Patients with impaired post-operative LV function had larger left atrial volumes, a higher LVESV, a lower LVEF and a higher PASP than patients with normal post-operative LVEF. Global work index of myocardial work was lower in patients with post-operative LV dysfunction (1722 ± 633 mmHg % versus 2045 ± 392 mmHg, p-value = 0.022). Global constructive work, global wasted work and global work efficiency were similar in the two groups (p-value > 0.05).

Table 6.7 Clinical characteristics and baseline echocardiographic parameters according to the occurrence of post-operative left ventricle dysfunction.

Variables	post-operative LVEF≥ 50% (n=76, 87%)	Post-operative LVEF<50% (n=11, 13%)	P- value
Clinical Characteristics			
Age, years	61 ± 13	72 ±12	**.008**
Male, n (%)	46 (61)	6 (50)	.524

Body mass index, kg/m^2	25 ± 3	26 ± 5	.570
Heart rate, bpm	72 ± 14	79 ± 16	.206
Systolic BP, mmHg	133 ± 15	128 ± 18	.192
Diastolic BP, mmHg	77 ± 9	76 ± 12	.799
Pre-operative Echocardiography variables			
LAV indexed, ml/m^2	68 ± 28	94 ± 26	**.005**
LVEDD indexed, cm/m^2	3 ± 0.4	3.2 ± 0.6	.184
LVESD indexed, cm/m^2	1.9 ± 0.3	2.1 ± 0.4	.055
LVEDV indexed, ml/m^2	84 ± 21	96 ± 28	.080
LVESV indexed, ml/m^2	31 ± 9	40 ± 11	**.020**
LVEF, %	63 ± 5	57 ± 8	**.003**
LV S' average, m/s	9.9 ± 2.6	8.7 ± 1.8	.151
PASP, mmHg	28 ±17	37 ± 13	**.021**
E/A ratio	1.8 ± 0.7	2.2 ± 0.7	.098
E' wave, m/s	10.8 ± 2.8	10.1 ± 1.6	.441
E/E' ratio	10.8 ± 3.6	12.7 ± 2.8	.070

GLS, %	-21% ± 3	-17 ± 5	**.002**
GWI, mmHg %	2045 ± 392	1722 ± 633	**.022**
GCW, mmHg%	2619 ± 426	2390 ± 681	.399
GWW, mmHg%	141 ± 64	140 ± 78	.702
GWE, %	94 ± 3	92 ± 6	.103

LVEF; left ventricle ejection fraction, BP; blood pressure, LAV; left atrium volume, LVEDD; left ventricle end-diastolic diameter, LVESD; left ventricle end-systolic diameter, LVEDV; left ventricle end-diastolic volume, LVESV; left ventricle end-systolic volume, S'; left ventricle systolic velocity, PASP; pulmonary artery systolic pressure, E/A; ratio of the early to late ventricular filling velocities, E' wave; mitral annular early diastolic velocity, GLS; global longitudinal strain, GWI; global work index, GCW; global constructive work, GWW; global wasted work, GWE; global work efficiency.

The association between myocardial work and post-operative LVEF

A simple linear regression analysis was performed for a potential predictor of post-operative LVEF (*Table 6.8*). Global work index was significantly associated with post-operative LVEF (β -coefficient 0.003, 95% CI 0.000 to 0.005, p-value = 0.022). Left atrial volume indexed, LVESV indexed, LVEF and GLS were associated with LVEF after surgery in the univariate analysis. Age and PASP showed no association with dependent variables. In addition, there was no association between GWW and GWE and post-operative LVEF.

In multivariate analysis, GWI showed no independent association with post-operative LVEF (p-value = 0.477). Independent predictors of LVEF after MV surgery were lower

GLS (β -coefficient -0.561, 95% CI -1.044 to 0.079, p-value = 0.023) and higher LA volume indexed (β -coefficient -0.048, 95% CI -.090 to -.007, p-value = 0.024). The overall model fit was $R^2 = 0.22$, p value 0.001. GLS was superior to GWI in predicting LV systolic function after mitral valve surgical correction. The predictor variables were not highly correlated with each other. VIF values were less than 3.

Table 6.8 Univariate and multivariate regression analysis with post-operative LVEF as the dependent variable.

Variables	**Univariate analysis**		
	β -coefficient	**95% CI**	**P value**
Univariate analysis			
Age, years	-.074	-.165 to .016	.107
LAVI, ml/m^2	-.047	-.088 to -.007	**.023**
LVESVI, ml/m^2	-.183	-.302 to -.064	**.003**
LVEF, %	.292	.098 to .486	**.004**
PASP, mmHg	-.014	-.089 to .060	.702
GLS, %	-.530	-.869 to -.191	**.003**
GWI, mmHg %	.003	.000 to .005	**.049**

GCW, mmHg %	.001	-.001 to .004	.321
GWW, mmHg %	-.009	-.028 to .010	.345
GWE, %	.338	-.035 to .710	.075

Variables	**Multivariate analysis**		
	β -coefficient	**95% CI**	**P value**
LAVI, ml/m^2	-.048	-.090 to -.007	**.024**
LVESVI, cm/m^2	-.094	-.237 to .049	.195
LVEF, %	.062	-.225 to .349	.669
GLS, %	-.561	-1.044 to .079	**.023**
GWI, mmHg %	-.001	-.005 to .002	.477

CI; confidence interval, LAVI; left atrial volume indexed, LVESDI; left ventricular end-systolic diameter indexed, LVEF; left ventricle ejection fraction, PASP; pulmonary artery systolic pressure. GLS; global longitudinal strain, GWI; global work index.

6.5 Discussion

In this prospective cohort of primary significant MR patients, we examined the prognostic value of myocardial work. We observed that 1. GWI was independently associated with the occurrence of symptoms even after multivariable adjustment for other

predictors of the outcome, 2. Myocardial work parameters were not associated with CPET parameters ($VO_{2\ peak}$ and VE/VCO_2 slope), 3. GWI was associated with post-operative LVEF, however, was not an independent predictor, and GLS was superior to GWI in predicting LVEF after surgery.

Various echocardiographic parameters are used to evaluate LV systolic function. In clinical practice, LVEF is the most widely used parameter. However, it has many limitations, and it may not reflect the true myocardial mechanics as it relies on LV geometric assumptions and is dependent on loading conditions (187). Global longitudinal strain has been advocated as a more sensitive marker of myocardial function in primary mitral regurgitation (191). Yet, GLS remains limited by its load dependency (190). Myocardial work is a novel echocardiography parameter which is less load-dependent and incorporates left ventricle pressure, and therefore, provides incremental information to LVEF and strain which are sensitive to left ventricle afterload. In chronic mitral regurgitation, severe regurgitation is characterised by volume overload. Afterload gradually increases as the ventricle adapts to the chronic overload and enlarges. Eventually, afterload goes beyond the normal, particularly in decompensated MR which may contribute to LVEF impairment (192). According to Laplace's law, LV wall stress is linearly proportional to ventricular pressure and ventricular size and inversely proportional to the wall thickness of the left ventricle. Thus, LV enlargement will indicate a high afterload unless there is a proportional increase in LV wall thickness. Even with all evidence to the contrary, the prevailing view persists that afterload in chronic MR is low. Previous studies debunked this misconception and have shown that end-systolic stress is greatly elevated in decompensated MR and peak systolic stress is increased in both the compensated and decompensated ventricle (193, 194). An understanding the afterload concepts in chronic mitral regurgitation is important when evaluation LV

systolic performance and function. Myocardial work allows the quantification of myocardial systolic performance to be corrected by afterload.

Several studies reported promising results showing the incremental prognostic value of myocardial work in patients with heart failure, aortic stenosis, myocardial infarction, and hypertrophic cardiomyopathy (95, 195-197). A previous study investigated the prognostic value of GWI in functional MR and found that GWI was independently associated with cardiovascular mortality or hospitalisation for heart failure (198). In the present study, we included patients with primary mitral regurgitation and found that patients with symptoms are characterised by reduced GWI. There was a significant association between lower GWI and the occurrence of symptoms, even after multivariable adjustment. However, in a group of asymptomatic MR patients, myocardial work parameters were not associated with the subsequent need for mitral valve surgery with no difference between the surgery group and follow-up group.

Lower GWI was associated with decreasing LVEF and was a predictor of postoperative LVEF. However, the only independent predictors of post-operative LVEF were GLS and LAVI after multivariable analysis. This result supports our previous conclusion in chapter four that GLS was superior to the other echocardiographic parameters in predicting LVEF after mitral surgical correction. There was no association between myocardial work components and $VO_{2\ peak}$ and VE/VCO_2 slope quantified by cardiopulmonary exercise test. The reason to account for this observation may be that patients included in this analysis had compensated MR with normal LVEF.

6.6 Limitation

The small sample size is a limitation of this study. The evaluation and documentation of symptoms may be considered subjective. Myocardial work parameters presume that end-

diastolic pressure (preload) is low as in a normal heart, and LV end-diastolic pressure does not affect the pressure loop area. In the future, myocardial work methodology should take preload into account for accurate results in volume overload conditions. The end-point of post-operative LV function is important. However, longer follow-up would allow investigation of the impact of this end-point on heart failure hospitalisations and mortality.

6.7 Conclusion

In primary MR, reduced GWI was associated with the occurrence of symptoms and post-operative LV dysfunction. However, GLS was superior to GWI in predicting post-operative LVEF. Further large studies are required to investigate the prognostic role of myocardial work in primary MR.

Chapter 7

Prognostic Utility of Blood Biomarkers in Patients with Significant Primary Mitral Regurgitation: N-Terminal Pro-B-Type Natriuretic Peptide and Soluble ST2

7.1 Abstract

Background and objective: In primary severe MR, the timing of surgery is crucial, however, still controversial. Cardiac biomarkers are objective markers for clinical LV dysfunction and heart failure. The aim of this study was to investigate the utility of serum brain natriuretic peptide (BNP) and soluble ST2 (sST2) in patients with significant primary MR. **Methods:** NT-proBNP was measured in 167 patients with primary moderate to severe or severe MR. sST2 was measured in 76 patients. Transthoracic echocardiography was performed for all patients. Two cohort were included, asymptomatic cohort: asymptomatic MR patients underwent exercise echocardiography combined with CPET, and surgery cohort: patients who had MV surgery underwent baseline and post-operative echocardiography 12 months after surgery. **Results:** In the overall study, median NT-proBNP was 168 pg/ml, (IQR 78 to 422 pg/ml). Median sST2 was 23 pg/ml, (IQR 17 to 34 pg/ml). In univariate analysis, elevated baseline NT-proBNP was associated with the presence of symptoms (p-value = 0.001), however it was not an independent association. Determinants of increased NT-proBNP levels were LA volume index, LV end-systolic dimension, reservoir LA strain, workload and VE/VCO2 slope. In the surgery cohort, baseline NT-proBNP was higher in patients with impaired LVEF after mitral surgical correction (p-value = 0.017). NT-proBNP was an independent predictor of post-operative LV dysfunction. sST2 showed no association with outcomes or echocardiographic parameters. **Conclusions:** In primary MR patients, NT-proBNP is higher in symptomatic than in asymptomatic patients. The main determinants of NT-proBNP in this population are the consequences of MR rather than severity. sST2 showed a non-significant result with functional capacity and post-operative LV dysfunction. Additional studies will be needed for additional information about sST2 testing on clinical outcomes in primary MR patients.

7.2 Introduction

Surgery is recommended for severe primary mitral regurgitation if symptoms occur or if there is evidence of left ventricular dysfunction, new atrial fibrillation, or pulmonary hypertension (1, 2). Previous studies demonstrated that there is an association between the standard surgery indications, such as symptoms or LV dysfunction, and long-term poor outcomes (post-operative mortality and heart failure) (199). It would be desirable to identify objective markers to guide the timing of surgical intervention before these complications develop. Therefore, a non-invasive marker of early cardiac remodelling would be beneficial in evaluating patients with degenerative MR. Clinical data has shown promising findings for cardiac biomarkers for clinical LV dysfunction and heart failure. NT-proBNP is a useful marker in evaluating the severity and prognosis of primary mitral regurgitation(114-117, 200). Soluble ST2 (sST2) is another promising biomarker which has the potential to be used for the diagnosis and management of patients with heart failure and several cardiovascular diseases (201-203). However, data are sparse on the role of these cardiac biomarkers in mitral regurgitation patients, especially sST2. The aims of this study were 1. to describe NT-proBNP and sST2 levels in patients with primary MR, 2. to assess the correlation of NT-proBNP and sST2 with other echocardiographic parameters, 3. to examine the incremental utility of these biomarkers and explore their relation to symptoms, exercise capacity, and LV remodelling in patients with significant primary mitral regurgitation.

7.3 Methods

7.3.1 Study population

A total of 167 patients with moderate to severe or severe mitral regurgitation (due to a prolapse or flail leaflet) were included. All patients underwent baseline echocardiography and NT-proBNP testing. When we had the facility for sST2 measurements. We obtained the ethical approval for sST2 measurements later for the remaining patients. we did a nested comparison of sST2 in 76 patients. as we thought that very little attention has been paid to investigating the role of sST2 in primary MR patients. ST2 is upregulated by cardiac myocytes in response to injury or stress. ST2 correlates with inversely with ejection fraction and increased levels are associated with increased mortality (207). There is no data regarding the utility of ST2 in predicting LV decompensation in primary MR. The study population was divided into 2 groups. The asymptomatic group: 95 patients with asymptomatic MR underwent exercise echocardiography combined with CPET. The Surgery group: 84 patients who had MV surgery underwent follow-up echocardiography 12 months after surgery.

7.3.2 Clinical assessments and blood biomarkers

Venous blood sampling for baseline cardiac biomarkers was performed immediately before echocardiography. Venous blood samples were drawn from an antecubital vein. Blood samples were collected using chilled ethylenediaminetetraacetic acid Vacutainer test tubes. Serum samples were separated and stored at −70 °C until further analysis. Plasma NT-proBNP levels were measured and analysed according to standard clinical laboratory routine. Measurement of sST2 was performed with Aspect Plus ST2 Rapid

Test. A detailed methodology of echocardiography, exercise stress test and blood biomarkers used in the study is given in the method chapter (chapter 2).

7.3.3 Follow-up and outcome analysis

Patients who had mitral valve surgery were asked to return for follow-up echocardiography 12 months after surgery. The primary outcome of this study was the presence of symptoms (defined as ≥ NYHA II), symptoms were classified according to NYHA functional classification. The secondary outcomes were: 1. Reduced functional capacity (defined as a predicted $VO_{2\ peak}$ less than 84%) for the asymptomatic group, and 2. Post-operative LV dysfunction (defined as an LV ejection fraction less than 50%) for the surgery group.

7.3.4 Statistical analysis

Continuous variables are reported as mean ± standard deviation, or as median and interquartile range (Q1 to Q3) when the variable is highly skewed. Categorical variables are presented as absolute values and percentages.The distribution of the NT-proBNP and sST2 were non-normal as the original data were skewed (Appendix E). We log transform NT-proBNP and sST2 to make it as normally distributed as possible and reduce the data's variability. so that the statistical analysis results from this data become more valid. Spearman's correlation coefficient was used to assess the correlation between continuous variables. Differences between groups (1. symptomatic versus asymptomatic, 2. patients with reduced functional capacity versus patients with normal functional capacity and 3. patients with postoperative LV dysfunction versus those with normal post-operative LV dysfunction) were analysed for statistical significance with Student t-test or Mann-Whitney test, or x^2 test, as appropriate. Independent predictors of NT-proBNP level were obtained by univariate and multivariate linear regressions analysis. Univariate and

multivariate logistic regression analysis were performed to determine whether cardiac biomarkers parameters could predict symptoms. To test if blood biomarkers are associated with post-operative LV dysfunction, univariable and multivariable linear regression analyses were performed, introducing other well-established independent predictors. Multivariate models' fit was assessed by the Hosmer–Lemeshow approach. A collinearity diagnostic test was performed to test the multicollinearity. A variance inflation factor (VIF) cut-off value of 5 was used for the multivariable model, and only variables with a VIF under 5 were included(153). A p-value less than 0.05 was considered statistically significant. SPSS 27.0 (SPSS Inc., Chicago, IL, USA) was used for all statistical analyses.

7.4 Results

7.4.1 Baseline characteristic

In total, 167 patients with moderate to severe primary MR were enrolled prospectively. 64 (38%) patients had symptoms (≥ NYHA II), and 103 (62%) patients were free of symptoms. The baseline clinical and laboratory characteristics of the whole cohort are presented in *Table 7.1*. The mean age of the total study was 61 ± 15 years. Symptomatic patients were older than asymptomatic patients (65 ± 14 years versus 59 ± 16 years, p-value = 0.053). 101 of 167 patients were male (61%). Height, weight, body mass index and heart rate were similar in both groups. The symptomatic group had a lower systolic blood pressure compared to the asymptomatic group (131 ±17 mmHg versus 139 ± 16 mmHg, p-value = 0.004). However, diastolic blood pressure did not significantly differ between the groups. A higher prevalence of atrial fibrillation, hypertension, and

hypercholesterolaemia were found in symptomatic patients compared to the patients without symptoms. In addition, smoking was more frequent in patients with symptoms (p-value = 0.044).

7.4.2 Blood biomarkers

NT-proBNP varied widely from 13 pg/ml to 5582 pg/ml (median 168 pg/ml, interquartile range (IQR): 78 to 422 pg/ml). sST2 varied from 12 to 85 pg/ml (median 23 pg/ml, IQR: 17 to 34 pg/ml). Median NT-proBNP concentrations were 248 pg/ml (IQR: 113 to761) in patients with symptoms and 141 pg/ml (IQR 70 to 277) in those without symptoms, p-value = 0.001. Median (IQR) sST2 were similar between the two groups (p-value = 0.806).

Table 7.1 Baseline clinical and laboratory characteristics of the patient population according to the occurrence of symptoms.

Variables	All patients (n= 167)	(-) Asymptomatic n=103 (62%)	(+) Symptomatic n=64 (38%)	P-value
Age, years	61 ± 15	59 ± 16	65 ± 14	**.053**
Male, n (%)	101 (61)	69 (67)	32 (50)	**.029**
Height, cm	171 ± 10	172 ± 10	169 ± 11	.065
Weight, kg	73 ± 14	73 ± 13	72 ± 16	.608
Body mass index, kg/m^2	25 ± 4	25 ± 3	25± 4	.646
Heart rate, bpm	72 ± 14	72 ± 13	73 ± 14	.795

Systolic BP, mmHg	136 ± 17	139 ± 16	131 ±17	**.004**
Diastolic BP, mmHg	77 ± 10	78 ± 10	75 ±12	.089
Risk Factors, n (%)				
AF	14 (8)	2 (2)	12 (19)	**.000**
Hypertension	52 (31)	26 (25)	26 (41)	**.037**
Hypercholesterolaemia	29 (17)	10 (10)	19 (30)	**.001**
Smoking	36 (22)	17 (17)	19 (30)	**.044**
Medications n, (%)				
Beta Blocker	47 (28)	27 (26)	20 (31)	.482
ACE inhibitors	28 (17)	9 (9)	19 (30)	**.000**
Diuretics	20 (12)	7 (7)	13 (20)	**.009**
Warfarin	7 (4)	1 (1)	6 (9)	**.009**
Antiplatelet agent	16 (10)	10 (10)	6 (9)	.943
Statin	29 (17)	19 (19)	10 (16)	.640
Amlodipine	13 (8)	9 (9)	4 (6)	.560
Anticoagulant	18 (11)	9 (9)	9 (14)	.281

ARBs	12 (7)	5 (5)	7 (11)	.139
Biomarkers				
NT-ProBNP, ng/ml	168 (78-422)	141 (70-277)	248 (113 -761)	
Log NT-ProBNP, ng/ml	2.3 ± .6	2.2 ± .5	2.5 ±.6	**.001**
sST2, ng/ml (n=76)	23 (17 - 34)	23 (17- 34)	23 (18-38)	
Log sST2, ng/ml (n=76)	1.3 ±.2	1.4 ±.2	1.4 ±.2	.806

Values are mean ± SD, n (%), or median (25th to 75th percentile). AF; Atrial fibrillation, BP; blood pressure; ACE; Angiotensin-converting enzyme, ARBs; Angiotensin receptor blockers. NT-ProBNP; N-terminal pro-B-type natriuretic peptide, sST2; Plasma soluble ST2.

7.4.3 Echocardiography data

Table 7.2 shows the difference in baseline echocardiographic parameters between symptomatic and asymptomatic patients. Measures of left atrial size showed that LA diameter, area and volume were significantly larger in patients with symptoms compared to patients without symptoms. Left ventricle systolic function assessed by LVEF, S' velocity and GLS were comparable in both groups. LV volumes and LV end-diastolic diameter were not significantly different between the groups. LV end-systolic diameter indexed was higher in the symptomatic group (1.9 ± 0.4 cm/m^2 versus 1.8 ± 0.3 cm/m^2, p-value = 0.014) than the asymptomatic group, however un-indexed LV end-systolic diameter did not differ between the group.

Patients with symptoms had significantly higher pulmonary artery systolic pressure than those without symptoms (PASP 32 ± 16 mmHg versus 21 ± 10 mmHg, p-value < 0.0001). Measures of diastolic function showed that patients with symptoms had a higher E wave (1.2 ± 0.3 m/s versus 1.0 ± 0.3 m/s, p-value =0.003) , lower deceleration time, lower E' wave (9.8 ± 2.7 m/s versus 10.7 ± 2.7 m/s , p-value = 0.017) and higher E/E' ratio (12.5 ± 4.3 versus 10.0 ± 3.3 p-value = 0.001), but the E/A ratio did not differ between the two groups.

Table 7.2 Baseline echocardiographic parameters according to the occurrence of symptoms.

Variables	All patients (n=167)	(-) Asymptomatic n=103 (62%)	(+) Symptomatic n=64 (38%)	P-value
LAD, cm	4.3 ± 0.8	4.2 ± 0.8	4.5 ± 0.9	**.009**
LAD indexed, cm/m^2	2.4 ± 0.5	2.3 ± 0.4	2.5 ± 0.5	**.000**
LAA, cm^2	29 ± 9	27 ± 8	32 ± 10	**.000**
LAV, ml	113 ± 51	102 ± 47	130 ± 53	**.000**
LAV indexed, ml/cm^2	62 ± 28	55 ± 25	72 ± 30	**.000**
LVEDD, cm	5.5 ± 0.7	5.4 ± 0.7	5.5 ± 0.8	.548
LVEDD indexed, cm/m^2	3.0 ± 0.5	3.0 ± 0.4	3.1 ± 0.5	.065

LVESD, cm	3.4 ± 0.6	3.4 ± .6	3.5 ± 0.6	.254
LVESD indexed, cm/m^2	1.9 ± 0.3	1.8 ± 0.3	1.9 ± 0.4	**.014**
LVEDV, ml	144 ± 45	142 ± 41	149 ± 51	.604
LVEDV indexed, ml/cm^2	78 ± 21	76 ± 20	81 ± 22	.181
LVESV, ml	54 ± 20	52 ± 17	58 ± 23	.286
LVESV indexed, ml/cm^2	29 ± 9	28 ± 8	31 ± 10	.063
LVEF, %	63 ± 6	63 ± 5	62 ± 6	.295
LV S' average, m/s	9.7 ± 2.6	10 ± 2.7	9.1 ± 2.3	.070
PASP, mmHg	25 ± 14	21 ± 10	32 ± 16	**.000**
RV S', m/s	15 ± 3	15 ± 3	15 ± 3	.814
TAPSE, mm	24 ± 5	25 ± 5	24 ± 5	.275
E/A ratio	1.6 ± 0.6	1.6 ± 0.6	1.7 ± 0.7	.343
E wave, m/s	1.1 ± 0.3	1.0 ± 0.3	1.2 ± 0.3	**.003**
DT, ms	214 ± 66	223 ± 69	199 ± 56	**.016**
E' wave, m/s	10.4 ± 2.7	10.7±2.7	9.8 ± 2.7	**.017**
E/E' ratio	10.9 ± 3.8	10 ± 3.3	12.5 ± 4.3	**.001**

GLS, %	- 20 ± 3	-21 ± 3	-20 ± 3	.754
Peak SL dispersion	40 ± 15	41 ± 16	39 ± 15	.596

LAD; left atrium diameter, LAA; left atrium area, LAV; left atrial volume, LVEDD; left ventricular end-diastolic diameter, LVESD; left ventricular end-systolic diameter, LVEDV; left ventricular end-diastolic volume, LVESV; left ventricular end-systolic volume, LVEF ; left ventricle ejection fraction, RV; right ventricle, PASP; pulmonary artery systolic pressure, S'; systolic velocity, TAPSE; tricuspid annular plane systolic excursion, E/A; ratio of the early to late ventricular filling velocities, DT; deceleration time, E; early passive filling of the left ventricle, E'; mitral annular early diastolic velocity, E/E'- ratio between early mitral inflow velocity and mitral annular early diastolic velocity, GLS; global longitudinal strain.

7.4.4 The association between the presence of symptoms and biomarkers

Table 7.3 shows the results for the logistic regression models with the presence of symptoms as the dependent variable. In univariate analysis, log NT-proBNP showed significant association with symptoms (Wald statistic 9.095, odds ratio: 2.929, 95% CI: 1.578 to 5.439; p-value = 0.001). However, log sST2 showed no association with symptoms (p-value = 0.580). The other variables which had an association with symptoms were age, LA volume, PASP and E/E' ratio. Other parameters such as LV size, LVEF and GLS were not associated with symptoms.

The result of the multiple logistic regression after sequential inclusion of all parameters from univariate analysis revealed that PASP (Wald statistic 8.375, odds ratio: 1.063, 95% CI: 1.020 to 1.109; p-value = 0.004) was the only independent predictor of symptoms. The model explained 26% (Nagelkerke R^2) of the variance and correctly classified 71% of cases. The Hosmer and Lemeshow test showed that the model was a good fit to the data given the p-value was 0.594 (>.05).

Log NT-proBNP was associated with symptoms. However, the association was no longer present when included in a multivariate logistic regression model (p-value = 0.373). The value for VIF was less than 2 for all predictor variables, indicating that multicollinearity was not a problem in the regression model.

Table 7.3 Univariable and multivariable logistic regression analysis for variables associated with symptoms

Variable	**Univariable**		
	Wald statistic	Odds ratio (95% CI)	P value
Age, years	4.519	1.024 (1.002 to 1.047)	**.034**
LAVI, ml/m^2	11.850	1.022 (1.010 to 1.035)	**.001**
PASP, mmHg	20.158	1.074 (1.041 to 1.108)	**.000**
E/E' ratio	11.937	1.189 (1.078 to 1.312)	**.001**
Log NT-ProBNP	11.588	2.929 (1.578 to 5.439)	**.001**
Log sST2	3.923	1.009 (.978 to 1.041)	.580
Variables	**Multivariable**		
	Wald statistic	Odds ratio (95% CI)	P value

Age, years	.214	.993 (.963 to 1.024)	.644
LAVI, ml/m^2	.183	1.003 (.988 to 1.019)	.669
PASP, mmHg	8.375	1.063 (1.020 to 1.109)	**.004**
E/E' ratio	.685	1.054 (.930 to 1.194)	.408
Log NT-ProBNP	.793	1.495 (.617 to 3.619)	.373

CI; confidence interval, LAVI; left atrial volume indexed, PASP; pulmonary artery systolic pressure. E'; mitral annular early diastolic velocity, GWI; global work index, GCW; global constructive work, GWW; global wasted work, GWE; global work efficiency, NT-ProBNP; N-terminal pro-B-type natriuretic peptide, sST2; Plasma soluble ST2.

Prediction of symptoms

The receiver-operator curve analysis was performed for predicting symptoms on the basis of rest PASP and NT-proBNP (*Figure 7.1*). The area under the curve (AUC) for PASP; AUC = 0.742; 95% CI: 0.663- 0.820, for NT-proBNP; AUC = 0.663; 95% CI: 0.576-0.820 (*Table 7.4).* The ROC curve confirmed the result of the regression analysis that PASP was superior to NT-proBNP in predicting symptoms. The optimal cut-off point derived from the ROC curve analysis was 25 mmHg for PASP, with a sensitivity of 60 % and specificity of 71%, and for NT-proBNP 171 pg/ml with a sensitivity of 64 % and specificity of 60%.

Table 7.4 The area under curve of PASP and NT-proBNP for detecting symptoms.

Variables	AUC	95% CI	p value
PASP, mmHg	.742	.663-.820	.000
NT-proBNP	.663	.576-.751	.000

PASP; pulmonary artery systolic pressure, NT-proBNP; N-terminal pro-BNP, AUC; area under curve, CI; confidence interval.

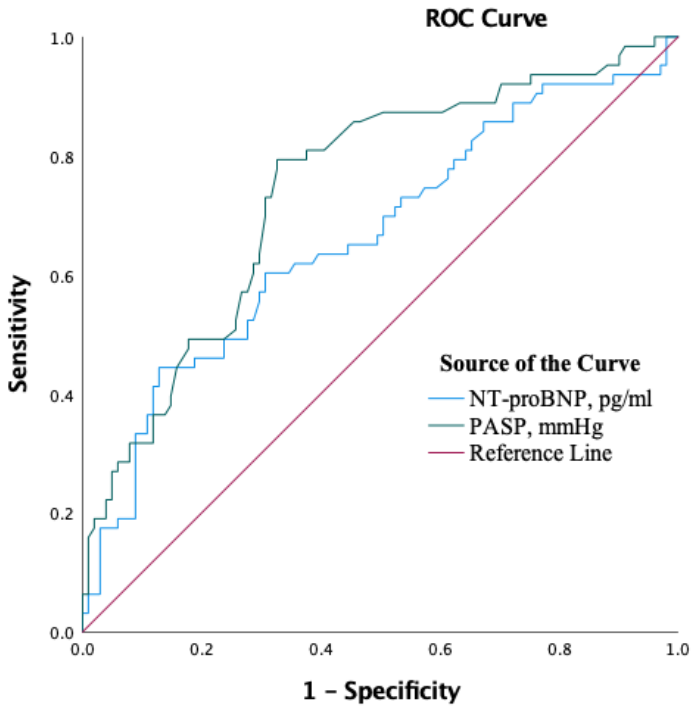


Figure 7.1 Receiver operating characteristic curves of PASP and NT-proBNP for detecting symptoms.

7.4.5 Determinants of biomarkers level

7.4.5.1 The association between biomarkers and echocardiographic parameters

Table 7.5 showed the relationship of the log transformation of NT-ProBNP and sST2 with echocardiographic parameters. The log NT-proBNP was positively correlated with age, indexed LV diameters, E wave, E/E' ratio, deceleration time, indexed LA diameters and indexed LA volume, and with PASP. The log NT-proBNP had a negative correlation with LV S' wave, global work index, global work efficiency and reservoir left atrial strain. All showed significant but weak correlation. The best correlation with log NT-proBNP was found with the reservoir left atrial strain (rho -.502, p-value < 0.0001) (*Figure 7.2*). Log NT-proBNP did not correlate with LVEF (p-value = 0.095) or GLS (p-value = 0.223). Log NT-proBNP was not related to the severity of MR (ERO, p-value = 0.833 and R Vol p-value = 0.108). There was no association between sST2 and any of the echocardiographic parameters.

Table 7.5 Correlation of log NT-ProBNP and log sST2 with echocardiographic parameters.

variables	Log NT-ProBNP		Log sST2	
	rho	p-value	rho	p-value
Age	.460	**.000**	.209	.070
LADI, cm/m2	.487	**.010**	.010	.935

LAVI, ml/m2	.449	**.000**	.019	.871
LVDDI, cm/m2	.308	**.000**	.113	.343
LVSDI, cm/m2	.340	**.000**	-.033	.779
LVDVI, ml/m2	.130	.100	.067	.571
LVSVI, ml/m2	.166	**.034**	-.018	.881
PASP, mmHg	.444	**.000**	.101	.391
S’ wave, m/s	-.254	**.001**	.028	.819
LVEF	-.130	.095	.095	.420
GLS	.023	.775	-.029	.809
ERO	.019	.833	-.102	.429
R Vol	.108	.223	.014	.912
E wave, m/s	.210	**.010**	.034	.788
E/E’	.291	**.000**	.140	.272
GWI, mmHg %	-.227	**.005**	.035	.774
GWE, %	-.256	**.002**	-.089	.467
Reservoir LAS, %	-.502	**.000**	.010	.932

Conduit LAS, %	.321	**.000**	-.034	.780
Contractile LAS, %	.432	**.000**	.004	.970

NT-ProBNP; N-terminal pro-B-type natriuretic peptide, sST2; Plasma soluble ST2, LADI; left atrium diameter indexed, LAVI; left atrial volume indexed, LVEDDI; left ventricular end-diastolic diameter indexed, LVESDI; left ventricular end-systolic diameter indexed, LVEDVI; left ventricular end-diastolic volume indexed, LVESVI; left ventricular end-systolic volume indexed, LVEF ; left ventricle ejection fraction, PASP; pulmonary artery systolic pressure, S'; systolic velocity, E'; mitral annular early diastolic velocity, E/E'- ratio between early mitral inflow velocity and mitral annular early diastolic velocity, GLS; global longitudinal strain. GWI; global work index, GWE; global work efficiency, LAS; left atrial strain.

7.4.5.2 The association between biomarkers and CPET parameters

The relationships between NT-proBNP and sST2 and cardiopulmonary exercise test parameters are listed in *Table 7.6.* There was no association between log NT-proBNP and blood pressure or heart rate at rest and during exercise. However, there was a weak negative relationship with maximum heart rate during exercise. Workload, time exercised, absolute and relative VO_2 peak, oxygen uptake efficiency slope and O_2 pulse were negatively associated with higher NT-proBNP. Higher VE/VCO_2 slope was positively associated with higher NT-proBNP. The best correlation with log NT-proBNP was found with the workload (rho -.543, p-value < 0.0001) (*Figure 7.2*). sST2 was correlated with diastolic blood pressure at rest (rho .348, p-value = 0.002) and diastolic blood pressure during exercise (rho .455 p-value =0.001), however, the correlation was significant but weak (*Figure 7.3).*

Table 7.6 Correlation of NT-ProBNP and sST2 with CPET parameters.

Variables	NT-ProBNP (ng/ml)		sST2 (ng/ml)	
	rho	p-value	rho	p-value
Systolic BP, mmHg	.132	.202	.080	.492
Diastolic BP, mmHg	.034	.745	.157	.157
HR, BPM	.036	.641	.081	.487
Systolic BP $_{peak}$, mmHg	-.163	.114	.309	**.034**
Diastolic BP $_{peak}$, mmHg	-.108	.297	.455	**.001**
HR max, BPM	-.225	**.030**	-.076	.612
% HR max, BPM	.018	.866	.123	.408
Workload, watts	-.543	**.000**	.013	.929
Time exercised, min: sec	-.227	**.028**	.021	.891
$VO_{2\ peak}$, ml /min	-.474	**.000**	.148	.320
Relative $VO_{2\ peak}$, ml /kg/min	-.372	**.000**	.154	.302
Predicted $VO_{2\ peak}$, %	.086	.409	.051	.734
VE/VCO_2 slope	.423	**.000**	-.045	.762

RER	-.100	.335	-.135	.367
OUES	-.389	**.000**	.170	.253
O_2 pulse, ml/beat	-.363	**.000**	.129	.388
Predicted O_2 pulse, %	.122	.244	.076	.612
VO_2/WR	-.105	.318	.159	.286

NT-ProBNP; N-terminal pro-B-type natriuretic peptide, sST2; Plasma soluble ST2.VO2; oxygen uptake, RER; raspatory exchange ratio, BP; blood pressure, VE; ventilation, VCO2; carbon dioxide, O2, oxygen, OUES; oxygen uptake efficiency slope, WR; work rate, HR, heart rate.

7.4.5.3 Regression analysis to predict NT-proBNP level

Table 7.7 showed a univariate and a multivariate regression analysis with NT-proBNP as the dependent variable. In univariate linear regression analysis for rest echocardiographic parameters: there was a positive association between age, LA volume, LVESD, PASP and E/E' ratio with NT-proBNP. S' wave, reservoir LA strain and global work index were negatively associated with higher NT-proBNP. For cardiopulmonary exercise test parameters, there was a negative association between workload, $VO_{2\ peak}$ and $O_{2\ pulse}$ with higher NT-proBNP. Higher VE/VCO_2 slope was associated with elevated NT-proBNP.

Multivariable linear regression analysis was performed for the identification of the independent determinants of NT-proBNP with adjustment for age, sex, and body mass index. The independent determinants of NT-proBNP were indexed LA volume (β - coefficient .007, 95% CI: 0.003 to 0.010, p-value < 0.0001), LV end-systolic diameter (β

-coefficient .345, 95% CI: .053 to .637, p-value = .021), reservoir left atrial strain (β -coefficient -.018, 95% CI: -0.030 to -0.006, p-value = .004) and workload during exercise (β -coefficient -.005, 95% CI: -0.009 to -0.002, p-value =.004) and VE/VCO_2 slope (β -coefficient .023, 95% CI: -0.003 to 0.043, p-value = .026).The overall model fit was R^2 = .611. The data in the multivariate regression analysis (table 7.7) met the assumption that multicollinearity was not a problem, VIF values were less than 4.

Table 7.7 Univariate and multivariate regression analysis with NT-proBNP as the dependent variable.

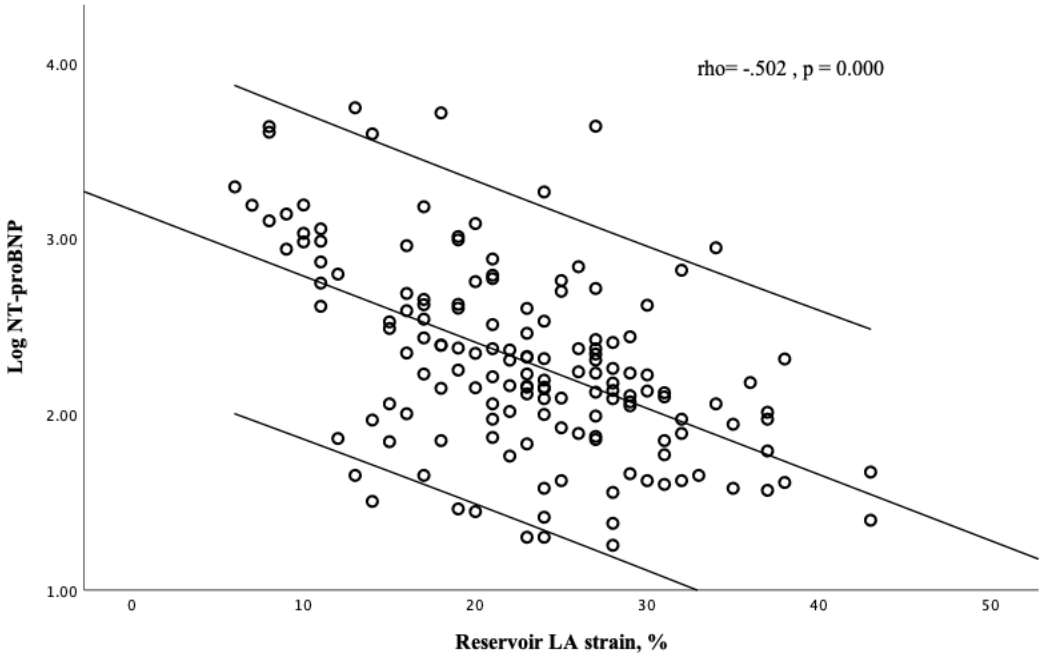
Variables	**Univariate analysis**		
	β -coefficient	**95% CI**	**P value**
Univariate analysis			
Age, years	.016	.011 to .021	**.000**
BMI	-.030	-.054 to -.007	**.012**
Gender	.233	.064 to .402	**.007**
LAVI, ml/m^2	.009	.006 to .012	**.000**
LVESDI, cm/m^2	.610	.362 to .857	**.000**
PASP, mmHg	.018	.013 to .024	**.000**
S' wave	-.057	-.089 to -.025	**.001**

E/E’	.046	.023 to .069	**.000**
Reservoir LAS, %	-.038	-.048 to -.028	**.000**
Workload, watts	-.006	-.008 to -.004	**.000**
Relative $VO_{2\ peak}$, ml /kg/min	-.028	-.047 to -.010	**.003**
VE/VCO_2 slope	.045	.025 to .064	**.000**
O_2 pulse, ml/beat	-.056	-.090 to -.021	**.002**

Variables	**Multivariate analysis**		
	β -coefficient	**95% CI**	**P value**
Age, years	-.001	-.008 to .006	.775
Sex	-.058	-.248 to .131	.543
BMI, kg/m^2	.005	-.024 to .034	.719
LAVI, ml/m^2	.007	.003 to .010	**.000**
LVESDI, cm/m^2	.345	.053 to .637	**.021**
Reservoir LAS, %	-.018	-.030 to -.006	**.004**
Workload, watts	-.005	-.009 to -.002	**.002**

$VO_{2\ peak}$, ml/kg/min	.018	-.008 to .043	.167
$VE/VCO_{2\ slope}$	.023	-.003 to .043	**.026**

CI; confidence interval, LAVI; left atrial volume indexed, LVESDI; left ventricular end-systolic diameter indexed, LVEF; left ventricle ejection fraction, PASP; pulmonary artery systolic pressure. GLS; global longitudinal strain, GWI; global work index.



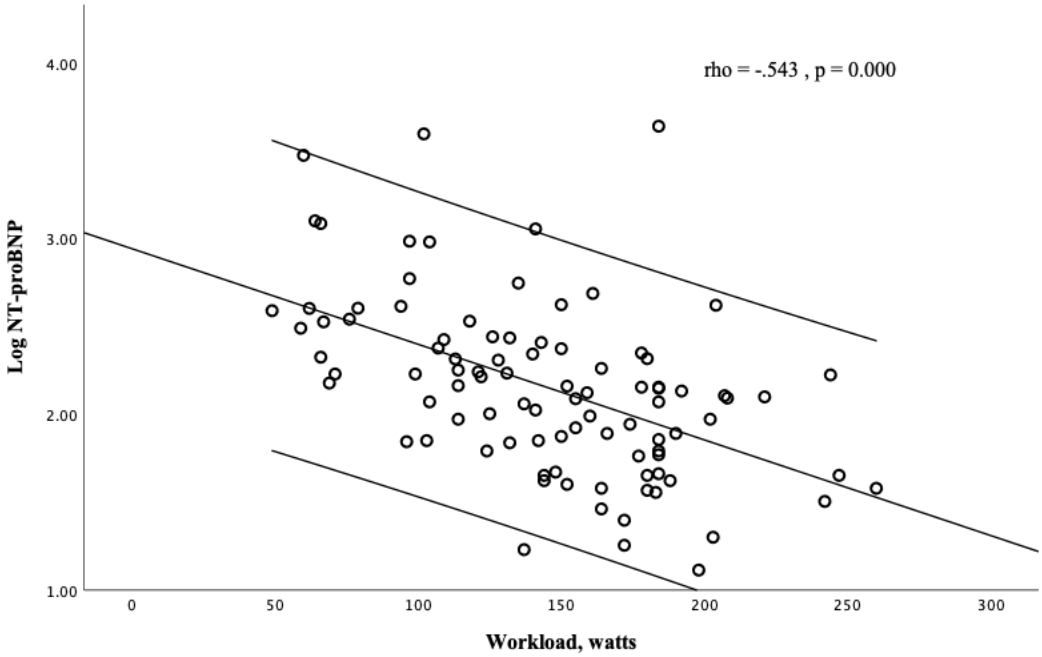


Figure 7.2 Scatterplots for the relationship between log NT-proBNP and (reservoir left atrial strain- top and workload - bottom)

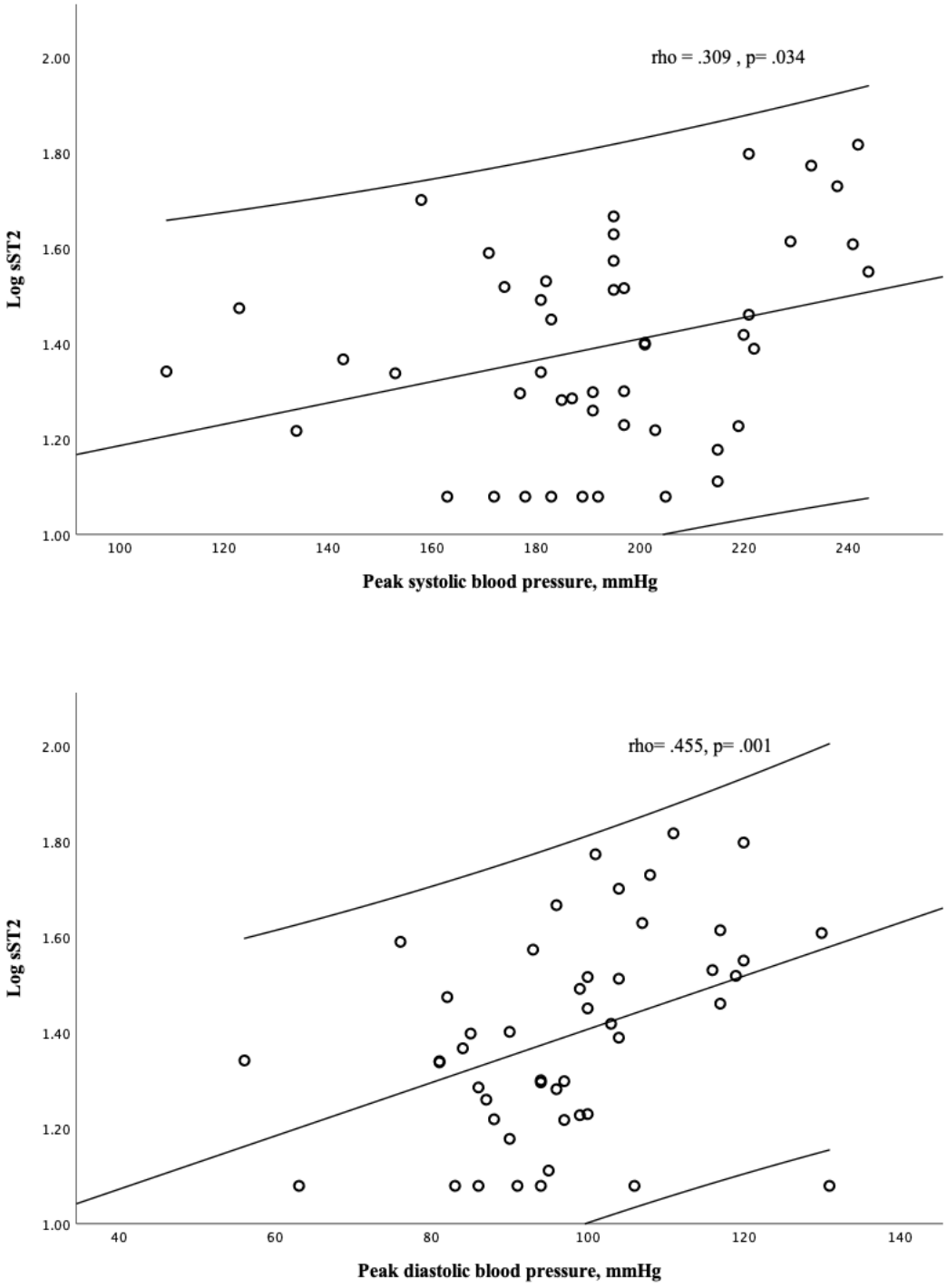


Figure 7.3 Scatterplots for the relationship between log sST2 and (peak systolic blood pressure during exercise- top and peak diastolic blood pressure during exercise - bottom)

7.4.6 The association between biomarkers and post-operative left ventricle dysfunction

A total of 84 patients with severe MR underwent mitral valve surgery. 9 (11%) patients had post-operative LV dysfunction (post-operative LVEF< 50%) and 75 (89%) patients had normal post-operative LV function (LVEF ≥ 50%). *Table 7.8* shows a comparison of the main clinical characteristics and baseline echocardiography parameters according to post-operative LV function.

Stratified by post-operative LVEF, patients with impaired post-operative LV function were older than patients with normal post-operative LV function, however, the difference was not significant (p-value = 0.073). Post-operative LV dysfunction group had a higher baseline left atrial volume indexed (95 ± 26 ml/m^2 versus 67 ± 28, ml/m^2, p-value = 0.004), bigger baseline left ventricle end-systolic dimension indexed (2.2 ± 0.3cm/m^2 versus 1.9 ± 0.3 cm/m^2, p-value = 0.033), bigger baseline left ventricle end-systolic and end-diastolic volume (97 ± 18 ml/m2 versus 83 ± 21 ml/m2, p-value = .038 and 41 ± 8 ml/m2 versus 31 ± 9 ml/m2, p-value = 0.002) and lower baseline LVEF (57 ± 9 % versus 63 ± 5 %, p-value = 0.002). Pre-operative pulmonary artery systolic pressure was higher in patients with impaired LVEF (36 ± 14 mmHg versus 28 ±15 mmHg, p-value =0.043) than in those with normal LVEF. Patients with post-operative impaired LV function had higher baseline E wave and lower baseline deceleration time than patients with normal post-operative LV function. Pre-operative GLS was lower in patients with post-operative LV dysfunction compared to patients with normal post-operative LVEF (-18 ± 5 % versus -21% ± 3 %, p-value = 0.011). Pre-operative median NT-proBNP concentrations were higher 1267 pg/ml (IQR 380 to 1769) in patients with post-operative LV dysfunction than 152 pg/ml (IQR 75 to 452) in those with normal post-operative LV function (p-value =

0.002). Pre-operative median sST2 was higher in patients with LV dysfunction compared to patients with normal post-operative LVEF (29 pg/ml (IQR 15 to 38 versus 21 pg/ml, IQR: 16 to 26) however, the difference was not significant.

Table 7.8 Clinical characteristics and baseline echocardiographic parameters according to the occurrence of post-operative left ventricle dysfunction

Variables	post-operative LVEF≥ 50% (n=75, 89%)	Post-operative LVEF<50% (n=9, 11%)	P- value
Clinical Characteristics			
Age, years	61 ± 13	70 ± 12	.073
Male, n (%)	44 (59)	5 (56)	.858
Body mass index, kg/m^2	25 ± 4	26 ± 5	.570
Heart rate, bpm	72 ± 14	80 ± 16	.206
Systolic BP, mmHg	133 ± 16	129 ± 19	.192
Diastolic BP, mmHg	76 ± 10	78 ± 11	.799
Pre-operative Echocardiography variables			
LAV indexed, ml/m^2	67 ± 28	95 ± 26	**.004**
LVEDD indexed, cm/m^2	3 ± 0.4	3.2 ± 0.6	.128

LVESD indexed, cm/m^2	1.9 ± 0.3	2.2 ± 0.3	**.033**
LVEDV indexed, ml/m^2	83 ± 21	97 ± 18	**.038**
LVESV indexed, ml/m^2	31 ± 9	41 ± 8	**.002**
LVEF, %	63 ± 5	57 ± 9	**.002**
LV S' average, m/s	9.7 ± 2.5	8.6 ± 2.0	.200
PASP, mmHg	28 ± 15	36 ± 14	**.043**
E/A ratio	1.8 ± 0.7	2.0 ± 0.4	.214
E wave	1.1 ± .3	1.4 ± .2	**.039**
DT, ms	205 ± 62	161 ± 28	**.026**
E' wave, m/s	10.7 ± 2.7	10.6 ± 1.2	.901
E/E' ratio	11.2 ± 4.0	12.7 ± 3.0	.148
GLS, %	-21% ± 3	-18 ± 5	**.011**
NT-ProBNP, ng/ml	152 (IQR 75 - 452)	1267 (IQR 380 - 1769)	
log NT-proBNP	2.3 ± .6	2.9 ± .5	**.002**
sST2, ng/ml (n=23)	21 (IQR 16 - 26), n=19	29 (IQR 15 - 38), n=4	
Log sST2	1.4 ± .2	1.4 ± .2	.667

LVEF; left ventricle ejection fraction, BP; blood pressure, LAV; left atrium volume, LVEDD; left ventricle end-diastolic diameter, LVESD; left ventricle end-systolic diameter, LVEDV; left ventricle end-diastolic volume, LVESV; left ventricle end-systolic volume, S'; left ventricle systolic velocity, PASP; pulmonary artery systolic pressure, E/A; ratio of the early to late ventricular filling velocities, E' wave; mitral annular early diastolic velocity, GLS; global longitudinal strain, NT-ProBNP; N-terminal pro-B-type natriuretic peptide, sST2; Plasma soluble ST2.

7.4.6.1 Regression analysis to predict post-operative left ventricle dysfunction

Table 7.9 shows regression analysis for potential predictors of post-operative LV dysfunction. In univariate linear analysis the log NT-proBNP was a predictor for LVEF after surgery (β -coefficient -2.599, 95% CI -4.725 to -0.474, p-value = 0.017). In addition, baseline LVESD, LVEF and GLS were associated with post-operative LVEF. In multivariate linear regression analysis, none of the included parameters were independently associated with post-operative LVEF including NT-proBNP (p-value = 0.075). The overall model fit was $R^2 = 0.24$, p-value < 0.0001.

Multivariable logistic regression analysis was performed to determine if NT-proBNP can predict post-operative LV dysfunction (LVEF<50%) rather than post-operative LVEF. When NT-proBNP was adjusted for other significant predictors in the multivariate logistic model, it remained an independent predictor of LV dysfunction (Wald statistic 4.165, P-value = 0.041). The model explained 34% (Nagelkerke R^2) of the variance and correctly classified 90% of cases. The Hosmer and Lemeshow test showed that the model was a good fit to the data as the p-value was 0.775 (>.05). The value for VIF was less than 2 for all predictor variables, indicating that multicollinearity was not a concern in the regression model.

Table 7.9 Univariate and multivariate linear regression analysis with post-operative LVEF as the dependent variable

Variables	**Univariate linear analysis**		
	β -coefficient	**95% CI**	**P value**
Univariate analysis			
Age, years	-.033	-.126 to .061	.487
LVESD, cm	-2.99	-4.876 to -1.104	**.002**
LVEF, %	.298	.107 to .489	**.003**
PASP, mmHg	-.003	-.084 to .078	.938
GLS, %	-.501	-.857 to -.145	**.006**
Log NT-proBNP	-2.599	-4.725 to -.474	**.017**
Variables	**Multivariate linear analysis**		
	β -coefficient	**95% CI**	**P value**
LVESD, cm	-1.572	-.258 to .040	.134
LVEF, %	.184	-.178 to .364	.119
GLS, %	-.303	-.805 to .116	.181

Log NT-proBNP	-1.908	-3.993 to .233	.075

Variables	**Multivariate logistic analysis**		
	Wald statistic	**Odds ratio (95% CI)**	**P value**
LVESD, cm	1.298	.498 to 13.934	.255
LVEF, %	.501	.778 to 1.125	.479
GLS, %	.192	.762 to 1.535	.661
Log NT-proBNP	4.165	1.060 to 17.651	**.041**

CI; confidence interval, LVESD; left ventricular end-systolic diameter, LVEF; left ventricle ejection fraction, PASP; pulmonary artery systolic pressure. GLS; global longitudinal strain.

7.4.6.2 Prediction of post-operative left ventricle dysfunction.

The receiver operator curve analysis was performed for predicting post-operative LV dysfunction on the basis of NT-proBNP level. ROC produced an area under curve for NT-proBNP of .814, (95% CI: 0.666 - 0.962) for predicting the post-operative LV dysfunction. AUC values for baseline LV end-systolic diameters was AUC = 0.734, (95% CI: 0.581- 0.888), for baseline LVEF was AUC = 0.746, (95% CI: 0.595- 0.898), and for GLS was AUC = 0.694, (95% CI: 0.499- 0.888). NT-proBNP was superior to the predictive association with post-operative LV dysfunction than baseline LVESD, LVEF and GLS. Table 7.10 shows the sensitivity and specificity values for different cut-off values of NT-proBNP. The optimal cut-off point derived from the ROC curve analysis was 252.5 pg/ml for NT–pro-BNP, with the highest sensitivity and specificity.

Table 7.10 The area under curve of NT-proBNP for predicting post-operative left ventricle dysfunction.

	AUC (95% CI)	p-value	Cut-off pg/ml	Sensitivity, %	Specificity, %
NT-proBNP	.814 (.666 - .962)	.002	252.5	89	66
			477.5	78	76
			646.6	67	81

NT-proBNP; N-terminal pro-BNP, AUC; area under curve, CI; confidence interval.

7.5 Discussion

The results of this chapter showed that in patients with moderate to severe or severe degenerative MR, 1) elevated baseline NT-proBNP was associated with presence of symptoms with symptomatic patients having higher NT-proBNP than asymptomatic patients, 2) baseline sST2 was not associated with symptoms, 3) the main determinants of NT-proBNP level were LA volume, LV end-systolic diameter, reservoir LA strain and workload during exercise, and 4) baseline NT-proBNP was higher in patients with impaired LVEF after mitral surgical correction than in patients with normal post-operative LVEF.

In primary mitral regurgitation, it is important to identify patients at high risk to determine the best clinical management, particularly to indicate when surgery is required.

Symptoms and left ventricle dysfunction are risk factors in primary MR. Current guidelines recommended mitral valve surgery for symptomatic patients with severe primary MR. In asymptomatic patients, mitral valve surgery can be considered in the presence of LV dilatation and/or LV dysfunction, LA dilatation, high pulmonary artery systolic pressure or in case of new-onset atrial fibrillation (1, 2, 204). Many patients with ventricular dysfunction are unaware of their condition because they do not have any symptoms. In addition, if they have symptoms, it may be unclear whether symptoms are connected to the regurgitation, particularly in elderly, obese, or physically inactive patients or those with pulmonary disorders. Therefore, an objective, non-invasive marker of early cardiac remodelling would be beneficial in evaluating patients with degenerative MR. Clinical data has shown promising results for cardiac biomarkers including NT-proBNP and sST2 for clinical left ventricle dysfunction and heart failure.

7.5.1 NT-proBNP role in mitral regurgitation

Several previous studies have evaluated the incremental utility of plasma levels of BNP in primary MR. In a study of 87 asymptomatic patients with severe MR and preserved LV function, Klaar et al. (115) reported higher serum BNP levels predicted development of symptoms and LV dysfunction during follow-up. In another study by Magne et al, (114) elevated serum BNP level in 135 patients was associated with a higher rate of MV surgery, indicated by the development of symptoms or ventricular dysfunction. Pizarro et al. (116) reported that higher serum BNP levels were associated with the occurrence of a combined end-point including symptoms, LV dysfunction, MV surgery, or cardiovascular death in severe asymptomatic organic MR. Our results extend findings of those of previous studies and indicate that elevated NT-proBNP level is associated with symptoms occurrence. However, our end-point was only the presence of symptoms not combined with LV dysfunction. Our findings are similar to those of Potocki et al (119) who found

that symptomatic patients had higher NT–pro-BNP levels than asymptomatic patients. However, in our study after further multivariate adjustment, only pulmonary artery systolic pressure remains independently associated with symptoms.

Determinants of NT-proBNP

Determinants of natriuretic peptides remained controversial. In general, natriuretic peptides have been found to be related to the symptoms but inconsistently related to left ventricle size or function, left atrial size, PASP or degree of MR. Sutton et al (205) reported that natriuretic peptide levels were elevated with increased severity of MR and were also higher in symptomatic compared to asymptomatic patients. In our study, MR severity measures such as effective regurgitant orifice and mitral regurgitant volume were not associated with the level of NT-proBNP. This is in line with the findings of Detaint et al, (118) who reported that higher BNP levels reflect the impact of MR on haemodynamics, myocardial structure and function rather than the degree of MR. Furthermore, the same group found that indexed LV end-systolic volume is the best independent determinant of BNP activation in both organic and functional MR (206). Our results are in line with previous studies and indicate that LV end-systolic diameter and LA volume and strain are independently associated with higher NT-proBNP. Magne et al (114) found that GLS is the main determinant of BNP level, whereas in our study there was no correlation between GLS and NT-proBNP. In our study, workload and VE/VCO_2 slope was independently associated with NT-proBNP in multivariate analysis. Suzuki et al (156) found a correlation between $VO_{2\ peak}$ and VE/VCO_2 slope and BNP and reported that patients with low exercise capacity had higher BNP than the patients with maintained exercise capacity. In this study, we found no significant difference in NT-proBNP between patients with reduced exercise capacity and patients with normal exercise

capacity. However higher NT-proBNP was related to lower $VO_{2\ peak}$ and higher VE/VCO_2 slope.

Previous studies have reported that BNP release was influenced by age and sex in the general population (207) and in patients with primary MR (118). In our study, age and sex and body mass index were adjusted in the multivariable analysis to identify independent determinants of NT-proBNP. Age, sex, and body mass index were associated with NT-proBNP levels in univariable analysis. However, in the multivariable model, none of them was an independent predictor of NT-proBNP.

Post-operative left ventricle dysfunction

Despite successful surgical interventions and having followed the current recommendations, postoperative dysfunction and heart failure may still occur. Therefore, identifying patients with subtle myocardial dysfunction is crucial. Standard echocardiographic parameters may fail to detect subclinical LV dysfunction because of their load dependency or their low sensitivity (170). Thus, there has been increased interest in identifying new parameters that would be able to detect subtle changes in myocardial function in primary MR patients. Previous studies reported that elevated plasma BNP levels might indicate subtle myocardial dysfunction and predict the occurrence of symptoms in asymptomatic MR patients (115, 116). Routine monitoring of these biomarkers may assist with deciding when to operate. In this chapter, we studied the association between NT-proBNP and post-operative LV dysfunction and found that patients with post-operative LV dysfunction had higher pre-operative NT-proBNP and NT-proBNP was associated with postoperative LVEF.

In addition, NT-proBNP was an independent predictor of post-operative LV dysfunction with an area under curve of .814, (95% confidence interval: 0.666 to 0.962). The optimal

cut-off value to predict LV systolic dysfunction after surgery was 252.5 pg/ml. Park et al (200) demonstrated that an NT-pro BNP level of 100 pg/ml was the best cut-off value to predict mitral valve surgery or LV systolic dysfunction. Pizarro et al. (116) reported that BNP ≥ 105 pg/ml discriminates patients at higher risk. Our study's cut-off value was higher than in previous studies, possibly because previous studies included asymptomatic patients with moderate to severe or severe MR. Our study included severe MR patients who had mitral valve surgery and the majority of patients were symptomatic.

The result of the present study suggests that NT-proBNP might help to improve the clinical assessment in patients with primary MR. Patients with elevated NT-proBNP are more likely to have symptoms and develop post-operative LV dysfunction.

7.5.2 sST2 clinical value

Natriuretic peptides are well-established biomarkers for heart failure diagnosis. Soluble ST2, ‘suppression of tumorigenicity 2’ is a member of the interleukin-1 receptor family. It is a promising biomarker in the diagnosis and monitoring of patients with different cardiovascular diseases. Weinberg et al. reported that sST2 is produced in cardiac cells as a response to myocardial stress or injury after MI and biomechanical overload (208). This novel biomarker shows promising results for various diseases including coronary artery disease, myocarditis, arrhythmia, and hypertension (201-203). In addition, sST2 is considered a valuable biomarker for risk stratification and for monitoring patients with heart failure (209). However, there is no previous study on the role of sST2 in mitral regurgitation patients. Our findings showed no relationship between echocardiography parameters and sST2. In addition, there was no association between the severity of mitral regurgitation or functional capacity to the sST2 levels. Furthermore, pre-operative sST2 levels showed no significant difference between patients with post-operative left ventricle

dysfunction and those with normal post-operative left ventricle function. The non-significant results may be related to the relatively small sample size of the study and the short follow-up period. To this end, further studies of the role of sST2 in the outcome and risk stratification of mitral regurgitation are needed.

7.6 Limitations

The sample size was relatively small. The study population consisted of pure primary MR due to mitral valve prolapse or flail leaflet, therefore, these findings cannot be extrapolated to all MR patients. As in clinical practice, assessment of the occurrence of symptoms remains subjective. Serial changes in biomarkers are not available in this study. To address the role of sST2 in the mitral regurgitation population, a large population with longer follow-up will be required.

7.7 Conclusions

In primary MR patients, the range of NT-proBNP levels may vary substantially among patients. NT-proBNP is higher in symptomatic than in asymptomatic patients. The main determinants of NT-proBNP in this population are LA size, LA strain and LV end-systolic diameters which are the consequences of MR. NT-proBNP is associated with workload and VE/VCO_2 level. Adding NT-proBNP measurements may be useful to enhance the clinical diagnostic power of clinical data and resting echocardiography variables and may help to improve the timing of intervention. sST2 showed a non-significant result with functional capacity and post-operative LV dysfunction. Additional studies will be needed to quantify the impact of sST2 testing on clinical outcomes in primary MR patients.

Chapter 8

General Discussion

In this thesis, we investigated patients with primary mitral regurgitation in order to help us understand the optimal timing for intervention. Uncertainty remains of the timing for intervention in primary mitral regurgitation. The incremental and clinical value of newer techniques including left ventricle and left atrium deformation, 3D LV volumes, myocardial work and cardiac biomarkers are poorly understood. We, therefore, examined their relationship to the symptomatic status and postoperative outcomes. In addition, in asymptomatic patients with moderate to severe primary MR, the correlation between myocardial mechanics and myocardial work parameters and cardiac biomarkers to exercise testing parameters from CPET including $VO_{2\ peak}$ and VE/VCO_2 slope was assessed.

8.1 Summary of thesis findings and novelty of the conducted research

The insidious onset of symptoms may mean patients do not recognise symptoms. The role of exercise testing for symptoms in MR is not clearly defined. The current guidelines for the management of MR indicate that the presence of symptoms is a critical element (1, 2), but our study has shown that identifying symptomatic status can be difficult. Many patients who were deemed to be asymptomatic developed symptoms during exercise or demonstrated a functional impairment on objective CPET testing. Therefore, the current method of evaluating symptom status based solely on clinical history is insufficient. Routine exercise echocardiography together with cardiopulmonary exercise testing is useful in the managements of asymptomatic patients with primary mitral regurgitation.

Current guidelines recommended surgery for symptomatic patients or for asymptomatic patients in the presence of LV dysfunction and/or LV dilation (1, 2). Despite these

recommendations, LVESD does not take into consideration mid-to-apical LV remodelling, it does not accurately indicate the extent of LV remodelling in response to mitral regurgitation (150). Data on how LV volumes impact outcomes in chronic mitral regurgitation are scarce. Our research demonstrates that LVEDV was superior to LVESD on resting echocardiography in predicting the need for surgery.

Myocardial work has been evaluated in a variety of myocardial and valve diseases (194, 195), however, the role of Myocardial work in primary MR is not defined. This thesis demonstrated a link between a lower myocardial work index and a poor prognosis. In addition, we found that GLS not LVEF was the best indicator of post-operative LV dysfunction. However, LVEF is the recommended measurement in current guidelines (1, 2). LA strain, myocardial work, and NT-proBNP were predictors of post-operative LV impairment, however, were not independent ones.

This research aimed to examine whether advanced echocardiographic imaging techniques and cardiopulmonary exercise tests may be able to identify the earliest signs of left ventricle dysfunction and objectively detect symptoms in patients with primary degenerative mitral regurgitation. In addition, we aimed to identify clinical, blood and echocardiographic biomarkers which predict post-operative outcomes and may help guide timing of intervention.

8.1.1 Evaluation of symptoms

The work within this thesis demonstrates that the accurate assessment of symptomatic status in primary mitral regurgitation patients can be challenging. Chapter three showed a proportion of patients who were deemed to be asymptomatic by experienced clinicians had reduced exercise capacity on an objective cardiopulmonary exercise test or developed dyspnoea on exercise stress echocardiography. In addition, we found that asymptomatic

MR patients who had an elevated rest pulmonary artery systolic pressure were more likely to develop symptoms during exercise stress echocardiography. Therefore, exercise testing may be appropriate in patients with asymptomatic primary MR who have elevated rest PASP since they are the most likely to develop symptoms on exercise (demonstrated in chapter 3). This confirms our belief that we need additional methods to the current approach of assessing symptom status from purely clinical history only, and that there is a role for routine exercise echocardiography combined with cardiopulmonary exercise testing in asymptomatic patients with primary mitral regurgitation for objective assessment of symptom status.

The association between advanced echocardiographic parameters and symptoms occurrence was examined in patients with moderate to severe or severe primary MR in subsequent studies to find a better method for assessing symptoms. Chapter five showed that reservoir LA strain was significantly associated with heart failure symptoms (≥NYHA II), and symptomatic patients had impaired LA strain compared to asymptomatic patients. In chapter six, we investigated whether myocardial work parameters were able to predict the occurrence of symptoms. Myocardial work is a novel echocardiography parameter that incorporates LV pressure. It is less load-dependent and, therefore, provides incremental information to LVEF and strain which are sensitive to LV afterload (94). Myocardial work has been shown to have promising results in various cardiac conditions such as heart failure patients, coronary artery disease, aortic stenosis and functional MR (95, 197, 210, 211). However, myocardial work in primary MR has not previously been studied. Our results demonstrated that there was an independent association between global myocardial index and symptoms. Both LA strain and global myocardial index were better at predicting symptoms than conventional echocardiography parameters such as LVEF, LV size and GLS. However, after

multivariable adjustments, PASP was a better independent parameter for predicting the occurrence of the symptoms than these advanced echocardiographic parameters.

8.1.2 Cardiopulmonary Exercise Test

Often symptoms developed when cardiac dysfunction has progressed to a very advanced stage. Cardiac function is usually assessed by resting echocardiography. Symptoms are graded by NYHA classification, which is the recommended method for functional assessment of mitral valve intervention requirements (1, 2). Despite this, a previous study reported that patients' assessment of their walking distance does not correlate with formally measured exercise capacity by cardiopulmonary exercise testing (212). This suggests that this subjective classification approach is poorly reproducible and may have significant consequences on treatment decisions.

Exercise testing may help to unmask the symptoms which may not be noticeable at rest. Cardiopulmonary exercise testing is an objective test for evaluation and quantification of functional capacity. It is a non-invasive and safe test and provides reproducible measurements (213, 214). In addition, CPET plays a major role in risk stratification and prediction of long-term outcomes in cardiac patients (215). CPET offers a general evaluation of cardiopulmonary function, but not anatomical and pathological function. Echocardiographic imaging provides pathological assessment and detailed information about cardiac anatomy. Exercise echocardiography allows us to assess the haemodynamic and cardiac function response to exercise. Combining an exercise echocardiography test with CPET offers an effective and simple approach which may be valuable for the management of MR patients. In chapter three, we investigated the benefits of integrating exercise echocardiography with CPET testing in asymptomatic patients with moderate to severe primary MR. A significant number of patients who were

considered to be asymptomatic had an impaired functional capacity on objective CPET testing. One of the aims of this research study was to determine whether resting echocardiography parameters can predict functional capacity (assessed by CPET). We found no relationship between rest echocardiography parameters and predicted $VO_{2\ peak}$. Therefore, the determinants of the CPET functional capacity parameters in primary MR are uncertain. $VO_{2\ peak}$ represents functional capacity and is a well-established parameter for prognostic evaluation. VE/VCO2 slope reflects exercise ventilatory efficiency which is a useful index for the prognosis of heart failure patients (216). Chapter five demonstrated that reservoir LA strain was an independent determinant of relative $VO_{2\ peak}$ and $VE/VCO_{2\ slope}$, besides diastolic function parameters. However, there was no difference in echocardiography variables between patients with impaired functional capacity and normal functional capacity. Chapter six showed that myocardial work parameters were not related to $VO_{2\ peak}$ or VE/VCO_2 slope. Therefore, CPET offers distinct information on functional capacity which cannot be obtained by any echocardiographic parameter alone.

8.1.3 Requirements for Cardiac Surgery

In chapter three, we studied the association between echocardiography and cardiopulmonary exercise test parameters and the subsequent need for mitral valve surgery in asymptomatic MR patients who had no conventional guideline indications for surgery at entry into the study. We found that LV end-diastolic volume was the only parameter independently associated with subsequent mitral surgery. In addition, LV end-diastolic volume was a better predictor of the development of symptoms and requirement for surgery during follow-up than LV end-systolic diameter, which is the recommended parameter for surgical intervention. Current guidelines recommend mitral valve

intervention in asymptomatic patients if LV ejection fraction ≤60% or LV end-systolic diameter is dilated. Linear measurements for LV dimensions are simple and quick to measure. However, linear measurements are limited by geometric assumptions and may underestimate size of the ventricle if not properly aligned to the short axis of the ventricle. There is a good correlation between LV diameters and volumes, however, the relationship is curvilinear with a wide error in enlarged ventricles (160). Therefore, LV volumes may provide a better quantification of LV size. Confirmation of our finding in a multi-centre study with a larger cohort is required. We also examined the predictive value of LA strain and myocardial work parameters for mitral valve surgery. However, there was no association between LA strain and myocardial work and the subsequent need for mitral valve surgery (chapters five and six).

8.1.4 Post-operative LV Dysfunction

The appropriate timing of surgery for patients with primary MR is crucial, specifically deciding which patients benefit from early intervention. Current guidelines recommended surgical intervention for symptomatic patients or for asymptomatic patients in the presence of LV dysfunction and/or LV dilation. Despite these recommendations, optimal timing of mitral valve surgery remains controversial, since symptoms recognition may be difficult, and assessment of LV systolic function accurately remains challenging. Despite much investigation into various echocardiographic parameters over the years, there is still no reliable alternative to conventional guideline directed measures. LV dimensions and LV function are the most widely used parameters in clinical practice to evaluate LV function in the context of severe primary mitral regurgitation. These parameters may not reflect true myocardial function as they depend on LV geometric assumptions and are dependent on loading conditions (187). In chronic severe MR, LV ejection fraction is often overestimated by the compensatory mechanism

of ventricular volume overload. The work presented in this thesis aimed to establish whether advanced echocardiographic imaging techniques including LV and LA deformation and myocardial work may be able to identify the earliest signs of LV decompensation and predict post-operative outcomes.

In chapter four, we found that approximately 12% of patients developed LV dysfunction (EF<50%). Baseline GLS was independently associated with post-operative LV dysfunction better than pre-operative LVEF and LV end-systolic diameter. Chapter five showed an association between reservoir LA strain and post-operative LVEF, however, GLS was a better predictor than LA strain. Similarly in chapter sex, myocardial work index was lower in patients with post-operative LV dysfunction than in patients with normal post-operative LVEF, however, GLS was better as a predictor factor for postoperative LV dysfunction. Therefore, GLS is the best predictor of post-operative LV impairment.

8.1.5 Blood biomarkers

NT-proBNP is a blood biomarker which is commonly used to detect heart failure. Previous studies have shown NT-proBNP has prognostic value in patients with MR.

In chapter seven, we investigated the role of baseline NT-proBNP and sST2 for identification of symptoms and post-operative LV dysfunction. We found that a higher NT-proBNP level was associated with the presence of symptoms, with symptomatic patients having a higher NT-proBNP than asymptomatic patients. However, again, pulmonary artery systolic pressure was a better independent predictor of symptoms than NT-proBNP. In addition, NT-proBNP level was significantly associated with left atrial size and LV end-systolic diameters. However, NT-proBNP was not associated with LVEF, GLS or the severity of MR. This is in contrast to previous studies that have

suggested that LV function or MR severity are determinants of higher BNP levels in primary MR (114, 205).

In the cohort of asymptomatic MR patients with normal LV function, we found there was a relationship between NT-proBNP and exercise capacity on CPET testing. Elevated NT-proBNP level was related to lower $VO_{2\ peak}$ and workload and higher VE/VCO_2 slope, although we found no significant difference in NT-proBNP between patients with reduced exercise capacity and patients with normal exercise capacity.

We studied the association between NT-proBNP and post-operative LV dysfunction. We identified that patients with post-operative LV dysfunction had higher levels of pre-operative NT-proBNP and it was associated with postoperative LVEF. The optimal cut-off value to predict LV systolic dysfunction after surgery was 252.5 pg/ml. Our study's cut-off value was higher than in previous studies (200). There were differences in study design between our study (included severe MR in patients who had mitral valve surgery) and previously published studies (including asymptomatic patients with moderate to severe or severe MR). The findings suggest that NT-proBNP can be useful as a prognostic tool regardless of the MR severity in patients with primary MR.

sST2 is a promising marker for the diagnosis and follow-up of patients with different cardiovascular diseases. However, sST2 had not previously been studied in patients with primary MR. In chapter seven, sST2 showed non-significant results and it was not related to any echocardiography parameters, MR severity or functional capacity by CPET. Further research to assess whether sST2 has prognostic utility is required.

8.2 Study limitations

The main limitation of our studies has been the sample size and modest number of patients recruited. In addition, the number of patients in the surgery group with the post-operative outcome events was small. This may limit the analysis power to detect difference between different groups. The follow-up period of patients with post-operative LV function was relatively short. Longer follow-up would be important to establish the impact of this end-point on subsequent heart failure hospitalisations and mortality. The absence of repeated NT-proBNP and sST2 measurement is another limitation, further investigation in this field is needed. The COVID-19 pandemic limited the recruitment and follow-up of patients due to the temporary cessation of elective cardiac surgery, out-patients and research appointments during the three main COVID-19 waves.

8.3 Future direction and clinical implication

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We have shown that asymptomatic patients that remain under routine follow-up based on standard assessment criteria have significantly abnormal functional capacity. Routine exercise echocardiography with CPET can identify patients with reduced functional capacity or exercise-induced symptoms. Future work is required to understand if patients who are asymptomatic but have reduced functional capacity on CPET exercise echocardiography are at greater risk of long-term mortality. LA strain and NT-proBNP were predictors of symptom status but not independent predictors. Only myocardial work and PASP were independent predictors of symptoms which can be identified from the resting echocardiogram.

Our study shows LVESD on a resting echocardiogram was a predictor of the development of symptoms leading to surgery however LVEDV was better. Further studies with larger sample size and prolonged follow-up are needed to examine the relationship between LV volumes and outcomes in primary MR to determine whether LV volumes could be used to identify the best time to intervene.

The best predictor of post-operative LV impairment was GLS and not LVEF. LA strain, myocardial work and NT-proBNP were predictors of post-operative LV impairment but not independent predictors. Current guidelines recommend using LVESD and LVEF, future studies need to be focussed on large, multi-centre trials evaluating the impact of decision-making algorithms based on LV volume and GLS.

8.4 Conclusion

This thesis demonstrated that presence of adverse features markers such as impaired myocardial deformation, reduced myocardial work index, pulmonary hypertension and high NT-proBNP was associated with poor prognosis. These markers are non-invasive, safe and relatively easy to obtain.

In addition, this research indicates the combination of CPET and exercise echocardiography provides unique data. The presence of symptoms is a vital component for the management of MR in the current guidelines, however, this study has highlighted that assessment of symptomatic status can be uncertain. In particular, some patients who were considered to be asymptomatic had poor exercise capacity. Integrating exercise echocardiography with CPET offers an objective definition of a patient's exercise capacity. Exercise echocardiography should be used much more frequently in the assessment of MR and perhaps even incorporated into routine clinical practice.

Important information about cardiac function can be obtained through the simple and effective test of echocardiography. Myocardial deformation and NT-proBNP measurements are increasingly recognised as adding diagnostic and prognostic value in mitral regurgitation patients. Advanced echocardiography including myocardial work is a novel non-invasive approach that may have potential value in MR patients.

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Appendix A: REC Ethical Approval

Health Research Authority

Dear Dr Sanjeev Bhattacharyya

Letter of HRA Approval

Study title:	**Determine Optimal Intervention Time Cut-Off for Degenerative Mitral Regurgitation by Left Ventricle Mechanics.**
IRAS project ID:	
REC reference:	
Sponsor	**Barts Health NHS Trust**

I am pleased to confirm that **HRA Approval** has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications noted in this letter.

Participation of NHS Organisations in England

The sponsor should now provide a copy of this letter to all participating NHS organisations in England.

Appendix B provides important information for sponsors and participating NHS organisations in England for arranging and confirming capacity and capability. **Please read *Appendix B* carefully**, in particular the following sections:

- *Participating NHS organisations in England* – this clarifies the types of participating organisations in the study and whether or not all organisations will be undertaking the same activities
- *Confirmation of capacity and capability* - this confirms whether or not each type of participating NHS organisation in England is expected to give formal confirmation of capacity and capability. Where formal confirmation is not expected, the section also provides details on the time limit given to participating organisations to opt out of the study, or request additional time, before their participation is assumed.
- *Allocation of responsibilities and rights are agreed and documented (4.1 of HRA assessment criteria)* - this provides detail on the form of agreement to be used in the study to confirm capacity and capability, where applicable.

Further information on funding, HR processes, and compliance with HRA criteria and standards is also provided.

Appendix B: Consent Form

Barts Heart Centre

Barts Health NHS
NHS Trust

LV mechanics in MR Study: Patient Declaration of Consent

Centre Number:

Study Number:

Participant Identification Number for this trial:

Title of Project: Determine Optimal Intervention Time Cut-Off for Degenerative Mitral Regurgitation by Left Ventricle Mechanics (LV mechanics in MR). IRAS number

Please initial box

1. I confirm that I have read the information sheet dated 3.10.2019 (Version 1.5) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected. ☐
3. I agree to provide a sample of blood for this study, blood sample will be kept and used for testing until study activities are completed ☐
4. (If appropriate) I understand that relevant sections of my medical notes and data collected during the study, may be looked at by individuals from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐
5. I understand that the information collected about me will be used to support other research in the future, and may be shared anonymously with other researchers. ☐
6. I agree to my General Practitioner being informed of my participation in the study. ☐
7. I agree to take part in the above study. ☐

Name of Participant	Date	Signature
Name of Person taking consent	Date	Signature

When completed: 1 for participant; 1 for researcher site file; 1 (original) to be kept in medical notes. LV mechanics in MR consent form v1.303/10/2019

Appendix C: Additional Statistics Measurements

Chapter 5

Further analysis showed that there was no association between left atrial strain parameters and the subsequent need for mitral valve surgery in asymptomatic mitral regurgitation patients (*Table A.1*).

Table A.1 Regression analysis of left atrial strain parameters with mitral valve surgery as the dependent variable.

Variables	**Univariate**	
	Wald statistics	**P-value**
Reservoir LAS, %	.656	.418
Conduit LAS, %	.548	.445
Contractile LAS, %	.003	.956

LAS; left atrial strain.

Echocardiographic data according to referral status to cardiac surgery for the asymptomatic cohort are presented in *Table A.2*. Echocardiographic parameters did not differ between patients who were referred to cardiac surgery and patients who were under follow-up.

Table A.2 Clinical demographics and baseline Echocardiographic parameters of the population according to the functional capacity.

Variable	**Normal functional capacity (n= 43 (49%))**	**Reduce functional capacity (n= 44(51%))**	***p-value***
Age, year	61±15	56±17	.064
Sex, male, n (%)	30 (47)	36 (72)	.388
BMI, kg/m^2	24 ± 3	25 ± 3	.802
Systolic BP, mmHg	140 ± 14	141 ± 17	.983
Diastolic BP, mmHg	80 ± 9	79 ± 8	.845
Heart rate, beat/min	73 ±13	74 ±15	.359
LAA, cm2	28 ± 9	25 ± 8	.308
LAV, ml	110 ± 54	90 ± 36	.081
LVEDD, cm	5.6 ± 0.6	5.4 ± 0.6	.146
LVESD, cm	3.4 ± 0.6	3.5 ± 0.5	.753
LVEDV, ml	148 ± 43	136 ± 39	.209
LVESV, ml	56 ±16	51 ±17	.108

LVEF (%)	62 ± 5	63 ± 5	.353
PASP, mmHg	20 ±10	19 ±10	.410
LV S' velocity, m/s	10.3 ± 2.7	10.1 ± 2.7	.619
LV-GLS, %	-21 ± 3	-20 ± 3	.284
ERO, mm^2	0.5 ± 0.2	0.5 ± 0.3	.902
E/E'	10.1 ± 3	9.9 ± 4	.764

LAD; left atrium diameter, LAA; left atrial area, LAV; left atrial volume, LVEDD; left ventricular end-diastolic diameter, LVESD; left ventricular end-systolic diameter, LVEDV; left ventricular end-diastolic volume, LVESV; left ventricular end-systolic volume, LVEF; left ventricle ejection fraction, GLS; global longitudinal strain, S'; left ventricle systolic velocity, PASP; pulmonary artery systolic pressure, BP; blood pressure.

Appendix D: Additional Statistics Measurements

Chapter 6

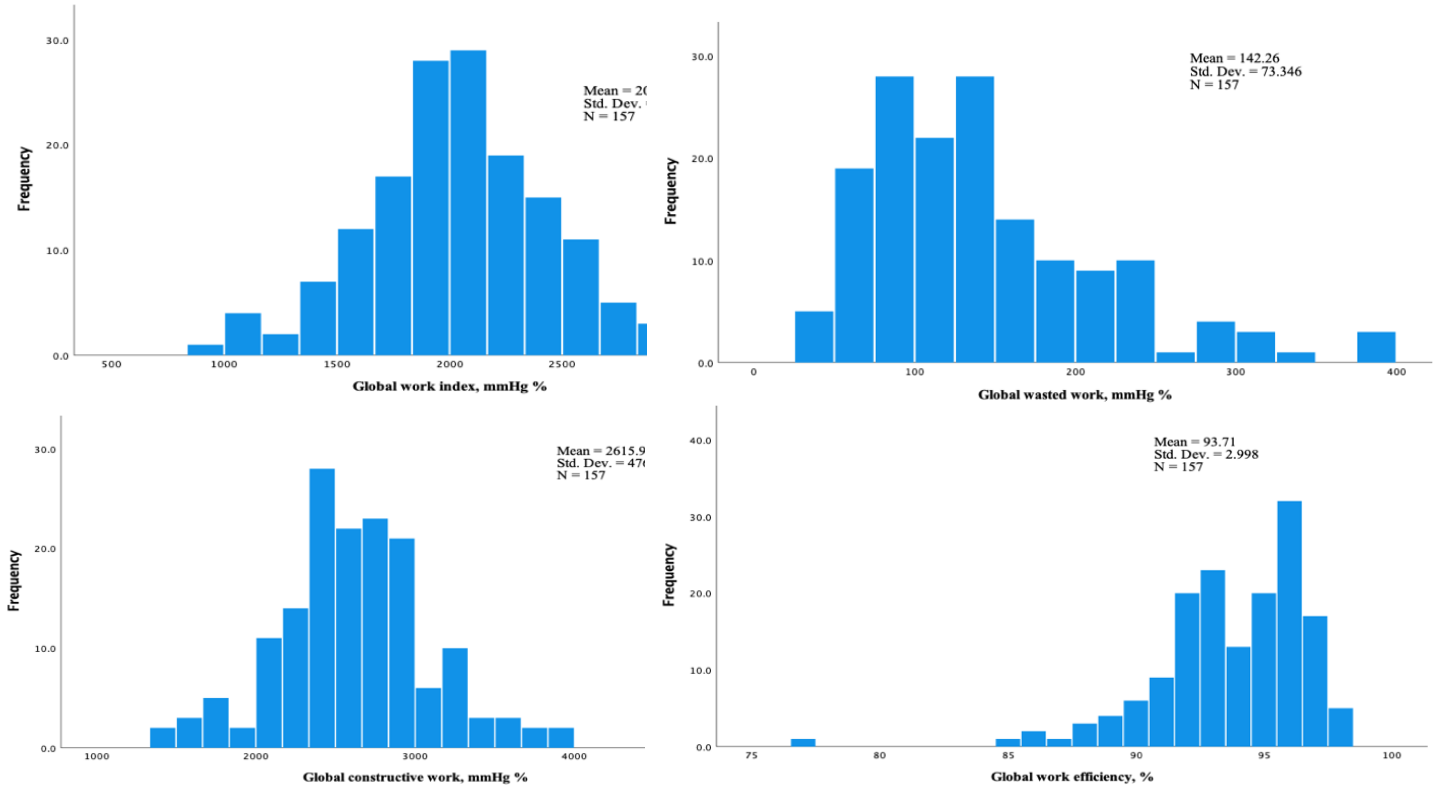

Figure A.1 Distribution of global work index (top left), global wasted work (top right), global constructive work (bottom left) and global work efficiency (bottom right).

Appendix E: Additional Statistics Measurements

Chapter 7

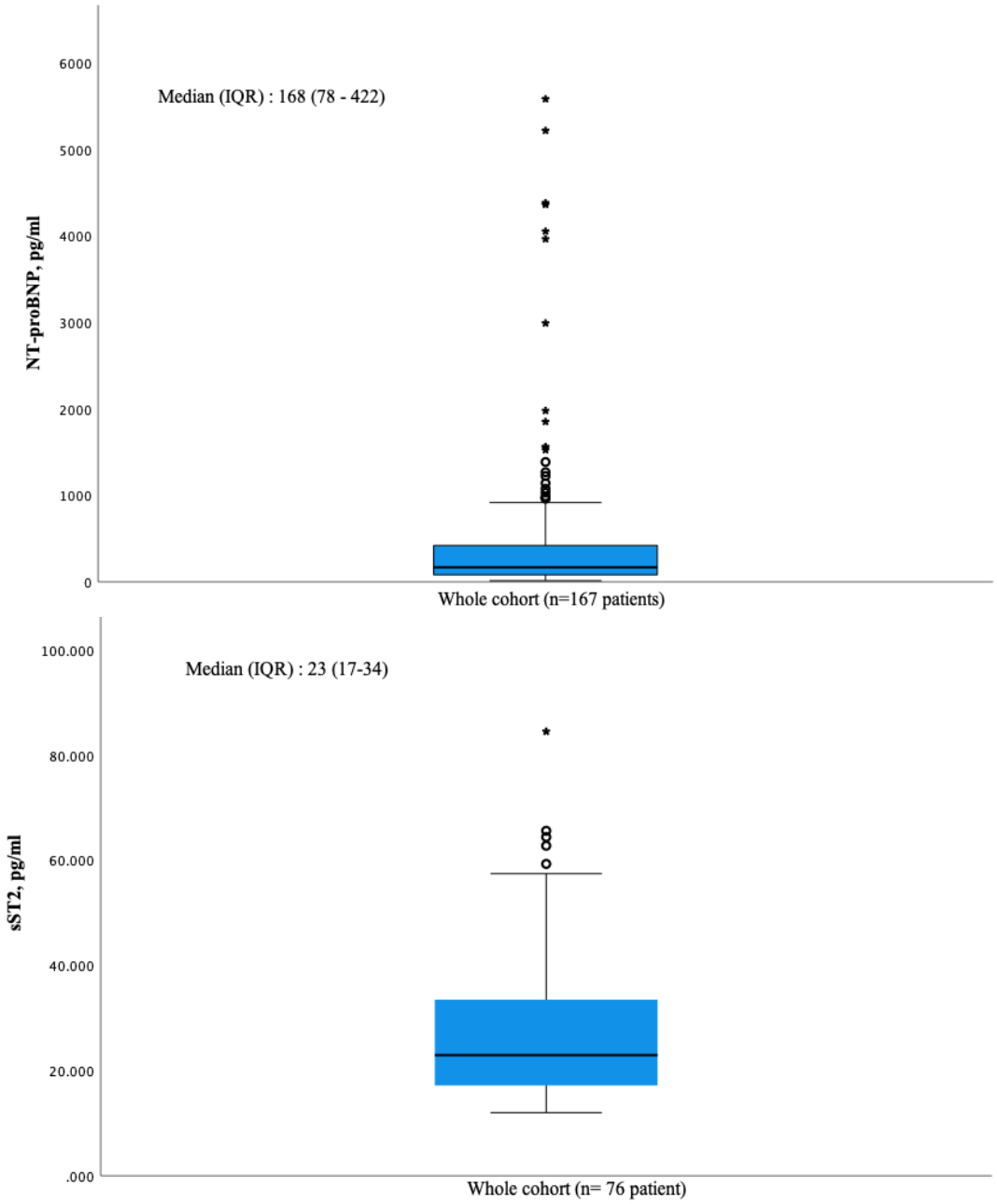

Figure A.2 Distribution of NT-proBNP (top) and sST2 (bottom) in the whole population, the box plots shows that the distribution of the blood biomarker is not normally distributed.