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SPECKLE TRACKING EVALUATION OF RIGHT VENTRICULAR FUNCTION POST LEFT-SIDED VALVE REPLACEMENT

By

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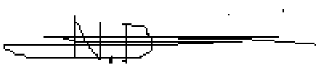
DECLARATION

I Nompilo Dlamini, student number 21119227 declare that:

With the exception of a few instances, the research presented in this dissertation is entirely original with no submissions made in the past for credit toward any other degree at any university or other higher education establishment. The research includes acknowledgements for any information taken from other people's published and unpublished works.



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PREFACE

The research described in this dissertation was carried out in the cardiac clinic at Port Elizabeth (Gqeberha) Provincial Hospital, Eastern Cape, from 2020-2022 and was supervised by:

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This study is intended to add knowledge to existing theories about the importance of the right ventricle as a determinant of clinical symptoms, peri-operative survival and postoperative outcome through dimensional (2D) echocardiographic and speckle tracking echocardiography.

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ABSTRACT

Background: The right ventricle dilates due to increased pulmonary wedge pressure caused by mitral and/or aortic valve disease, which lowers the right ventricular (RV) ejection fraction. This dilation can lead to tricuspid regurgitation (TR) with secondary right ventricular volume overload. Surgically correcting the left heart valves is thought to result in more favourable RV reverse remodelling, however, a growing number of patients have been observed in the cardiac unit at Port Elizabeth Provincial Hospital (PEPH) with worsening symptoms after left valvular correction. Due to the idea that tricuspid regurgitation (TR) would disappear after the original left-sided valve disease was corrected, surgical correction of the tricuspid valve (TV) has, up to now, been avoided in patients with secondary STR at the time of left valvular surgical correction. Much too little is known about how critical right ventricular (RV) function is and how it affects the cardiovascular patient's prognosis. When selecting surgical procedures for the mitral valve (MV) and/or aortic valve (AO), RV performance is not the key determining factor.

Aims: To determine changes in the right heart after mitral and/or aortic valve surgery, as well as to determine predictors of early signs of tricuspid regurgitation progression post-left valve surgery using two-dimensional Doppler and speckle tracking echocardiography.

Study population and design: This study included 30 patients, 12 males and 18 females between the ages of 18 and 65. This was a prospective clinical study on the preoperative and postoperative echocardiographic parameters and their interaction in patients with severe mitral and/or aortic valve disease who were candidates for valve surgical correction. All echocardiographic examinations were conducted in the cardiac clinic of Port Elizabeth (Gqeberha) Hospital in the years 2020 to 2022.

Subjects and methods: Participants were subjected to complete clinical examination and transthoracic echocardiography using the Ultra-Premium Aloka Prosound F75 Hitachi system, equipped with S3 transducer under very strict COVID-19 protocols. Standard 2D, M-mode, right ventricular global longitudinal strain, right ventricular free wall longitudinal strain, and Doppler echocardiography in the parasternal and apical views were recorded.

Results: The population comprised 30 patients undergoing cardiac surgery for severe mitral and or aortic valve surgery. The study's results revealed that the mean age of patients was 45.83 years with the majority being females (60%) and males at 40%. The predominant aetiology of valve diseases was degenerative valve disease (43.3%), and the most common valve disease was mitral regurgitation and aortic regurgitation, respectively at 23.3%. Tricuspid valve replacement reduced tricuspid regurgitation significantly, however, due to the small number of patients (n = 1) who progressed to significant tricuspid regurgitation further analysis was not undertaken. All correlations between tricuspid valve annulus, right ventricular systolic pressures and right ventricular diameter 6 months post-op were significant with a p-value of < 0.001.

There were significant differences in left ventricular end-diastolic diameter (LVEDD) [5.46 ±.867vs 5.11 ±.850, (p=0.027)] as well as ejection fraction (EF) [65.33 ± 11.902 vs 61.50 ± 15.543, (p=0.037)] 6 months post op. There was no significant global longitudinal strain (GLS) change demonstrated in right ventricular function using speckle tracking imaging [-5.02 ± 7.400 vs -6.07 ± 9.373, p>0.005). The study demonstrated a significant decline in regional basal inferior septum (BIS) segments at 6 months follow-up [-9.67 ± 19.626 vs -4.86 ± 23.126 (p 0.034)]. The study also demonstrated a significant decrease in right ventricular function measured with TAPSE [23.20 ± 6.483 vs 19.182 ± 5.7738 (p<0.001) and FAC [60.63 ± 17.76 vs 41.33 ± 19.62 (p=0.18) 6 months post-op, with an immediate decline in mean measurements directly (72 hours) after surgery, a slight gradual mean increase was noted at 6 months follow up after surgery. A significant negative correlation was seen between RV dimensions and TAPSE 6 months post-op. There was no correlation seen between EF and GLS and TAPSE, LVEDD and GLS 72 hours post-op and again 6 months post-op (p >0.05).

Conclusion: The global and/or regional systolic RV function was appropriately estimated using the 2D Doppler measurements and speckle tracking imaging. Together, these echocardiographic parameters measurements allowed for an accurate RV evaluation, improving disease diagnosis and management. Immediately following surgery, a thorough examination that includes TAPSE, S', and RVFAC assessment should be conducted. This examination should be repeated in three and six months to verify whether RV longitudinal function may have fully recovered and to enhance early management of RV failure.

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ABBREVIATIONS

2D	two dimensional
3D	Three dimensional
ACC/AHA	American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines.
ApS	Apical septum
A2C	Apical two-chamber
A3C	Apical long axis three-chamber
A4C	Apical four-chamber
ACE	angiotensin-converting enzyme
ACEI	angiotensin-converting enzyme inhibitor
ASE	The American Society of Echocardiography
AHA/ACC	American Heart Association/American College of Cardiology
ASE/EACVI	American Society of Echocardiography/European Association of Cardiovascular Imaging
ACS	acute coronary syndromes
AMI	acute myocardial infarction
AF	atrial fibrillation
AR	aortic regurgitation
AS	aortic stenosis
AV	Aortic valve
AVR	aortic valve replacement
ApL	Apical lateral
BAV	balloon aortic valvotomy
BAL	Basal inferior wall
BIS	Basal inferior septum
BMV	Balloon mitral valvotomy
CO	cardiac output

CHF	congestive heart failure
CABG	coronary artery bypass grafting
CAD	coronary artery disease
CM	Centimeters
ESC/ERS	European Society of Cardiology/European Respiratory Society guidelines
CAVD	Calcified aortic valve disease
CFM	color-flow mapping
CHD	coronary heart disease
CHF	chronic heart failure
COPD	chronic obstructive pulmonary disease
CNS	central nervous system
CMRI	cardiac magnetic resonance imaging
CPR	cardiopulmonary resuscitation
CT	computed tomography
CW	continuous wave
DCM	dilated cardiomyopathy
EDV	end-diastolic volume
ESV	end-systolic volume
E wave	early wave
ERO	effective regurgitant orifice
EACVI	European Association of Cardiovascular Imaging
ESC/EACTS	European Society of Cardiology/European Association of Cardiothoracic Surgery
ECG	electrocardiogram
LVEDV	Left ventricular end diastolic volume
EF	ejection fraction
FTR	Functional tricuspid regurgitation
FAC	Fractional area change
GFR	glomerular filtration rate

HFrEF	Heart failure with reduced ejection fraction
HFpEf	Heart failure with preserved ejection fraction
HCM	hypertrophic cardiomyopathy
ICH	intracranial hemorrhage
IVSLS	interventricular septal wall longitudinal strain
IE	infective endocarditis
IM	intramuscular
INR	international normalized ratio
IVS	Interventricular septum
IVSd	Interventricular septum in diastole
IVS/LVPW	Ratio of Inter-ventricular septum/ left ventricle posterior wall
IVC	inferior vena cava
JVP	jugular venous pressure
LA	left atrium
LAP	left atrial filling pressure
LGE CMR	late gadolinium enhancement cardiac magnetic resonance
LV	left ventricle
LVOT	Left ventricular outflow tract
LVEF	left ventricle ejection fraction
LVESD	left ventricular end-systolic dimension
LVIDd	Left ventricular internal diameter
LVPWs	Left ventricular posterior wall in systole
LVH	left ventricular hypertrophy
mPAP	mean pulmonary arterial pressure
mm^2	millimeters squared
mmHg	millimetres per mercury

MI	myocardial infarction
MIS	Mid inferior septum
MAL	Mid anterior wall
MVD	Mixed valvular disease
MR	mitral regurgitation
MRI	magnetic resonance imaging
MS	mitral stenosis
MV	mitral valve
MVR	Mitral valve replacement
MVP	mitral valve prolapse
MVA	mitral valve area
MVP	mitral valve prolapse
NYHA	New York Heart Association
PLAX	Parasternal long axis view
PSAX	Parasternal short axis view
PHTN PH	pulmonary hypertension
PH-LHD	Pulmonary hypertension due to left heart disease
PCWP	pulmonary capillary wedge pressure
PAWP	pulmonary arterial wedge pressure
PEPH	Port Elizabeth Provincial Hospital
PTCA	percutaneous transluminal coronary angioplasty
PRF	pulse repetition frequency
PVR	pulmonary vascular resistance
PW	pulsed wave
PV	Pulmonary valve
PS	Pulmonary stenosis
PISA	proximal isovelocity surface area
PR	Pulmonary regurgitation stenosis
RA	right atrium

ROI	region of interest
RVGS	Right ventricle global strain
RVol	Regurgitant volume
RV	right ventricle
RVVO	Right ventricular volume overload
RVPO	Right ventricular pressure overload
RVF	Right ventricular function
RVEF	Right ventricular ejection function
RVF	Right ventricular dysfunction
RVOT	right ventricular outflow tract
RVSP	Right ventricular systolic pressure
RVGLS	RV global longitudinal strain
RVFWS	RV free wall longitudinal strain
RVH	right ventricular hypertrophy
RHD	Rheumatic heart disease
RF	rheumatic fever
SAVR	Surgical aortic valve replacement
SDI	sociodemographic index
SLE	systemic lupus erythematosus
STR	secondary tricuspid regurgitation
STI	Speckle tracking imaging
STE	Speckle tracking echocardiography
STR	secondary tricuspid regurgitation
SR	sinus rhythm
SVC	superior vena cava
sPAP	Systolic pulmonary artery pressure
TAVI	transcatheter aortic valve Implantation
TAPSE	Tricuspid annular plane systolic excursion

TEE	transesophageal echocardiography
TDI	Tissue doppler imaging
TR	tricuspid regurgitation
TA	tricuspid annular
TA	tricuspid annuloplasty
TS	Tricuspid stenosis
TV	Tricuspid valve
TVR	Tricuspid valve replacement
TAVR	Transcatheter Aortic valve replacement
UK	United Kingdom
VAS	Valvular aortic stenosis
VHD	Valvular heart disease
VC	Vena contracta

CHAPTER 1: INTRODUCTION

Cardiac remodeling due to aortic or mitral valve disease results in right ventricular ejection fraction reduction and ventricle dilatation. [1]The right ventricle (RV) and pulmonary circulation are low-resistance systems[2],and variations in ventricular pressure affect the septum's shape and mobility. [3]When the left ventricle experiences volume overload, pulmonary hypertension (PHTN) results.[2]Despite the potential for PHTN reversibility after left valve surgery, a significant portion of postoperative patients have RV dysfunction indications.[4]

Postoperative RV dysfunction is linked to factors such as poor collateral network, direct exposure to the atmosphere, rapid temperature increase, hypoperfusion during cold cardioplegic arrest[5], non-venting of venous blood returning to the RV, myocardial hypothermia, and size or location of the pericardial opening.[6]Postoperatively, RV systolic function can be reduced for months or years. However, surgically correcting left heart valves can significantly improve depressed RV function and reverse remodeling.[7] Perioperative RV dysfunction is a predictor of morbidity and death following mitral and/or aortic valve replacements[7, 8], but is not the main factor to consider when choosing mitral valve (MV) and/or aortic valve (AV) replacements. [9]

RV function is crucial for heart failure patients' symptoms and survival. [7] Post-surgery, the RV may continue to worsen, potentially indicating a poorer prognosis for morbidity and death. Early surgical referral and considering RV function in intervention criteria are essential. Imaging technologies like speckle tracking echocardiography (STE) are essential for detecting early RV depression or function.[10] However, sub-Saharan Africa lacks knowledge on STE's usefulness in evaluating right ventricular remodelling due to limited specialized personnel availability and high costs.[11]

This study used two-dimensional Doppler and speckle tracking echocardiography to examine the changes in the right heart following left valvular intervention and identify independent predictors of postoperative RV dysfunction and TR progression.

This study included 30 patients (12 men and 18 women) between the ages of 18 and 65 years. This was a prospective clinical study on the preoperative and postoperative echocardiographic parameters and their interaction in patients with severe mitral and/or aortic valve disease who were candidates for valve surgical correction. All echocardiographic examinations were conducted in the cardiac clinic of Port Elizabeth (Gqeberha) Hospital between the years 2020-2022. Participants were subjected to complete clinical examination and transthoracic echocardiography using the Ultra-Premium Aloka Prosound F75 Hitachi system, equipped with an S3 transducer under very strict coronavirus disease of 2019 (COVID-19) protocols. Standard 2D, M-mode, RV global longitudinal strain (RVGS), RV free wall longitudinal strain (RVFWS) and Doppler echocardiography were recorded in the parasternal and apical views.

1.1 Aim and objectives

The aim of this study was to determine changes in the right heart after mitral and/or aortic valve surgery, as well as to determine predictors of early signs of TR progression post left valve surgery that could possibly be used as an indication for TV surgery at time of left valve surgery.

The objectives were:

1. To determine echocardiographic parameters of tricuspid regurgitation, pulmonary arterial pressure and RV function at specific intervals pre and post left sided valve surgery.
2. To determine and describe the progression, regression and interaction of these parameters in the pre- and post-operative periods.
3. To determine echocardiographic parameters that indicate TV intervention at time of left side valve surgery.
4. To determine echocardiographic parameters that indicate early signs of progression of tricuspid regurgitation (if not intervened on) after left valve surgery.
5. To compare the degree of change in RV structure and function pre and post left valve surgery

CHAPTER 2: LITERATURE REVIEW

2.1 Right ventricular function

The role that the right ventricle plays in maintaining proper cardiac function is well-established. Its primary duties include maintaining a low systemic venous pressure to prevent congestion of tissues and organs and maintaining an adequate pulmonary perfusion pressure under varying circulatory and loading conditions to deliver desaturated venous blood to the gas exchange membranes of the lungs.[12] The pulmonary circulation and the right ventricle are low-resistance systems[2] in contrast to the left ventricle and the systemic circulation.[12] Right ventricular ejection performance and stroke volume are influenced by several parameters, such as cardiac rhythm, ventricular interdependence, contractility, myocardial wall thickness, preload, afterload, and limitation from the intact pericardium.[13]

Right ventricular afterload and, consequently, left ventricular or left atrial filling pressure are necessary for proper right ventricular function.[2]Increased left ventricular afterload causes a reduction in left ventricular wall stress when muscle mass increases. However, because the right ventricle has less muscle mass and, thus, higher wall stress under any given load, it is more susceptible to fluctuations in load. As such, a reduction in right ventricular function concomitant with an elevation in pulmonary artery pressure has been reported in individuals suffering from valvular or coronary artery disease.[14] RV afterload, RV contractility, RV preload, ventricular interdependence, and cause-related arrhythmias can all be affected by these conditions, which can be present alone, in combination, or new to the patient.[15] These conditions account for the majority of RV failure cases. The most frequent cause of persistent left-sided heart failure is RV dysfunction. According to Nishimura et al (2017),[16] the leading cause of morbidity and death in both industrialized and developing nations is valve heart disease. In terms of valve disease, aortic stenosis (AS) and primary mitral regurgitation (MR) are the two most prevalent forms.[17]

2.2 Right ventricular dysfunction vs failure

A condition known as right ventricular dysfunction occurs when the RV end-diastolic volume increases, but the stroke volume continues to rise.[18]

The inability of the heart's right ventricle to pump enough blood through the circulation in the lungs at a normal central venous pressure as a result of decreased RV output, with the ensuing hypoperfusion and indications of organ dysfunction, is known as right ventricular failure.[19]

2.3 Left-to-right interaction

Systolic forces between the ventricles are transmitted through the interventricular septum and are mechanically influenced by the common muscle fibres surrounding their free walls. This phenomenon is known as left-to-right systolic ventricular interaction, which is why the left ventricle produces two-thirds of the pressure and the majority of the flow produced by the right ventricle.[20] Consequently, any decrease in the function of the left ventricle's free wall results in a decrease in the pressure or function of the right ventricle.[20] Given that the right ventricle remains non-dilated, the septum can maintain cardiac output. A respectable right ventricular ejection fraction is associated with scarring of the right ventricular myocardium caused by cauterization of the ventricle using a noncontractile pericardial patch.[21]

Hoffman et al. (1994)[22] found that the left ventricle might contribute twenty-four percent of its own stroke effort toward the stroke work produced by the right ventricle because of the interventricular septum. In cases of pulmonary hypertension, this percentage rose to 35%. It was demonstrated that the right ventricular size and left or right ventricular stroke work had a negative linear connection. This means that even though left-to-right ventricular interaction may counteract a decline in right ventricular function, insufficient contraction of the right ventricle will prevent it from being sufficient to maintain adequate cardiac output in the presence of right ventricular pressure or volume overload.

2.4 Volume vs pressure overload of the right ventricle

Right ventricular volume overload (RVVO) can result from several conditions, including tricuspid regurgitation, atrial septal defect, and pulmonary regurgitation.[23] It preserves systolic function but reduces the left ventricle's end-diastolic volume and systolic function.[24] Urabe et al. (1993)[25] demonstrated that in a cat model, cardiomyocytes remained normal despite hypertrophied and dilated left and right ventricles. RVVO can be tolerated for extended periods but eventually stops functioning, similar to the left ventricle. In patients overloaded, right ventricular ejection fraction maintenance may be aided by the septal paradox.[23]

Louie et al. (1995)[26]research explains the varying reactions of left ventricular ejection fraction to right ventricular volume loading. They found no apparent limitation to total left ventricular filling due to RVVO impairment of late diastolic filling. The ejection percentage of the underfilled left ventricle in RVVO is lowered, and individuals with primary pulmonary hypertension have an intact pericardium compared to those with tricuspid valve excision.

Right ventricular dilatation can be measured using various techniques and comparing the size of the right and left ventricles.[23] The apex is formed by the right ventricle, and the interventricular septum's motion can be observed. The septum flattens during diastole and shifts to the left during volume overload, creating a "D-shaped" left ventricle.[23] The septal flattening sequence can reduce left ventricular contraction force. In patients with volume overload, the systolic movement of the interventricular septum towards the right ventricle may help maintain the right ventricular ejection fraction during systole.[27]

Experimental animals show acute pulmonary vasoconstriction or embolism is linked to right ventricle pressure overload, resulting in an enlarged ventricle and lower ejection fraction. Left ventricular volumes drop, but ejection fraction remains stable.[28]

Research[29, 30] differentiates patients with tricuspid regurgitation and right ventricular pressure overload. [29]

Badke (1982)[31] study on left ventricular systolic shortening in dogs showed that chronic pulmonary artery constriction did not change left ventricular ejection fraction. Active end-systolic ventricular septal displacement towards the left ventricle's center maintained global left ventricular ejection and septal contribution to left ventricular contraction. Louie et al. (1995)[26] study found that individuals with RV volume overload had lower resting left ventricular systolic function than those with RV pressure overload. Patients with RVVO had significantly reduced left ventricular ejection fraction.[26]

Echocardiographic studies show that patients with isolated tricuspid regurgitation and pulmonary arterial hypertension experience distinct effects of pressure and volume overload in the right ventricle. [32]When right ventricular pressure overload occurs, left ventricular ejection fraction remains, while when right ventricular volume overflow occurs, it may be reduced. Severe pulmonary hypertension is associated with increased right ventricular contractility, maintaining stroke volume and allowing moderately expanded right ventricular dimensions.[33] In prolonged pulmonary hypertension or rapid lung pressure increase, the right ventricle expands and the right ventricular-arterial coupling deteriorates, but in severe phases, the afterloaded right ventricle's systolic function remains higher than usual.[33]

2.5 The role of the right ventricle in left heart surgery prognostication

The right ventricle is crucial for postoperative recovery and survival in patients with heart valve disease. Valvular heart surgery patients have varying prognoses based on their right ventricular function.[3] RV failure is associated with high morbidity and mortality rates, with only 28% of patients still alive after 75 months [34] Preoperative RV dysfunction predicts adverse events and a higher postoperative mortality rate.[35]Patients with a preoperative ejection fraction of less than 30% have more enduring symptoms after surgery compared to those with more than 30%.[2]

RV failure is linked to a high mortality rate of 44% to 86% after heart surgery.[36]According to Pinzani et al. (1993)[34],only 28% of patients survive after six years and two months of follow-up in mitral or mitral-aortic repair or replacement cases.[34] Patients with ongoing right heart failure have a higher 5-year mortality rate (39%) compared to those without (4%). Preexisting RV dysfunction is a reliable indicator of RV failure postoperatively.[34]

Patients with pulmonary arterial dysfunction had a poor prognosis, 72% of them pass away within 75 months of having surgery. Likewise, in research by Di Mauro et al. (2018)[37], 3% of patients with normal PASP had RV dysfunction. PASP, LV end-diastolic diameter index, and LV septal function are all independently correlated with right ventricular ejection fraction (RVEF).[38]RV function may be more significantly predicted by left ventricular remodeling and left ventricular septal function. In 26% of patients with maintained RVEF and 44% of patients with compromised RVEF, significant PHTN (PASP > 50 mmHg) was detected. [38]

Hahn (2018)[39] highlights the prevalence of functional TR in MV disease, suggesting that even after correcting lesions, surgically disregarded functional TR may persist. Groves et al. (1991)[40] found that patients with late tricuspid regurgitation had shorter exercise durations and decreased oxygen intake.

Rana et al. (2019)[13] and Wang et al. (2008)[41] found that tricuspid annulus dilatation progression and PH are key risk factors for late TR in patients following left-sided valve replacement. Severe tricuspid regurgitation often leads to right ventricular dysfunction or failure[42], resulting in reduced exercise tolerance, low functional capacity, reduced cardiac output, and increased end-organ damage.[43] Patients with aortic regurgitation generally have better postoperative outcomes and survival than those with mitral regurgitation.[44]Operational mortality related to isolated mitral valve replacement is predicted to be between 4% and 7% of patients[45], with early mortality influenced by age, left ventricular function, history of valve surgery, aortic/mitral insufficiency, and coronary artery disease.

Acute RV dysfunction and altered contractility are primarily caused by intraoperative RV ischaemia, which can occur due to factors like inadequate cardiac shielding, incomplete revascularization, microparticulate embolisms, increased RV wall tension, and decreased coronary perfusion. Isolated LV dysfunction or transient global myocardial dysfunction can also impair RV function. [46]

According to the current guidelines[47], numerous standard measures should be used to assess the systolic RV function, however, several authors[48, 49] have questioned the use of these parameters as prognostic and diagnostic markers. Recent advancements in myocardial deformation imaging methods such as tissue Doppler imaging (TDI), two and three dimensional and 3D speckle-tracking echocardiography have made it possible to examine the right heart chambers and better understand the role that RV function plays in the pathophysiology of several cardiovascular diseases. However, the true utility of this new tool remains unclear.[50]

Myocardial deformation imaging techniques are more sensitive than traditional echocardiographic systolic function parameters for early detection of myocardial impairment.[51] These parameters have prognostic and diagnostic values in various cardiac disorders. Two-dimensional speckle-tracking echocardiography (STE) and three-dimensional STE have been introduced to measure myocardial strain[50] enabling a more thorough evaluation of deformation in all spatial dimensions.[52]These techniques have been proven effective in clinical investigations[53, 54], for pulmonary hypertension, heart failure, pulmonary embolism, myocardial infarction, valvular heart disorders, and cardiomyopathies.

Shah et al. (2012)[52] highlight the limitations of 2D strain analysis in evaluating the systolic function of the RV. Cardiac deformation imaging techniques are limited, requiring specialized pictures at high frame rates.[52]Different techniques and software versions have different strain values[55], making it difficult to track speckles from frame to frame. The right ventricle was added to the 2D strain software, but the geometry and spatial orientation of LVs differ from RVs.[56] The RV chamber's thin wall makes tracking speckles challenging[56], restricting the region of interest to heart muscles and pericardium. Additionally, the majority of methods have inadequate validation compared to absolute and objective reference standards[57], impacting the repeatability of measurements. There are no sizable multicenter studies to measure variations in RV strain outcomes between institutions and user skill levels.[56]

2.6 Aortic stenosis

2.6.1 Definition

The inability of blood to pass through the aortic valve is known as aortic stenosis (AS),either as a result of or resulting from congenital (bicuspid/unicuspid), calcific, or rheumatic disease.[58]

2.6.2 Epidemiology

Valvular heart disease significantly impacts physical function, lifespan, and quality of life[59]. Its incidence varies between high- and low-income countries, with rheumatic heart disease being the most prevalent.[59] Degenerative mitral valve disease and calcific aortic stenosis are also prevalent.[59] Calcified aortic valve disease (CAVD) is the third most common cardiac disorder in the Western world[60], with frequency in older people ranging from 2% to 4%.[61]However, a small percentage of elderly people experience calcification, suggesting other pathological factors may be involved.[62]

Rheumatic heart disease (RHD) is now the primary cause of aortic valve disease (AVD) in high-income and developed countries. Infectious endocarditis is a common cause, with 3-7 cases per 100,000 person-years. [63]The global population's rapid aging and economic growth, particularly in the elderly, contribute to the rise in non-rheumatic VHD (NRVHD) cases.[64] A prospective population-based study[65] found an increase in AS prevalence with age, with the lowest prevalence in ages 50-59 at 0.2%. This presents a significant management and financial burden on a global scale.

The African continent is a major source of rheumatic fever (RF), a congenital heart defect that affects children and young adults. [66]Valvular aortic stenosis (VAS) is a common issue, affecting men more frequently than women.[67]High sociodemographic index (SDI) nations have successfully reduced RHD incidence, but it still affects disadvantaged, marginalized, and older adult populations.[68]Improvements in socioeconomic status, healthcare system performance, control program implementation, and the use of penicillin G benzathine to treat streptococcal pharyngitis have contributed to the decrease in RHD burden.[69]

South Africa, a developed nation in Sub-Saharan Africa, faces a significant global burden of RF and RHD, with a 1.5% yearly death rate. [70]RHD is more common in

Sub-Saharan Africa than North Africa or industrialized nations.[71] Active RF surveillance is difficult, and a 15-year decline in RF cases has been observed, with inadequate and underreported case counts by Western Cape health officials.[71] This undercounting may have contributed to the observed decline in instances in Africa.[72] (Figure 2.1 and 2.2).

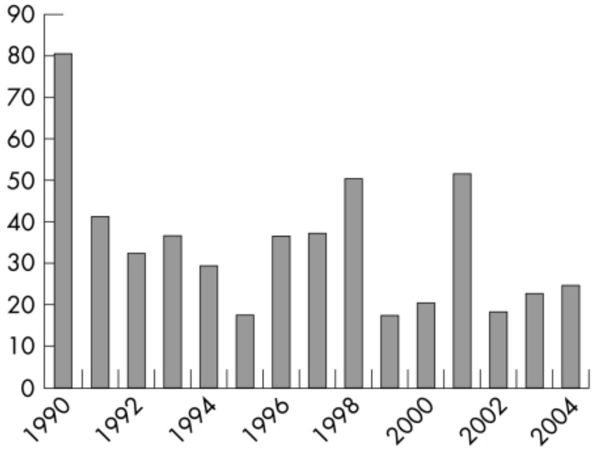


Figure 2.1: Number of cases of rheumatic fever reported to South Africa's National Department of Health per year. Source: Reproduced from Nkgudi et al. (2006)[72]

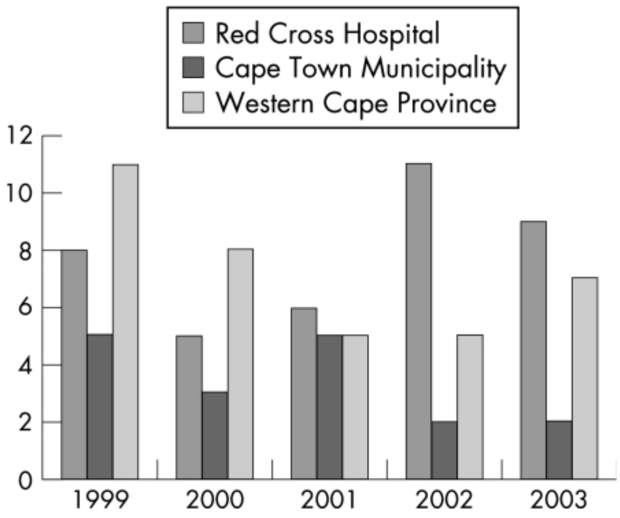


Figure 2.2: Number of rheumatic fever cases recorded by the province's Department of Health,Cape Town City Health Department, and Red Cross Children's Hospital[71]

The death rate from rheumatic heart disease has remained relatively constant since 2000, but calcific aortic stenosis-related deaths have increased over the past 20 years.[60] Patients with calcific aortic valve disease have higher morbidity and mortality rates. The Western Cape is expected to have a larger incidence of rheumatic heart disease. [73]

2.6.3 Pathophysiology of AS in right ventricular dysfunction

Aortic stenosis is a pathophysiologic process that involves both the valvular and extravalvular systems. Pressure overload caused by progressive aortic stenosis leads to compensatory left ventricular hypertrophy, enlargement of the left atrium, development of mitral and tricuspid regurgitation, and elevation of pulmonary artery pressures.[74] Biventricular dysfunction is a highly developed process that tends to occur in later stages.[74]

Myocardial oxygen requirements are raised when aortic stenosis causes progressive left ventricular hypertrophy[75], while the intramural coronary arteries may be compressed by myocardial thickening as they carry blood to the endocardium. These changes, together with reduced coronary artery diastolic filling, can induce typical angina even in the absence of CAD.[76] Additionally, cardiac output decreases with exercise as aortic stenosis gets worse.[77] In this situation, hypotension and syncope may result from decrease systemic vascular resistance, which typically happens with exertion.[78]

Once symptoms of aortic stenosis appear, mortality rises sharply. When symptomatic patients receive no surgical intervention, the total rate of survival is typically 2-3 years. For senior members of this community, one- and three-year death rates of 44% and 75%, respectively, have been documented.[77]

2.6.4 Surgical management of AS

Balloon aortic valvotomy (BAV) is the simplest but least successful mechanical therapy for severe AS.[16] As a result, it is used to palliate the symptoms of patients whose major concomitant conditions prevent them from having an aortic valve replacement or, in the case of patients with severe AS and hemodynamic instability, as a stopgap measure before aortic valve replacement.[16] Aortic valve replacement or transcatheter aortic valve implantation (TAVI) is the only validated and proven therapy for hemodynamically severe aortic stenosis.[79] Although TAVI is a valuable and well-researched treatment used in select patient population, the gold standard for aortic valve replacement is still surgical aortic valve replacement (SAVR).[16] Patients with severe AS who are asymptomatic or undergoing cardiac surgery for another reason, as well as those who are asymptomatic but have a left ventricular ejection fraction

(LVEF) < 50%, are typically advised to have an aortic valve replacement.[16]There is a 4% average perioperative mortality rate after the surgery, and there is a 1% annual risk of prosthetic valve failure.[77]

2.7 Mitral regurgitation

2.7.1 Definition

Primary and secondary causes can be distinguished in mitral regurgitation. Any MR brought on by a structural chordae malformation or injury, papillary muscles, and/or leaflets that causes the leaflets to close insufficiently during systole is referred to as primary MR, also known as degenerative or organic MR.[80] Papillary muscle rupture, mitral valve prolapse (MVP), and leaflet perforation are common causes.[80] Certain connective tissue diseases have been reported to result in MR, such as osteogenesis imperfecta, pseudoxanthoma elasticum, Ehlers-Danlos syndrome, Marfan syndrome, MASS phenotype, and systemic lupus erythematosus (SLE), are responsible for secondary MVP.[81] Secondary mitral regurgitation, also called functional regurgitation, results from abnormalities in the left ventricular wall motion (ischemic cardiomyopathy) or left ventricular remodelling (dilated cardiomyopathy)[16]. These can cause the dilatation of the mitral annulus or the displacement of papillary muscles,resulting in retrograde flow from improperly closed mitral valve leaflets.[16]

2.7.2 Epidemiology

Mitral valvular disease is thought to be the most common cardiac condition worldwide, affecting 2% to 3% of the population. RHD is still frequent in underdeveloped nations and is the most common cause of mitral valvular disease that necessitates hospital stays. The Framingham Heart study[82] evaluated the prevalence and severity of mitral regurgitation (MR) and other valve diseases in 1,696 men and 1,893 women.[82]Results showed that MR affects men and women differently, with 91.5% of women and 87.7% of men having MR. The prevalence of MR increases with age, with 19% of men and 19% of women having MR with a severity of ≥ mild after eliminating trace regurgitation.

Table 2.1 and Table 2.2 show the prevalence of MR in men and women by age and severity based on the Framingham Heart Study findings.[82]

Table **2.1: Prevalence of MR by age in men.**

Severity of MR	**Prevalence of MR by age in men**				
	26-29	**40-49**	**50-59**	**60-69**	**70-83**
No MR (%)	14.4	13.3	11.3	12.7	9.0
Trace (%)	76.7	72.9	74.6	60.3	51.7
Mild (%)	8.9	13.5	12.5	24.6	28.1
Moderate or severe (%)	0	0.3	1.6	2.4	11.2

Source: Adapted from Singh et al. (1999).[82]

Table 2.2: Prevalence of MR by age in women

Severity of MR	**Prevalence of MR by age in women**				
	26-29	**40-49**	**50-59**	**60-69**	**70-83**
No MR (%)	14.0	8.6	9.0	7.2	5.6
Trace (%)	76.3	75	74	66.5	70.8
Mild (%)	9.7	15.5	16	24	23.6
Moderate or severe (%)	0	0.9	1	2.3	0

Source: Adapted from Singh et al. (1999).[82]

Regurgitation, associated with pancarditis, happens in almost all instances of chronic RHD due to scarring of the valve and valve apparatus.[83] Papillary muscle rupture is an extremely rare syndrome that affects 1% to 2% of people following myocardial infarction (MI) or infective endocarditis.[84]

Systolic congestive heart failure (CHF) patients make up 24% of the patient population with secondary or functional MR, which accounts for 65% of incidents of moderate to severe MR. It originates from morphological enlargement of the left ventricle or atrium without modification of the mitral valve leaflets. Secondary MR is common in industrialized nations with high rates of atherosclerosis, CAD, and congestive heart failure (CHF). All of these disorders are connected to secondary MR and contribute to it.[85]

2.7.3 Pathophysiology of MR in right ventricular dysfunction

LA volume initially increases as a result of MR. The pulmonary venous pressure and LA can be initially kept normal due to the highly compliant LA, however, as enlargement progresses, the LA pressure rises. As pulmonary vascular compliance decreases over time, RV end-diastolic pressure and afterload rise. The condition has a poor long-term prognosis, including a decreased likelihood of survival, a worse quality of life, and a higher burden of symptoms associated with heart failure (HF) and atrial fibrillation (AF), if therapy is not obtained. The disease will gradually develop. The aforementioned process is characteristic of pulmonary hypertension (PH) brought on by left heart disease.[86]

According to a retrospective cohort study, functional MR is brought on by dilated valve annulus and atrial size, resulting from AF. Controlling AF and reestablishing sinus rhythm in these patients led to a greater decrease in functional magnetic resonance imaging.[87]Additionally, a randomised trial revealed a connection between deteriorating valvular disease and AF.[88]

Patel et al (2004)[89] studied patients with severe congestive heart failure (EF less than or equal to 35%) and demonstrated that MR was either absent or present in 10.4% of cases, mild to moderate in 11.8% of cases, moderate in 21.9%, moderate to severe in 12.5% of cases and severe in 4.3% of cases.[89] This study identified the correlation between severe CHF and MR and their association.

2.7.4 Surgical management of MR

MR surgery is necessary for patients with infective endocarditis, chordal or papillary muscle rupture, valvular damage, or ischaemia.[90]For the purpose of this study, we will focus more on data based on primary MR.

The 2014 American Heart Association/American College of Cardiology (AHA/ACC)[9] Recommendation recommends surgery for individuals with severe mitral regurgitation, left ventricular failure, or symptoms. This is particularly important for patients with persistent severe primary mitral regurgitation undergoing cardiac surgery.[9]The 2017 AHA/ACC Focused Update, updated the 2014 AHA/ACC Guideline for the care of patients with valvular heart disease.[9] Surgery is advised for patients with chronic severe primary MR, LV dilatation, asymptomatic patients, and those undergoing cardiac surgery. The recommendation for replacement of the mitral valve may vary depending on local anatomy, leaflet presence, and the likelihood of successful repair.[91]

Mitral valve repair is the preferred surgical correction technique for degenerative MR due to its high success rate and low recurrence risk. [92]However, older patients with severe sub-valvular thickening, rheumatic heart disease, or calcified deformed valves may require mitral valve replacement.[93] This treatment has drawbacks, such as declining left ventricular function and ejection fraction, increasing the risk of morbidity and mortality. [94]

Maharaj et al. (2021) [95] examined the response of patients with severe rheumatic mitral regurgitation to mitral valve replacement. The study involved 132 individuals, 66% of whom were in NYHA class III-IV and 38% had heart failure-related clinical characteristics. The majority had significant chamber size enlargement, with 28% having impaired LV function. After surgery, the percentage of patients with an EF > 55% decreased to 20%. The study found that severe MR patients often present late, have significant LV function impairment, and do not fully recover after surgery. Early evaluation and prompt surgery are crucial to preserve LV function. Mechanical prosthesis increases the risk of thrombosis, bleeding, and thromboembolism, necessitating lifelong anticoagulation. Bioprostheses are linked to late-stage structural degradation and recurrent intervention requirements[16], increasing the chance of infective endocarditis. Mitraclip, a successful surgical technique, has a low morbidity and death rate in high-risk individuals. [96]

Both MV replacement and repair in severe MR caused by acute IE have comparable clinical outcomes.[97] Transcatheter MV repair combined with percutaneous edge-to-edge clip technique is a safe option for patients with significant degenerative MR but high-risk surgical mortality, avoiding complete sternotomy and early recovery. [98]

When evaluating individuals for MV replacement, factors like MV structure, patient preference, surgical expertise, risk of bleeding, healthcare access, and anticoagulation monitoring should be considered.[92]The recurrence rate for ischemic mitral regurgitation (MR) increases from 30% at three years to 70% at five years[99], leading to left ventricular negative remodeling and tethered mitral leaflets, worsening the condition. Prognosis is linked to significant postoperative ischemic mitral regurgitation.[100]

2.8 Aortic regurgitation

2.8.1 Definition

Aortic regurgitation (AR), also known as aortic insufficiency, is a form of valvular heart disease that allows for the retrograde flow of blood back into the left ventricle during ventricular diastole and, with time, results in stress of the left ventricle.[82] Dysfunction associated with the ascending aorta, annulus, aortic root, or aortic valve leaflets can result in aortic insufficiency. Acute AR is frequently caused by infectious endocarditis, traumatic and non-traumatic ascending aortic rupture with aortic cusp prolapse, iatrogenic AR from percutaneous aortic balloon valvuloplasty, malfunctioning prosthetic valves, and perivalvular leak or dehiscence of a prosthetic valve.[82]

2.8.2 Epidemiology

The Framingham Heart Study[82], initiated in 1948, aimed to identify risk factors for coronary heart disease. The study involved 5209 patients aged 28 to 62. Aortic insufficiency affected 4.9% of patients, while moderate or greater severity AR affected 0.5%.[82] Age-related increases in AR prevalence and severity peak between the 4th and 6th decades of life, affecting 2% of the population over 70. Clinically significant AR is more common in men.(Table 2.3).

Table 2.3: The Framingham Offspring Study on prevalence of AR.

	Age, y				
	26–39	40–49	50–59	60–69	70–83
Age and gender were the only factors that multivariate analysis used to predict AR prevalence. Adapted from Singh and colleagues.					
Men	(n = 91)	(n = 352)	(n = 433)	(n = 359)	(n = 91)
None	96.7%	95.4%	91.1%	74.3%	75.6%
Trace	3.3%	2.9%	4.7%	13.0%	10.0%
Mild	0%	1.4%	3.7%	12.1%	12.2%
≥ Moderate	0%	0.3%	0.5%	0.6%	2.2%
Women	(n = 93)	(n = 451)	(n = 515)	(n = 390)	(n = 90)

	Age, y				
	26–39	40–49	50–59	60–69	70–83
None	98.9%	96.6%	92.4%	86.9%	73.0%
Trace	1.1%	2.7%	5.5%	6.3%	10.1%
Mild	0%	0.7%	1.9%	6.0%	14.6%
≥ Moderate	0%	0%	0.2%	0.8%	2.3%

Source: Adapted from Singh et al. (1999).[82]

The Strong Heart Study on native Americans found that aortic root size and age were independent predictors of arteriosclerosis (AR), but not gender. Hypertension did not predict AR, contradicting previous research.[101]The Strong Heart Study[102] found a 10% prevalence of AR, with most cases having mild severity.

Aortic insufficiency (AR) presentation varies globally, with industrialized countries more common in older individuals and linked to comorbidities.[103]In developing nations, AR is more prevalent in younger patients with faster onset, with risk factors including rheumatic heart disease and infective endocarditis. The frequency of AR varies by gender and region.[103]

2.8.3 Pathophysiology of AR in right ventricular dysfunction

Chronic severe aortic regurgitation causes severe volume and pressure overload in the left ventricle (LV), leading to structural changes in the myocardium. Despite asymptomatic individuals staying asymptomatic, the LV fails to sustain this compensated condition, resulting in reduced LVEF and heart failure symptoms. Systolic hypertension increases total aortic stroke volume, causing pressure overload.[104] This may be linked to a cycle where the aortic root dilates and the aortic arch worsens.[105] Despite high regurgitant volume, eccentric hypertrophy preserves LV diastolic compliance, allowing filling pressures to remain normal or slightly raised.[106]

Acute AR can be fatal due to the inability of LV dilatation and compensatory mechanisms to prevent hemodynamic deterioration.[107] This can lead to a decrease in stroke volume and an increase in left ventricular end-diastolic pressure, causing hypotension, pulmonary oedema, and cardiogenic shock.[107] Rapid decompensation and reduced LV diastolic compliance can result in severe hypotension instead of systolic hypertension.[107] Decompensated severe AR can also cause heart failure symptoms, with exertional dyspnea being the most common symptom. [108] In addition to causing LV systolic dysfunction due to hypertrophy and fibrosis, decompensated severe AR also results in reduced LV diastolic compliance, which increases filling pressures and produces heart failure symptoms. Though angina can be more prominent from a reduction in coronary flow reserve, which predominantly impacts systolic coronary flow, exertional dyspnea is the most common symptom.[108]

In Figure 2.3, the various stages of AR are displayed. Top left: in mild AR, LV size, function, and hemodynamics are normal. As noted in the upper right, in acute severe AR, the aortic and LV pressures have equalized (80/40 mmHg in this case). Prolonged left atrial pressure causes pulmonary oedema. Bottom left: In chronic severe compensated AR, the left ventricle (LV) may enlarge, although increasing preload often maintains the LVEF within normal limits. There is systolic arterial hypertension as well as a broad pulse pressure. However, because LV filling pressures are either normal or just slightly raised, dyspnea is not present. Bottom right: In decompensated chronic severe AR, the LV is dilated and hypertrophied, and LV function is typically compromised by excess afterload.[109]

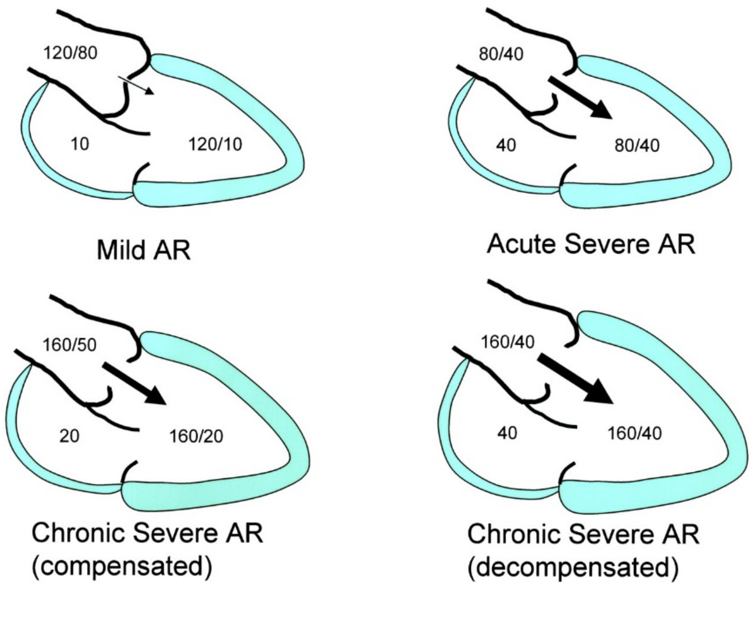


Figure 2.3: Different stages of AR
Source: Adapted from Bonow et al. (1984).[109]

Severe acute coronary syndrome (ACS) patients have higher morbidity and mortality rates than general individuals.[110] Studies[111, 112] show that less than 5% of patients experience LV dysfunction, symptoms, or mortality, and only 0.4% of patients experience unexpected fatalities. Despite this, 58% of individuals with normal LV systolic function remain asymptomatic after 11 years. The New York Heart Association's functional classes III-IV, including those with severe symptoms, have an annual death rate of 25%.[110] Even asymptomatic patients with lower LV ejection fraction have a worse prognosis. [109] (Figure 2.4)

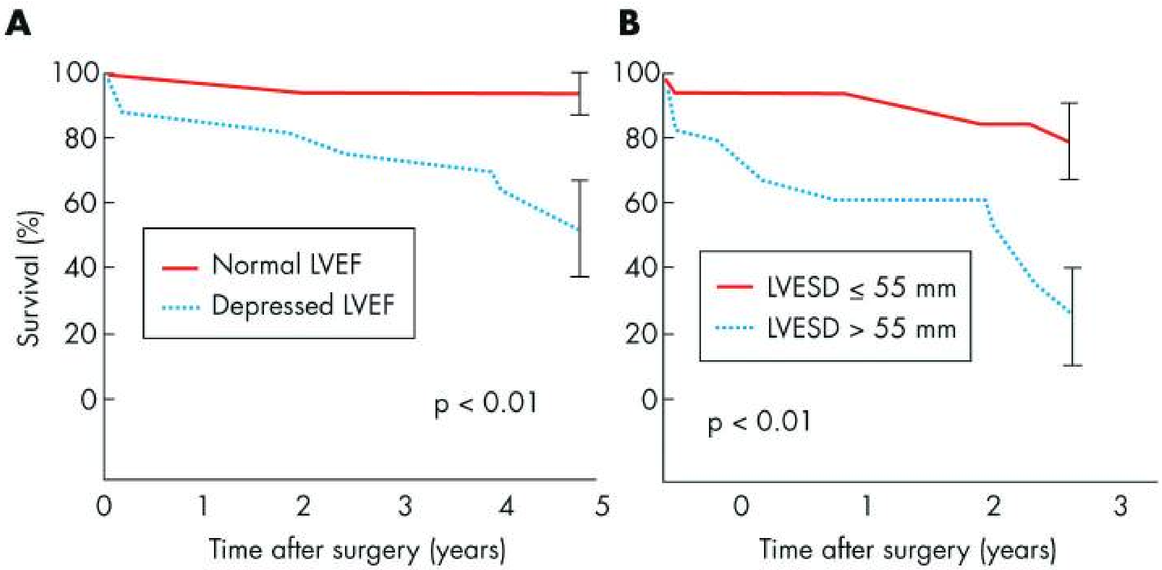


Figure 2.4: Patients with preoperative decreased vs normal left ventricular function (panel A) and those with preoperative left ventricular end-systolic diameter (LVESD) < 55 mm against > 55 mm (panel B) showed different postoperative survival rates. Left ventricular ejection fraction, or LVEF. various phases of AR. Adapted from Bonow et al. (1984).[109]

However, short-term LV failure is typically reversible.[111] However, short-term LV failure is typically reversible.[113] For these individuals, serial evaluation of LV function is therefore frequently recommended, and consideration of surgery should be made as soon as the ejection fraction starts to decline. An LV enlargement by itself might potentially indicate the need for surgery.[113]

2.9 Mitral stenosis

2.9.1 Definition

A valvular cardiac condition known as MS is typified by the narrowing of the mitral valve opening. Among the less common causes of mitral stenosis (MS), rheumatic heart disease (RHD) is the most prevalent cause.[114] RHD is still a significant public health issue in countries with inadequate resources.[115] Congenital heart disease and calcification of the mitral valve leaflets are uncommon causes of mitral stenosis. Additional factors contributing to mitral stenosis comprise endomyocardial fibroelastosis, mitral annular calcification, infectious endocarditis, malignant carcinoid syndrome, systemic lupus erythematosus, Fabry disease, Whipple disease, and rheumatoid arthritis.[114]

2.9.2 Epidemiology

Rheumatic disease (RHD) is a common cause of aortic stenosis, with an estimated incidence of 1 in 100,000. It is decreasing in developed nations, but developing countries have a higher prevalence, with 35 cases per 100,000 people in Africa. RHD is more prevalent in women and manifests in one's third or fourth decade of life. [116]The World Health Organization (WHO)[117] expert consultation found that RHD is often identified in affluent countries around the age of 50 when symptoms first appear, compared to developing countries where symptoms appear earlier in life. A study[118] in South Africa found that 76% of children with acute RHD developed RHD, while 57% had carditis. The disease progresses at varying rates depending on the geographic location and standard of care. [118]

Asymptomatic patients with aortic valve calcification have a 10-year survival rate of over 80%, largely due to the gradual narrowing of the valve. The survival rate varies from 0% to 15%, with the first surgical or percutaneous procedure typically performed at age 70. Due to age-related comorbidities and degraded valve features, surgical replacement is not recommended for senior patients. Percutaneous balloon valvotomy is the preferred method for patients over 70 years.[119, 120]

Mitral annular calcification, a condition characterized by reduced leaflet mobility and impaired diastolic annular dilation, can lead to significant obstruction and is linked to various risk factors such as age, mechanical stress, hypertension, diabetes, renal disease, atherosclerosis, systemic inflammation, and mineral abnormalities.[121] This process is similar to aortic valve calcification and atherosclerosis, involving progressive calcium deposition, white blood cell infiltration, and tissue remodeling at the annular C shape. [122]The process shares a common basis with atherosclerosis and aortic calcifications, with factors such as inflammation markers, fetuin-A, and fibroblast growth factor playing roles.[123]

Tyagi et al. (2014)[124], found that as degenerative mitral stenosis progressed, the transmitral gradient increased by 0.8 ± 2.4 mmHg annually. Pasca et al. (2016)[125] large single-center study found that patients with severe mitral annular calcification had a 78% and 47% survival rate.

2.9.3 Pathophysiology of MS in right ventricular dysfunction

Both pulmonary capillary wedge pressure (PCWP) and pulmonary arterial pressure (PAP) are raised when mitral stenosis (MS) causes retroactive elevation of pulmonary venous pressure (post-capillary).[91] (Figure 2.5).

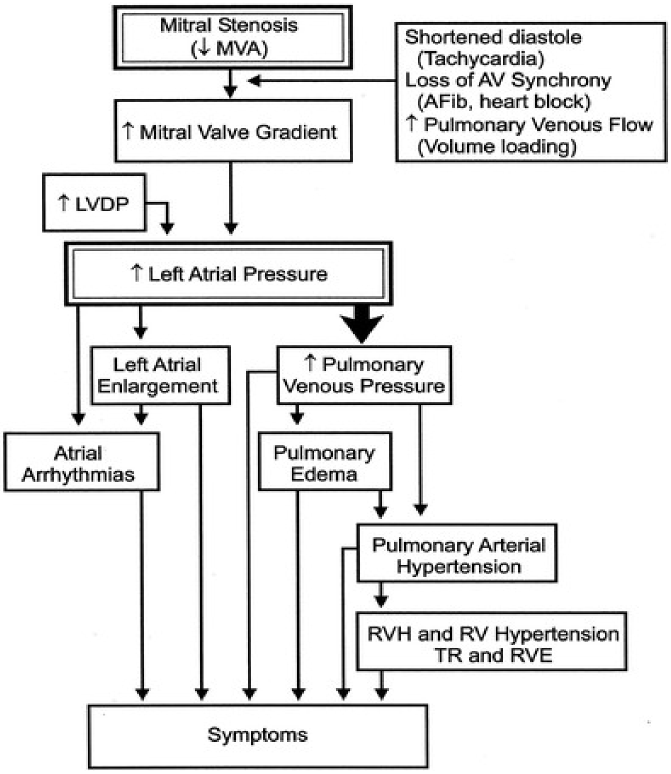


Figure 2.5: MS pathophysiology. The degree of LA hypertension and MS severity are significant determinants of the results. TR stands for tricuspid regurgitation, RV stands for right ventricular hypertrophy, and RVE is for right ventricular enlargement.

Adapted from Rahimtoola et al.(2002)[126]

2.9.4 Surgical management of MS

The European Society of Cardiology/European Association of Cardiothoracic Surgery[127] recommends balloon valvotomy or surgery for individuals with symptomatic significant MS, particularly moderate or severe MS, with a mitral valve area (MVA) of less than 1.5 cm^2[127].Good initial outcomes include a valve area more than 1.5 cm^2 and no mitral regurgitation greater than 2/4. [127]Common complications include severe mitral regurgitation, hemopericardium, systemic embolism, and procedural mortality. [128]Severe mitral regurgitation following percutaneous balloon mitral valvuloplasty often requires intensive care and immediate surgery. [128]

Mitral valve replacement is the recommended treatment due to improved valve and clinical results. [129]The surgical mortality rate is between 3% and 5%, but long-term outcomes are unpredictable.[130] Patients typically receive a bioprosthetic valve between 60% and 70% of the time.[131] However, bioprosthetic valves degenerate, impacting short- and long-term outcomes. Up to one-third of patients may need repeat surgery after 8 years, with younger patients experiencing faster degeneration. Mortality rates for mitral valve reoperation range from 8% to 14%, with individual risks varying.[132]

The choice between mechanical and bioprosthetic prosthesis for prosthetic mitral valve replacement surgery is influenced by factors like age, antiplatelet drug requirements, perceived longevity, and reoperation risk. While bioprosthetic valves have similar death rates[131], research[132] shows that patients under 70 with a bioprosthetic valve in the mitral position have higher long-term all-cause mortality.[132] Critics argue that co-morbidities and technological changes could impact life expectancy. Percutaneous mitral valve replacement is considered a viable treatment option in case of bioprosthetic valve failure, especially in young patients requiring multiple sternotomies. However, the death rates of patients with bioprosthetic valves may be higher than those with mechanical valves.[132]

2.10 Tricuspid regurgitation

2.10.1 Definition

The backflow of blood into the right ventricle during ventricular diastole is a frequent disorder called tricuspid regurgitation, often referred to as tricuspid insufficiency. Anatomical anomalies in any component of the tricuspid valve system can be the cause of this disorder. This may involve changes to the annulus, chordae tendinea, valve leaflets, or papillary muscles.[133] When intrinsic anomalies in the tricuspid valvular apparatus are the cause of lesions leading to tricuspid regurgitation, they are categorized as primary, when right ventricular dilatation is the reason, they are classed as secondary. [133]

Secondary disorders, such as tethering of tricuspid valve leaflets, annular size dilation, and leaflet tethering, primarily cause tricuspid regurgitation.[134] These disorders can be caused by an elevation in the ventricle's systolic pressure, pulmonary hypertension, or problems with the right ventricle.[134]Cardiomyopathies and ischemic heart disorders, as well as chronic left-sided heart failure, mitral stenosis, pulmonary embolism, pulmonary hypertension, and pulmonic valve or pulmonary artery stenosis, can also cause tricuspid regurgitation. [135, 136]

2.10.2 Epidemiology

Tricuspid regurgitation (TR) is the most common cause of tricuspid regurgitation in adults, with secondary causes including tricuspid annulus dilation, right atrial and ventricle dilatation, and normal structural leaflets and chords.[137] TR is the least common primary valvular pathology, linked to a higher death rate. [133]The prevalence of TR varies globally, with 2.7% of older people in the United Kingdom (UK) exhibiting moderate-severe TR compared to 1.1% in China. The age-adjusted death rate from TR was stable until 2013, when it began to rise by 25% annually. [138]The most common cause is functional, also known as secondary TR, with only about 10% due to a primary cause. [139]

TR is a common cardiac condition primarily caused by right ventricle or atrial dilatation, with 92% of cases linked to left heart failure.[140] Even in moderate cases, TR remains a risk factor for morbidity and death.[140] Patients with underlying right ventricle dilatation have a higher risk of developing TR, a feared complication of intracardiac pacemaker implantation, and worse prognosis after the procedure.[141]TR has also been linked to Staphylococcus aureus-caused infective endocarditis.[142]

Rheumatic heart disease-related tricuspid regurgitation is typically linked to mitral and aortic valve pathology, with the Ebstein anomaly being the most common cause.[143] Secondary or functional TR is mostly caused by left-sided pathology with pulmonary hypertension, right-sided pathology with pulmonary hypertension, and global or regional right ventricular dysfunction. [144]

2.10.3 Pathophysiology of TR in right ventricular dysfunction

The most common kind of tricuspid valve regurgitation is called secondary TR, which is unrelated to main organic disease of the valve. The etiology of secondary TR involves cardiac remodelling brought on by elevated pulmonary wedge pressure from aortic or mitral valve disease[145]. This dilatation of the right ventricle (Figure 2.6) lowers the right ventricular (RV) ejection fraction.[1] The tricuspid valve annulus enlarges as a result, which may lead to tricuspid regurgitation (TR) and subsequent right ventricular volume overload.[13]

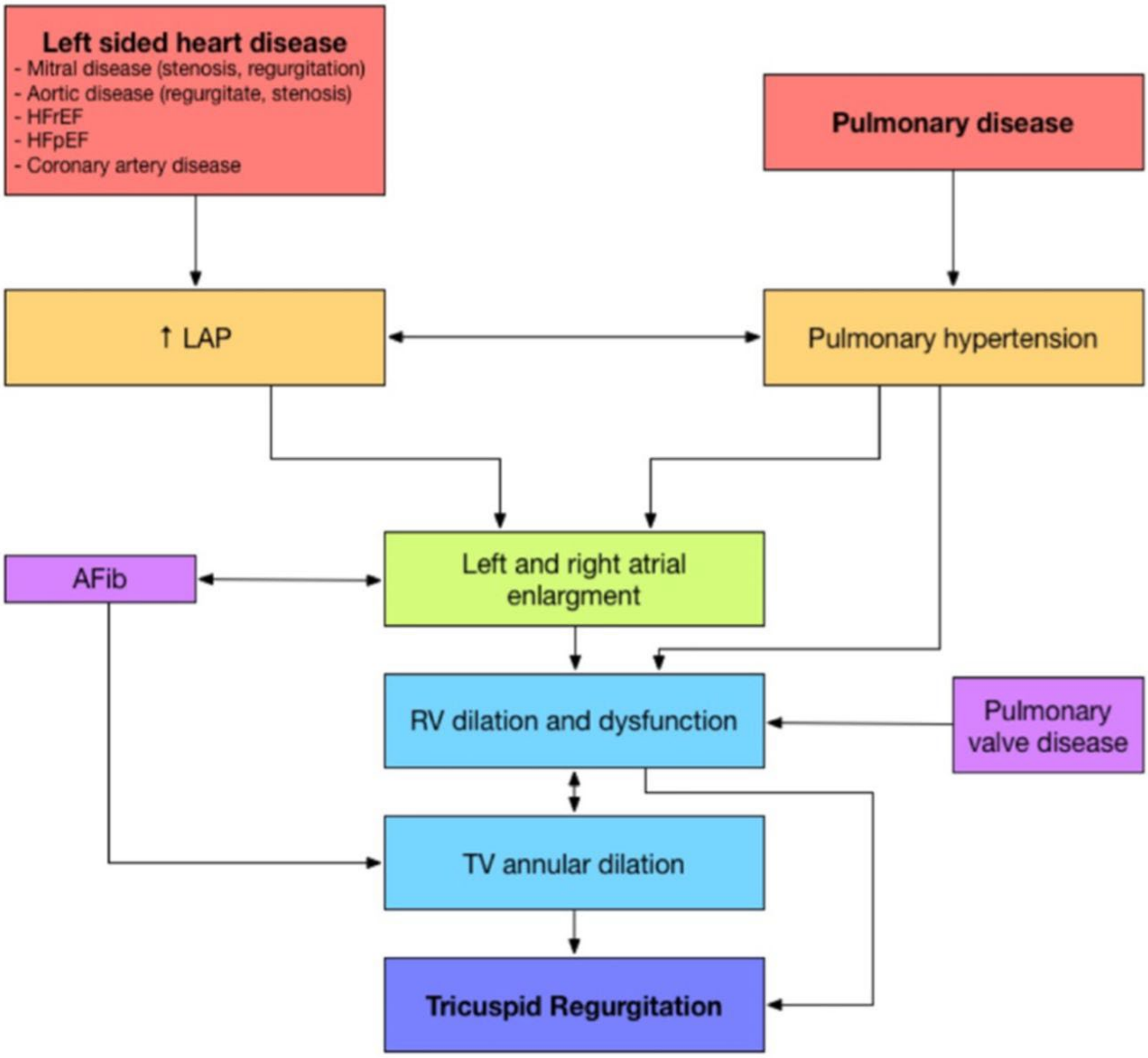


Figure 2.6: Pathophysiology of tricuspid regurgitation. Source: Adapted from Nagel et al. (1996).[1]

The first evaluation of TR's prognostic implications was conducted on a sizable echocardiographic registry comprising 5 223 predominately male patients.[146] Severe TR was associated with higher mortality at 4-year follow-up, even after controlling for multiple echocardiographic parameters that suggested PH, LV and RV dysfunction (hazard ratio [HR] 1.31, 95% confidence interval [CI] 1.05–1.66, p< 0.001).[146] This seminal study proposed that TR was an independent prognostic predictor rather than just a marker of biventricular disease. More outcome information about the different TR etiologies has been published in recent years.[147, 148] In a small retrospective study (n= 239), significant lead-induced TR has been linked to more adverse events related to heart failure (HR 1.64, 95% CI 1.09–2.48, p = 0.019) and lower survival (HR 1.69, 95% CI 1.02–2.78, p = 0.040) at 4-year follow-up.[149]

2.10.4 Surgical management of TR

The latest guidelines[17] recommend tricuspid annuloplasty (TA) for treating TR concurrently with left-side valve surgery for concomitant TV surgery. This treatment is preferred for moderate TR with annular dilatation (≥ 4 cm) and prior to RV failure. Concurrent TA is safe and enhances long-term RV remodeling in mild TR patients.[131]Early referral for isolated TV surgery is crucial[150], with better results in patients with NYHA class II symptoms. Early mortality drops to about 6% in severe TR patients who are operated on before severe symptoms.[151]

The American Heart Association/American College of Cardiology (AHA/ACC)[152] has recommended surgical repair as the gold standard for treating severe TR. This recommendation applies to patients with progressive TR, symptomatic patients with primary severe TR, coexisting annular dilation, functional TR poorly responsive to optimal medical therapy, patients without severe PH or RV systolic dysfunction, and asymptomatic patients. (Table 2.7).

Surgical TV repair recommended in:
1.Patients with severe TR at the time of left-sided valve surgery
2.Symptomatic patients with primary severe TR
3.Symptomatic patients with FTR poorly responsive to optimal medical therapy,, in which annular dilation coexists, in absence of severe PH or left-sided disease
4.Patients with progressive TR at the time of left-sided valve surgery if they have suffered from right heart failure or in case of coexistent annular dilation ≥ 40 mm or ≥ 21 mm/m 2
5.Symptomatic patients with severe TR, who underwent prior left-sided valve surgery, in absence of severe PH or RV systolic dysfunction
Asymptomatic patients with severe primary TR and progressive RV dilation or systolic dysfunction.

Table 2.7: Surgical TV repair recommendations as per the 2020 ACC/AHA Guideline for the Management of Patients with Valvular Heart Disease.
Adapted from Otto et al. (2021).[152]

When combined with left-sided surgery, concurrent tricuspid surgical repair has been shown to not impose extra surgical risk. Additionally, it has been connected to RV reverse remodelling and enhanced functioning condition.[153]TV repair is generally preferred over replacement for aortic valve replacement (TR) due to lower risk of thrombosis, bioprosthetic valve degradation, and long-term anticoagulant usage. [154]

The surgical procedure chosen depends on the natural history of TR. Prosthetic rings are recommended for annuloplasty when there is TA dilatation and little tethering.[155] In mild or moderate TR, prosthetic ring annuloplasty results in excellent functional class and negligible residual TR. However, severe TR has less-than-ideal results.

Preoperative predictors of TR relapse include TA dilation, RV dilation/dysfunction, LV dysfunction, PH, persistent atrial fibrillation, and intraventricular pacemaker lead presence.[156] Prosthetic ring annuloplasty is preferred over direct suture for better outcomes. [155]

The high mortality rate of surgical TV replacement is primarily due to advanced diseases causing end-organ damage. Bioprosthesis, with lower thromboembolic complications, is recommended for valve replacement. [157]However, many patients are turned down due to excessive perioperative risk, often due to repeat surgery or advanced disease stages. [158]

2.10.5 Surgical management of TS

Surgery for severe tricuspid stenosis (TS) is typically done in combination with surgery for left-sided valve disease[9], most frequently mitral valve stenosis, according to the 2014 AHA/ACC guideline[9]for the treatment of patients with valvular heart disease.Rheumatoid heart disease is the most prevalent cause of TS, carcinoid disease is less common. For symptomatic alleviation of TS, TV surgery is preferable to percutaneous balloon tricuspid commissurotomy because most severe instances of TS have considerable associated TR (congenital, rheumatic, or carcinoid).[159] For people with stage C or D TS, who may or may not have symptoms, surgery is advised. These individuals have valve areas less than 1.0 cm^2 and T1/2 > 190 milliseconds. Although it needs more frequent reoperation, primary TS repair is feasible.[159]

2.11 Pulmonary valve stenosis and regurgitation

2.11.1 Definition

A pulmonic valve abnormality called pulmonic stenosis causes the valve to harden, obstructing flow. Usually identified in pediatric children, this disease is benign, congenital, and may be treated with medication. Adults can also have pulmonary stenosis, frequently in addition to serious structural heart problems.[160]

2.11.2 Epidemiology

It is difficult to pinpoint the precise prevalence because pulmonary hypertension, which can result in pulmonary regurgitation (PR), has many different causes. There is no racial or ethnic bias. Men and women experience PR at different frequencies, which is consistent with the unique aetiology of this condition. As a result of balloon valvuloplasty or surgical correction of congenital anomalies, pulmonary insufficiency is frequently observed following Tetralogy of Fallot (TOF) repair.[160] After TOF repair, residual PR is initially well tolerated but eventually increases the risk of sudden death, arrhythmias, RV enlargement, and decreased exercise tolerance.[161] PR is less frequently observed in conjunction with carcinoid syndrome or infective endocarditis. It is rare to experience secondary PR following prolonged PH and annular dilatation.[161]

Conversely, pulmonary stenosis is responsible for 7% to 10% of congenital cardiac conditions. There is a slight female predominance,[162] and 2% of familial occurrences are without a genetic cause.[163]

2.11.3 Pathophysiology of pulmonary valve disease in right ventricular dysfunction

PR shows an increase in afterload as well as preload. The diastolic murmur is decrescendo in nature due to a reverse pressure gradient that gradually decreases from the pulmonary artery to the right ventricle (RV), which is the driver of the PR. The right ventricle's end-diastolic volume stays higher than normal when there is pulmonary regurgitation.[164] The backflow causes the right ventricular diastolic pressure and cavity size to rise as the disease worsens. Although the forward cardiac output (CO) does not always rise with exercise and falls over time, it is preserved during the early stages of the disease. A lower RV ejection fraction could be a sign of hemodynamic compromise before it becomes too late. The right atrium (RA) and ventricle (RV) are noticeably larger.[164]

2.11.4 Surgical management of pulmonary valve

When PR is severe and there are symptoms or signs of RVD, surgery may be considered. Surgery is typically advised for severe PR that is asymptomatic when there are symptomatic atrial and ventricular arrhythmias, severe RV dilation, or both.[161] Additionally, transcatheter PV replacement is now feasible. Transcatheter PV replacement led to a clinically significant decrease in TR in patients with concurrent severe TR, and this reduction remained over a 5-year follow-up period.[165]

Percutaneous balloon PV commissurotomy or valve replacement are two possible treatments for PS. Patients with severe PR, subvalvular PS, supravalvular PS, or severe PS with an associated hypoplastic pulmonary annulus are advised to undergo surgical therapy rather than percutaneous therapy. In cases of dysplastic PV, severe TR that is associated with it, or when a surgical Maze procedure is required, surgical therapy is also typically preferred.[161]

2.12 Multivalvular disease

Multivalvular disease (MVD) affects 10% of patients after valvular surgery, characterized by the co-occurrence of stenotic or regurgitant lesions in two or more heart valves. Research on this topic is limited, but it is more prevalent in clinical practice.[166] Multivalvular disease (MR) affects 20% to 80% of aortic valve disease (AS) patients[167, 168], and 20% of patients undergoing transcatheter or surgical aortic valve replacement also have MR concurrently. [169]

A nationwide study[166] in Sweden found that multiple valvular dysfunction (VHD) accounts for 11% of patients with aortic valve disease (AS). Functional MR is more common in AS patients than degenerative MR[170], and determining whether to perform a simultaneous operation on the mitral valve requires a thorough assessment of the MR mechanism.[171] Obstructive hypertrophic cardiomyopathy should be taken seriously as it can cause high gradients in the LVOT and MR due to systolic anterior movement. [172]

Concurrent MR is associated with increased left ventricle size in patients with AS, which is linked to higher afterload. This is due to volume overload, which lowers stroke volume and afterload, creating a low flow-low gradient condition. Although MR is typically mild in severity, it may lead to inaccurate underestimation of the transvalvular aortic valvular gradient.[170] The presence of MR also raises ejection fraction and decreases total afterload, potentially concealing subclinical myocardial dysfunction.[173] Katte et al. (2018) [174] found that a reduction in forward stroke volume from severe MR significantly reduces both the mean pressure gradient and peak velocity. Patients with severe MR may experience atrial fibrillation with preload impairment, which is poorly tolerated and associated with left atrial enlargement. [74]

Generaux et al.(2017)[175] new AS staging system considers factors like pulmonary hypertension, concurrent MR, decreased left ventricular function, and TR when assessing disease severity. This approach offers additional predictive value for patients undergoing surgical and percutaneous aortic valve replacement (AVR) with moderate to severe AS.[176] Pighi et al. (2020)[177] study found that cardiac damage categorization is an independent predictor of 12-month all-cause death and strongly correlates with increased risk of acute renal damage after percutaneous AVR. (Figure 2.8).

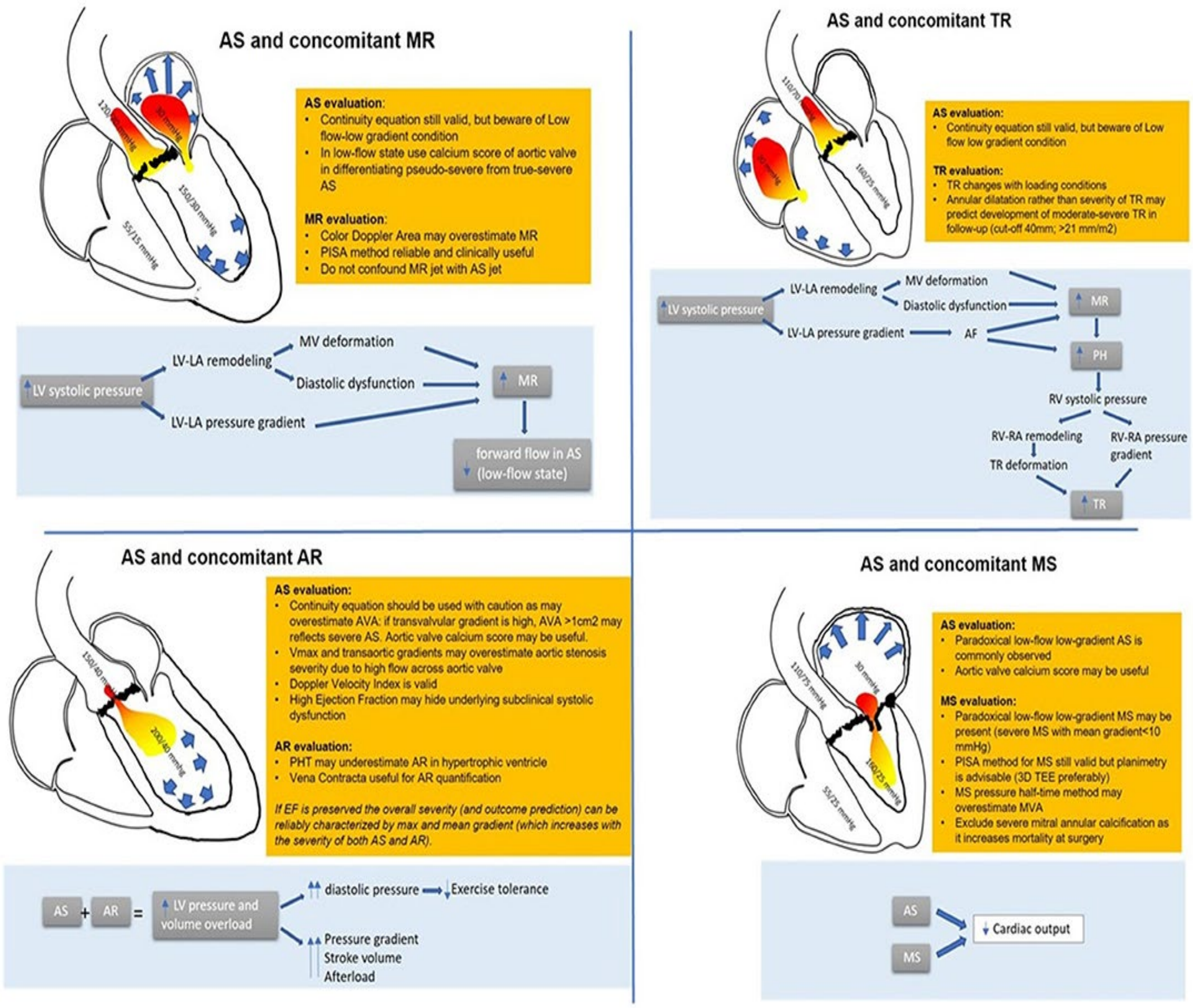


Figure 2.8: Combination of AS and other valvular heart disease: hemodynamic interactions and diagnostic pitfalls and tricks.
Source: Adapted from Pighi et al. (2020). [177]

Between 1995 and 2001, rheumatic heart disease (RHD) accounted for 26.5% of cardiovascular fatalities, with 70% of patients dying from congestive heart failure.[178] Most patients had both aortic and mitral valve regurgitation, challenging the idea that myocarditis is the root cause of heart failure in rheumatic carditis. The pathophysiological mechanism of mitral regurgitation during active carditis is related to annular dilatation, chordal elongation, and anterior mitral leaflet prolapse. [76]

The prevalence of mitral stenosis from chronic rheumatic valvulitis increases with age, and in young people with severe active rheumatic carditis, pure mitral valve regurgitation without stenosis leading to heart failure is common. (Fig 2.9 and 2.10). Rare occurrences that can happen with or without aortic regurgitation and without mitral regurgitation include left ventricular dilatation and cardiac failure. Heart failure can only improve with surgical repair of valve regurgitation, which results in left ventricular reverse remodelling.[179]

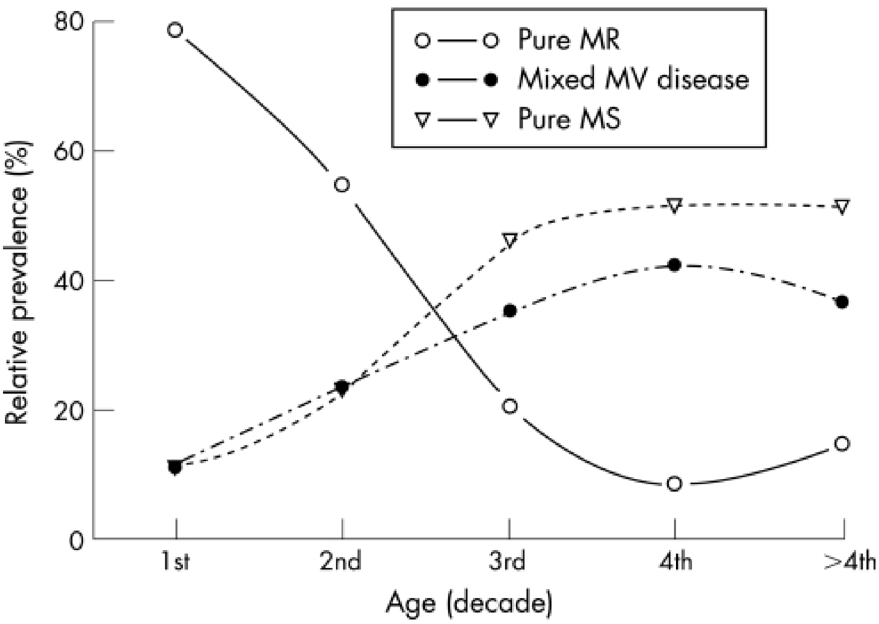


Figure 2.9: A decade-by-decade time-course examination of the relative frequencies of mixed mitral valve disease (MVD), pure mitral stenosis (MS), and pure mitral regurgitation (MR).
Source: Reproduced from Marcus et al. (1982).[76]**Error! Bookmark not defined.**

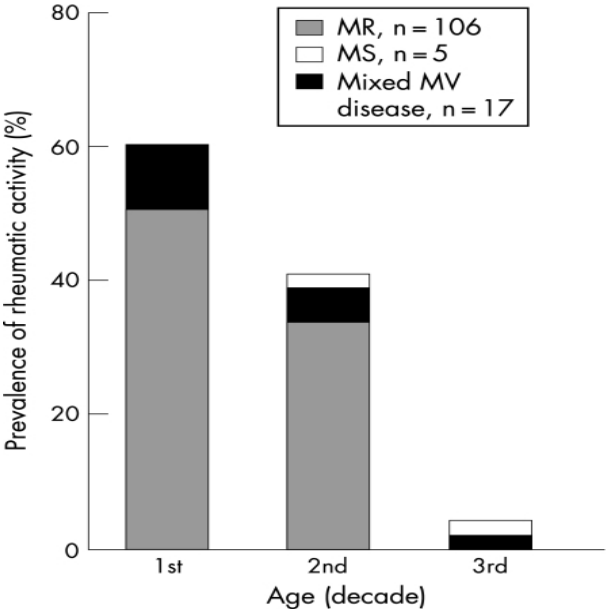


Figure 2.10: Relationships between valve lesion, disease activity, and age. In individuals presenting with severe mitral valve disease throughout the first three decades of life, histograms illustrate the predominance of rheumatic activity. Mitral regurgitation (MR), mitral stenosis (MS), and mitral valve (MV) diseases.
Source: Reproduced from Marcus et al. (1982).[76]

The most prevalent valve pathologies globally are rheumatic heart disease, mitral regurgitation, aortic valve stenotic disease, and aortic regurgitation. Aortic valve stenotic disease is more prevalent in industrialized countries.[58] Sixty one percent of deaths from valvular heart disease are caused by diseases of the aortic valve, whereas 15% are caused by diseases of the mitral valve.[180] (Figure 2.11).

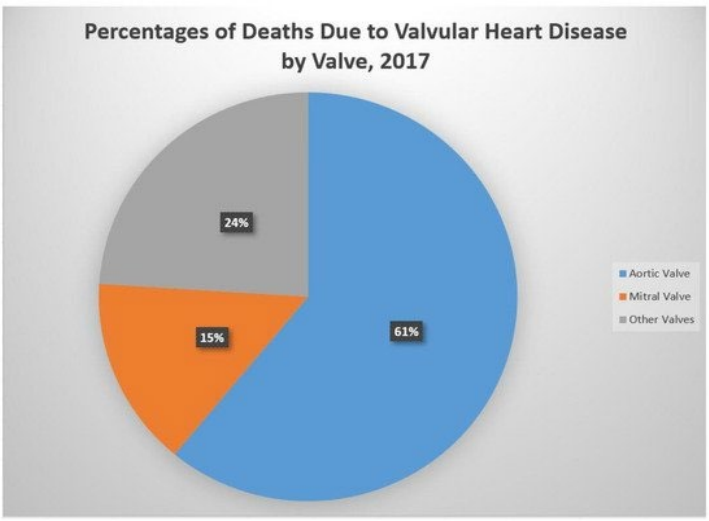


Figure 2.11: Percentages of deaths due to valvular heart disease
Source: Percentages of deaths due to valvular heart disease, by valve, 2017[180] -data obtained from CDC, Atlanta, GA, USA. Available online: https://www.cdc.gov/heartdisease/valvular_disease.htm

Chronic cardiovascular conditions, aging populations, and aortic valve disorders are linked to rheumatic heart disease, a disease caused by overcrowding and inadequate treatment. Infected endocarditis is more common in industrialized countries and the elderly. Women are underrepresented in studies influencing treatment guidelines and postoperative outcomes, despite their higher percentage of cases.[181]

Echocardiography is the gold standard for diagnosing valvular disease, and monitoring patients with progressive conditions is crucial. Intervention is necessary for those with symptoms or reduced ventricular function. Transcatheter valve replacement, often guided by echocardiography, is more common than open heart surgery, potentially improving prognosis for certain valvular heart diseases.[85]

2.13 Pulmonary hypertension due to left heart disease (PH-LHD)

Pulmonary hypertension caused by left heart disease (PH-LHD) is a common form of pulmonary hypertension caused by left heart disease, characterized by a pulmonary arterial wedge pressure greater than 15 mmHg and an elevated mean pulmonary arterial pressure of ≥ 25 mmHg.[182] This condition often worsens the prognosis and exacerbates heart failure, with decreased ejection fraction (HFrEF) or preserved ejection fraction (HFpEF), especially when a precapillary component is present. [183]

Pulmonary artery pressure (PH) is the main factor influencing RV dysfunction in left-sided heart disorders. [184]Patients with left-sided valve disease fall into group II PH due to pulmonary hypertension and pressure overload of the RV[91], which may lead to RV ischaemia and aggravate ventricular dysfunction. [185]However, some patients with PH experience an earlier onset of RV failure due to changes in neurohormonal activation and gene expression.[186] The RV generally adjusts to volume overload more readily than pressure overload[187] ,but persistent volume overload may raise morbidity and death rates.[187] A prospective study[183] involving 1,413 adults found that pulmonary artery systolic pressure(PASP) increased with age, systemic vascular stiffening, and elevated LV filling pressures. Moderate to severe acquired pulmonary wedge pressure often results in RV dilatation and failure in adults, primarily due to mitral and/or aortic valve disease.[1]

Death risk is associated with estimates of PASP. Increased mortality in the general population (A) and in patients without obvious cardiopulmonary disease (B), as well as heart failure with preserved (C) or reduced ejection fraction (D), are linked to elevation in PASP as measured noninvasively by Doppler echocardiography. PASP, HFrEF, HFpEF, and TR velocity are all indicated.Figure 2.12[188]

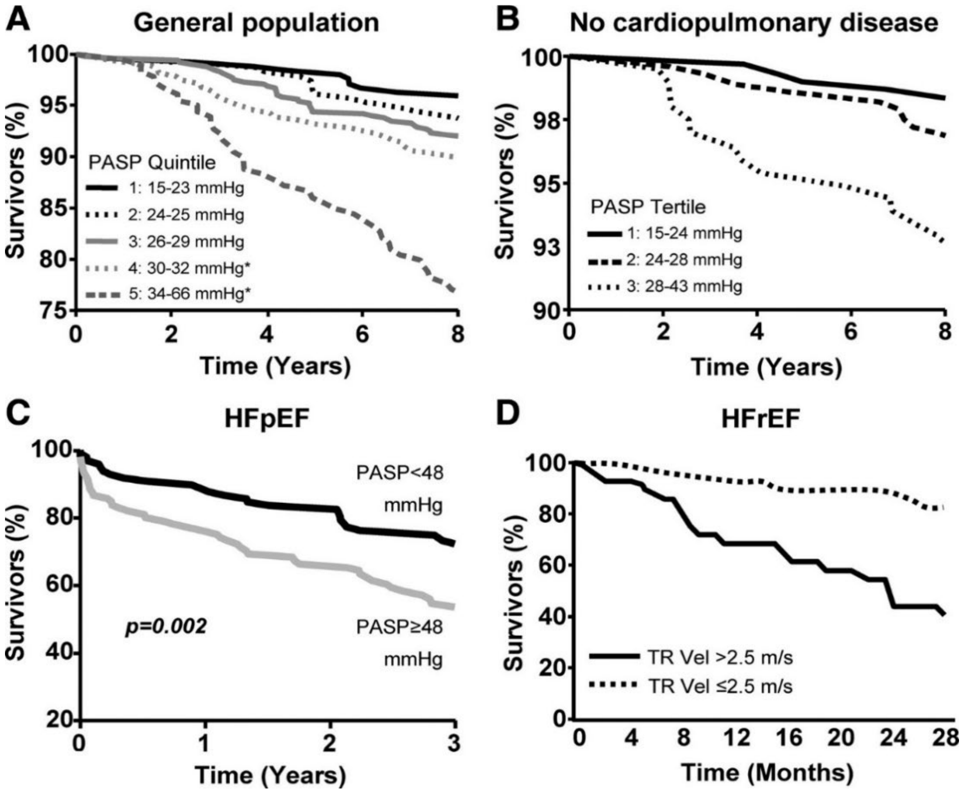


Figure 2.12: Pulmonary artery systolic pressure (PASP).
Source: Adapted from Lam et al. (2009).[188]

While some individuals will not experience significant PH and RV dysfunction, others will. Haddad et al. (2007)[8] discovered that 22% of the participants in a small cohort of patients undergoing MV and aortic valve replacement had prior RV dysfunction. In a single-center cohort of 324 individuals having dilated ischemic cardiomyopathy treated with LV reconstruction, Garatti et al. (2015)[189] reported an incidence of 21%. Although the exact causes of this susceptibility are unknown, co-morbidities, genetic and environmental settings, and the amount of time since the onset of left-sided heart disease are all plausible candidates.[190]

Lam et al. (2009)[188] conducted a prospective study to look at the significance and prevalence of PH in a population with HFpEF. A comparison was made between hypertensive patients without HF (n=719) and patients with HFpEF (n=224, 96% of whom had hypertension). The median PASP was 28 mmHg in those without hypertension symptoms and 48 mmHg ($p<0.0001$) in individuals with HFpEF. In 83% of HFpEF patients and 8% of hypertensive subjects, elevated PASP (>35 mmHg) was found. Similar to the overall population, PASP demonstrated a strong correlation with survival in HFpEF (Figure 2.12C). The authors suggest that the presence of elevated PASP should prompt additional consideration for the diagnosis of HFpEF. These findings emphasize the importance of increased PASP as an additional echocardiographic marker of aberrant PCW.[188] LV diastolic dysfunction is included as the main cause of group 2 PH according to the most recent update on the Dana Point guidelines.[191]

Most of the epidemiological data regarding PH in HFrEF come from populations with advanced (stage D) HF[192].Echocardiography-estimated PH was linked to significantly higher morbidity and mortality in HFrEF, according to Abramson et al. (1992) [193],(Figure 2.12D). Ghio et al. (2001) [194]demonstrated that RV dysfunction has significant effects on risk stratification in group 2 PH above and beyond PAP. More than 60% of the patients with moderate or severe HF had PH.[194] In an echo-based investigation involving 388 heart failure patients, the presence of PH (defined as PASP>39 mmHg) was associated with worse survival in both HFrEF and HFpEF. The size of the impact did not differ significantly across groups.[135]

2.13.1 Pathophysiology of PH-LHD

It is well recognized that heart failure (HF) affects the pulmonary circulation. An early increase in LA filling pressure brought on by HF results in a "passive" rise in PAP. Subsequently, this increase is then passed on to the pulmonary veins and capillaries.[195] A rise in LAP, which is often assessed by the pulmonary artery wedge (PAWP), is the single factor that may explain how PH develops (Figure 2.13). On the other hand, mean PAP (mPAP) may increase in addition to the rise in LAP/PAWP in the presence of several other variables including chronic conditions. Pulmonary vascular resistance (PVR) rises as a result of this, which is associated with a more severe clinical state and leads to the formation of a precapillary component.[195]

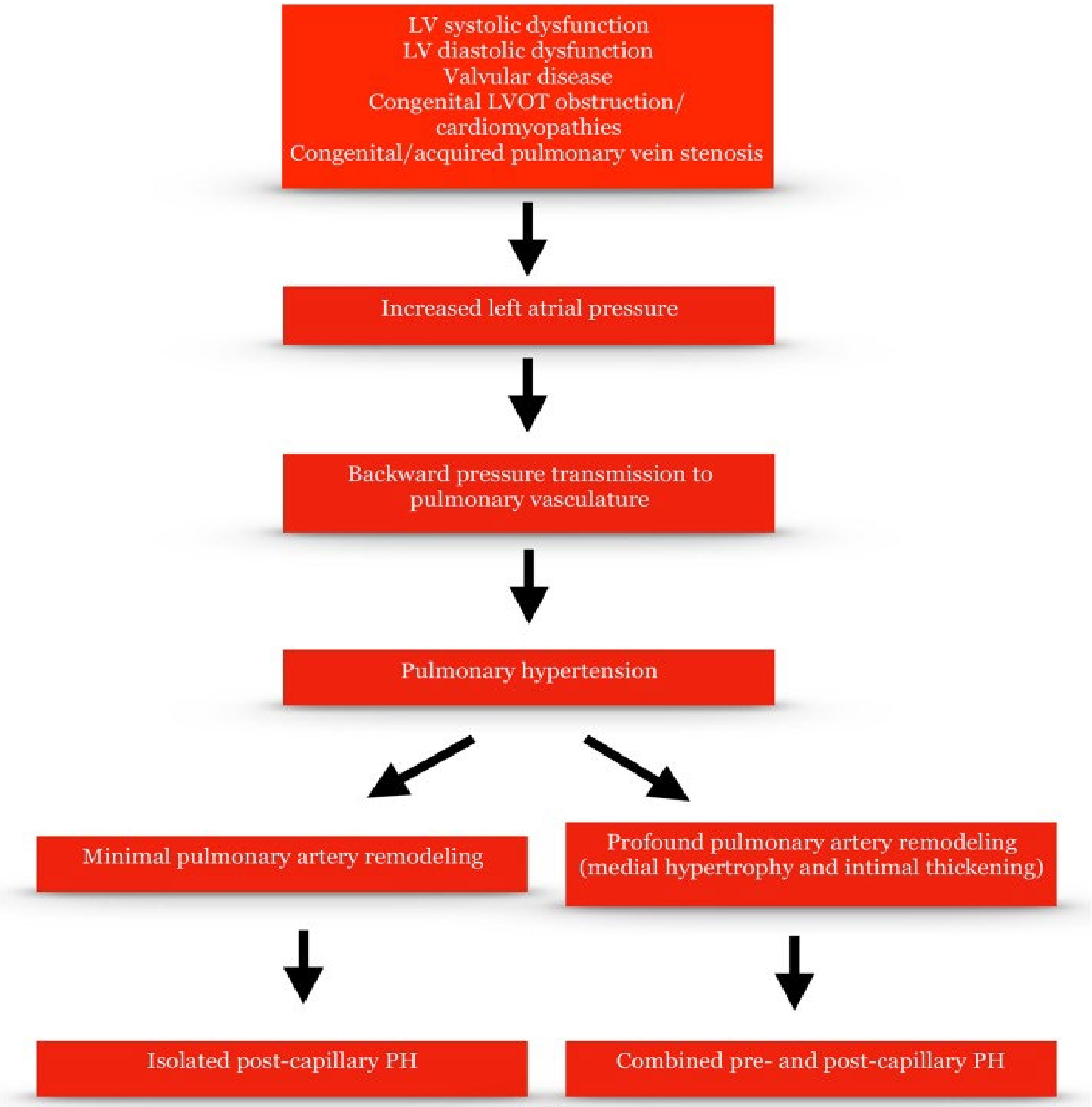


Figure 2.13: Pathophysiological mechanisms of pulmonary hypertension due to left heart disease.
Source: Adapted from Charalampopoulos et al. (2018).[196]

When the diastolic pressure gradient (DPG) is less than 7 mmHg and/or the PVR is less than 3 Wood Units (WU), two conditions must be met as identified at the 5th World Symposium on Pulmonary Hypertension (WSPH) in 2013: (1) isolated postcapillary PH, and (2) combined post- and precapillary PH (CpcPH). This hemodynamic categorization of PH was recently amended by the 6th World Symposium on Pulmonary Hypertension, which decreased the normal value for mPAP from 25 to 20 mmHg and included PVR in the overall definition.[195] However, this definition has not yet been implemented in international guidelines.

According to Butler et al. (1999)[197], 28% of heart failure patients had normal pulmonary vascular resistance (PVR,< 1.5 WU), 36% had mildly elevated PVR (1.5–2.49 WU), 17% had moderately elevated PVR (2.5-3.49 WU), and 19% had severely elevated PVR (>3.5 WU). The study also looked at exercise intolerance and pulmonary hypertension in these patients. A more recent study by Meader et al (2021)[198] found that in reality, 80-90% of patients with HFpEF and HFrEF had PVR > 1.7 WU, and more than half had PVR >3 WU or TPG >5 mmHg. Figure 2.14

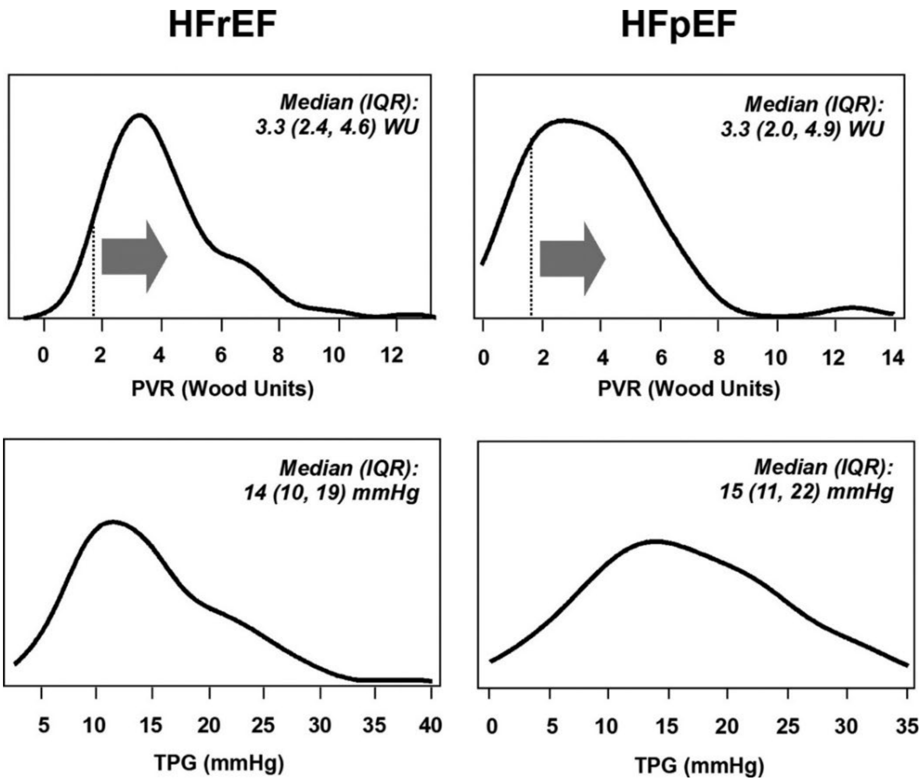


Figure 2.14: Distribution of PVR and TPG in a patients with group 2 PH due to HFrEF and HFpEF. Source: Adapted from Schwartzenberg et al. (2012). [199]

2.13.2 Pulmonary hypertension due to left heart diseases and prognosis

Mitral stenosis is often used as a model disease due to its association with worse prognosis after valve replacement[200] and postcapillary pulmonary hypertension, a risk factor for patients with primary or functional mitral regurgitation. [200]

Pulmonary hypertension due to left heart diseases (PH-LHD) is a significant risk factor for heart failure patients, with a 12-month mortality rate of up to 32% predicted.[135] Factors such as male sex, advanced age, right ventricular failure, renal disease, and poorer functional class contribute to death.[201] In a study of 244 patients with heart failure, peak systolic PAP was found to be an independent predictor of mortality.[188] Patients with severe heart failure with a reduced right ventricular ejection fraction (RVEF) are more likely to die or require immediate transplants.[193] PH is also an independent predictor of mortality and hospitalization for heart failure.[193] Patients with pre-capillary PH in chronic HFrEF are at a higher risk of dying than those with PH-LHD. RVEF calculations may provide a better prognosis for heart failure patients[202, 203]

RVEF is an independent predictor of survival in mild congestive heart failure, with 1-year survival rates of 80%, 90%, and 95%.[202] Shorter patient survival is associated with higher PAP paired with low RVEF. [204]Treating pulmonary hypertension in LHD may improve prognosis, as it is associated with poorer prognosis. High echocardiographic systolic pulmonary pressure indicates heart failure mortality and cardiovascular events. [205]

2.13.3 Management of PH-LHD

Patients with PH-LHD are not covered by the Cardiology/European Respiratory Society (ESC/ERS) guidelines treatment algorithm, which was created for group 1 PH (PAH).[206] The ESC/ERS guidelines advise optimizing the treatment of underlying conditions and ruling out any other causes of PH before assessing patients for PH-LHD.[206] Supplemental oxygen, diuretics, oral anticoagulants, and digoxin are examples of general supportive therapies for PAH, and specific drug therapies include rostanoids, endothelin receptor agonists, calcium channel blockers, endothelin receptor agonists, soluble guanylyl cyclase stimulators, and phosphodiesterase type-5 inhibitors.[206] One of the most crucial initial steps in treating PH-LHD is managing the underlying etiology of PH.[207] For example, in the event of valve-related left heart disease, surgical repair or replacement of the aortic or mitral valves can improve patient outcomes. Baumgartner et al. (2017) [127]stated that, effective decongestion of the pulmonary vasculature may also be a useful strategy. With cases of mitral valve disease, mitral valve intervention is recommended and often results in improved PH. Lowering left ventricular filling pressures is another benefit of standard heart failure therapies.[208]

2.14 Two-dimensional Doppler and speckle tracking echocardiography for the assessment of RV function and left heart valves

A new algorithm called speckle tracking echocardiography (STE) can analyze echocardiographic images and provide an objective, repeatable measurement of both global and regional myocardial function[209]. It is now considered a crucial tool for evaluating RV myocardial deformation, which is a strong indicator of a patients ability to function and the likelihood of survival.[53]

According to early studies[210, 211], MRI is a reliable method for estimating RV volumes and function, but it is more expensive and not always accessible. A study Mitchell et al. (2019)[212] found that Cardiac magnetic resonance imaging (CMRI), considered the gold standard for RV evaluation, correlates well with the global longitudinal strain of the RV.[212]

Altiok et al. (2014) [213]found that two-dimensional speckle tracking imaging (STE) is as accurate as late gadolinium enhancement cardiac magnetic resonance (LGE CMR) in predicting global functional recovery and left ventricular remodeling after acute myocardial infarction. Global longitudinal strain (GLS) is a sensitive indicator of myocardial systolic function and an independent predictor of cardiovascular outcomes.[214]

2D speckle-tracking echocardiography (2DSTE) quantifies RV myocardial longitudinal strain (RVLS), a less load- and angle-dependent indices than typical RV function indices. [215]This imaging has significant implications for patient diagnosis, prognosis, and treatment, and has shown utility as a prognostic tool for various cardiovascular diseases. Strain echocardiography, a non-invasive, objective indicator of myocardial contractility, can now measure myocardial strain, representing regional and global myocardial systolic function.[55]

RV global longitudinal strain (RVGLS) is a more accurate and sensitive indicator of RV function than conventional echocardiographic markers, and is recommended in 2015 guidelines for chamber quantification by echocardiography in adults due to its ability to predict certain cardiovascular conditions. [215]

Research[216-219] has shown the importance of right ventricular (RV) strain in heart failure and congenital disease, as well as in conditions that predominantly affect the RV, such as pulmonary hypertension and pulmonary embolism. When compared to LV strain alone, RV strain offered an independent extra prognostic value. [216]

Research[220, 221] has shown that elevated afterload can lead to decreased RV systolic function in MS patients undergoing balloon mitral valvotomy (BMV). However, after BMV, there was a significant increase in global and septal strain, but not in the RV free wall (RVFW). This could also apply to aortic stenosis.[220] Medvedofsky et al. (2020)[222] found that 19% of patients had impaired right ventricular systolic function before and after Transcatheter Aortic valve replacement (TAVR), but no significant differences in right ventricular free wall strain.

RV dysfunction is caused by a complex interplay of enlarged and remodelled LV, septal function, and PASP, with or without degenerative MR.[3] Research Chowdekar et al. (2021) [223]found no improvement in RVGLS in patients with rheumatic[224] mitral valve disease after surgery. The authors hypothesize that open sternotomy affects RV free wall's longitudinal motion, and RV dysfunction may take a long time to improve due to pericardiotomy-induced longitudinal deformation. [225]

RV global and free wall systolic strain are not used to define normal RV longitudinal systolic function. A study by Tong et al. (2008)[226] used 2D speckle-tracking echocardiography to analyze healthy subjects, but the normal range of RV global and free wall systolic strain could not be determined due to the limited number of patients studied.[226] The three main indicators within right ventricular strain are right ventricular global longitudinal strain (RVGLS), right ventricular free wall longitudinal Strain (RVFWLS), and interventricular septal wall longitudinal strain (IVSLS). However, the reference ranges for these characteristics have not yet been established.[215] And because of that reason we adapted those used by Morris et al. 2017[224].The normal range of RV systolic strain measured in healthy subjects was -17% and -19% for RV global strain and RV free wall strain, , at -24.5±3.8 and -28.5 ± 4.8, respectively. The American Society of Echocardiography/European Association of Cardiovascular Imaging (ASE/EACVI) guidelines have recognized the need for standardization in strain imaging, recommending using the same vendor machine and software version for serial evaluation of global strain. The strain results produced by various echocardiography machines and software programs can vary, making it difficult to compare them over time for a particular patient. As a result of their recent efforts to reduce intervendor variability of strain measurement, the American Society of Echocardiography/European Association of Cardiovascular Imaging (ASE/EACVI) guidelines have recognized the critical need for standardization in strain imaging.[227] One recommendation is to use the same vendor machine and software version for the serial evaluation of global strain.

CHAPTER 3: RESEARCH METHODOLOGY

Increased filling pressures in the left heart are linked to left valvular heart disease. These increases set off a sequence of unfavorable pathological and functional alterations in the pulmonary vasculature, ultimately affecting the right heart (pulmonary hypertension, tricuspid regurgitation, and RV dysfunction). Surgery to repair any of the left heart valves frequently, though not always, results in the remodelling of the right heart or the return of tricuspid valve function, RV function, and pulmonary hypertension to normal.[228] However, the reduction/normalisation in pulmonary hypertension (PH), tricuspid regurgitation (TR) and right ventricular (RV) function are often modest and a few studies[13, 229] have been conducted to show the interaction of PH, TR and RV function pre and post valve surgery in patients with left valvular disease.[230] The aim of this study was to determine changes in the right heart after mitral and/or aortic valve surgery, as well as to determine predictors of early signs of TR progression/regression post-left valve surgery that could possibly be used as an indication for TV surgery at the time of left valve surgery.

Flow diagram highlighting and study layout conceptual framework of the study

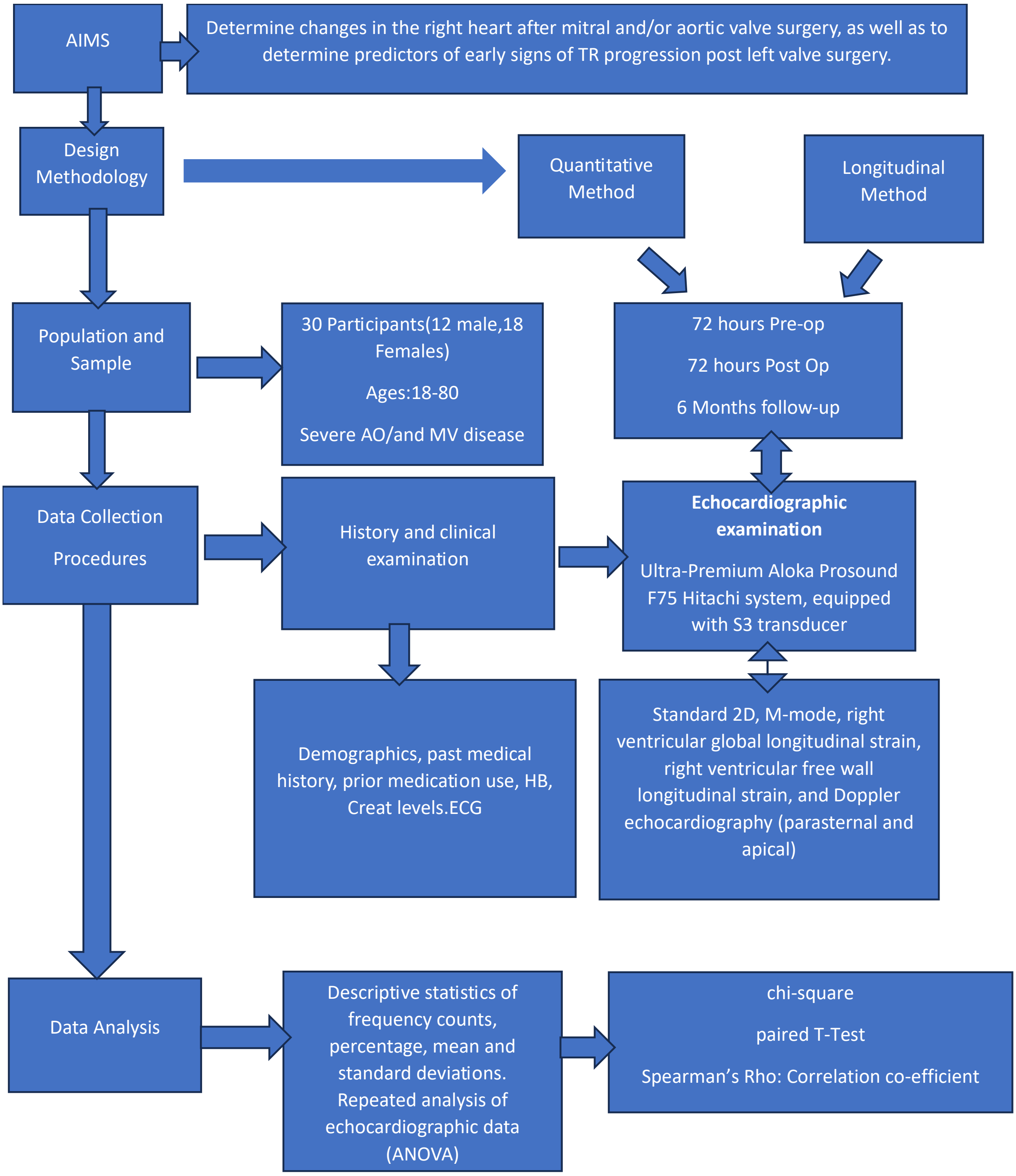


Figure 3: flow diagram of the study layout and conceptual framework

3.1 Study design

This was a clinical prospective observational study on the preoperative and postoperative echocardiographic parameters and their interaction in patients with severe mitral and or aortic valve disease and were candidates for valve surgical correction.

3.2 Study area

The study was conducted at Port Elizabeth Provincial Hospital which is based in the Eastern Cape. According to the Income and Expenditure Survey/Labour Force Survey (IES/LFS) 2000[231] and Census 2001[232], Eastern Cape is home to approximately 6.8 million people and the vast majority of the population is Africans (87.9%).

3.3 Study population

The study included 30 patients (12 men and 18 women) between the ages of 18 and 65.

3.4 Inclusion criteria

Inclusion criteria were South African citizens between the ages of 18 and 65 years, patients with severe mitral and/or aortic valve disease requiring valve surgery, patients with no history of myocardial infarction, and patients with no history of previous heart or valve operation.

3.5 Exclusion criteria

We excluded all patients who were under the age of 18 and over the age of 65 years, patients with chronic obstructive pulmonary disease (COPD), patients requiring coronary artery bypass grafting, patients who have had previous valve intervention and are returning for reoperations or correction of valve, individuals who tested positive for Human Immunodeficiency Virus(HIV) and had a viral load more than 10,000 copies/ml or a CD4 count of fewer than 200 cells/cc3, and patients not proficient in English, Afrikaans or isiXhosa/isiZulu (as investigators and other persons involved were only fluent in English, isiXhosa/isiZulu and Afrikaans). Medications including angiotensin-converting enzyme inhibitors and beta-blockers were adjusted as per the decision of the cardiologist and the cardio-thoracic surgeon who were treating. Postoperatively, all patients with a prosthetic valve received oral anticoagulation.

3.6 The recruitment process

All participants recruited gave their informed written consent (Appendix 1a,b,c). Thirty consecutive randomised patients with severe mitral and or aortic valve disease coming for elective cardiac surgery were recruited as participants (Appendix 2a,b,c). Departmental approval was obtained from the Livingstone Tertiary Hospital (Appendix 3). Certificate for the Introduction to Research Ethics was obtained from the Training and Resources in Research Ethics Evaluation (TRREE) online training program(Appendix 4). The study was approved by the Durban University of Technology Institutional Research Ethics Committee (Ethics Clearance Number: IREC 004/21) (Appendix 5) and by the Eastern Cape Health Research Committee (Appendix 6). Upon approval by IREC and Health Research Committee, various tests and measurement were collected as variables of the study (Appendix 7). All patients underwent a detailed history and clinical examination by the cardiologist and a 2D and 2D speckle tracking echocardiographic examination was performed (Appendix 8) following strict COVID-19 protocols.

3.7 Sample size calculation

Considering a paired t-test for pre- and post-variable comparisons and using a 5% level of significance, a power of 80% and an effect size of 0.40 for the difference in pre- and post-means, the ideal sample size was found to be 52. The minimum sample size when using a 5% level of significance, a power of 80% and an effect size of 0.50 for the difference in pre- and post-means, the sample size is found to be 30. Therefore, the sample size used for the purpose of this research was 30. The sample size calculator GPower 3.1.9.2[233] was used to determine the sample size in consultation with a biostatistician.

3.8 Data collection

All patients recruited by the principal investigator, myself, underwent a detailed history and clinical examination by a cardiologist. They also underwent an echocardiographic examination 72 hours before and 72 hours after the surgeon completed the interventional procedure. This examination was repeated six months later as part of the standard cardiologist visit, using the Ultra-Premium Aloka Prosound F75 Hitachi system, equipped with an S3 transducer, and adhering to strict COVID-19 protocols.

The echocardiographic procedure was briefly explained to the participants. Clothes were removed to expose the chest and patient asked to lie in a left decubitus posture with their arms stretched behind their head. The heart and chest wall are in close touch in this posture.

Variables such as demographics, past medical history, prior medication use, cardiac catheterization results, present clinical presentation, type of surgery, myocardial protection techniques employed, intraoperative complications, and postoperative data, Including ICU stay, number of hours of post-operative mechanical ventilation, and postoperative hemodynamic inotropic support dose was entered in Microsoft Excel and imported into SPSS for statistical analysis.

A three-lead electrocardiogram (ECG) was connected to the patient, allowing identification of arrhythmias and timing of cardiac events during the echocardiographic examination. Standard views (Appendix 8) were recorded as per the 2014 ESC/ESA Guidelines for non-cardiac surgery [234]

Echocardiographic parameters that were measured and recorded as variables in this study were as follows:

- RV global longitudinal strain (RVGS)
- RV free wall longitudinal strain (RVFWS)
- M-mode echocardiography:
    - LV/RV EDD(mm)
    - LV/RV ESD(mm)
    - LV EF(%)
    - LV FS (%)
    - LAD (mm)
    - TAD (mm)
    - RV FAC (%)
    - TAPSE (mm)

Two-dimensional and conventional colour Doppler echocardiography:

- S'(cm/s)
- E' (cm/s)
- RV E/E'
- Severity of valve disease (through the use of velocity and colour Doppler)

Pressure gradients (mmHg):

- AO/MV mean and peak gradients
- Valve area
- Peak RV pressure

All echocardiographic data was saved on the internal memory of the echocardiographic machine and hard drive using the patient's PE number. This data will be accessible upon request in case of any need to check uncertainty regarding data analysis.

3.9 Research tool / data measurement instruments

3.9.1 Data analysis plan

All results obtained from the data collection process was be captured on a Microsoft excel spread sheet. Analysis was done using ***SPSS software (V28)*** after variables were pooled, edited and scored. Nominal values were assigned to the items according to scales. Descriptive statistics of frequency counts, percentage, mean and standard deviations were used to present baseline characteristics and prevalence data. Continuous echocardiography data was analysed at baseline, immediately post-operatively and at 6 months using ANOVA, while categorical data was analysed using Chi-square to determine significant associations across the timeframes. The paired T-Test was used to compare echocardiography data preoperatively and postoperatively at 6 months to ascertain longer term characteristics. RV strain was also compared preoperatively and postoperatively at 6 months using the paired T-Test. Spearman's Rho was used to determine the correlation between specific echocardiography parameters to establish any relationship at preoperative levels and then at 6 months. Correlation co-efficient between 0.8 and 1.0 was considered very strong, 0.6-0.79 was considered to be a strong correlation, 0.4-0.59 was considered to be a moderate correlation, 0.2-0.39 was considered to be a weak correlation, while 0.0- 0.19 was considered to be a very weak correlation.[235] Odds ratio and the 95% confidence interval were calculated, and a p-value ≤ 0.05 was considered statistically significant.

3.9.2 Intra-observer variability

The researcher undertook testing for intra-observer variability, in accordance with the guidelines by Popović & Thomas.[236] The researcher performed two measurements on each of the series of samples, where individual differences between first and second measurements were calculated as follows:

$$A-B/[(A+B)/2]$$

The relative differences (%) are shown in Appendix 9, and all fall under 9% of each other.

3.9.3 Ethics considerations

Upon approval by the Institutional Research Ethics Committee (Ethics clearance no: **IREC 004/21)**, participants were recruited without being coerced into participating. Education on the aims, potential outcomes, risks and or benefits of the study was clearly communicated to potential participants before they gave consent. All patients are and were treated fairly and indiscriminately, irrespective of their age, gender and race. A memorandum of understanding was signed by the interpreter/witness to ensure no information about the participant would be shared. In addition, participants were not exposed to additional invasive procedures, as echocardiogram is a non-invasive and a ‘risk free’ assessment of the heart.

3.9.4 Confidentiality and anonymity

Confidentiality and anonymity were prioritised by coding each participant into a ‘PE’ number that is known only by the researcher and supervisor as the South African constitution allows and respects an individual’s privacy regarding their health status.

3.10 Echocardiographic measurements and methods applied

3.10.1 Left ventricular ejection fraction LVEF%

The left ventricular ejection fraction (LVEF) is the primary measure of left ventricular systolic function. LVEF is the ratio of the chamber volume expelled in systole (stroke volume) to the amount of blood in the ventricle at the end of diastole (end-diastolic volume, EDV). The stroke volume (SV) (end systolic volume, ESV) is the difference between the EDV and ESV.[237] LVEF is calculated as follows[237]:

LVEF: [SV/EDV] x 100

Left ventricular ejection fraction was calculated from these measurements by an automated computer program which displays the output as follows:

The EF is composed of the following: LVIDd is the left ventricular internal diameter in diastole, IVSd is the interventricular septum in diastole, LVPWs is the left ventricular posterior wall in systole, EDV is the end-diastolic volume, IVS/LVPW: the ratio of posterior wall thickness to interventricular septum (Figure 3.1). [238]

Surgery is generally recommended when LVEF is reduced below 60% but greater than 30%. LV dimensions were considered as seen in Table 3.1

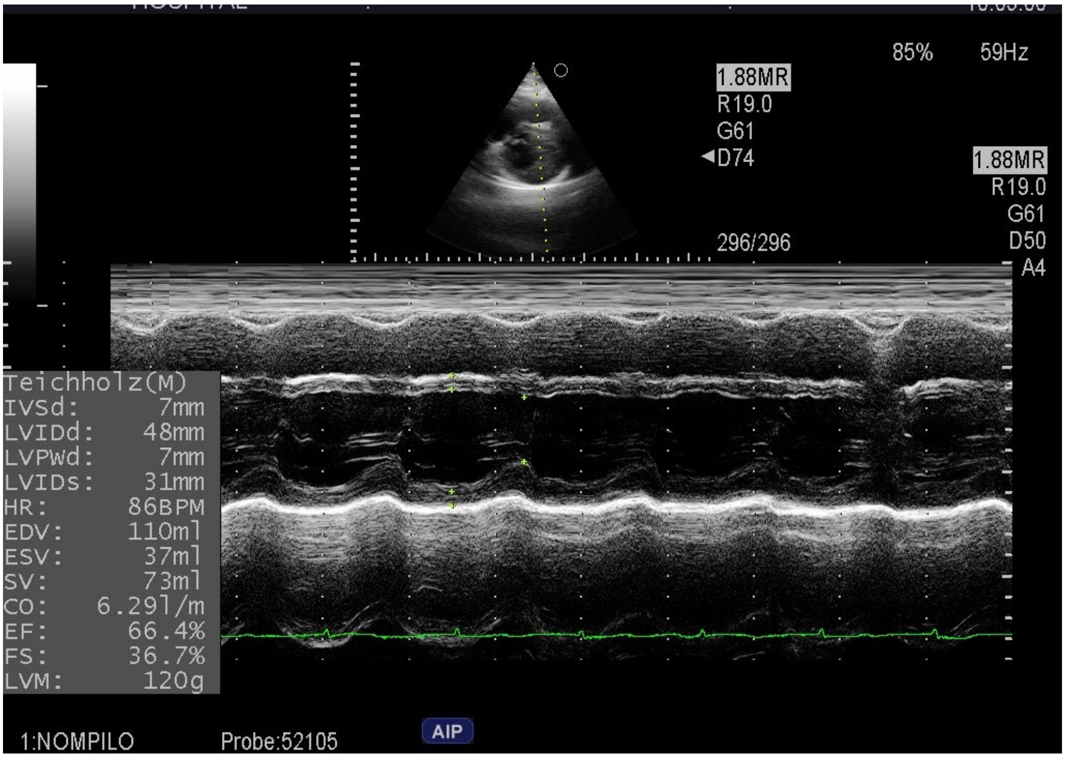


Figure 3.1: M-mode in parasternal long axis view for LV dimension and ejection fraction.

Table 3.1: Classification of LV ventricular size and function.

LV VENTRICULAR SIZE AND FUNCTION				
	NORMAL	MILD	MODERATE	SEVERE
LV DIMENSION (WOMAN)				
LVID (cm)	3.9-5.3	5.7-5.7	5.8-6.1	>6.2
LV DIMENSION (MAN)				
LVID(cm)	4.2-5.9	6.0-6.3	6.4-6.8	>6.9
LV WALL THICKNESS				
IVSd/PWd(cm)	0.6-1.2	1.3-1.5	1.6-1.9	>2.0
LV FUNCTION				
EJECTION FRACTION(%)	>55	45-54	36-44	<35
FRACTIONAL SHORTNING(%)	25-43	20-24	15-19	<15

Source: Adapted from Lang et al. (2015).[215]

3.10.2 LA diameter

The measurement of the left atrial size occurs at end-systole when the left atrium is at its most dilated. The parasternal long-axis view was used to acquire measurements using M-mode echocardiography (Figure 3.2). The biggest anteroposterior diameter was obtained by measuring from the leading edge of the posterior LA wall to the trailing edge of the posterior aortic wall. Although the standard procedure for measuring M-mode is to measure from the leading edge to the leading edge, the American Society of Echocardiography advises measuring from the trailing edge of the posterior aortic root.[215] This lessens the chance of an irregular gap forming between the left atrium and the aortic root. LA dimensions were in accordance with the recommendation for the 2015 recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of cardiovascular Imaging[215], as shown in Table 3.2.

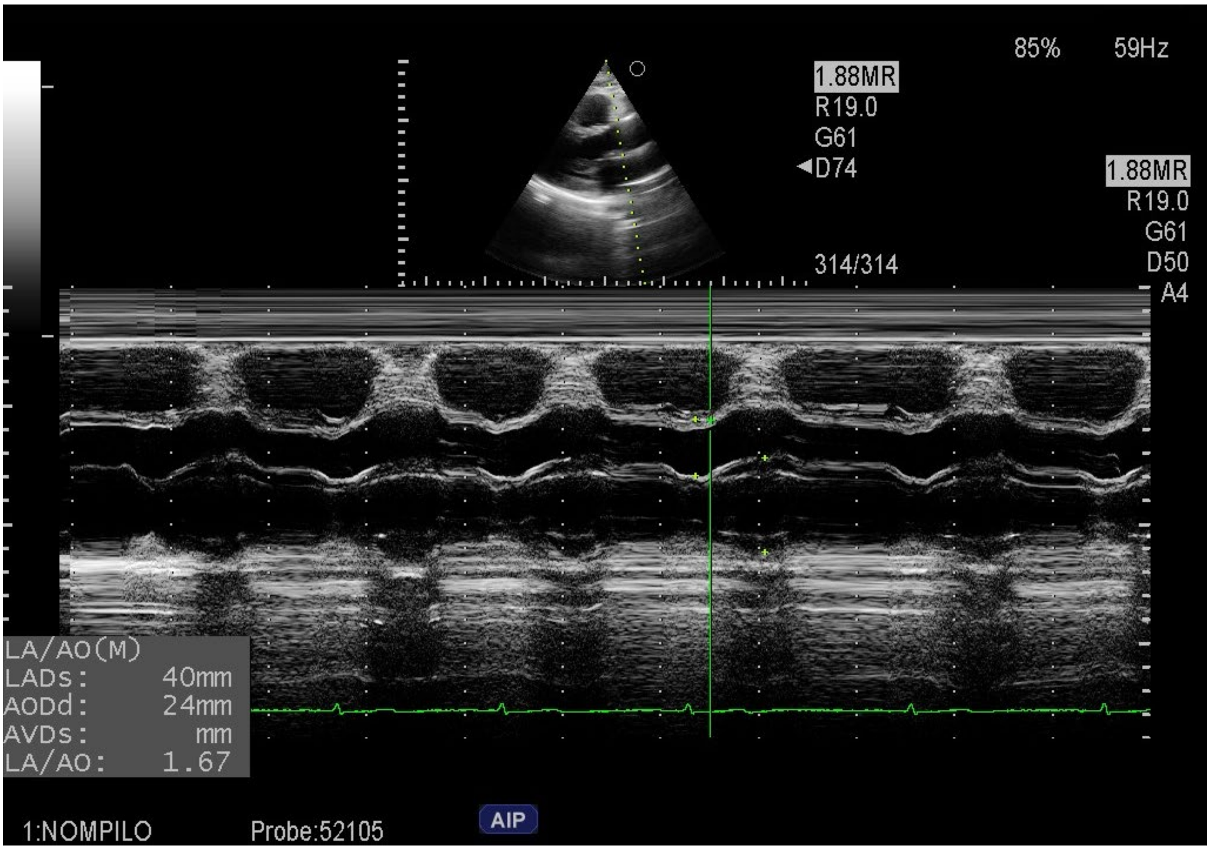


Figure 3.2: Parasternal long-axis view of LA/AO diameter using M-mode echocardiography.

Table 3.2: Classification of left atrial size.

LEFT ATRIAL SIZE				
	NORMAL	MILD	MODERATE	SEVERE
LA SIZE WOMAN (mm)	2.7-3.8	3.9-4.2	4.6-4.6	>4.7
LA SIZE MEN (mm)	3.0-4.0	4.1-4.6	4.7-5.2	>5.3

Source: Adapted from Lang et al. (2015).[215]

3.10.3 Right heart dimensions

RV dimension was best estimated at end-diastole using an apical 4-chamber view with the right ventricle in focus.[215] The picture showing the right ventricle's maximum diameter was carefully captured without foreshortening. Making sure the heart's apex and crux are visible (Figure 3.3). RV dilatation was indicated by a diameter of > 42 mm at the base and > 35 mm at the midpoint. RV enlargement was also indicated by a longitudinal dimension greater than 86 mm (Table 3.3).

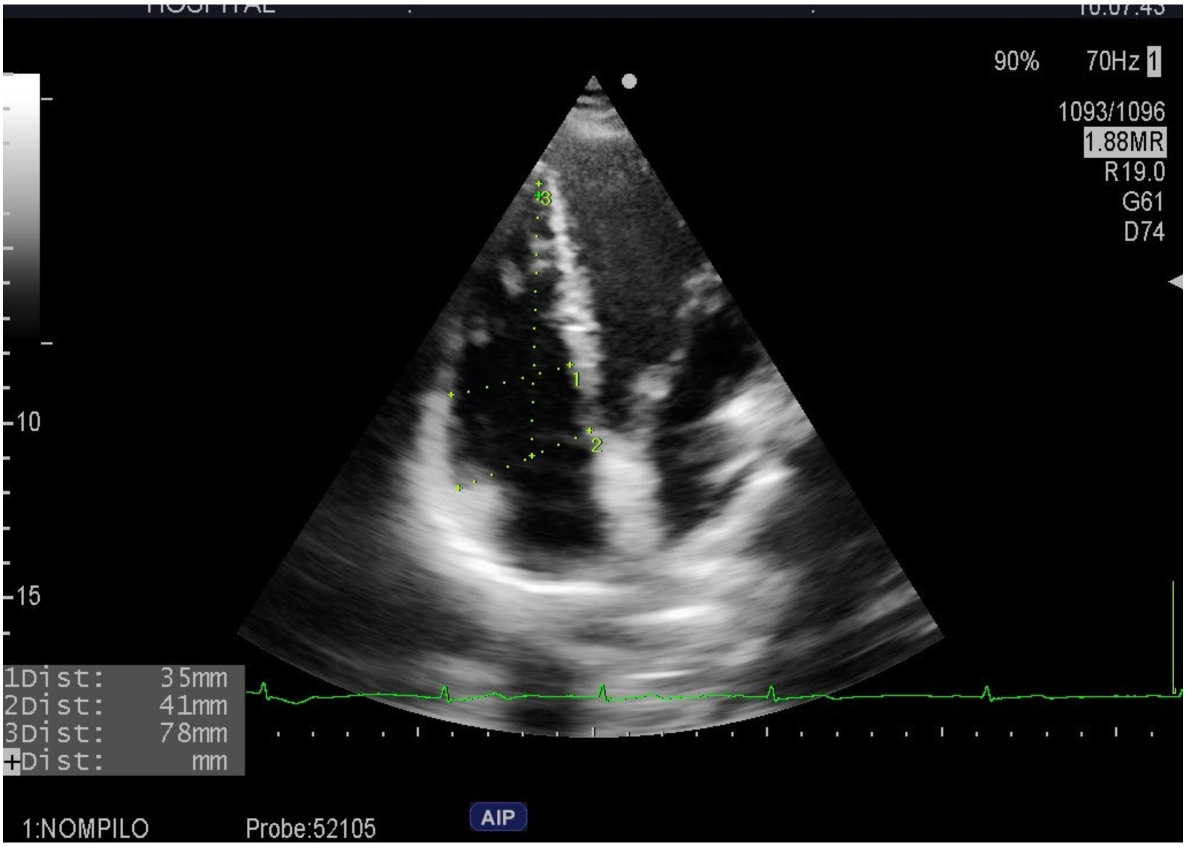


Figure 3.3: Right ventricular end-diastolic and -systolic area measurement from 2D apical 4-chamber view.

Table 3.3: Classification of RV ventricular size and function

RV VENTRICULAR SIZE AND FUNCTION	
RV DIMENSION APICAL 4 CHAMBER	**ABNORMAL**
BASAL RV DIAMETER(RVD1) cm	>4.2
MID RV DIAMETER (RVD2) cm	>3.5
BASE TO APEX LENGTH (RVD3) cm	>8.6
RV FUNCTION	
FRACTIONAL AREA CHANGE (%)	<35
TAPSE	<16

Source: Adapted from Lang et al. (2015).[215]

3.10.4 IVC measurement

The subcostal view evaluates inspiratory collapsibility and allows for imaging and measurement of the IVC. An accurate method for determining the volume status of individuals who are hemodynamically stable was to measure the interstitial lung space circumference (IVC) at various stages of the respiratory cycle.[239]. IVC was measured immediately in front of the hepatic vein entrance (Figure 3.4, A and B). An IVC diameter of less than 2.1 cm that collapses more than 50% at sniffing suggested a normal RA pressure of 3 mmHg (range, 0–5), whereas an IVC diameter of more than 2.1 cm that collapses less than 50% upon sniffing suggested a high RA pressure of 15 mmHg (range, 10–20 mmHg). 8 mmHg, with a range of 5 to 10 mmHg, was used as an intermediate value when IVC diameter and collapse deviate from these models.[215]

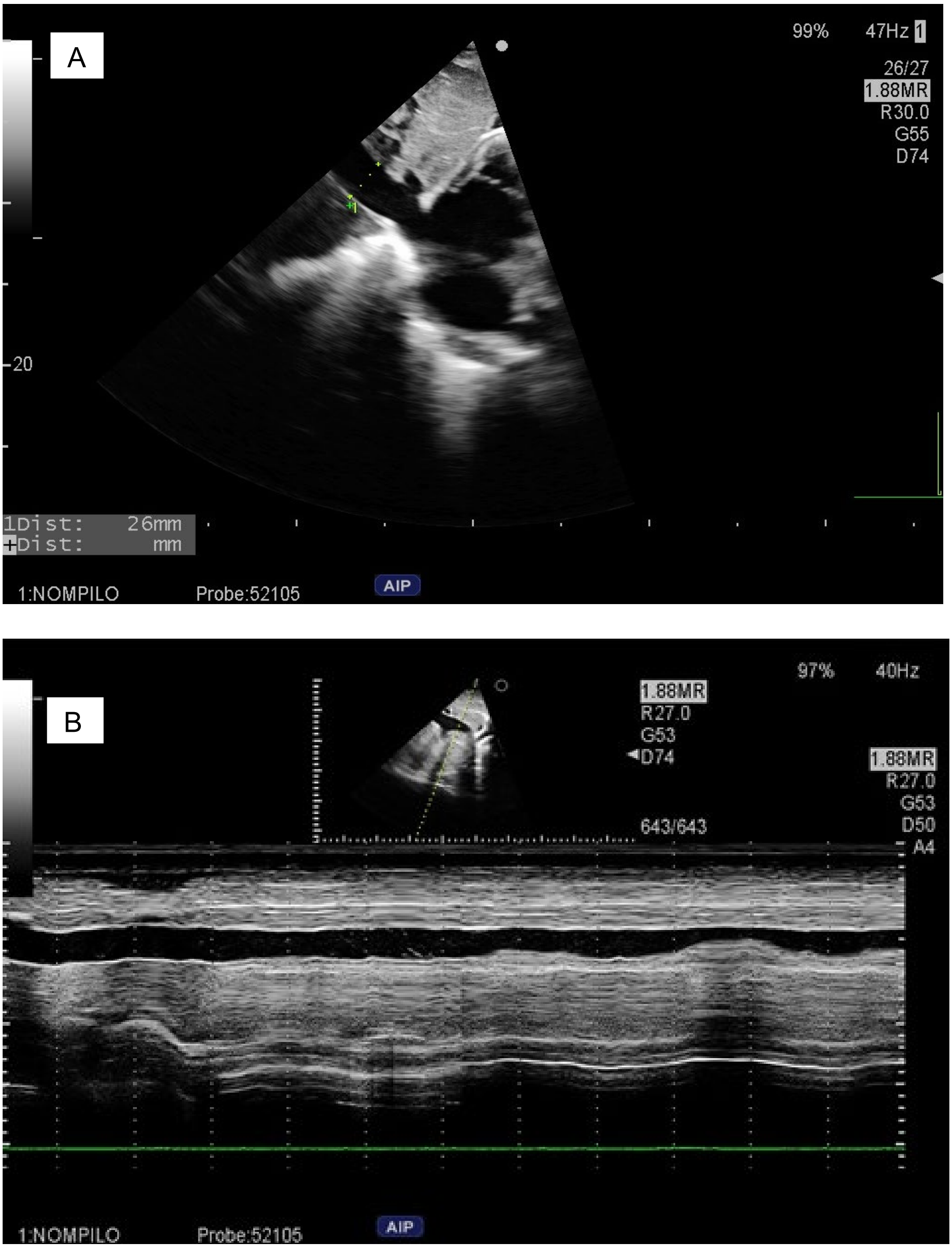


Figure 3.4: A. Two-dimensional subcoastal view of IVC. B. Two-dimensional M-mode across subcoastal IVC.

3.10.5 RV systolic function

This study examined a variety of echocardiographic indices, including the following, because there isn't a single best sign for RV systolic performance[240]. Tricuspid annular plane systolic excursion (TAPSE) and fractional area change of RV (RVFAC). In investigations of patients following pulmonary embolism, Khemasuwan et al (2015)[241] discovered that RVFAC was an independent predictor of heart failure, sudden death, stroke, and/or mortality.

RV systolic dysfunction was indicated by TAPSE < 16 mm.[215] The tricuspid lateral annulus is the source of TAPSE measurement (Figure 3.5). It has demonstrated a strong correlation with methods for estimating RV global systolic function, including radionuclide-derived RV EF, 2D RV FAC, and 2D RV EF, despite measuring longitudinal function.[47]

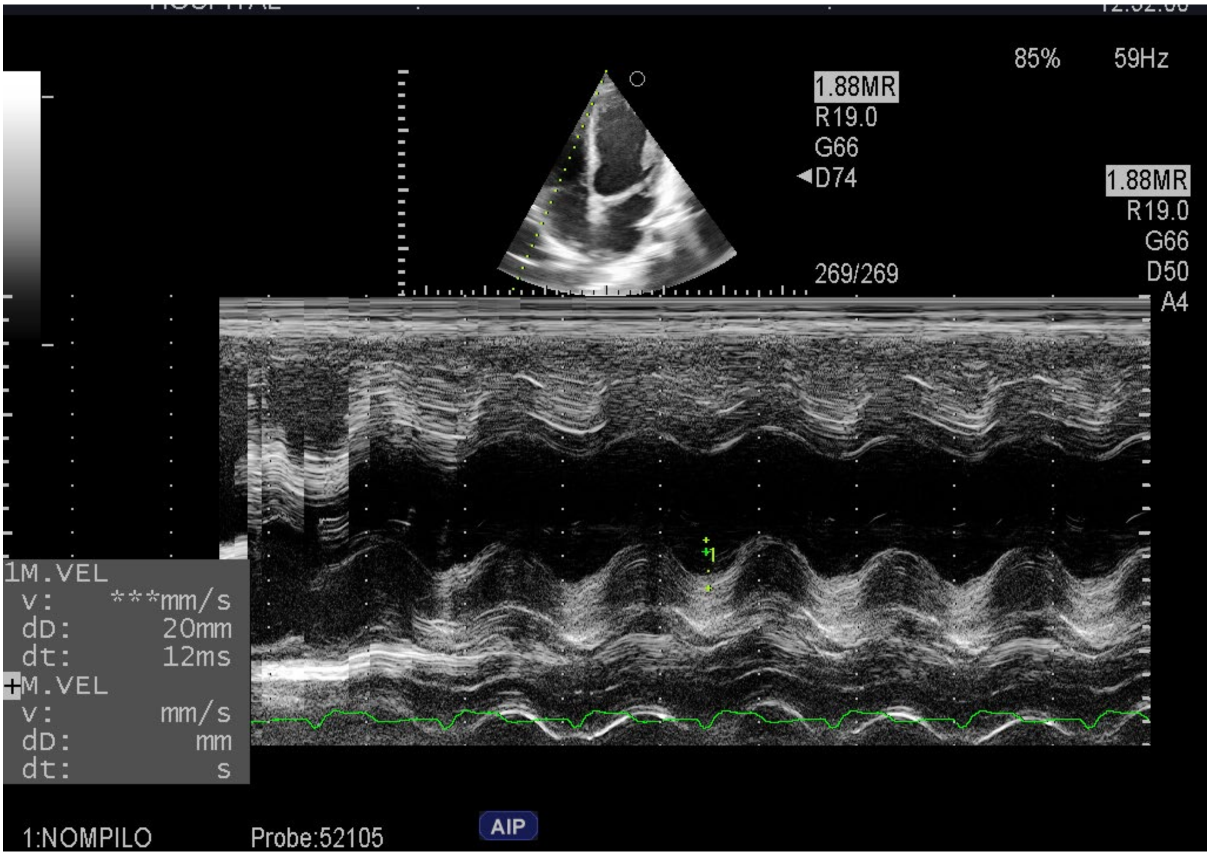


Figure 3.5: TAPSE, M-mode across tricuspid lateral annulus.

<u>Two-dimensional FAC</u> (as a percentage) provides the RV systolic function estimate. RV systolic dysfunction was indicated by a two-dimensional FAC < 35%. The apex and the lateral wall in both systole and diastole of the right ventricle were visible. When tracing the RV area, caution was used to rule out trabeculations (Figure 3.6). The graph displays (A) FAC 60% in a normal subject (B) a noticeably dilated left

ventricle (LV), a moderately dilated right ventricle (RV), and a 40% FAC. (C) Due to the right ventricular chamber's optimal view, the left ventricle (LV) was foreshortened, the RV was dilated, and the FAC was 20%.[47]

Tricuspid annular tissue Doppler Thus, S' is easy to measure, reliable, and repeatable. When the velocity of S" is less than 10 cm/s, RV systolic dysfunction was suspected. The tricuspid annular S' velocity also indicates the RV longitudinal systolic function. It was measured by tissue Doppler application of the lateral tricuspid annulus (Figure 3.7). The tricuspid annular S velocity typically ranges from 14.1 ± 2.3 cm/sec.[47]

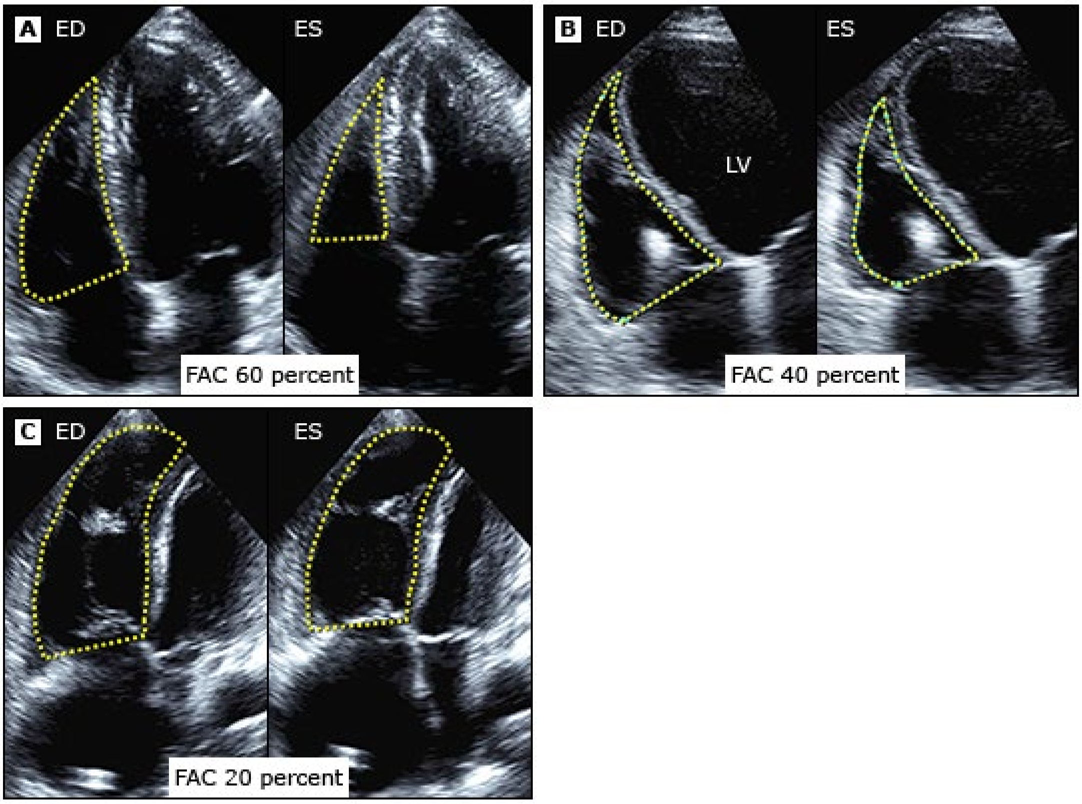


Figure 3.6: Measurement of fractional area change (FAC). Right ventricular end-diastolic and end-systolic area measurements. Source: Adapted from Rudski et al. (2010).[47]

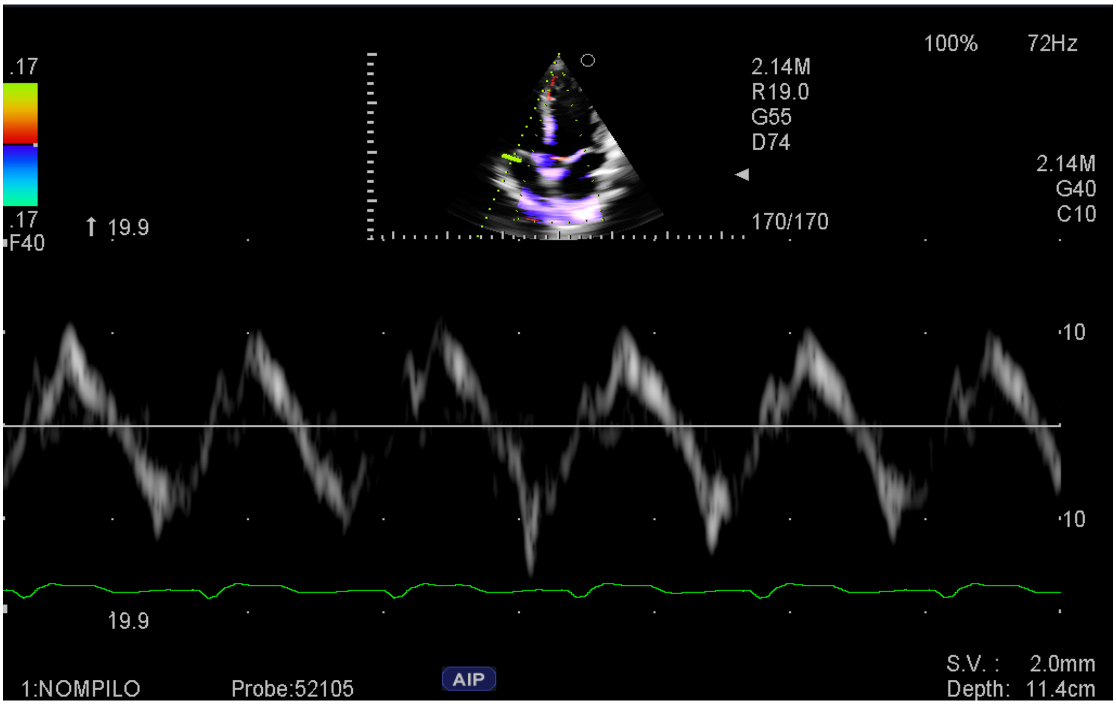


Figure 3.7: Tricuspid annular tissue Doppler imaging.

RV diastolic dysfunction assessment of RV diastolic function was carried out using pulsed Doppler of the tricuspid inflow, tissue Doppler of the lateral tricuspid annulus (Figure 3.8), pulsed Doppler of the hepatic vein (Figure 3.9), and measurements of IVC size and collapsibility (Figure 3.10). These measurements were made either as an average of five consecutive beats or at the end of expiration during quiet breathing; however, they might not be reliable if there is severe tricuspid regurgitation (TR).[47]

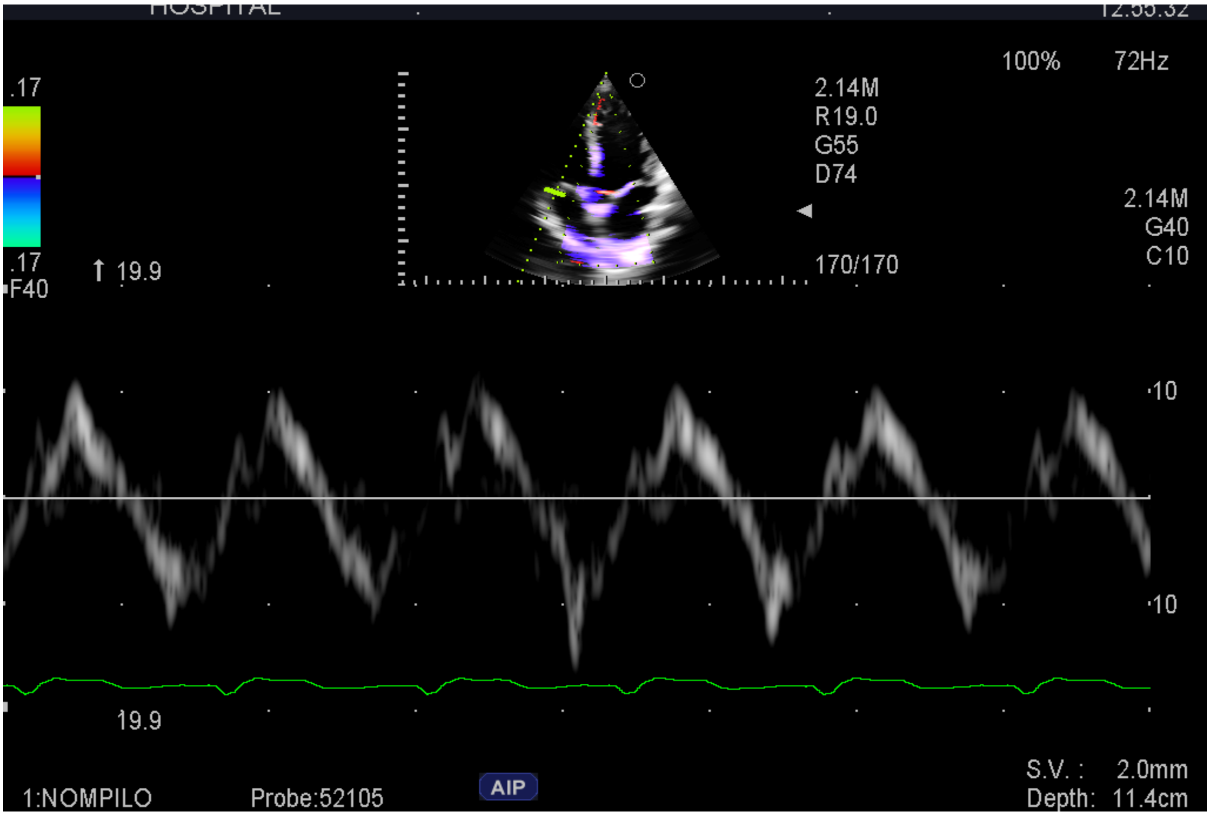


Figure 3.8: Pulsed Doppler of the tricuspid inflow, tissue Doppler of the lateral tricuspid annulus.

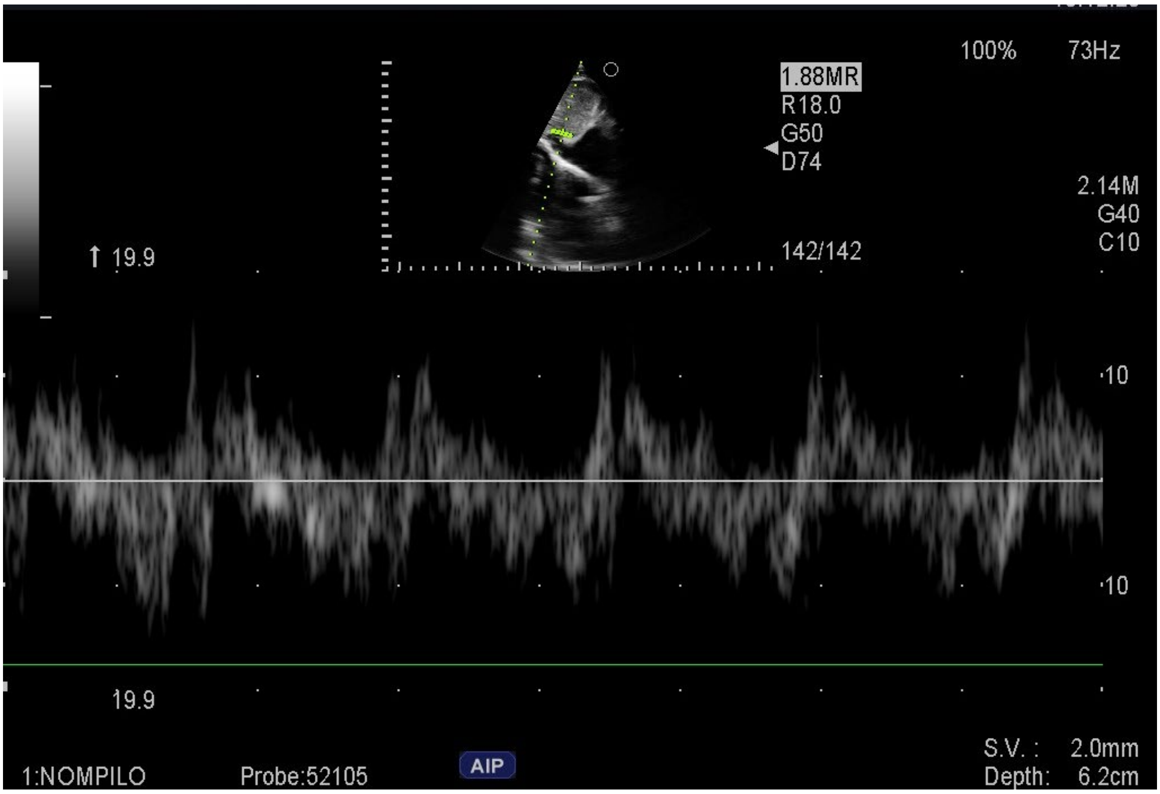


Figure 3.9: Pulsed Doppler of the hepatic vein.

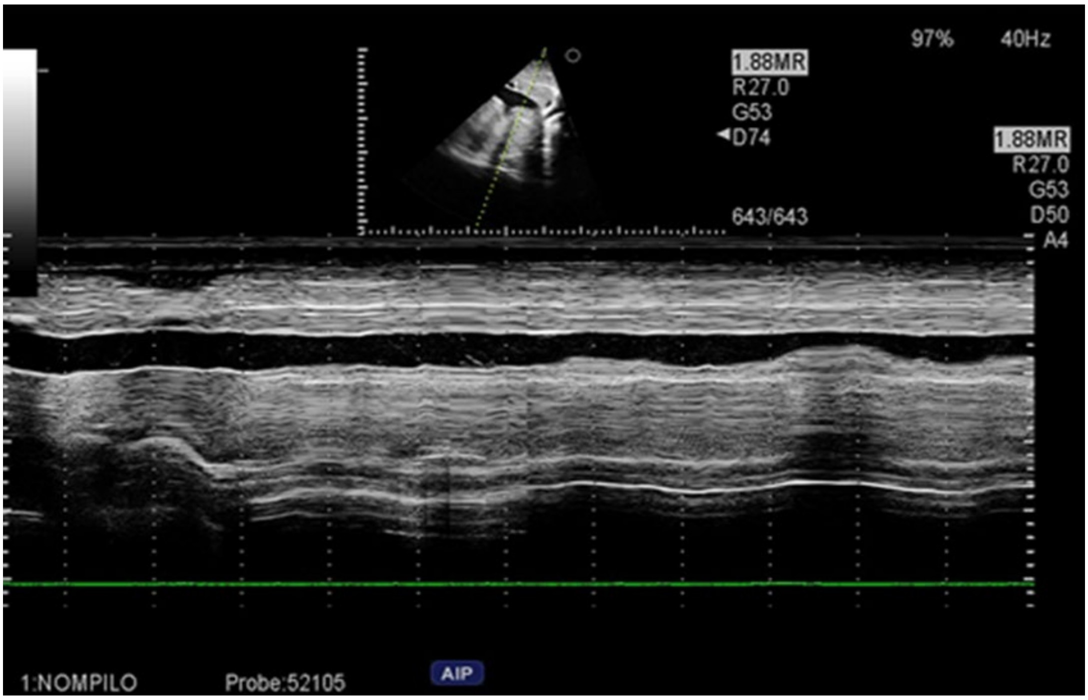


Figure 3.10: Measurements of IVC size and collapsibility. Adapted from Patil et al. (2016)[242]

TR velocity reliably allowed for the estimation of RVSP with the addition of RA pressure, assuming no significant RVOT obstruction was present (Figure 3.11). Using the RA pressure estimated from IVC and its collapsibility is advised by the 2010 guidelines for the echocardiographic assessment of the adult right heart rather than arbitrary RA pressure assignment.[47]

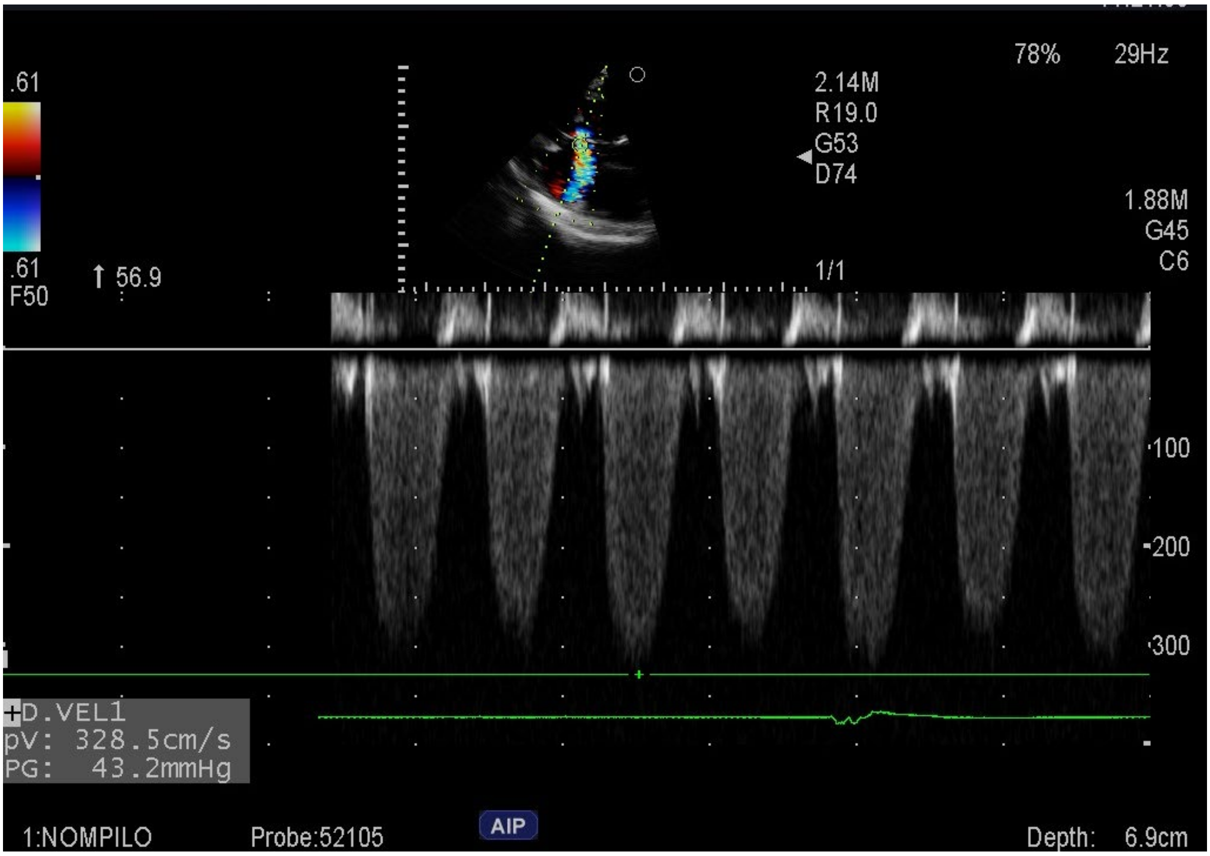


Figure 3.11: Pulmonary systolic pressure/RVSP. TR velocity.

3.10.6 2D speckle tracking imaging (STE)

RV-focused apical 4-chamber 2D speckle tracking imaging (STE) (Figure 3.12) yielded measures of RV myocardial deformation that were evaluated using the Q-Analysis program (Echo Pac). Two-dimensional speckle tracking echocardiography was used to assess the longitudinal strain of the RV global (RVGS) and free wall (RVFWS). Because there is no dedicated software for RVGLS and RVFWLS,[240] we adapted the software designed for the LV for the purpose of our study. After manually tracing the end-systolic RV endocardial boundary (Figure 3.12), an automatically produced region of interest (ROI) was created (Figure 3.13). The width and position of the ROI were then manually modified to encompass the whole myocardial wall and exclude the pericardium.[240] The RV outflow tract's pulse-wave Doppler tracing revealed the presence of a pulmonary valve closure.[240]

The interventricular septum and the RV free wall were automatically divided into three segments each by the program, resulting in a six segment model (basal, mid, and apical).[56]

The tracking quality was automatically confirmed by software, and visual confirmation was given by the 2D images. Even after making an effort to modify the ROI position and breadth, subjects who continuously showed poor tracking in more than two segments were excluded from the study. Once the endocardial boundary was outlined on an end-diastolic frame by clicking on the apical, lateral, and septal points of the tricuspid annulus, or by putting more than six points across the endocardial border, the program tracked the contour automatically on consecutive frames.

The region of interest was automatically estimated and could be adjusted to determine the thickness of the septum and RV-free wall.[240] Adequate tracking was verified in real-time and was corrected by adjusting the ROI or manually correcting the contour to ensure optimal tracking.

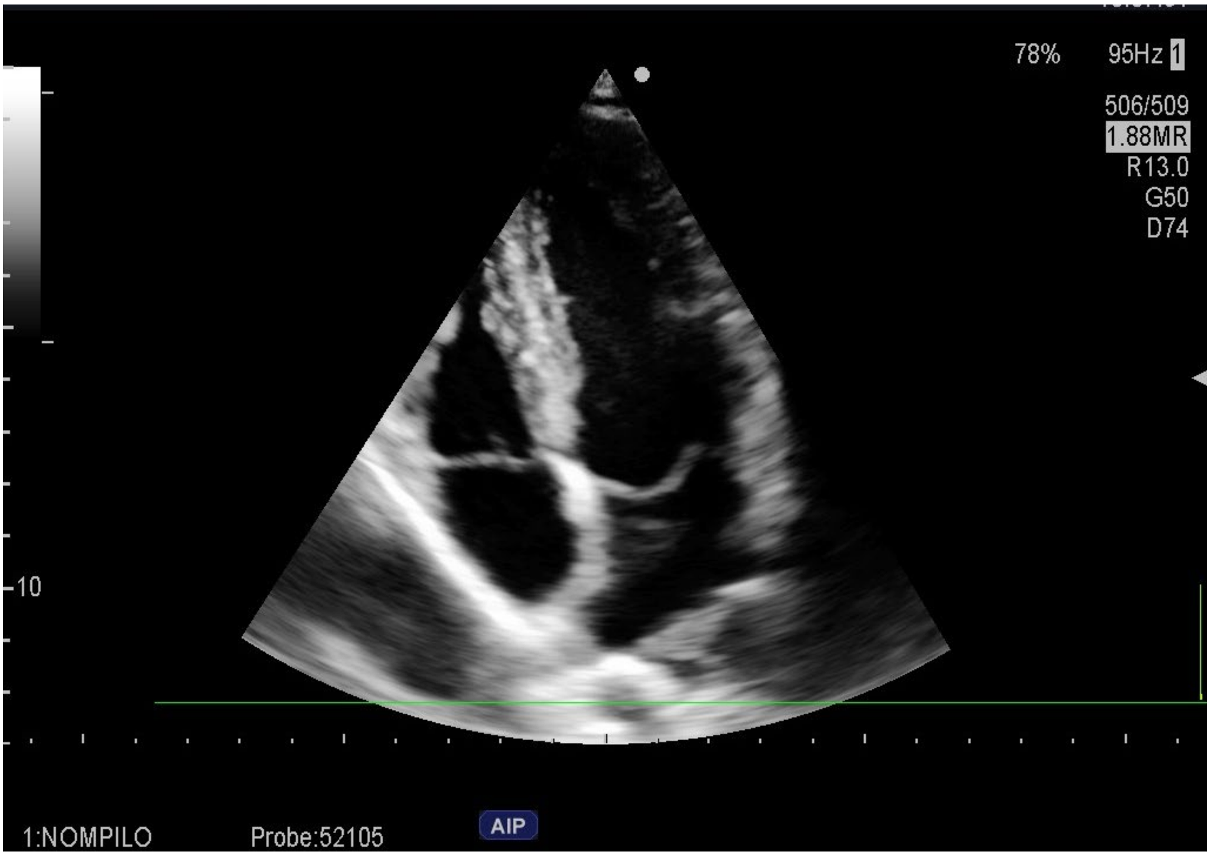


Figure 3.12: RV-focused apical 4-chamber.

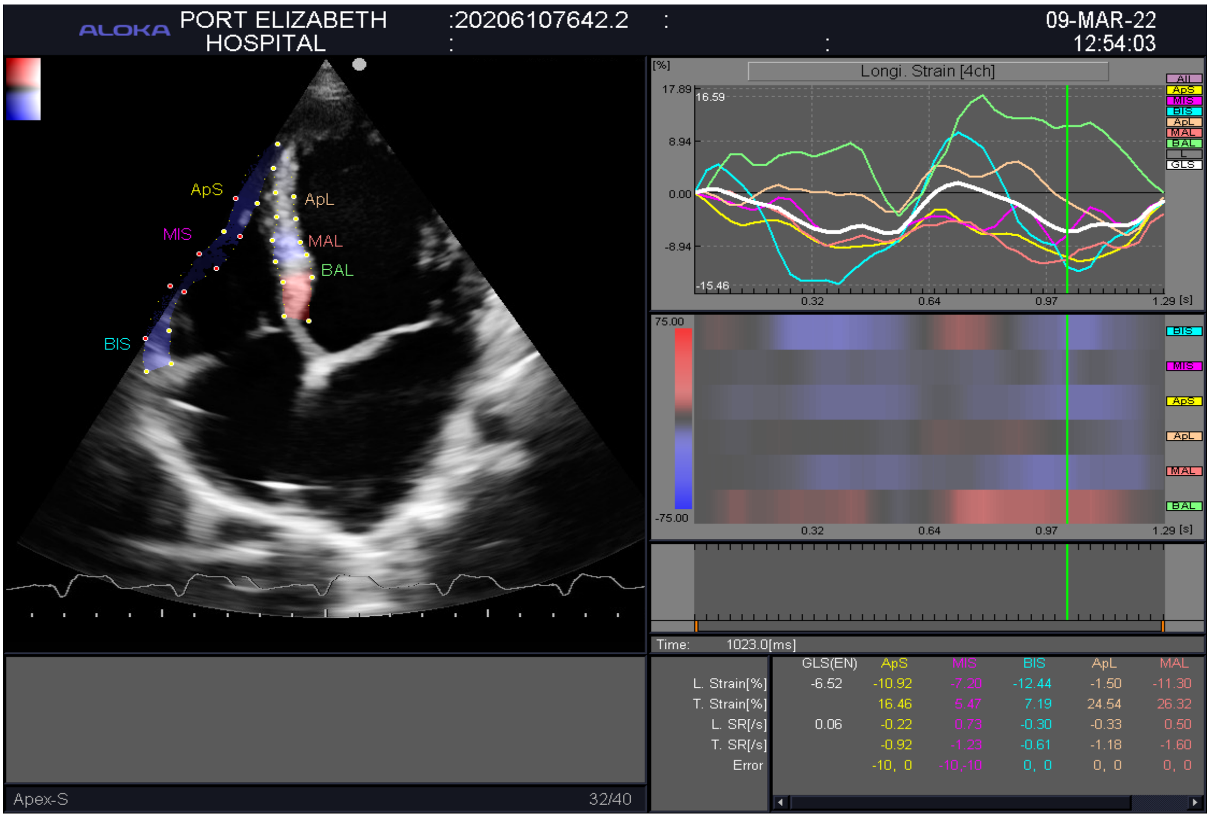


Figure 3.13: A region of interest (ROI) that is automatically generated.

First off, since there isn't specific software for RVGLS and RVFWLS, there are modifications in segment labeling that one must consider, because we modified the software meant for the LV for the RV. It makes sense to believe that the LV geometry and spatial orientation are different from RVs. The shape of the RV chamber is more complex due to the location of the inflow and outflow sections in different planes and the thin RV wall. This makes it difficult to track speckles from frame to frame and limits the width of the ROI to the myocardium excluding the pericardium, especially in low-quality images.[56] Tables 3.4 and 3.5 compare the LV geometry and spatial orientation with the RV geometry and spatial orientation.

Table 3.4: Modifications in segment labeling of RV wall.[56]

SEPTAL WALL TRACING	BECOMES ⇔	RV LATERAL WALLTRACING
BASAL INFEROSEPTUM (BIS)		BASAL LATERAL RV WALL
MID INFERO SEPTUM (MIS)		MID LATERAL RV WALL
APICAL SEPTUM (ApS)		APICAL LATERAL SEPTUM
LV ANTERIOR WALL TRACING	**BECOMES** ⇔	SEPTAL WALL TRACING
BASAL ANTERIOR WALL (BAL)		BASAL INFEROSEPTUM
MID ANTERIOR WALL (MAL)		MID INFERO SEPTUM
APICAL LATERAL (ApL)		APICAL SEPTUM

The reference ranges for the STE parameters are still not established,[215] therefore we adapted those used by Morris and colleagues[224] in their research study titled: Normal range and usefulness of right ventricular systolic strain to detect subtle right ventricular systolic abnormalities in patients with heart failure: a multicentre study. RV global strain -24.5 ± 3.8 and RV free wall strain -28.5 ± 4.8 (lowest anticipated value -17 and -19, respectively) were the usual range of RV systolic strain analysed in the healthy patients in that research.

Table 3.5: Normal ranges of RV strain.

NORMAL RANGE OF RV SYSTOLIC STRAIN	
RV global strain	-24.5 ± 3.8
RV free wall strain	-28.5 ± 4.8
Lowest expected value	-17-19

Source: Adapted from Morris et al. (2017).[224]

VALVE DOPPLER AND QUANTIFICATION

3.10.7 Mitral regurgitation

The main and most crucial diagnostic test for mitral regurgitation diagnosis and assessment is echocardiography.[9]

The apical four-chamber and parasternal long-axis views were used for color flow imaging. We did not examine short-axis views because it was very difficult to detect the vena contracta (VC) from the parasternal short-axis plane and because it was difficult to have the ultrasound beam perpendicular to the mitral regurgitation flow. The transducer was modified as necessary to obtain the maximum MR jet size.

The width of the regurgitant jet as it exits the regurgitant orifice is known as the vena contracta, or VC width (Figure 3.14 A and B). This represents the area of the regurgitant orifice, and it was anticipated that the effective regurgitant orifice (ERO) diameter and the vena contracta width would match. More than 7 mm of vena contracta was indicative of severe MR.[243]

A B

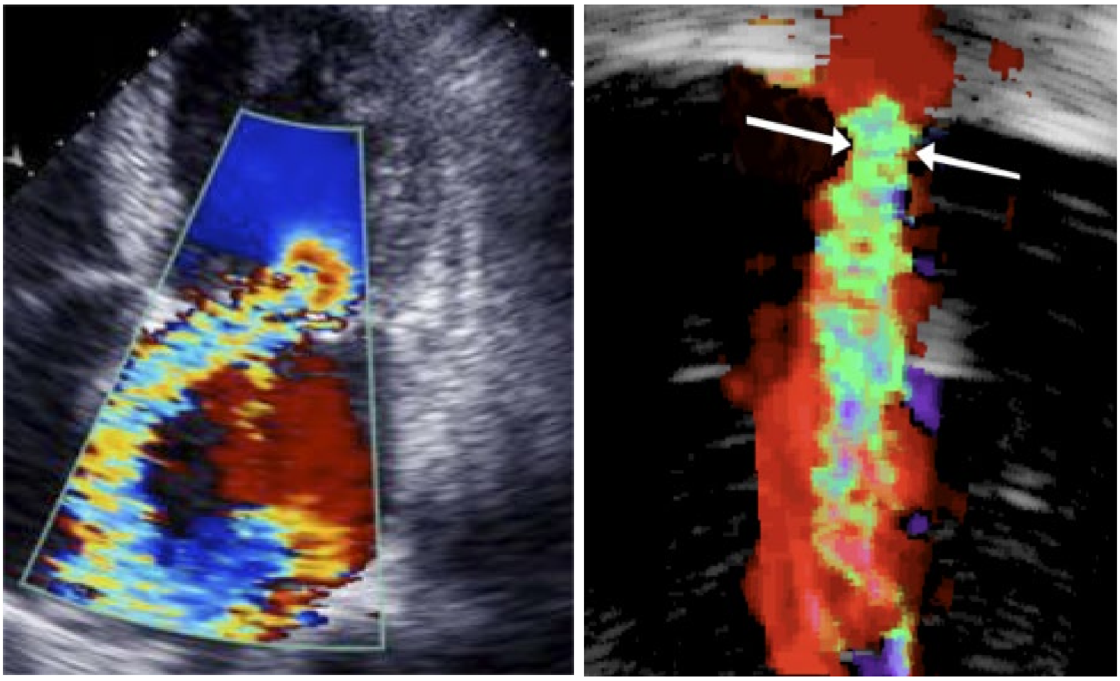


Figure 3.14: A and B. The width of the regurgitant jet as it escapes the regurgitant orifice. Adapted from Lancellotti et al. (2013).[243]

The volume of regurgitation was calculated using the proximal isovelocity surface area (PISA) approach (Figure 3.15), which was made possible by the proximal flow convergence zone. The basic idea behind this technique is the correspondence between the flow convergence zone and regurgitant flow. The blood flow accelerates as it gets closer to the regurgitant orifice. Consequently, "hemispheric shells" that characterize the proximal flow convergence zone are those in which the surface velocity of each shell is the same.[244] Once the radius of the shell and the velocity at its surface were measured, the amount of blood flow (regurgitant flow) was computed as follows[244] :

Q is 2 x r2 x π x Nyquist vel for the regurgitant flow.

Applying the PISA approach, we used the shell where aliasing occurs, i.e., where the color quickly shifted from an identifiable red or blue to a turbulent (multicolored) flow. The velocity (aliasing velocity) was measured exactly at that spot. We also measured the radius (r) of the hemisphere at this point. Severity was indicated when the regurgitant volume (RVol) was greater than 60 milliliters. RVol is the volume of blood that, during a beat or cardiac cycle, passes through the valve plane in the opposite direction or backwards (Table 3.6).

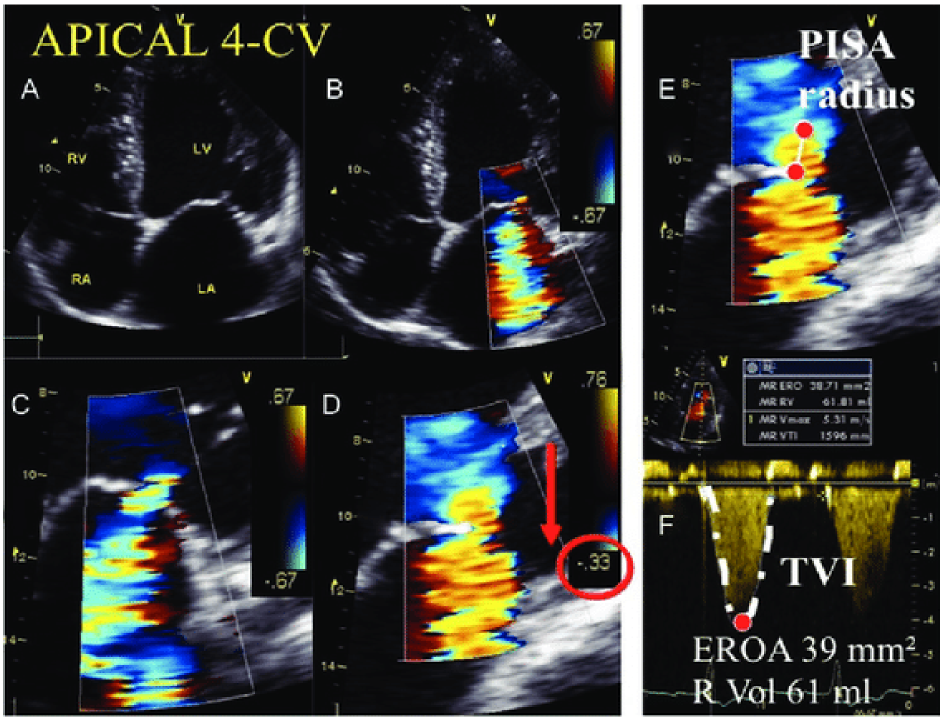


Figure 3.15: Employing the PISA approach to quantitatively quantify the severity of MR. Step-by-step MR analysis: A hemispheric PISA is obtained by shifting the zero baseline lower; (B) colorflow is displayed; (C) the select zone is zoomed in; (D) the apical four-chamber view (CV) is measured using the first aliasing; (F) MR jet continuous wave Doppler that enables the determination of the regurgitant volume (R Vol) and effective regurgitant orifice area (EROA). Time-velocity integral, or TVI. Source: Adapted from Lancellotti et al. (2013).[243]

Table 3.6: Recommendations for classification of MR severity.[245]

Recommendations for classification of mitral regurgitation severity				
Variables	Mild	Moderate	Severe	
VC width	<0,3	0,3-0,6	>7	
Rvol(mls)	<30	30-59	>60	
LA Size	Normal 2-4cm	Normal to <5,5cm	>5,5cm	

As qualitative measures for rating the severity of MR, measurements were made of the left atrial (LA) size, mitral valve structure, color flow regurgitant jet, continuous wave signal of regurgitant jet, and flow convergence zone. Table 3.7 provides a summary of all the measurements that were made.

Table 3.7: Echocardiographic criteria for definition of severe mitral regurgitation

Echocardiographic criteria for the definition of severe mitral regurgitation	
Qualitative	
Mitral valve morphology	Flail leaflet/ ruptured papillary muscle
Colour flow regurgitant jet	Very large central or eccentric jet adhering, swirling and reaching the posterior wall of the left atrium
Continuous wave signal of regurgitant jet	Dense/triangular
Flow convergence zone	Large
Semi-quantitative	
Vena contracta width (mm)	≥7(>8 for biplane)
TVI mitral/TVI aortic	Systolic flow reversal. E wave dominant> 1.5ms
Quantitative	
EROA (mm^2)	>40(Primary) or > 20 (secondary)
Regurgitant volume (mL/beat)	>60(Primary) or > 30 (secondary)

Echo criteria for the definition of severe mitral regurgitation. Source: Adapted from De Bonis et al. (2016).[246]

3.10.8 Aortic regurgitation

The parasternal long-axis view was used to quantify the following anatomical structures: the ascending aorta, prolapse, leaflet thickening, aortic sinuses, aortic annulus, and sino tubular junction (Figure 3.16). Doppler assessed the regurgitant orifice's size using the parasternal long axis window. Right below the aortic valve, to within one centimeter, the diastole of the color jet diameter (or breadth) was measured. The relationship between jet diameter and left ventricular outflow tract diameter was ascertained. A semi-quantitative measure of the degree of regurgitation was provided by this ratio (Table 3.8), with 45% to 64% indicating moderate to severe AR and more than 65% implying severe AR.

The vena contracta was identified by measuring the diameter of the regurgitant jet as it leaves the regurgitant orifice (Figure 3.17). In long axis view, this occurs during LV diastole. Severe AR is indicated by a jet width of six millimeters or more. The colour wave (CW) doppler in five chamber view, which is used to quantify the regurgitant flow velocities of the AR jet, reflects the diastolic pressure gradient between the aorta and the LV. A pressure half-time (PHT) of less than 200 ms indicates severe AR (Figure 3.18). CW Doppler used the effective regurgitant orifice area (EROA) to calculate the regurgitant stroke volume and the regurgitant jet velocity time integral. An EROA of 30 indicates severe AR.[247]

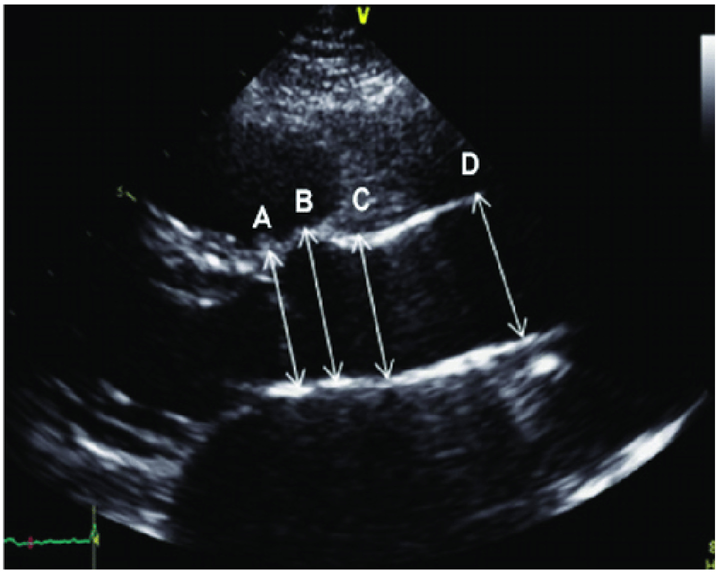


Figure 3.16: The parasternal long-axis view: A aortic annulus tract, B aortic sinuses, C sinotubular junction and D ascending aorta. Source: Adapted from Upadhyaya et al. 2021.[248]

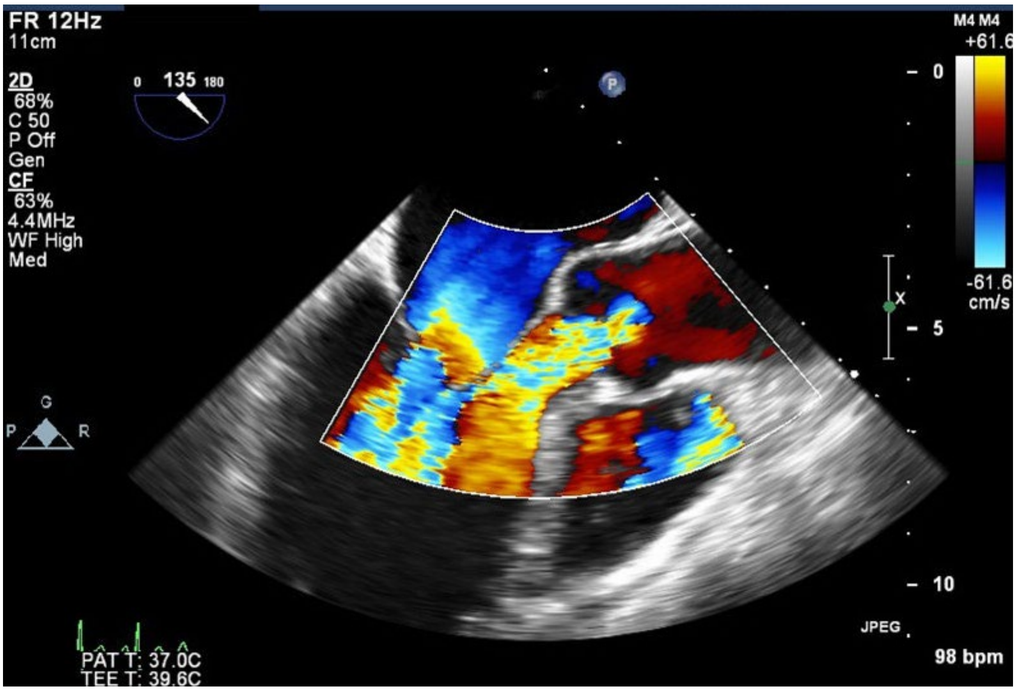


Figure 3.17: Measurement of Vena Contracta in parasternal long axis view. Source: Adapted from Smer et al. 2020.[247]

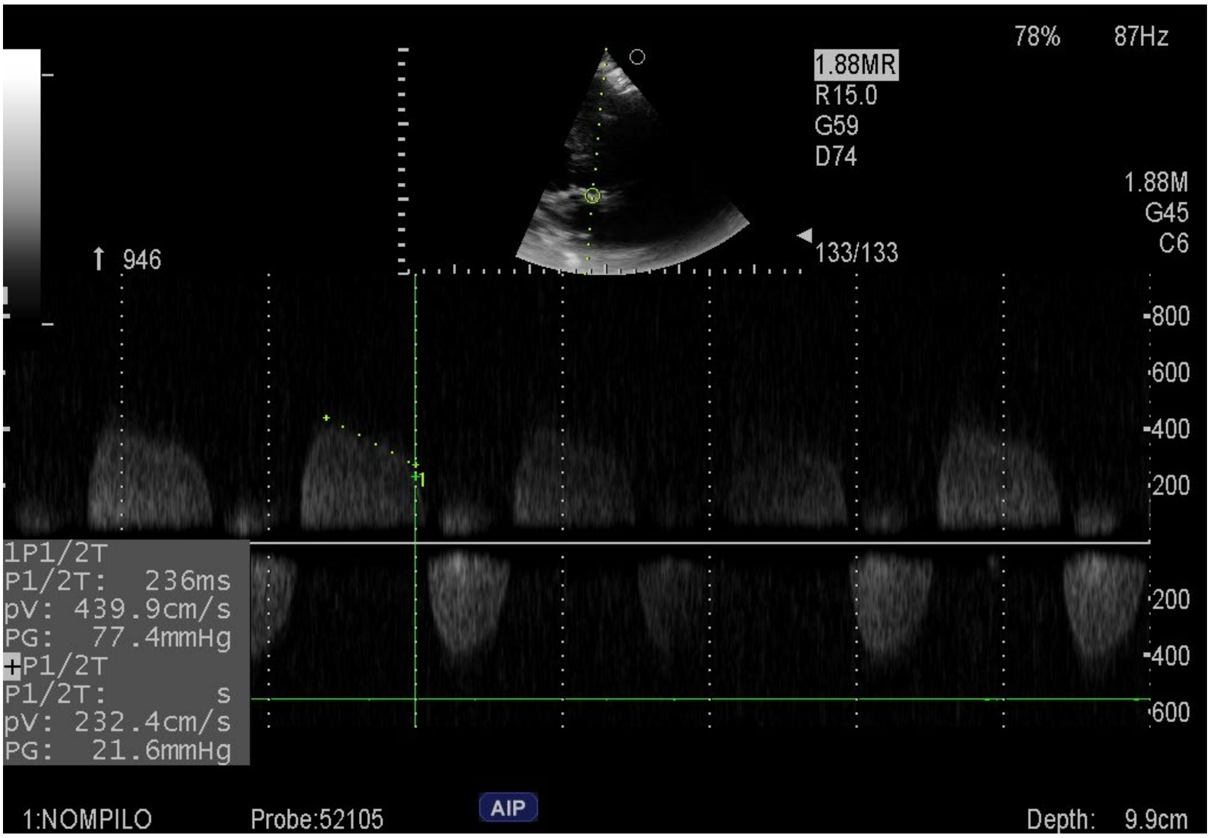


Figure 3.18: Measurement of PHT is apical five chamber view.

Table 3.8 summarises the semi-quantitative methods used for the assessment of aortic regurgitation severity by Doppler echocardiography.

Table 3.8: Assessment of aortic regurgitation severity by Doppler echocardiography: a summary or semi-quantitative methods.

Classification of aortic regurgitation severity				
Variable	Mild	Mild-Moderate	Moderate-severe	Severe
Jet/LVOT width	<25%	25–44%	45–64%	≥65%
Vena contracta width (mm)	<3	3–5.9	3–5.9	≥6
Regurgitant volume (mL/beat)	<30	30–44	45–59	≥60
Regurgitant fraction	<30%	30–39%	40–49%	≥50%
Effective regurgitant orifice area (mm2)	<10	10–19	20–29	≥30
Pressure half time (P 1/2 t) (ms)	>500	350–500	200–350	<200

Source: Adapted from Nishimura et al. (2017)[16]

3.10.9 Aortic stenosis

The left ventricular outflow tract (LVOT) diameter was measured in a 2D parasternal long-axis view by moving a diameter calliper from the inner edge to the inner edge of the LVOT.

Cardiac output and cardiac systolic function are measured by LVOT velocity.[249] Using the feedback from the spectral velocity display and the audio signal, precise adjustments were made to the transducer's location and direction to measure the maximum velocity jet at each site. Using pulse wave (PW) directly below the AO valve in the apical five-chamber view (Figure 3.19), the LVOT velocity was measured at the maximum velocity from the peak of the dense velocity curve. Using the continuous wave Doppler at the aortic valve level, the velocity curve was traced to determine the mean pressure gradient at the same viewpoint. Severe AS was indicated by an aortic jet velocity greater than 40 m/s and mean gradients greater than 40 mmHg (Figure 3.20).

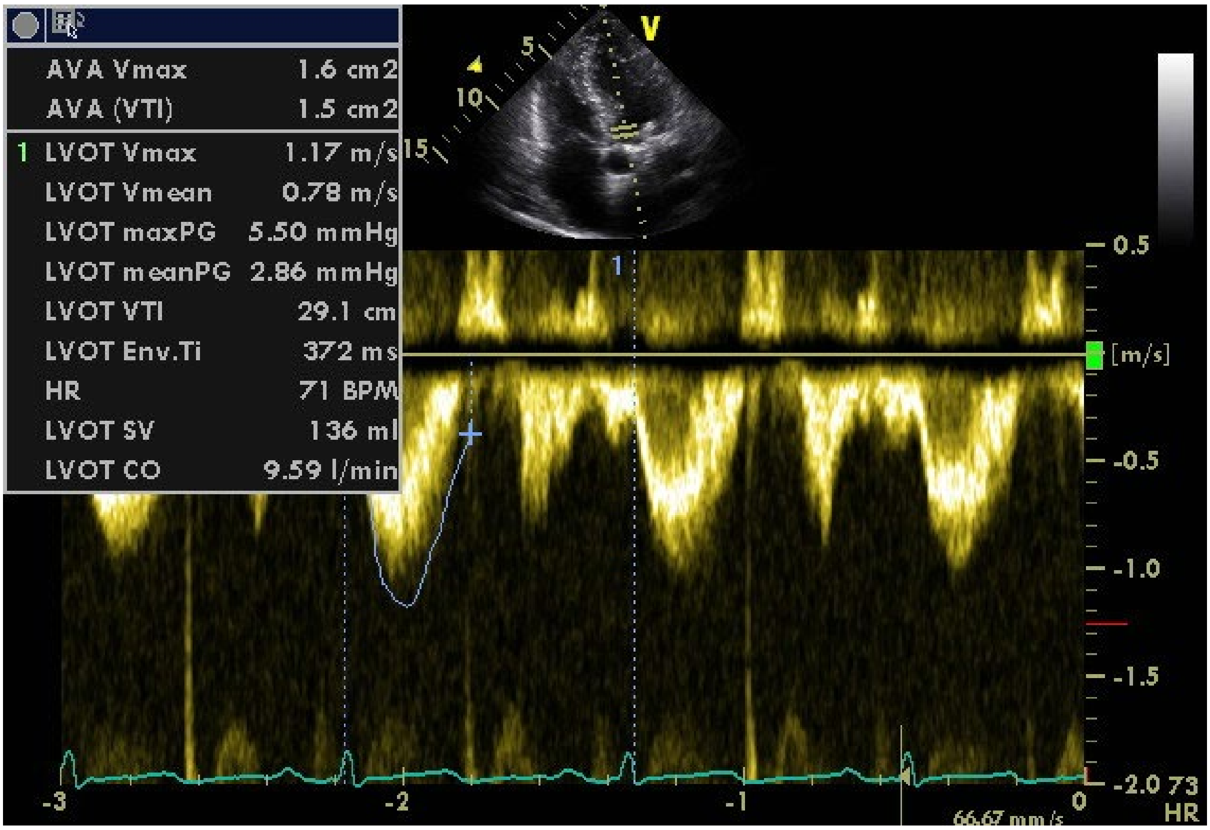


Figure 3.19: Measurement of LVOT velocity in apical five chamber view. Adapted from Hagendorff et al. (2020).[249]

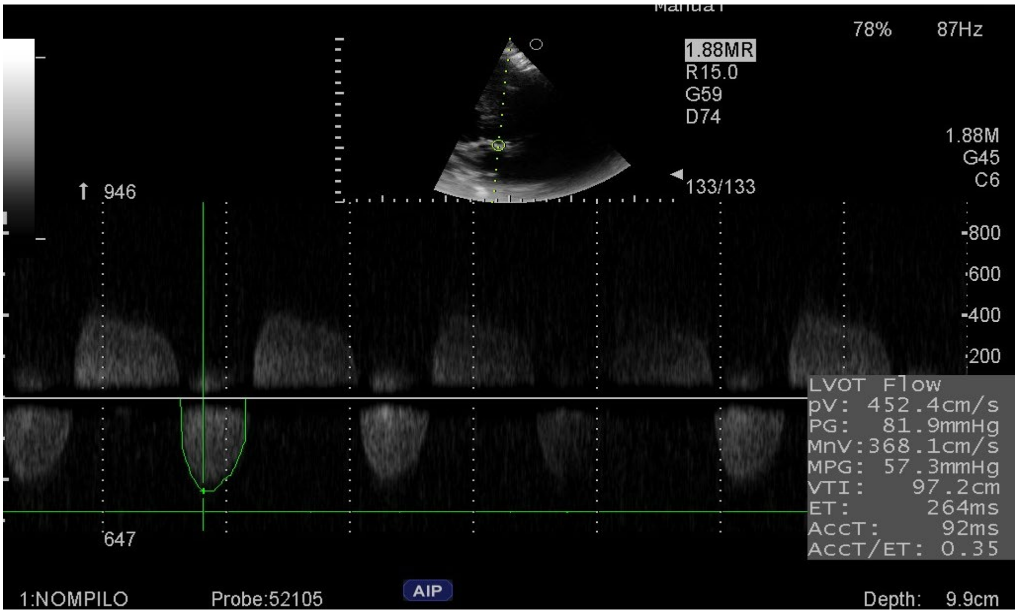


Figure 3.20: Measurement of AV mean gradients in apical five-chamber view by manual tracing of velocity waveform. Adapted from Hagendorff et al. (2020).[249]

Utilizing planimetry, a manual tracing of the aortic valve opening (Figure 3.21) in a still image taken during ventricular systole, when the valve is supposed to be open-the area of the aortic valve was measured in the parasternal short axis view at the aortic level. If the area of the aortic valve was less than 1 cm^2, AS was severe (Table 3.9).

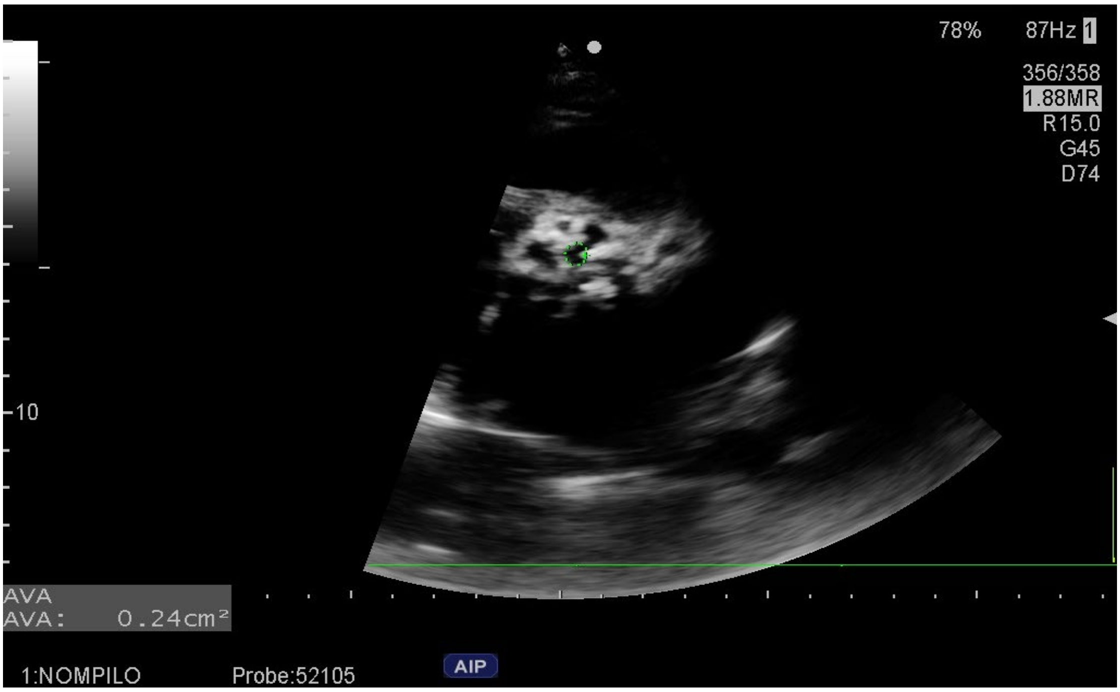


Figure 3.21: AV area tracing of aortic valve orifice.

Table 3.9: Classification of aortic stenosis severity.

Classification of aortic stenosis severity				
Variables	Aortic Sclerosis	Mild	Moderate	Severe
Aortic jet velocity (m/s)	≤2,5m/s	2,6-2,9	4-Mar	
Mean gradient (mmhg)		<20	30-40	>40
AVA (CM2)		>1,5	1-1,5	<1

Source: Adapted from Nishimura et al. (2017)[16]

3.10.10 Mitral stenosis

To determine the MV area, the planimetry of the mitral valve was obtained at the level of the leaflets tips in the parasternal short axis view (Figure 3.22). A less than 1 cm^2 MV area was indicative of severe MS (Table 3.10). The mitral valve's mean pressure gradient was measured in the apical four-chamber view. The dense shape of the mitral diastolic inflow was traced to estimate the gradient, and the mean pressure gradient was automatically calculated (Figure 3.23). Mean pressure gradients greater than 10 mmHg were indicative of severe MS.[250]

Mitral valve area (MVA) might also be computed by pressure half-time using CW Doppler in the apical four chamber view.[251] The right ventricular systolic pressure (RVSP) and the pulmonary artery systolic pressure (PAS) were estimated using the tricuspid regurgitation velocity at the parasternal short axis (PSAX) and apical 4-chamber (A4C) perspectives. The regurgitant volume's center was where the CW Doppler was placed, and the maximum velocity throughout the whole TR envelope was observed.

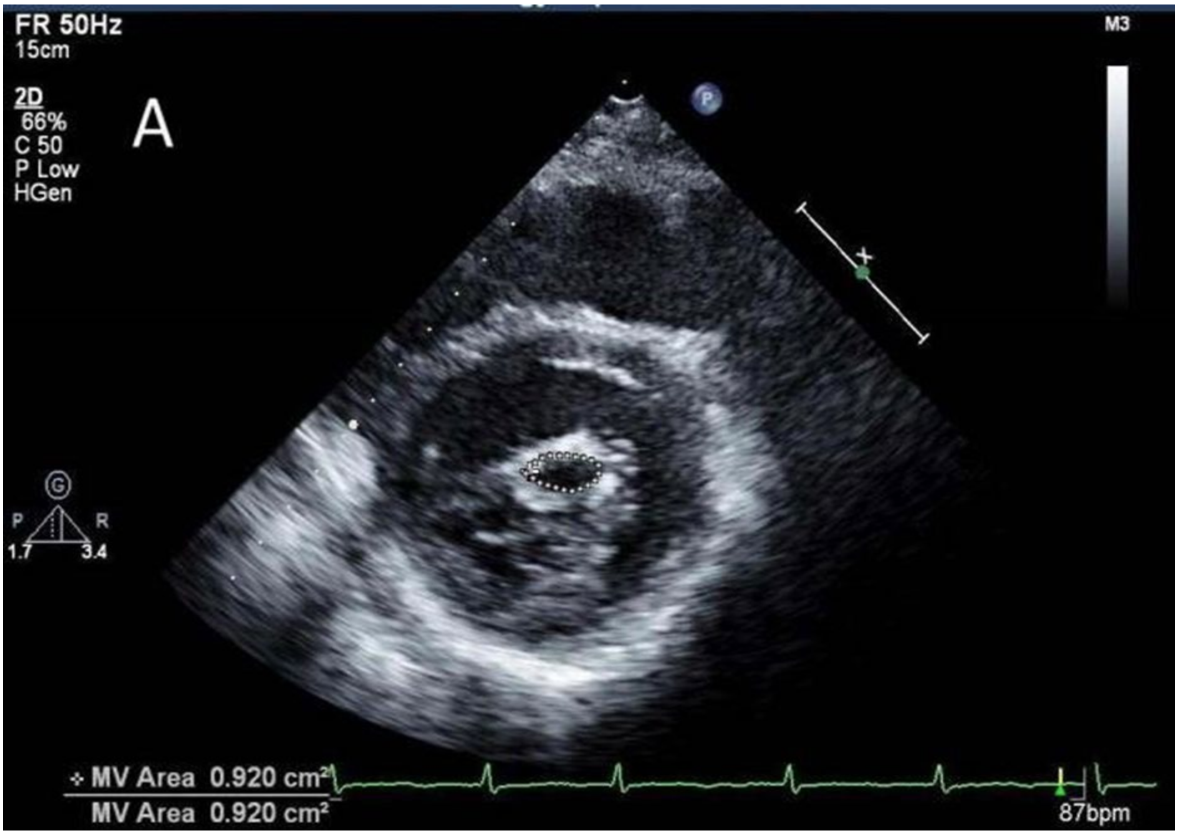


Figure 3.22: Planimetry measurement of the mitral valve. Source: Adapted from Libanoff et al. (1968)[252]

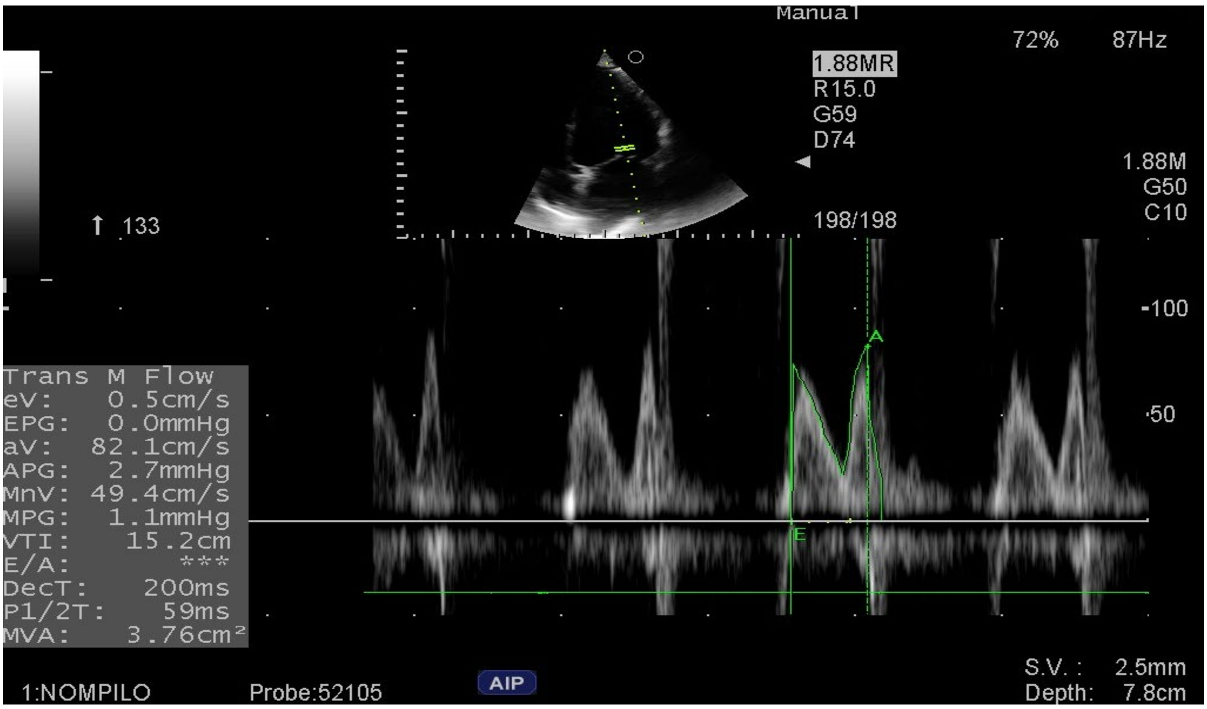


Figure 3.23: Measurement of mean pressure gradient across the mitral valve. Source: Adapted from Libanoff et al. (1968).[252]

Table 3.10: Recommendations for classification of MV stenosis.

Recommendations for classification of mitral stenosis severity			
Variables	Mild	Moderate	Severe
MVA (cm2)	>1,5	1-1,5	<1
Mean grad	<5	5–10	>10
Pulmonary artery pressures	<30	30-50	>50

Source: Adapted from Nishimura et al. (2017)[16]

3.10.11 Tricuspid regurgitation

Using visual color Doppler on 2D echocardiography in all three views-parasternal long, short axis, and apical four-chamber view—tricuspid regurgitation was visually estimated. The best views to measure VC width were the apical four-chamber view and the parasternal short axis view (Figure 3.24). As shown in Table 3.11, VC widths of 7 to 13 mm indicate severe TR, while VC widths larger than 21 mm indicate torrential TR.

Using a color flow doppler of the TR Jet and a good PISA formation in a zoomed-in view, EROA by PISA was obtained (Figure 3.24). Next, the PISA radius's diameter was determined. After following the diastolic flow profile, a VTI of the regurgitant jet was produced. A 180° angle was found to be the PISA formation angle. According to Table 3.11, an EROA by PISA of 50 to 59 mm^2 indicated severe TR, while an EROA of more than 70 mm^2 indicated torrential TR.

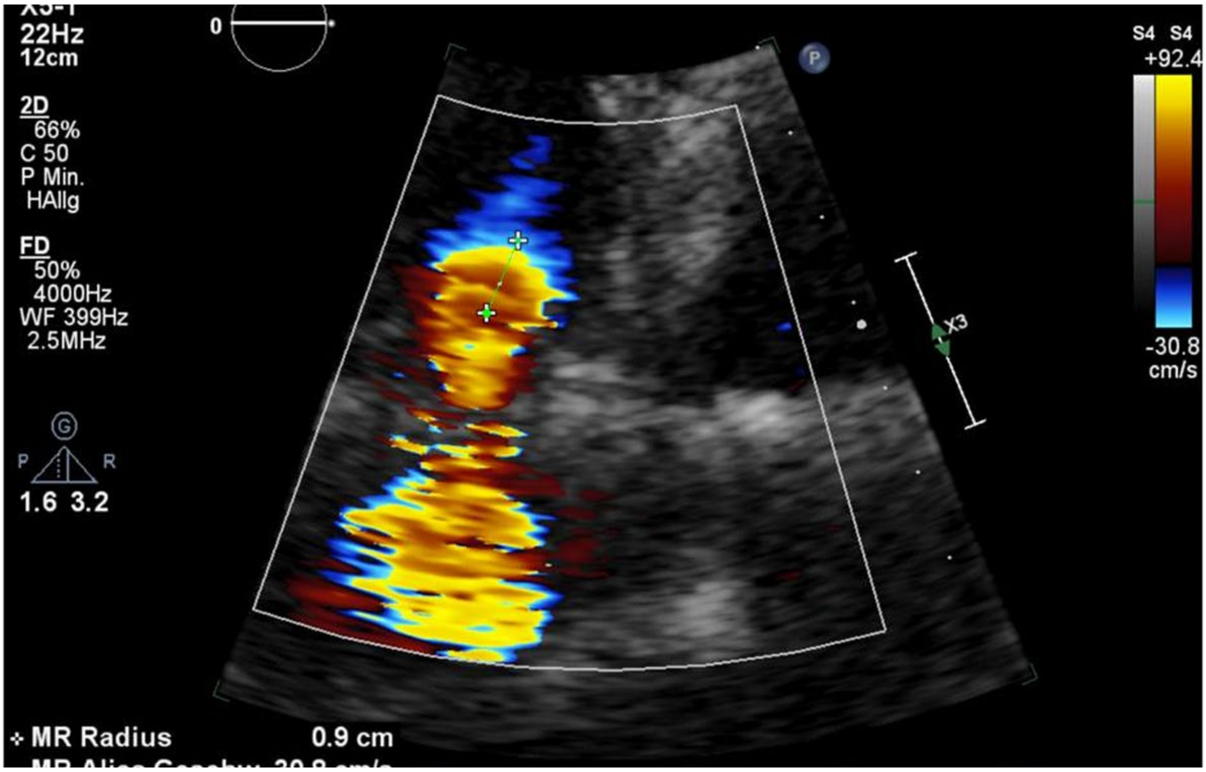


Figure 3.24: Measurement of VC width in apical 4 chamber zoomed view.Source: Adapted from Manjunath et al. (2020)[253]

Table 3.11: Recommendations for classification of TR severity.

Recommendations for classification of tricuspid regurgitation severity					
Variables	Mild	Moderate	Severe	Massive	Torential
VC width mm	<3	3-6,9	7–13	14-20	>21
EROA by PISA mm2	<20	20-39	40-59	60-79	>80

Source: Adapted from Nishimura et al. (2017)[16]

CHAPTER 4: RESULTS

The right ventricle dilates as a result of heart remodelling brought on by elevated pulmonary wedge pressure from mitral and/or aortic valve disease[145], which lowers the right ventricular (RV) ejection fraction.[1] Pulmonary hypertension (PHTN) develops when the left ventricle becomes volume-loaded, as in severe MV and/or AO disease. This condition eventually causes RV dilatation, tricuspid regurgitation, and RV failure.[2] Due to the belief that TR would go away once the primary left-sided defect was treated, surgical correction of the tricuspid valve (TV) was, until recently, avoided in patients with secondary tricuspid regurgitation (STR) at the time of left valvular surgical correction. There is evidence of RV dysfunction in a considerable percentage of postoperative patients, despite the link between PHTN and the decline in RV function and the possible reversibility of PHTN following left valve intervention.[4]

Baseline characteristics

The clinical and echocardiographic characteristics of the study population are summarised in Table 4.1. In this clinical, prospective study a total of 30 patients with severe mitral and or aortic valve disease were enrolled, 12 males (40%) and 18 females (60%) between the ages of 18 and 65 years. The mean age was 45.83 years. Two patients demised before the completion of the data collection, thus, the final study group consisted of 28 patients.

Of the 30 patients, a total of 23 patients (76.6%) were in normal sinus rhythm, 3 patients (10%) were in sinus tachycardia with a heart rate (HR) exceeding 100 bpm, 2 patients (6.6%) were in sinus bradycardia with a HR of less than 100 bpm, 1 patient (3.3%) was in a paced ventricular rhythm and 1 patient (3.3%) was in atrial fibrillation. The baseline measurements are summarized in Table 4.1.

Table 4.1: Baseline characteristics

BASELINE CHARACTERISTICS			
Parameters	**Preoperative (mean ± SD)**	**Postoperative (mean ± SD)**	**At 6 months Follow-up (mean ± SD)**
Age (years)	45.83 ± 15.04		
Mass (kg)	75.88 ± 21.41	76.28 ± 21.12	75.76 ± 19.31
Systolic (mmHg)	117.57 ± 15.43	123.52 ± 17.44	119.39 ± 13.56
Diastolic (mmHg)	65.03 ± 10.93	67.45 ± 10.58	67.82 ± 9.85

HR (bpm)	83.90 ± 17.91	85.79 ± 11.20	82.25 ± 11.48
HB (g/dl)	11.18 ± 1.98	10.72 ± 1.76	11.35 ± 1.67
Creatinine (umol/L)	91.73 ± 34.70	88.41 ± 28.93	87.89 ± 28.12
Heart Rhythm & Ejection Fraction			
	Pre-Op n (%) n=30	**Post-Op n (%) n=29**	**6-months n (%) n=28**
Normal sinus	23(76.7)	24(82.8)	25(89.3)
Sinus tachycardia	3(10)	2(6.9)	1(3.6)
Sinus bradycardia	2(6.7)	0(0)	0(0)
Heart-block/paced vent rh	1(3.3)	2(6.9)	1(3.6)
AF	1(3.3)	1(3.4)	1(3.6)
EF > 50%	25(83,3)	24(80)	23(82)
EF< 50%	5(16.6)	5(17.2)	5(28.5)
Aetiology of valve diseases preoperative n (%)			
Degenerative aetiology	13(43.3)		
Vegetations	7(23.3)		
Calcified	6(20)		
Rheumatic	2(6.7)		
MV aneurysm	1 (3.3)		
Congenital	1(3.3)		
Valve disease preoperative n (%)			
AR	7(23.3)		
AS	4(13.3)		
MR	7(23.3)		
MS	2(6.6)		
Mixed MV disease	4(13.3)		
Mixed AV disease	0(0)		
AR/MR	3(10)		
Bicuspid	1(3.3)		
I.E	2(6.6)		
Valve replacements/repairs postoperatively n (%)			
Mechanical mitral valve	12(41.3)		
Mechanical aortic valve replacement	6(20.6)		
Double (mitral and aortic) mechanical valve	5(17.2)		
Bioprosthetic AVR	2(6.8)		
Bioprosthetic MVR	2(6.8)		
Mechanical AVR+MVR+ Bioprosthetic TVR	1(3.4)		
Mechanical MVR+ Bio prosthetic TVR	1(3.4)		

HR: heart rate; HB: heamoglobin; AF:atrial fibrillation; MR: mitral regurgitation; AR: aortic regurgitation; MS: mitral stenosis; AS: aortic stenosi; IE: infective endocarditis; AVR: aortic valve replacement; MVR: mitral valve replacement; TVR: tricuspid valve replacement.

Degenerative valve disease (43.3%) was the most common assessment in the age group of 41 to 65 years (Table 4.1 and Figure 4.1), followed by vegetation (23.3%). The most common valve disease was found to be MR and AR, both at 23.3% (Table 4.1).

The highest number of surgical cases was mechanical mitral valve replacement (41.3%) followed by mechanical aortic valve replacement (20.6%) double (mitral and aortic) mechanical valve replacement (17.2%), bioprosthetic AVR and MVR (6.8% and 6.8%), mechanical AVR + MVR + bioprosthetic TVR (3.4%), and mechanical MVR + bioprosthetic TVR (3.4%) (Table 4.1).

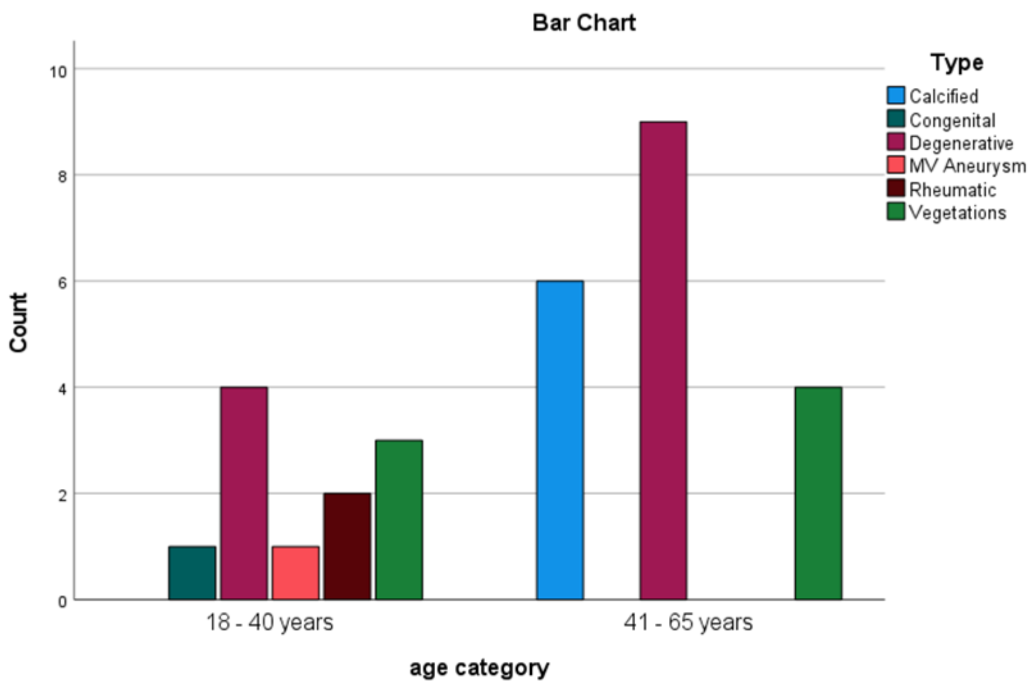


Figure 4.1: Aetiology of valve disease vs age.

4.1 Objective 1: To determine echocardiographic parameters of tricuspid regurgitation, pulmonary arterial pressure and RV function at specific intervals pre and post left-sided valve surgery

4.1.1 Left ventricular M-mode echocardiographic parameters

The mean and standard deviation values of M-mode echocardiographic parameters of LV/LA/AO dimension aswell as LV systolic function summarized in Table 4.2.

Table 4.2: Left ventricular M-mode echocardiographic parameters.

Left ventricular M-mode echocardiographic parameters			
Parameters	**Preoperative**	**Postoperative**	**At 6 months follow-up**
	(mean ± SD)	**(mean ± SD)**	**(mean ± SD)**
LVEDD (cm)	5.46 ± 0.87	5.25 ±0.70	5.11 ±0.85
LVESD (cm)	3.54 ± 0.84	3.51 ±0.88	3.31 ± 1.03
IVSS (cm)	1.26 ±0.35	1.76 ± 2.03	1.65 ± 1.93
IVSD (cm)	1.31 ± 1.66	.97 ± 0.23	1.39 ± 2.29
LVPWS (cm)	2.03 ± 2.61	1.28 ± 0.35	1.63 ± 2.06
LVPWD (cm)	1.21 ± 1.31	1.24 ± 1.17	1.26 ± 1.93
EF %	65.33 ± 11.90	61.03 ± 12.87	61.50 ± 15.54
FS %	34.34 ± 8.01	30.52 ± 7.79	32.26 ± 9.78
LA (mm)	41.98 ± 11.97	41.78 ± 7.89	39.47 ± 10.97
AO (mm)	26.91 ± 4.44	25.79 ± 3.501	24.52 ± 3.37

LVEDD: left ventricular end-diastolic dimension; LVESD: left ventricular end-systolic dimension; IVSS: interventricular septum in systole; IVSD: interventricular septum in diastole; LVPWD: left ventricle posterior wall in diastole; LVPWS: left ventricle posterior wall in systole; EF: ejection fraction; FS: fractional shortening; LA: left atrium; AO: Aorta.

Changes in LV mean parameters are displayed in Table 4.2. Left ventricular end-diastolic (LVEDD) dimensions and left ventricular posterior wall in systole (LVPWS) dimension decreased after 6 months of surgery. The interventricular septum during systole (IVSS) increased, while the diastolic interventricular septum (IVSD) dimension remained relatively unchanged.

A small decrease in mean ejection fraction (EF) values was noticed 72 hours post-surgery with a slight gradual increase at 6 months follow-up post-surgery. A steady decrease was also observed in the LA mean diameter over a period of 6 months (Table 4.2).

4.1.2 Right ventricular M-Mode and two-dimensional strain

The p-values for the summary measurements in Table 4.3 were calculated between pre-operative and 6 months post-operative

Table 4.3: Right ventricular M-Mode and two-dimensional strain.

Right ventricular M-mode and 2-dimensional strain				
Parameters	Pre-operative	Post-operative	At 6 months follow-up	p-value
	(mean ± SD)	(mean ± SD)	(mean ± SD)	
TAPSE (mm)	23.20 ± 6.48	18.55 ± 7.24	19.18 ± 5.77	< 0.001
FAC %	60.63 ± 17.76	45.86 ± 21.32	41.33 ± 19.62	0.18
GLS	-5.02 ± 7.40	-5.96 ± 6.28	-6.07 ± 9.37	0.33
BIS	-9.67 ± 19.63	-11.16 ± 18.63	-4.86 ± 23.13	0.03
MIS	-6.73 ± 13.42	-7.41 ± 8.25	-10.04 ± 9.07	0.15
APS	-3.94 ± 8.54	-5.86 ± 10.73	-7.78 ± 8.19	0.03
APL	-4.78 ± 10.68	-4.03 ± 10.51	-5.45 ± 9.85	0.42
MAL	-4.31 ± 12.02	-2.61 ± 9.58	-.95 ± 7.92	0.11
BAL	.53 ± 11.96	.33 ± 12.44	-1.85 ± 14.96	0.21

TAPSE: Tricuspid annular plane systolic excursion; FAC: Fractional area change; GLS: Global longitudinal strain; BIS: Basal inferoseptal; MIS: Mid inferoseptum; ApS: Apical septum; APL: Apical lateral; MAL: Mid anterior wall; BAL: Basal anterior wall

The mean difference in TAPSE pre-op and TAPSE at 6 months follow-up was 3.99 with p-value<0.001. which was significantly higher. The mean difference between BIS pre-op and BIS 6 months post-op was 4.81. The p-value is 0.03, which indicates a significant difference in means. The data shows that BIS pre-op was higher than the mean BIS 6 months post-op. The mean difference of FAC pre-op and 6 months post-op was 19.3, which although high, was not significant (p-value=0.18). The mean for APS pre-op was significantly higher than the mean APS 6 months post-op (p-value 0.03).

There was no evidence that GLS and the other parameters (MIS, APL, MAL, BAL and FAC) differed significantly (Table 4.3).

4.2 Objective 2: To determine and describe the progression, regression and interaction of these parameters in the pre- and post-operative periods

4.2.1 Doppler assessment and M-mode of the right ventricle: tricuspid valve, RVSP, RV and TV annulus dimension

The summary measurements for the TV annulus, RVSP, longitudinal, basal, and mid RV dimensions taken from the Doppler assessment and M-mode of the right ventricle, are presented in Table 4.4.

Table 4. 4: Doppler and M-mode assessment in the right ventricle

	n	Minimum	Maximum	Mean	Std. Deviation
Pre-op					
TV Annulus (mm)	30	24.00	53.00	35.40	8.16
RVSP (mmHg)	30	7.00	63.00	23.73	17.44
Longitudinal RV dimension (cm)	30	5.8	9.1	7.94	1.09
Basal RV dimension (cm)	30	2.60	5.10	4.15	0.56
Mid RV dimension (cm)	30	2.10	4.80	3.48	0.63
Post-op					
TV Annulus (mm)	29	27.00	49.00	33.34	6.48
RVSP (mmHg)	29	7.00	60.00	21.45	14.63
Longitudinal RV dimension (cm)	29	5.8	9.0	8.01	1.02
Basal RV Dimension (cm)	29	2.70	5.40	4.11	0.51
Mid RV dimension (cm)	29	2.10	5.00	3.48	0.60
6 months-post op					
TV Annulus (mm)	28	24.00	51.00	33.04	7.09
RVSP (mmHg)	28	7.00	81.00	20.20	19.56
Longitudinal RV dimension (cm)	28	6.00	9.30	7.86	0.98
Basal RV dimension (cm)	28	3.10	5.50	4.10	0.58
Mid RV dimension (cm)	28	2.70	5.10	3.39	0.56

TV annulus: tricuspid valve annulus; RVSP:right ventricular systolic pressure; RV: right ventricle

Doppler echocardiographic findings showed that the means of right ventricular systolic pressure (RVSP) and TV annulus decreased 6 months post-surgery, mean difference of 2.37 and 3.53 respectively, p-value <0.001 (Table 4.5), while RV dimensions remained relatively the same (Table 4.4).

A paired t-test was conducted on TV Annulus, RVSP, RV Longitudinal, mid and base pre and post- operative. The results are summarized in Table 4.5.

Table 4.5: Paired sample t-test for TV annulus, RVSP, RV diameter Pre-and Post-op

		Mean	Std. Dev.	Std. Error Mean	t	df	Two-Sided p
	Pre TV Annullus – Post TV Annulllus (mm)	2.17	5.11	0.95	2.29	28	0.03
	Pre RVSP – Post RVSP (mmHg)	2.72	10.32	1.92	1.42	28	0.17
	Pre RV Longitudinal - Post RV Longitudinal (cm)	0.07	0.50	0.09	0.70	28	0.49
	Pre RV Base – Post RV_Base (cm)	0.07	0.34	0.06	1.10	27	0.28
	Pre_RV Mid - Post_RV_Mid (cm)	0.03	0.29	0.05	0.51	28	0.61

TV annulus:tricuspid valve annulus;RVSP:right ventricular systolic pressure; RV:right ventricle

The table above indicated that only TV annulus showed a significant difference in means pre and post-operative (p-value=0.03). The mean difference was 2.17mm with a standard deviation of 5.11mm.

A paired t-test was performed on LVEDD, LVESD, IVSD, LVPWS, LVPWD, EF, FS, LAD, AO-Root and TAPSE 72 hours pre-op and 6 months later. The summary statistics are provide in Table 4.6.

Table 4.6: Paired t-test pre-operative versus 6 months follow-up.

		Mean difference	Std. Deviation	Std. Error Mean	t	df	One-Sided p
	Pre LVEDD – LVEDD 6mth (cm)	0.34	0.90	0.17	2.01	27	0.03
	Pre LVESD – LVESD 6mth (cm)	0.15	0.84	0.16	0.95	26	0.18
	Pre IVSS – IVSS 6mth (cm)	-0.36	1.87	0.35	-1.02	27	0.16
	Pre IVSD – IVSD 6mth (cm)	-0.04	2.89	0.55	-0.07	27	0.47
	Pre LVPWS – LVPWS 6mth (cm)	0.48	3.40	0.64	0.74	27	0.23

	Pre LVPWD – LVPWD 6mth (cm)	-0.02	2.39	0.45	-0.04	27	0.48
	Pre EF – EF 6mth (%)	3.83	12.40	2.34	1.86	27	0.04
	Pre FS – FS 6mth (%)	3.21	8.84	1.67	1.92	27	0.03
	Pre LAD – LAD 6mth (mm)	3.46	13.63	2.58	1.34	27	0.10
	Pre AO ROOT – AO ROOT 6mth (mm)	2.60	3.72	0.70	3.69	27	<0 .001
	Pre TAPSE – TAPSE 6mth (mm)	4.00	5.97	1.13	3.55	27	< 0.001

LVEDD: left ventricular end-diastolic dimension; LVESD: left ventricular end-systolic dimension; IVSS: interventricular septum in systole; IVSD: interventricular septum in diastole; LVPWD: left ventricle posterior wall in diastole; LVPWS: left ventricle posterior wall in systole; EF: ejection fraction; FS: fractional shortening; LA: left atrium; AO: Aorta;TAPSE:tricuspid annular plane excursion.

The mean difference between LVEDD pre and LVEDD 6 months follow-up was 0.34cm. The p-value of 0.03 for the hypothesis test result indicates that the mean LVEDD pre-operatively is significantly higher than the mean LVEDD after 6 months follow-up. The mean difference between EF pre-operatively and EF 6 months follow-up was 3.83%. The p-value of 0.04 indicates that the mean ejection fraction pre-op was significantly higher than the mean ejection fraction 6 months follow-up (Table 4.6).

The mean difference between AO ROOT pre-op and AO-ROOT 6 months follow-up was 2.60mm with a p-value<0.001. The AO-ROOT pre-op was significantly higher than 6 months follow-up (Table 4.6). The mean difference for the TAPSE pre-op and TAPSE at 6 months follow-up was 4.00mm with a p-value<0.001. The mean for TAPSE pre- op was significantly higher than the mean for TAPSE 6 months follow-up (Table 4.6).

The variables for RV strain were compared pre-op and 6 months post-op and a paired t-test was performed on BIS, MIS, APS, MAL, BAL, and GLS. The mean difference, t-value and p-values are presented in Table 4.7.

Table 4.7: RV Strain pre-op vs 6 months post-op.

		Mean difference	Std. Deviation	Std. Error Mean	t	df	One-Sided p
	Pre BIS – BIS 6mth	-4.50	30.59	5.78	-0.78	27	0.221
	Pre MIS – MIS 6mth	3.33	16.42	3.10	1.07	27	0.147
	Pre APS – APS 6mth	3.70	10.32	1.95	1.90	27	0.034
	Pre APL – APL 6mth	0.40	10.49	1.98	0.20	27	0.421
	Pre MAL – MAL 6mth	-3.05	13.08	2.47	-1.23	27	0.114
	Pre BAL – BAL 6mth	2.61	17.18	3.25	0.80	27	0.214
	Pre GLS – GLS 6mth	1.13	13.45	2.54	0.44	27	0.330

BIS: basal inferior septum; MIS: mid inferior septum; APS: apical septum; APL: apical lateral wall; MAL: mid anterior wall; BAL: basal anterior wall; GLS: global longitudinal strain.

The mean difference between APS pre-op and APS at 6 months follow-up was 3.70. The one-sided p-value of 0.03 indicates that the mean APS pre-op was significantly larger than the mean APS 6 months later. There is no evidence that any of the other parameters differed significantly as all p-values were >0.05 (Table 4.7).

4.3 Objective 3: To determine echocardiographic parameters that indicate TV intervention at time of left-sided valve surgery

In this section correlation coefficients between the parameters TV annulus, RVSP, longitudinal, base and mid RV pre-op was assessed. Table 4.8 provides the pair-wise correlations for all the combinations and the associated p-value. The upper triangle of the correlation coefficients is displayed since for example the correlation between TV annulus and RVSP and the RVSP and TV annulus is the same.

Table 4.8: Correlations between TV annulus, RVSP and RV diameter pre op.

		Pre-op TV_ Annulus (mm)	Pre-op RVSP (mmHg)	Pre-op Longitudinal RV (cm)	Pre-op Base RV (cm)	Pre-op Mid RV (cm)
Pre-op TV Annulus (mm)	Pearson Correlation	1.00	0.70	0.46	0.72	0.74
	p-value		<0,001	0.01	<0,001	<0,001
Pre-op RVSP (mmHg)	Pearson Correlation		1.00	0.54	0.71	0.69
	p-value			<0.001	<0,001	<0,001
Pre-op Longitudinal RV (cm)	Pearson Correlation			1.00	0.85	0.74
	p-value				<0,001	<0,001
Pre-op Base RV (cm)	Pearson Correlation				1.00	0.91
	p-value					<0,001
Pre-op Mid RV (cm)	Pearson Correlation					1.00
	p-value					<0.001

TV annulus: tricuspid valve annulus; RVSP: right ventricular systolic pressure; RV: right ventricle

A correlation coefficient of 0.70 is seen between TV annulus and RVSP pre-op, with a p-value of <0.001, thus showing a strong positive correlation between these two variables. A strong positive correlation is also seen pre-op between TV annulus and RV base (r=0.72) and mid diameters (r=0.74), as well as in RVSP and RV base (r=0.71) and mid diameters (r=0.69), with a p-value of <0.001. The highest correlation value of r=0.91 is between pre-op RV base and pre-op mid RV with (p<0.001)(Table 4.8).

Similarly, correlation coefficients between the parameters TV annulus, RVSP, longitudinal, base and mid RV were calculated post 6 months. The results are shown in Table 4.9.

Table 4.9: Correlations between TV annulus, RVSP and RV diameter 6 months post-op

		TV Annul_6mth (mm)	RVSP 6mth (mmHg)	RVD Longit 6mth (cm)	RVD Base 6mth (cm)	RVD Mid 6mth (cm)
TV Annullus 6mth (mm)	Pearson Correlation	1.00	0.85	0.54	0.78	0.78
	p-value		<0.001	0.001	<0,001	<,001
RVSP 6mth (mmHg)	Pearson Correlation		1.00	0.53	0.72	0.69
	p-value			0.00	<0,001	<0,001
RV diameter Longitudinal 6mth (cm)	Pearson Correlation			1.00	0.80	0.74
	p-value				<0,001	<0,001
RV diameter Base 6mth (cm)	Pearson Correlation					0.91
	p-value					<0,001
RV diameter Mid 6mth (cm)	Pearson Correlation					1.00
	p-value					<0,001

TV annulus: tricuspid valve annulus; RVSP: right ventricular systolic pressure; RV: right ventricle

All the correlations were significant between all the variables mentioned in Table 4.9 as the p-value was <0.05 in each case. The magnitudes of the correlation coefficients calculated pre-op and then 6 months post-op have also remained fairly constant and in some cases exactly the same. A very strong correlation coefficient was seen between RV base diameter and RV mid diameter (r=0.91), TV annulus and RVSP (r=0.85), and Longitudinal RV diameter and RV base diameter(r=0.80) at 6 months follow-up.

Correlation coefficients between the parameters RV diameter, TAPSE and GLS post-op are displayed in Table 4.10

Table 4.10: Correlation between RV diameter, TAPSE and GLS 6 months post op

		RVD_Longit_6mth (cm)	RVD_Base _6mth (cm)	RVD_Mid _6mth (cm)	TAPSE6 mth (mm)	GLS6mth
RV diameter Longitudinal 6mth (cm)	Pearson Correlation	1.00	0.80	0.74	-0.40	0.08
	P value		<,001	<0,001	0.04	0.69
RV diameter Base 6mth (cm)	Pearson Correlation		1.00	0.91	-0.41	0.02
	Sig. (2-tailed)			<0,001	0.03	0.94
RV diameter Mid 6mth (cm)	Pearson Correlation			1.00	-0.35	-0.12
	Sig. (2-tailed)				0.07	0.54
TAPSE 6mth (mm)	Pearson Correlation				1.00	-0.03
	Sig. (2-tailed)					0.89
GLS 6mth	Pearson Correlation					1.00
	Sig. (2-tailed)					1.00

RV: right ventricle; TAPSE :tricuspid annular plane excursion; GLS: global longitudinal strain;mth:months

RV longitudinal diameter has a strong and significant correlation with RV mid (r=0.80) and base diameter (r=0.74) as well as TAPSE at 6 months post op. RV base diameter has a strong correlation between RV longitudinal, mid and TAPSE at 6 months post-op. RV mid diameter and TAPSE correlated significantly between RV longitudinal and base diameters at 6 months. All have p-values of < 0.05 and are thus significant.

RV longitudinal and RV base dimensions at 6 months are negatively correlated with TAPSE at 6 months (r=-0.40 with p-value=0.04 and r=-0.41 with p-value=0.03 respectively). RV dimensions are not correlated with GLS at 6 months as can be seen from the small correlation coefficients, for example RVD longitudinal with GLS has a correlation coefficient of 0.08 with p-value=0.69) (Table 4.10).

4.4 **Objective 4: To compare the degree of change in RV structure and function pre and post left valve surgery**

Table 4.11 displays the descriptive statistics of RV dimensions pre-operatively and post-operatively, and again at 6 months follow-up.

Table 4.11: Descriptive statistics of RV dimensions pre-op and post-op, and 6 months post follow-up

	n	Minimum	Maximum	Mean	Std. Deviation
Pre longitudinal (cm)	30	5.80	9.10	7.94	1.09
Pre Base (cm)	30	2.60	5.10	4.15	0.56
Pre Mid (cm)	30	2.10	4.80	3.48	0.63
Post longitudinal (cm)	29	5.8	9.00	8.01	1.02
Post RV Base (cm)	29	2.70	5.40	4.11	0.51
Post RV Mid (cm)	29	2.10	5.00	3.48	0.60
RV Longit_6mth (cm)	28	6.00	9.30	7.86	0.98
RV Base_6mth (cm)	28	3.10	5.50	4.10	0.58
RV Mid_6mth (cm)	28	2.70	5.10	3.39	0.56

RV: right ventricle;mth: months

The table demonstrates relatively no changes in mean RV diameter immediately post-surgery and at 6 months follow-up.

Paired t-tests were conducted on the RV dimensions pre-op and post-op to investigate whether there was a change. The results of the paired t-test are given in Table 4.12

Table 4.12: Paired sample test of RV dimensions pre-op and post-op.

	Mean difference	Std. Deviation	Std. Error Mean	t-value	df	Two-Sided p

	Pre RV longitudinal-Post RV Longitudinal (cm)	0.07	0.50	0.09	0.70	28	0.49
	Pre RV Base – Post RV_Base (cm)	0.07	0.34	0.06	1.11	27	0.28
	Pre RV Mid – Post RV_Mid (cm)	0.03	0.29	0.05	0.51	28	0.61

RV: right ventricle

As can be seen from Table 4.12 the mean differences for the RV dimension pre and post are small (0.07, 0.07 and 0.03, respectively), and all the p-values are larger than 0.05 indicating that there were no significant differences in means between longitudinal, base and mid RV diameters pre-op vs 72 hours post-op (Table 4.12).

Paired t-tests were also conducted to investigate whether there was a change in TV annulus, RVSP, and the RV dimensions 72 hours post-op and then 6 months post-op. These results are shown in Table 4.13.

Table 4.13: Paired sample test of RV dimensions 72 hours and 6 months post-op.

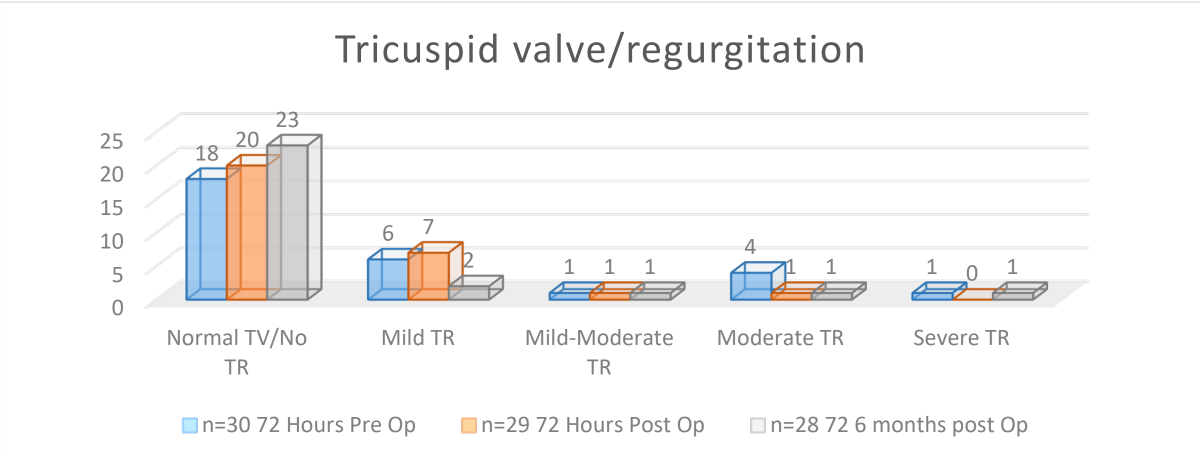
		Mean	Std. Deviation	Std. Error Mean	t-value	df	Two-Sided p
	TV annullus 6mth – Post TV annullus (mm)	0.29	3.76	0.71	-0.40	27	0.69
	RVSP_6mth – Post RVSP (mmHg)	1.41	11.16	2.11	-0.67	27	0.51
	RVD Longitudinal 6mth - Post RV Longitudinal (cm)	0.08	0.57	0.11	-0.70	27	0.49
	RV diameter Base 6mth - Post RV Base (cm)	0.03	0.38	0.07	-0.45	26	0.65
	RV diameter Mid 6mth – Post RV Mid (cm)	0.08	0.52	0.10	-0.80	27	0.43

TV annulus: tricuspid valve annulus; RVSP: right ventricular systolic pressure; RV: right ventricle

There were no significant differences in means for 72 hour post-op vs 6 months post-op, as all p-values were greater than 0.05. It appears that the RV dimensions remained relatively unchanged 72 hours post-op to 6 months post-op (Table 4.13).

4.5 Objective 5: To determine echocardiographic parameters that indicate early signs of progression of tricuspid regurgitation (If not intervened on) after left valve surgery.

Of 30 patients who underwent left valve surgery in the pre-operative stage, 18 patients (60%) presented with normal tricuspid valves, 6 patients (20%) with mild tricuspid regurgitation (TR), 1 patient (3.3%) mild to moderate TR, 4 patients (13.3%) moderate TR and 1 patient (3.3%) with severe TR 72 hours preoperatively (Figure 4.2).



TV:tricuspid valve; TR:tricuspid regurgitation

Figure 4.2: Bar graph of severity of TR regurgitation.

Upon echocardiographic examination 72 hours post-surgery, of a total of 29 patients that had successful surgery, 20 patients (69.0%) had no TR, 7 patients (24.1%) had mild TR, 1 patient (3.3%) had mild to moderate, 1 patient (3.3%) had moderate and no patients presented with severe TR. In comparison TR was significantly reduced in 13.8% of patients, especially those who presented with moderate or severe TR, while TR remained unchanged in 31.03% of patients and showed significant progression in

3.3% of patients. An additional 9.6% of patients returned at 6 months follow-up with no TR, showing a significant reduction in those who had mild TR 72 hours post-op, while 1 (3.6%) had a significant progression in TR severity. Due to the small number of patients (n = 1) who progressed to significant TR, no further analysis was undertaken.

CHAPTER 5: DISCUSSION

Heart remodelling caused by high pulmonary pressure from mitral and/or aortic valve disease causes the right ventricle to dilate, which reduces the right ventricular (RV) ejection fraction.[1] Pulmonary hypertension (PHTN), which results in RV dilatation, tricuspid regurgitation, and ultimately RV failure, occurs when the LV becomes volume-loaded, as in severe MV and/or AO disease.[2]

Early detection of RV function abnormalities is important in VHD because subclinical disease may suggest a worse clinical prognosis and can assist in deciding whether surgery is necessary. However, because of the intricate anatomy of the RV, 2D evaluation of the RV function is particularly difficult.[254] Early detection of RV depression through the use of imaging technologies such as speckle tracking echocardiography (STE) is important.[10] Nonetheless, sub-Saharan Africa lacks sufficient data on the usefulness of echocardiography in evaluating right ventricular remodelling.[255] This could be because of the low availability of highly specialized personnel to perform novel techniques like STE and the high cost of echocardiography in sub-Saharan Africa and southern Africa.

In this regard, the aim of this study was to determine changes in the right heart after mitral and/or aortic valve surgery, as well as to determine predictors of early signs of TR progression post left valve surgery that could possibly be used as an indication for TV surgery at the time of left valve surgery through the use of a two-dimensional doppler and speckle tracking echocardiography.

This clinical prospective research included 30 patients who were candidates for valve surgery due to severe mitral and/or aortic valve disease. Investigations were conducted on patients with severe mitral and/or aortic valve disease to examine preoperative and postoperative echocardiographic parameters and their interaction. The research included patients with combined mitral and/or aortic lesions, since these individuals typically presented with disease in more than one valve. Degenerative valve disease (43.3%) was the most frequent assessment of valve etiology in this study, followed by vegetations (23.3%) and calcified valve disease (20%). The most common valve disease was found to be MR and AR, both at 23.3%. Only prosthetic valves were placed in the tricuspid location in our research group, even though mechanical valves were used in most of left-sided valve replacement surgeries.

Post-valvular surgery assessment of the tricuspid valve showed a significant reduction at 6 months in the postoperative tricuspid annular diameter (p=0.030), pulmonary artery systolic pressure, and tricuspid regurgitation severity, especially in those patients presenting with no TR, trivial TR, and mild TR (Grade 0+, 1+ and 2+). Severe residual postoperative tricuspid regurgitation (previously ignored at the time of left valve surgery) was observed in 1 patient (3.6%) after follow-up, and because there was only one patient(n=1) who progressed to significant TR, no further analysis was undertaken. A further important finding of this study was that no significant GLS change was demonstrated in RV function using speckle tracking imaging, the study demonstrated a significant decline in regional APS and BIS segments at 6 months follow-up. The study demonstrated a significant decrease in RV function with TAPSE pre-op vs 6 months follow-up. Although the mean difference of FAC was high pre-op vs at 6 months follow-up, there was no significant change (p-value =0.18). There was a positive correlation seen between RVSP and TV annulus. A significant negative correlation was seen between RV dimensions 72 hours pre-op and TAPSE 6 months post op. There was no correlation seen between EF and GLS and TAPSE, LVEDD and GLS 72 hours post-op and again 6 months post-op.

5.1 The prevalence of valve heart disease

The results of the study revealed that the mean age of these patients with severe MV/AO disease was 45.83 years, with the majority being females (60%). The predominant aetiology of valve diseases was found to be degenerative valve disease (43.3%). RHD and degenerative VHD account for 70% of the causes of VHD in this study, sharing the disease burden (Table 4.1). Over 73.2% of all lesions were monovalvular, with MR and AR making up the majority of these at 23.3% each. As a result of the rarity of non-functional tricuspid valve or pulmonary VHD, as demonstrated by Nkoke et al. (2018)[256], our attention was more directed toward left-sided VHD.

There are some contrasts in the overall epidemiological picture of VHD in this community in Port Elizabeth, Eastern Cape, and what has been documented in other African research. For example, research conducted in Togo by Balaka et al. (2015)

[257] on 5412 patients found that 4.45% of patients who were followed up at a cardiac centre in Lomé had VHD.

Although lower than what we found, this proportion may have been similar if patients with primary left valvular heart disease had been included in the research. Consistent with our findings, 77% of their study sample had monovalvular lesions. Furthermore, aortic regurgitation (30.7%) and mitral regurgitation (50.8%), were the most prevalent lesions.

The VALVAFRIC study[258]: a multicenter hospital-based retrospective registry of 3441 patients with RHD hospitalized in African cardiology departments from 2004 to 2008 revealed that 52.7% and 22.3% of patients, respectively, had monovalvular mitral regurgitation and aortic regurgitation. Monovalvular mitral regurgitation was twice as common in the study mentioned (23.3% of cases) compared to our population. There are several reasons why the difference can exist. It's likely that the Lomé study[257] exaggerated mitral regurgitation as an anatomical defect by including functional regurgitation. The VALVAFRIC [258] study emphasis on RHD may assist in explaining the higher incidence of mitral regurgitation compared to our study, which discovered that degenerative VHD was quite prevalent, as RHD seems to be a more common cause of mitral regurgitation than a degenerative disease.[259]

Regarding aetiologies, we found that RHD (26.7%) and degenerative VHD (43.3%) were the two most prevalent causes of left-sided VHD in our cohort. Similar results were seen in Uganda, where Rwebembera et al. (2018)[260] reported that 41.8% of the 3,582 patients who underwent echocardiography at the Uganda Heart Institute had RHD, and 53.0% had degenerative VHD. In the Heart of Soweto Study in South Africa, 72% of patients with a de novo presentation of VHD had RHD, while 21% of patients had a degenerative etiology.[261] The Heart of Soweto Study participant’s mean age 43(32-56) years, which is comparable to our study population's mean age of 46(18-65) years, is the primary cause of the higher prevalence of RHD in that study.

Although it was not common in our sample, mitral valve prolapse is another cause of VHD. However, the prevalence was greater in our investigation compared to the 1.0% and 1.4% found in the Heart of Soweto Study and the Uganda Heart Institute.[260, 261] RHD was determined to be the most frequent cause of VHD in a major hospital-based research conducted in China, accounting for 37% of cases.[262] This is because RHD is endemic in China, as it is in the majority of sub-Saharan nations, according to Watkins et al. (2017)[69]. While the frequency of degenerative VHD (11.5%) is lower in the Chinese sample than in the African studies, the prevalence of congenital heart disease (13.9%) and ischemic-related valvular lesions (12.7%) is much greater.[263]

5.2 Echocardiographic parameters of tricuspid regurgitation, pulmonary arterial pressure and RV function at specific intervals pre and post left-sided valve surgery

RV function can be challenging to evaluate because RV anatomy is intricate. One parameter might not be enough to assess RV function or RVD to the right ventricle's intricate three-dimensional shape. In our study, we used 3 parameters of RV function that are easily obtainable by the vast majority of current echocardiographic machines, including 2-dimensional RVFAC, TAPSE and speckle tracking imaging. We demonstrated that echocardiographic measures, such as 2D echocardiography and speckle tracking imaging, can identify alterations in the structure and function of the RV following valve surgery in patients having left valvular surgery.

RV function measured by TAPSE and RV FAC showed a significant decline post-operatively in our study. However, RV function measured by speckle tracking echocardiography remained unchanged, suggesting that quantitative measures of RV function should not rely solely on conventional indices. A reduction in TAPSE after cardiac surgery is a well-known phenomenon and has been previously reported in both congenital and acquired diseases.[264] This observation has been interpreted as an isolated worsening of right ventricular performance, without changes in left ventricle parameters or exercise capacity and thus with poor clinical significance. Several hypotheses have been proposed to explain this loss in right ventricular performance detected along the long axis, including cardiopulmonary bypass use.[265] Geometrical changes of the right ventricular chamber (in association with interventricular septal paradoxical motion, intraoperative ischaemia, right atrial injury due to cannulation procedure[266], poor myocardial protection[267], and extramyocardial causes (pericardial disruption, changes in fossa ovale, and postoperative adherence of the right ventricle to the thoracic wall).[268] In more detail, investigators' attention was particularly addressed to the role played by pericardial injury but definitive conclusions concerning its real contribution failed to be drawn. Unsworth et al.(2009)[5] assessed temporal changes in right ventricular two-dimensional features according to the different surgical acts in order to narrow the range of factors that may cause the observed right ventricular functional loss. They demonstrated that peak systolic velocity and TAPSE are reduced within the first 3 minutes after opening the pericardium and hypothesized that the loss of pericardial support, which is fundamental for maintaining right ventricle chamber geometry, makes the right ventricle susceptible to changes when the pericardial constraint itself is lost. These findings support the hypothesis that geometric rather than functional changes happen in the right ventricle during surgery. On the contrary, such a theory was not proved by Lindqvist et al.(2012)[266] who, by examining the effect of pericardial suture after mitral surgery completion, found that it had no consequences on right ventricular function restoration.

Nevertheless, the assumption of a preeminent right ventricular chamber geometric modification seems to be confirmed by the paper of Tamborini et al.(2009)[269] who were able to demonstrate that despite the reduction in right ventricular performance measured after surgery along the ventricular long axis by TAPSE and peak systolic velocity, no associated decrease in three-dimensional right ventricular ejection fraction was found, leading to caution in the interpretation of two-dimensional and Doppler parameters.

Over the course of six months following surgery, both enlarged left and right atrial sizes were observed to somewhat show a steady decrease in size. This might be the result of a typical RV, which is thought to be able to handle PH and RVD that just started. Nevertheless, individuals with pre-operative RVD frequently cannot withstand these abrupt changes and go on to experience RV insufficiency, which results in low cardiac output syndrome.[159]

Although RV function by TAPSE and RV FAC decreased in our investigation, RV dimensions remained relatively unchanged, but the means of the right ventricular systolic pressure (RVSP) decreased six months after surgery, according to Doppler echocardiographic results. If TR was visible in the subcostal, apical four-chamber, or RV inflow views, RVSP was calculated. RVSP was computed using the modified Bernoulli equation for the view with the greatest tricuspid jet velocity. Previous research[270-272] has shown a strong correlation between patient populations, the accuracy of absolute PASP values derived from TR velocity (TRV)max has only been moderately established.

For every patient, a mean right atrial (RA) pressure of 10 mmHg was assumed for all participants with no TR in our study. RVSP gradually rose as tricuspid regurgitation got worse. In our study (n=30), the overall mean RVSP pre-operatively was 23.73 ± 17.44 mmHg pre-operatively. Previous studies, such as one by McQuillan et al. (2001)[273], reported a somewhat higher mean RVSP of 28.3 ± 4.9 mmHg (n=3 790), however, the mean age of the group was significantly lower (33 years), and their patients ranged in age from one to 89 years, whereas our patient range was 18 to 65 years. In our study, 7 patients (23.3%) were older than 60 years old, compared to just 199 people in the McQuillan research.[273] Two variables that may account for the greater mean RVSP in our group are the mean age and the age distribution. These differences may also account for the different reference ranges we propose for our adult population. It has been demonstrated that the Doppler TTE measurement of TV regurgitation jet peak velocity, which is used to estimate RV systolic pressure (RVSP), can reliably predict the PASP measured through invasive methods.[274] In addition to the severity of TR, it has been shown that RV dysfunction and increased PASP have unfavorable prognostic implications for long-term survival. It was demonstrated by Nath et al. (2004)[146]that TR predicted death without reference to PASP or RV function.

5.3 The progression, regression and interaction of these parameters in the pre- and post-operative periods

The reaction of reverse ventricle remodeling after left valve disease correction is discussed, along with a correlation between the response and preoperative variables. Our results show a considerable decrease in LV diastolic and systolic dimensions six months after surgery. Six months after surgery, we also saw a steady increase in the mean LV ejection percentage. The patients who did not have preoperative alterations indicative of chronic diseases, such as LV dilatation, LA enlargement, and LV dysfunction, had the best chance of achieving positive reverse remodeling. As stated by Lang et al. (2007)[18], in more advanced stages of left ventricular dysfunction, dilatation of the right ventricle and a decrease in its contractile strength are typically observed, highlighting the close connection between the two ventricles. Early intervention prior to the development of LV dysfunction or enlargement was found by Suri et al.(2009)[275] to be necessary for the recovery of LV function. This means that irreversible changes are brought about by the ventricular remodelling process, especially when patients experience ventricular dysfunction and chamber dilatation.[276] These results provide indirect support for an increasing amount of research that indicates early intervention for severe left valvular disease is beneficial.[277]

The decrease in EF after surgery in patients with aortic or mitral valve disease can be attributed to multiple mechanisms. The temporal response of the left ventricle to mitral valve replacement was described by Schuler et al. (1979)[278]and Zile et al. (1985)[279]in early echocardiographic studies. They also proposed that preoperative measurements of LV size and function could be predictive. After surgery, the LV end-diastolic dimension decreased significantly in most of these patients, but some did not show this beneficial reduction in LV size. Patients with normal LV end-diastolic dimension achieved better functional outcomes than those with persistent postoperative LV enlargement in both studies. Early research[280] also demonstrated a steady decrease in LV EF following mitral valve replacement. This was believed to result from a rise in left ventricular afterload, which was causally linked to the closure of the left atrial low-impedance leak. This process may account for the decline in EF seen in patients with decompensated MR, prolonged postoperative left ventricular hypertrophy, and afterload excess.[281]

Magne et al. (2010)[99] found that the slight changes in left ventricular (LV) function seen in MR could be linked to the emergence of pressure halftime (PHT) during exercise[99] and right ventricular (RV) dysfunction[38], which would indicate a poor prognosis and a quick onset of symptoms.

Due to the strict exclusion criteria, no signs of RV dysfunction and RV dimension changes were expected in our study. This was confirmed by the normal values of TAPSE, FAC and GLS in most of our patients pre-operatively. Similar results were seen by Bruhl et al. (2011) [282] in their assessment of 51 healthy adults without a history of cardiac disease, TAPSE, mitral annular plane of systolic excursion (MAPSE), and tissue Doppler imaging measures of the right and left ventricles were constant across age, gender, and body surface area.

These results demonstrate the systolic interdependence and the ventricular relationship. The symptoms and physical capabilities of patients with a variety of clinical conditions are correlated with RV size and function.

72 hours after cardiac surgery, although mean was higher 6 months post op, there was no significant difference in RV FAC in our patients. Our findings are consistent with several other studies[283][284] that have examined the impact of cardiothoracic surgery on the right ventricle (RV). After cardiac surgery, there are fundamental changes in the contractile pattern of the RV. Measures of longitudinal RV shortening, such as TAPSE or the systolic tricuspid annular velocity, typically decrease postoperatively. In contrast, RV ejection fraction and RV FAC appear to remain stable or even increase after cardiac surgery. It could be explained by deformation analysis of RV. Donauer et al.(2020)[285], demonstrated that RV circumferential and radial contraction do not show significant changes after cardiac surgery. However, there is a significant decrease in peak longitudinal systolic strain of the RV lateral wall. Like our study there were no changes observed in RV GLS. RV FAC, which encompasses both longitudinal and transverse contraction of the RV lateral free wall, remains preserved post-surgery.

5.4 Echocardiographic parameters that indicate TV intervention at time of left side valve surgery

In this study, we found that TV annulus and RSVP were the best markers that indicated TV intervention at the time of left-side valve surgery. However, RSVP has the potential to both overestimate and underestimate the degree of pulmonary hypertension, as it relies on accurate assessment of the tricuspid regurgitation jet velocity and inferior vena cava assessment. Further, estimation of RVSP is unable to predict an elevated

PVR, as it may be markedly elevated in both PAH and PVH[271], we relied mostly on TV annulus and severity of TR by colour Doppler as a marker for TV intervention.

When a patient has mild-to-moderate TR and an annulus diameter of less than 40 mm, cardiovascular surgeons frequently do not consider treating the TV because they believe that the volume load reduction that results from treating additional valve pathologies will be sufficient to lower the degree of TR.[286] According to current guidelines, the indications for TV intervention include severe TR and mild or moderate TR with a dilated TA.[287] In our study only a small fraction (5 patients, 16.6%) had clinically significant TR (moderate and or severe TR), while the remaining patients had moderate or less TR. TR surgery was only performed in 2 patients(6.8%). Therefore, the decision to perform TV repair was left to the surgeon's discretion or even was not specified, but is mainly based on the TA dimensions. This conclusion is supported by Dreyfus et al.[288] who suggested performing tricuspid annuloplasty regardless of the grade of tricuspid regurgitation, when the tricuspid annular diameter was greater than twice the normal size (>70 mm).

The TA end-diastolic diameter was easily measured pre-operatively with a 2D TTE, the mean measured TV annulus pre-op was 35.4mm and it is expected that 2D measurements reflect the degree of TA enlargement. However, Bieliauskienė et al. (2023)[289] demonstrated that 2D parameters, such as systolic apical 4Ch diameter and parasternal short axis diameter, are significantly smaller than the 3D major axis and correspond to the 3D minor axis. This conclusion is supported by some studies[290-292]that have reported that the TA diameter measured in the 4-chamber view by 2D echocardiography underestimates the 4Ch diameter obtained by 3D echocardiography. Thus, solely 2D measurements may not provide an accurate assessment of the degree of TA dilation, leading to a potential delay in the appropriate timing of TV intervention.

We hypothesise that the size of the TA is an essential factor in selecting the annuloplasty modality. Praz et al.(2021)[293], suggested that excessive annular dilatation is unsuitable for transcatheter annuloplasty procedures. Further studies on long-term outcomes are needed to evaluate the impact of TA size on different repair techniques. It is likely that for significantly enlarged TA with severe TR, suture annuloplasty may be insufficient, and ring annuloplasty may be necessary for better long-term results.

Additionally, we showed that an increased right ventricular pressure was associated with an increasing tricuspid annulus (p<.001). TV annulus and RVSP pre-op showed a 0.695 correlation coefficient. Pre-operatively, there was a noteworthy positive correlation observed between the RVSP and RV base and mid diameters, as well as between the TV annulus and these same diameters (p-values<0.001). However, comparing our study with other studies of functional TR[134, 294] revealed several differences. The study populations are defined and selected differently. Our population was defined by a multiple and mixed diagnosis of severe left valve disease, with or without TR. Fukuda et al (2006)[134] studied patients with severe TR (>2+) accompanying any left-sided heart disease, Kim et al (2006)[294] studied patients with enlarged RVs with any diagnosis and any degree of TR. In these and the present study, leaflet tethering and dilatation were correlated with the degree of TR, yet the weakness of the correlation suggests that the mechanism of TR is multifactorial and variable from case to case. TR is more than a simple consequence of RV dilatation. Unlike the linear relation of RVSP with increasing TR grade.

5.5 To compare the degree of change in RV structure and function pre and post left valve surgery

In our study RV function was evaluated, and the results showed a considerable drop in RV function suing TAPSE and RV FAC with a modest increase detected at 6 months post-surgery. Reduced RV performance has been repeatedly to a deterioration of the prognosis for patients. GLS and RV dimensions did not reveal any noteworthy alterations. Contrary to what we found, Rong et al. (2019)[295] reported that TAPSE did not predict RV dysfunction during chest closure, although FAC, GLS, and free wall strain did. After percutaneous mitral valve replacement (PMVR), most 2D-derived indicators of RV function showed no change in RV function according to Van Riel et al. (2014)[296]. Currently, a key question is how effectively TAPSE and FAC represent changes in RV function after surgery and RV function overall.

Given that TAPSE monitors regional RV longitudinal function (as defined by the motion of the tricuspid annulus), it only measures changes in regional RV longitudinal function. In contrast, strain examines global and regional right ventricular function and accesses longitudinal function in all right ventricular myocardial segments.[297] In the current study, no appreciable changes in longitudinal RV function (GLS) over the whole long-axis of the RV were found. By assessing both longitudinal and transverse shortening, FAC offers a comprehensive assessment of RV function. In the present investigation, FAC decreased 72 hours after surgery. FAC, which evaluates the systolic change in RV area by 2D echocardiography, may be less sensitive to changes in global and localized or regional myocardial contraction as compared to a direct measure of myocardial long-axis shortening, such as RV strain.[284]

Tamborini et al. (2009)[269] conducted two- and three-dimensional echocardiographic studies on 40 patients to assess whether the right ventricular systolic function is diminished following cardiac surgery. The results of their study compared favourably to ours. It was discovered that there was a significant decrease in TAPSE and S' (25.3 + 4 vs 15.5 + 3 mm and 17.8 + 4 vs 11.9 + 2 cm/s), respectively, with all p-values less than 0.0001). Conversely, 3D echocardiography did not show any variations in RV dimensions, and more importantly, RVEF did not align with these findings.

Similarly, Schuuring et al. (2012)[298] detected changes in RV shape, suggesting that the effects of valve surgery can be long-lasting. The TAPSE measured after valve surgery showed a significant drop in the valve, but the follow-up clearly indicated a significant improvement in the TAPSE. Similar changes in TAPSE were observed in our study, however, at the 6-month follow-up, no significant increase in TAPSE was observed.

In comparison to baseline, Singh et al. (2020)[67] found a significant decrease in RV function following CPB (TPSE 2.2 [Q1, Q3: 1.8, 2.5] vs 1.5 [1.1, 1.7] mm, RV strain -22 [-24, -18] vs -16 [-20, -14] %, FAC 45 [35, 51] vs 42 [34, 49] %), but not following pericardiotomy. They also stated that following chest closure, the following reduced RV functions persisted: RV strain -16 [-18, -13]%, FAC 38 [31, 46]%, and tricuspid annular plane systolic excursion 1.3 [1.0, 1.6] mm. In contrast to our study, which showed a steady and gradual increase in TAPSE at 6 months post-surgery, They displayed diminished functionality in all cardiac surgical techniques, procedures, including both main and reoperative surgery. Many theories have been put forth to explain the sharp decline in TAPSE after heart surgery, modifications to the RV's shape related to interventricular septal paradoxical motion and insufficient RV protection during cardiopulmonary bypass, which lowers the RV's long-axis performance.[49]

5.6 Echocardiographic parameters that indicate early signs of progression of Tricuspid regurgitation (If not intervened on) after left valve surgery (predictors of postoperative recurrent TR)

Oftentimes, abnormalities including tricuspid regurgitation, RV dysfunction, and pulmonary hypertension, coexist. The reasons for functional TR secondary to left-sided cardiac disease have been proposed to be changes in RV geometry, the size and structure of the TV annulus, and the relative displacement of papillary muscles.[137] This theory suggests that treating left-sided valve disease should cause reverse RV remodelling and lower TR. The results of our study demonstrate that, at six months following valve surgery, there was a significant decrease in the postoperative tricuspid annular diameter ($p=0.030$), pulmonary artery systolic pressure ($p<0.001$), and the severity of tricuspid regurgitation, particularly in patients who initially presented with no TR, trivial TR, or mild TR (Grades 0+, 1+, and 2+). In our study only one patient (3.6%) developed severe postoperative tricuspid regurgitation. Therefore, no additional analysis was carried out.

According to literature[299], echocardiographic predictors are pre-operative TR severity, TA diameter, advanced leaflet tethering (tethering distance, area, and volume), presence and persistence of severe pulmonary hypertension after TV repair, and reduced LV function

Vahanian et al.(2012)[300], suggests that after MV surgery, tricuspid annular dilatation measured by TTE may be a more reliable marker of severe late TR. Because of the linear association between annular diameter and tricuspid regurgitant volume, the annular diameter criteria have been employed as a stand-in for regurgitation volume. Significant annular dilatation, defined as a diastolic diameter of >40 mm, is the key imaging criterion used in the current American Heart Association/American College of Cardiology recommendations to diagnose severe TR.[9] Our study suggested that TV annulus differed significantly pre-op vs 72 hours post-op (p-value=0.03), suggesting that there was a decrease in TV annular size post-surgery, which may be contributed to the repair ring annulopasty techniques employed.

Fukuda et al. (2005),[134] state that together with annular dimensions, TTE values of tricuspid valve tethering diameter of >7.6 mm or tethering area of more than 16.3mm are further echocardiographic indicators of postoperative recurrent TR. Regrettably, these measurements were not included in the measured parameters for our study. Dreyfus et al. (2015)[292] investigated intraoperative predictors of worsening TR and discovered that, if a concomitant repair was made,TR will gradually deteriorate in 48% of patients if their TV annular size (septolateral dimension) was more than 7 cm (compared to 2% in patients who had a concurrent repair). These findings were consistent with those of Shiran et al.(2009)[301] .The grade of TR, which often indicates left-sided valvular disease, indicates the advanced stage of heart disease.[302]

According to research by Shiran et al. (2009)[301], patients with significant TR may not see improvement in their prognosis even after left-sided valvular abnormalities are corrected. In addition to the severity of TR, it has been shown that RV dysfunction and increased PASP have unfavorable prognostic implications for long-term survival. Nath et al. (2004)[146] showed that TR is a different predictor of death from PASP and RV function. They demonstrated an HR of 1.31 in individuals with moderate or greater TR, independent of PASP. A further investigation by Topilsky et al. (2014)[303] revealed that isolated severe TR had an adjusted HR of 1.78 (95% CI 1.10 to 2.82) and was linked to increased cardiac events and death. More recently, Meijerink et al. (2021) [304]discovered that severe left valve surgery, specifically MVR, was independently predicted by advanced age, the presence of AF, RV dysfunction, and a limited reduction of MR during the procedure. Although our study did not find any significant differences in AF or TAD.

CHAPTER 6: CONCLUSION AND RECOMMENDATIONS

Perioperative physicians must understand the impact of AO and/or MV disease on RV function. In the same way, the goal in managing this patient group should be to recognize individuals who are susceptible to RV failure, detect RV dysfunction early on, and initiate appropriate therapy as soon as possible to avoid acute RV failure. This will be particularly important for high-risk procedures such as LVAD installation, congenital heart disease, and multiple valve surgery.

We demonstrated that in patients with severe left-sided valve heart disease, there was no substantial global (GLS) change in RV function using speckle tracking imaging both before and after cardiac left valvular surgery. In contrast, an evaluation of RV function utilizing TAPSE and FAC 2D measures revealed that RV function was severely reduced and subsequently progressively improved at 6 months following surgery. Among the intriguing mechanistic hypotheses that our findings generated for further research into the aetiology of these differences are the various clinical and physiological differences among patients, the pericardial closure post valve repair, the sternotomy and instrumentation effect, and the location and size of the pericardial incision. It remains to be determined and needs further research if these physiologic variations lead to better clinical outcomes. The study could not determine early signs of tricuspid regurgitation since only one patient progressed to severe TR in this sample.

All things considered, the speckle tracking imaging and 2D Doppler measurements have produced accurate estimates of the global and/or regional systolic RV function. When all of these echocardiographic parameters are measured, an accurate evaluation of the RV can be made to diagnose and optimize the management of the condition.

6.1 RECOMMENDATIONS

As soon as feasible after surgery, a thorough examination encompassing TAPSE, S', RVFAC, and RV GLS assessment should be conducted. This examination should be repeated in three and six months to confirm the potential full restoration of RV longitudinal function and to enhance early management of RV failure.

6.2 LIMITATIONS OF THE STUDY

Our study had several limitations, Firstly, our findings must be validated in other studies involving a larger number of subjects. Our small sample size does not allow us to extrapolate these results to other populations. This was a clinical, uncontrolled study, which included consecutive patients with leftsided VHD from different aetiologies and mechanisms of valvular dysfunction, reflecting the population of patients currently treated in our clinical practice.

1. S' RV imaging was not performed routinely as part of this protocol and therefore, the effect of cardiac surgery on RV function using these parameters was not assessed.
2. Pulmonary artery pressure quantification was based on the presence of an adequate TR envelope. We did not look at any events which may have occurred between the time of the echocardiography examination being done.
3. 2D strain software currently used was originally created for the assessment of LV systolic function and adapted for the right ventricle for the purpose of our study.Therefore 2D echocardiography diameters of the RV may significantly vary just with minor rotation of the probe due to the lack of a precise and specific landmark, leading to a significant under- or over-estimation of RV size.
4. Due to the small number of patients (n = 1) who progressed to significant TR, no further analysis was undertaken.
5. Lastly, the population from our hospital-based single-centre study is not representative of the general population of South Africa.

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APPENDICES

APPENDIX 1: LETTER OF INFORMATION AND CONSENT FORM

LETTER OF INFORMATION

Title of the Research Study: Investigation of changes in the right heart function after mitral and/or aortic valve surgical replacement using a two dimensional Doppler and speckle tracking echocardiography.

Principal Investigator/s/researcher: (Name, qualifications)

Ms N.Dlamini,

Registered M-tech degree student :Clinical Technology(Cardiology) at Durban University of Technology, employed and conducting research in Port Elizabeth provincial Hospital

Co-Investigator/s/supervisor/s: (Name, qualifications)

Dr.D.R Prakashandra

Senior lecturer in the department of biomedical and clinical technology

Dr.J.J Koshe

Specialist cardiothoracic surgeon

Mr.M.K.E

Chief cardiovascular perfusionist

Brief Introduction and Purpose of the Study:

The right ventricle has not been an area of concern because of the lack of right ventricular focused diagnostic equipment in the early years of cardiac interventions, difficulty in assessment due to its complex structure and also due to lack of awareness of the crucial role it plays in cardiac and pulmonary vascular disease. The use of and demand for echocardiography have shown a marked increase worldwide (Bedeker,2015). However, there is a lack of data regarding the impact of echocardiography in the assessment of cardiovascular disease in sub-Saharan Africa (Bedekerl et al,2015). This is possibly due to limited access to echocardiography in sub Saharan Africa and southern Africa because of the costs of the technique and the lack of highly specialized personnel to perform it, therefore the aim of this study is to investigate changes in the right heart after left heart valvular intervention and also investigate whether or not there are independent predictors of post operative (after surgery) right ventricular dysfunction and tricuspid valve regurgitation progression using two dimensional Doppler and Speckle tracking.

Outline of the Procedures: This is a clinical prospective study on the preoperative and postoperative echocardiographic parameters and their interaction in patient undergoing left sided valve surgery to investigate changes in the right heart function after mitral and/or aortic valve surgical replacement using a two dimensional Doppler and speckle tracking echocardiography. The study will be conducted at Port Elizabeth Provincial Hospital and the target population will include African male and female between the ages 18-65 years.

All participants recruited will undergo a detailed history and clinical examination by the cardiologist. Echocardiographic evaluation will be done by the lead investigator of the research who is a qualified and experienced cardiac clinical technologist, using the Ultra-Premium Aloka Prosound F75 Hitachi system ,The evaluation will include conventional echocardiographic parameters of RV function and speckle-tracking derived 2DS indices: RV global longitudinal strain (RVGS) and RV free wall longitudinal strain (RVFWS). M-mode echocardiography, two-dimensional and conventional colour Doppler echocardiography. Echocardiographic examination will be performed 72 hours before and 72 hours after completion of the interventional procedure and repeated 6 months thereafter.

Risks or Discomforts to the Participant: There are no known risks associated with echocardiographic examination.

Benefits: Abnormalities of the heart often have a long period without any signs or symptoms or have their symptoms relating to another disease, such abnormalities are more common in the under developed areas where access to appropriate investigations are limited in primary and secondary care setting. This research study will empower participants by increasing their knowledge and giving them the opportunity to be examined with the newest technologies that is not yet available in other institutions in the Eastern Cape. Moreover to improve their condition, wellbeing and quality of life of the participants. Also bring about potential addition of knowledge to existing theories about the importance of RV as determinant of clinical symptoms, peri-operative survival and postoperative outcome.

Reason/s why the Participant May Be Withdrawn from the Study: Participants may be withdrawn from the study as soon as they feel they do not want to continue with the study and when they do not comply. There will be no adverse consequences should participants wish to withdraw from the study.

Remuneration: It has been clearly specified on with participants before any agreements that there will be no compensation, such as money or otherwise in return of their participation.

Costs of the Study: Nothing will be expected of participants besides their corporation and presence during the days/times given to them to come for echocardiographic follow-up. Hospital transport will be available for those participants residing out of Port Elizabeth.

Confidentiality: Because of the sensitivity nature of the data to be collected, maintaining the confidentiality of clinical information is of high priority. Measures to ensure confidentiality will include:

- Recruitment and personal interviews will be done in total privacy.
- Questionnaires that have a detachable section containing the persons identification data.
- Storage of questionnaires in a locked room accessible only to select personnel

- Data will be anonymised (removed identifying details and patients to be identified with CN number) and entered into a secure database.

Research-related Injury: Should there be any research related injuries the participants will be taken care of free of charge by our trained stuff.

Persons to Contact in the Event of Any Problems or Queries:

Please contact the researcher (073 670 9030), my supervisors Dr.Prachaschandra, Dr Koshy and Mr.Gojo (0834467735,082 867 1291.) or the Institutional Research Ethics Administrator on 031 373 2375. Complaints can be reported to the Director: Research and Postgraduate Support Dr L Linganiso on 031 373 2577 or researchdirector@dut.ac.za.

CONSENT

Statement of Agreement to Participate in the Research Study:

- I hereby confirm that I have been informed by the researcher, ***NOMPILO DLAMINI*** (name of researcher), about the nature, conduct, benefits and risks of this study - Research Ethics Clearance Number:…………………………………
- I have also received, read and understood the above written information (Participant Letter of Information) regarding the study.
- I am aware that the results of the study, including personal details regarding my sex, age, date of birth, initials and diagnosis will be anonymously processed into a study report.
- In view of the requirements of research, I agree that the data collected during this study can be processed in a computerised system by the researcher.
- I may, at any stage, without prejudice, withdraw my consent and participation in the study.
- I have had sufficient opportunity to ask questions and (of my own free will) declare myself prepared to participate in the study.
- I understand that significant new findings developed during the course of this research which may relate to my participation will be made available to me.

_______________________ ___________ _______ _________________

Full Name of Participant **Date** **Time** **Signature / Right Thumbprint**

I, (name of researcher) herewith confirm that the above participant has been fully informed about the nature, conduct and risks of the above study.

___________________ ___________ _____________________

Full Name of Researcher **Date** **Signature**

___________________ ___________ _____________________

Full Name of Witness (If applicable) **Date** **Signature**

_________________ __________ ___________________

Full Name of Legal Guardian (If applicable) **Date** **Signature**

APPENDIX 2: LETTER TO PROSPECTIVE PARTICIPANTS

Port Elizabeth Provincial Hospital

Buckingham Road

Mount Croix

Port Elizabeth

6001

18/08/2020

Dear prospective participant

My name is Nompilo Dlamini, a registered masters degree (MHCLT) part time student in clinical technology based and permanently employed in Port Elizabeth Provincial Hospital.

I am kindly requesting you to participate in a medical research study that I am conducting titled: ***Investigation of changes in the right heart function after mitral and/or aortic valve surgical replacement using a two dimensional Doppler and speckle tracking echocardiography****.* The intention of this research study is to study changes in the heart after you have undergone left heart valve operation that could possibly predict future damage of right heart valve (Tricuspid) and right heart muscle function using a special heart scan technology called Speckle tracking Imaging (STE).

The study will involve you as the possible participants to undergo an examination by the cardiologist and echocardiographic examination by the clinical technologist (myself). Personal details will be kept secret by coding/substituting them with a ‘PE’ number that will be known only by myself and supervisors.

Participation is completely voluntary and you may withdraw from the study at any time. If you would like to participate in the study please read the Informed Consent letter below before signing at the bottom.

Your participation in the research will be of great importance to assist in addition of knowledge to existing theories about the importance of the right heart as determinant of clinical symptoms, survival and outcome after valve operation.

Thank you for your time and participation

Sincerely

Nompilo Dlamini

(Clinical technology part time student)

APPENDIX 3: REQUEST FOR EASTERN CAPE HEALTH APPROVAL

APPENDIX 3

Appendix 3

Province of the
EASTERN CAPE
HEALTH

Clinical Technology - Cardiology • Ground floor • Port Elizabeth Provincial Hospital • Buckingham Road • Mount Croix • Port Elizabeth
PO Korsten • Port Elizabeth • 6014 • REPUBLIC OF SOUTH AFRICA
Tel.: +27 (0)41 392 3329/3507 Cell: 073 670 9030

INTERNAL MEMORANDUM

TO ;	Dr.M.Xamlashe
FROM:	Ms.N.Dlamini
CC;	Ms.Z.Mthembu,Dr.J.Koshy,Dr.A.Knock
SUBJECT	Request for permission to conduct a research study in PE Provincial Hospital
DATE	10 February 2021

My Name is Nompilo Dlamini, a qualified clinical technologist registered with the health professions counsel of South Africa (Hpcsa). I am currently based and employed in Port Elizabeth Provincial Hospital and recently registered as a part time student for MHSc in Clinical Technology. I hereby request permission to conduct/embark on the following research study for my qualification in MHSc in Clinical Technology.

My topic: **Investigation of changes in the right heart function after mitral and/or aortic valve surgical replacement using a two dimensional Doppler and speckle tracking echocardiography.**

This will be a clinical prospective study on the preoperative and postoperative echocardiographic parameters and their interaction in patients undergoing left sided valve surgery in Port Elizabeth provincial hospital to investigate changes in the right heart function after mitral and/or aortic valve surgical replacement using a two dimensional Doppler. Dr.Jithan Koshy, Specialist and head of the cardiothoracic surgery unit and Mr.M.K.E Gojo have offered me supervision and support. I strongly believe that this study will offer expansion of knowledge in Cardiology and the cardiovascular unit as a whole. I seek to begin this study as soon as it is ethically approved.

Ethical consideration

Confidentiality and anonymity will be prioritized, as the South African constitution allows and respects individual's privacy regarding their health statuses. Attached is a departmental letter as well as the DoH approval. Should you require any further information, please do not hesitate to contact me directly on 073 670 9030, 041 392 3347/48 and nomsdlamini@gmail.com.

Thank you for your time and consideration in this matter.

Together, moving the health system forward

Fraud prevention line: 0800 701 701
24 hour Call Centre: 0800 032 364
Website: www.echealth.gov.za

APPENDIX 4: ETHICS TRAINING CERTIFICATE

Appendix 4

Zertifikat

Certificado

Certificat

Certificate

Promouvoir les plus hauts standards éthiques dans la protection des participants à la recherche biomédicale
Promoting the highest ethical standards in the protection of biomedical research participants

TRREE

Clinical Trials Centre
The University of Hong Kong

Certificat de formation - Training Certificate

Ce document atteste que - this document certifies that

Nompilo Dlamini

a complété avec succès - has successfully completed

Introduction to Research Ethics

du programme de formation TRREE en évaluation éthique de la recherche
of the TRREE training programme in research ethics evaluation

Release Date: 2021/01/29
CID : PVd1EhFfKB

Professeur Dominique Sprumont
Coordinateur TRREE Coordinator

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Swiss Academy of Medical Science (SAMS/ASSM/SAMW) (www.samw.ch) Commission for Research Partnerships with Developing Countries (www.kfpe.ch)

[REV : 20170310]

APPENDIX 5: IREC FULL APPROVAL

Institutional Research Ethics Committee
Research and Postgraduate Support Directorate
2nd Floor, Berwyn Court
Gate 1, Steve Biko Campus
Durban University of Technology

P O Box 1334, Durban, South Africa, 4001

Tel: 031 373 2375
Email: lavishad@dut.ac.za
http://www.dut.ac.za/research/institutional_research_ethics

www.dut.ac.za

Appendix 5

2 August 2021

Ms N Dlamini
P O Box 60060
Richards Bay
3900

Dear Ms Dlamini

Investigation of changes in the right heart function after mitral and/or aortic valve surgical replacement using a two dimensional Doppler and speckle tracking echocardiography
Ethics Clearance Number: IREC 004/21

The Institutional Research Ethics Committee acknowledges receipt of your notification regarding the piloting of your data collection tool.

Kindly ensure that participants used for the pilot study are not part of the main study.

Please note that FULL APPROVAL is granted to your research proposal. You may proceed with data collection.

Any adverse events [serious or minor] which occur in connection with this study and/or which may alter its ethical consideration must be reported to the IREC according to the IREC SOP's.

Please note that any deviations from the approved proposal require the approval of the IREC as outlined in the IREC SOP's.

Yours Sincerely

Professor J K Adam
Chairperson: IREC

APPENDIX 6: APPROVAL LETTER EASTERN CAPE HEALTH

Province of the
EASTERN CAPE
HEALTH

Appendix 6

Enquiries: Yvonne Gixela

Tel no: 079 074 0859

Email: Yvonne.Gixela@echealth.gov.za / ygixela@gmail.com

Date: 10 September 2021

Investigation of changes in the right heart function after mitral and/or aortic valve surgical replacement using a two dimensional Doppler and speckle tracking echocardiography. (EC_202104_005)

Dear Ms N. Dlamini

The department would like to inform you that your application for the abovementioned research topic has been approved based on the following conditions:

1. During your study, you will follow the submitted protocol with ethical approval and can only deviate from it after having a written approval from the Department of Health in writing.

2. You are advised to ensure, observe and respect the rights and culture of your research participants and maintain confidentiality of their identities and shall remove or not collect any information which can be used to link the participants.

3. The Department of Health expects you to provide a progress update on your study every 3 months (from date you received this letter) in writing.

4. At the end of your study, you will be expected to send a full written report with your findings and implementable recommendations to the Eastern Cape Health Research Committee secretariat. You may also be invited to the department to come and present your research findings with your implementable recommendations.

5. Your results on the Eastern Cape will not be presented anywhere unless you have shared them with the Department of Health as indicated above.

Your compliance in this regard will be highly appreciated.

SECRETARIAT: EASTERN CAPE HEALTH RESEARCH COMMITTE

2030 NDP

TOGETHER, MOVING THE HEALTH SYSTEM FORWARD

APPENDIX 7: STUDY VARIABLES

Appendix 7

STUDY VARIABLE

Demographic	
Age (years)	
gender	
Body mass index (kg/m2)	
Smoking	
Vital signs	
Systolic blood pressure (mmHg)/ Diastolic blood pressure (mmHg)	
Heart rate (beats/min)	
Rhythm	
Blood biochemistry	
Creatinine (mg/dL)	
Hemoglobin (mg/dL)	
LDL-cholesterol (mg/dL)	
PT/PTT/INR	

ECHOCARDIOGRAPHIC VALVE ASSESSMENT					
AORTIC VALVE STENOSIS	LVOT DIAMETER	AVA	MEAN GRAD (mmhg)	JET VELOCITY (m/s)	
MITRAL VALVE STENOSIS	PISA	MVA	MEAN GRAD (mmhg)	SYSTOLIC PULM.ART PRESSURE	
AORTIC VALVE REGURGITATION	VC WIDTH	PHT	AR JET WIDTH	PISA	
MITRAL VALVE REGURGITATION	VC WIDTH	PISA	JET VELOCITY	LA SIZE	
TRICUSPID VALVE					
VALVE MORPHOLOGY AND FUNCTION					
PULMONARY VALVE					
VALVE MORPHOLOGY AND FUNCTION					

Appendix 7

SPECKLE TRACKING ECHOCARDIOGRAPHY							
RV Longitudinal strain	Basal inferiorseptum (BIS)	Mid inferior septum (MIS)	Apical septum (ApS)	Basal anterior wall (BAL)	Mid Anterior Wall (MAL)	Apical Lateral wall (ApL)
RV Global strain						

M-Mode 2D Echocardiographic parameters	**LV**	**RV**
LV/RV EDD(mm)		
LV/RV ESD(mm)		
LV Septum Systole (mm)		
LV Septum Diastole (mm)		
LV Post Systole (mm)		
LV Post Diastole (mm)		
LV EF(%)		
LV FS (%)		
LAD (mm)		
RAD (mm)		
TAD (mm)		
RV FAC (%)		
TAPSE (mm)		
AO root (mm)		

Appendix 8

PE PROVINCIAL HOSPITAL ECHOCARDIOGRAPHY PROTOCOL

EQUIPMENT

Following equipment is required for an echocardiographic examination.

- Echocardiographic machine
- Electrocardiographic desposable leads
- Gel, for good surface contact
- Defibrillator for emergency arrhythmias
- Alcohol prep pads, webcol (To clean the patients skin)
- Shaving blade (used when indicated)
- Paper towel (for cleaning assess gel when test complete)

Personnel

- Echocardiography technologist
- Registered cardiac nurse
- Cardiologist, an expert in echocardiography/imaging

Preparation

No special preparations are required for a standard transthoracic echocardiogram. Ideally, chest hairs should be removed in male patients for good probe contact and proper image acquisition.

Echocardiography Terms

Frequency: Sound waves are mechanical vibrations. The number of vibrations per unit time is called frequency, expressed in Hertz, 1 Hz = 1 vibration per second. Higher the frequency of the probe, the better the resolution but, the lesser the penetration.

Grayscale: This indicates the different amplitude detected by the ultrasound system. High amplitudes are displayed bright, low amplitudes as dark grey, and no signal as black.

Appendix 8

Depth and Sector: Adjusting depth helps to adjust the size of the image on the screen. Sector indicates the width of the scan area. Both influence frame rate. Higher the frame rate, the higher is the resolution.

Gain: Increasing gain increases the overall brightness of the image.

TGC (time gain compensation): This compensates for attenuation of ultrasound energy with depth. These knobs help to increase or decrease the brightness at different depth levels.

Frame Rate: The more the frame rate, the better the temporal resolution. Decreasing the depth, narrowing the sector width, or using live zoom can increase the frame rate.

Technique

Patient Position and Electrocardiography Lead Placement

For the parasternal and apical tomographic views, the patient is required to lie in the left lateral decubitus position, with the left arm extended behind the head. This position brings the heart into close contact with the chest wall. The subcostal and suprasternal views require the patient to be in the supine position(Mitchell, C and Rahko, P et al.2019). The electrocardiogram (ECG) leads are placed, which allow identification of arrhythmias and timing of cardiac events during the echocardiographic examination. An electrocardiogram is used as a timing marker for digital recording gating of echocardiographic images.

Echocardiographic Modes

M Mode

Initially, echocardiographic images were obtained by sending ultrasound waves along a single line followed by the display of amplitude of the reflected signal as well as the depth of that signal on an oscilloscope, which was called A-mode echocardiography. When these lines of ultrasound images were plotted concerning time, an M-mode (motion mode) was produced. Despite the increasing emphasis on 2D and 3D imaging, the M-mode remains a complementary part of the echocardiographic examination. M mode has a high sampling rate as compared to 2D echocardiography, which provides excellent temporal resolution. It is very useful in the timing of subtle cardiac events that can be missed in the 2D echocardiographic examination. Rapidly moving structures such as the aortic valve and mitral valve, and endocardium have characteristic movements in M-mode (Feigenbaum,H.2010).

2D Echocardiogram

Appendix 8

2D echocardiographic imaging provides tomographic views of various planes of the cardiac structures and acts as a guide for the M-mode and Doppler echocardiogram. In 2D echocardiographic imaging, instead of having a fixed line of sight, the scan line is swept back and forth across an arc. After complex manipulation of the data received by the transducer from the multiple scan lines, a 2D tomographic image is generated by the echocardiographic machine for display (Bonagura,J and Blissitt,K.1995).

Doppler Imaging

The introduction of the Doppler technique to the 2D echocardiography not only added new imaging capabilities but also transformed echocardiography into a modality that could provide a non-invasive hemodynamic assessment. The Doppler principle states that "the sound frequency increases as the source moves toward the observer and decreases as the source moves away." This change in frequency between the transmitter and the reflected sound waves is called the Doppler shift (Pellett,A and Kerut,E.2004) .This Doppler frequency shift is used to measure the velocity of the red blood cell by using the Doppler equation (Mao,Y and Zhao, B et al.2019).

Spectral Analysis: The term used to describe how Doppler images (pulsed wave Doppler and continuous wave Doppler) are displayed.

- **Pulsed Wave (PW) Doppler**: The purpose of PW Doppler mode is to measure the Doppler shift to assess a velocity at a specific location of interest within a small sample volume (e.g., mitral inflow velocity at the mitral valve leaflet tips, the systolic velocity at the LVOT, and blood flow within the pulmonary veins). A single crystal sends short bursts of ultrasound waves at a specific pulse repetition frequency (PRF) to a specific location in this mode. The sound waves are reflected from moving blood cells at this location and received by the same crystal (Mao,Y and Zhao, B et al.2019). The maximal velocity that can be measured is limited by the time required to transmit and receive the reflected ultrasound wave, which is called the Nyquist limit. If a velocity is greater than the Nyquist limit, the signal appears as a wrap around the baseline called aliasing**.** Color Doppler and tissue Doppler imaging (TDI) are based on the principle of pulsed-wave Doppler.
- **Continuous Wave (CW) Doppler**: CW Doppler utilizes two crystals; one of the crystals continuously sends ultrasound waves, and the other continuously receives the waves. Unlike PW Doppler, CW Doppler measures the maximal velocity along the entire ultrasound beam, and it does not help in localizing the precise position of that peak velocity (Bolger,A and Eidenvall,L et al.1997). Aliasing is not a feature of continuous-wave Doppler, so it is used to measure the higher velocities, e,g aortic stenosis.

Appendix 8

In general, CW Doppler is used to assessing a high-velocity flow, and PW Doppler is used to measuring the low-velocity flow in specific areas.

2D Echocardiographic Tomographic Views

Parasternal Views: The parasternal views are obtained in the left lateral decubitus position by placing the transducer at the left of the sternal border in the third or fourth intercostal space. A hybrid position between the steep left lateral and supine positions may be required to optimize the view. This position allows imaging of the long axis as well as the short axis of the heart (Remenyi, B and Davis, K et al.2020).

- **Parasternal long axis (PLAX) view**: The PLAX view is traditionally the first view of a standard transthoracic echocardiographic examination. The ultrasound beam is lined up between the patient's right shoulder and the left flank. The right ventricular outflow tract (RVOT) is located at the top of the image, the aorta to the right, the inferolateral (or posterior) wall on the bottom, and the cardiac apex on the left. The anteroseptal is visualized between the right ventricular outflow tract (RVOT) and the left ventricular (LV) cavity.Tilting the transducer towards the left shoulder with slight clockwise rotation brings the right ventricular (RV) inflow into view. This is good for obtaining the tricuspid regurgitation (TR) velocity and examining the tricuspid valve, RV apex, and the right atrium.
- **Parasternal short axis (PSAX) view**: While the transducer is in the parasternal long-axis position, rotating the transducer clockwise by approximately 90° displays the heart in the short axis. The ultrasound beam in this view is directed roughly from the left shoulder to the right flank. Using different degrees of transducer tilting, and moving up or down an intercostal space, results in different views of the heart. For example, on tilting from superior to inferior, the views obtained are aortic valve-RV outflow view, mitral valve level view, mid-ventricle at the papillary muscles, and the SAX view at the level of LV apex.
-

Apical Tomographic Views: The apical position is obtained with the patient in the left lateral position and the probe placed at the maximum apical impulse. This position allows imaging of the long axis of the heart (Mitchell, C and Rahko, P et al.2019).

- **Apical four-chamber (A4C) view**: The A4C the transducer is oriented to place the left ventricle on the right side of the screen and the right ventricle on the left side. The apex is at the top of the image, and the atria are at the bottom, regardless of the orientation. The inferoseptal and anterolateral walls and the apex of the left ventricle are assessed in this view. Assessment of the right ventricular structure and function is also done in this view.

- **Apical five-chamber (A5C) view**: A slight rotation of the transducer introduces the proximal aorta, a fifth "chamber," as well as the aortic valve and LVOT. This view allows for qualitative assessment of aortic valve morphology along with the hemodynamic assessment of the LVOT and aortic valve.
- **Apical two-chamber (A2C) view**: From the apical 4C view, 90° counterclockwise rotation gives the A2C view. In this view, in addition to the left atrium, the LV anterior wall, inferior wall, apex, and mitral valve are also well visualized.
- **Apical long axis/three-chamber (A3C) view**: A slightly more counterclockwise rotation (approximately 30°) from the A2C view brings the aorta back into the image, resulting in the A3C, or apical long-axis view. This view essentially has the same anatomical structures as those in the PLAX view with a different orientation. The apex is better visualized, and the RVOT usually drops out of the image. Additional information on mitral and aortic valve hemodynamics can also be obtained in this view.

Subcostal Tomographic Views: The subcostal view is obtained with the patient in the supine position and the probe located caudal to the xiphoid process. The transducer is placed in the midline nearly parallel to the long axis of the patient's body so that the ultrasound beam slices toward the spine. This shows the right ventricle at the top right, the left ventricle at the bottom right, and their respective atria on the left. (Figure.8) Clockwise rotation along with inferior tilting brings the inferior vena cava (IVC) and hepatic veins into view for right-sided hemodynamic assessments (Mitchell, C and Rahko, P et al.2019).

Suprasternal Tomographic Views: Suprasternal view is obtained by placing the transducer in the suprasternal notch and pointing inferiorly. It is used to assess the ascending aorta, aortic arch, and descending aorta. Hemodynamics from this position can better characterize AR, patent ductus arteriosus, and the presence of coarctation of the aorta (Mitchell, C and Rahko, P et al.2019).

Appendix 9
Table of Intravaraibility indices

1,7	LVOT DIAMETER(MM)
0,8	AVA(CM2)
1,8	JET VELOCITY(M/S)
0,3	MVA(CM2)
8,1	MEAN GRAD(MMHG)
5,5	VC WIDTH(MM)
3,0	BIS
8,6	Aps
2,6	BAL
2,5	MAL
6,6	Apl
1,2	RV GLS
3,9	RV BASE
2,8	RV MID
5,8	RV LONGITUDINAL
3,2	LVEDD(CM)
2,2	LVESD(CM)
1,0	LV SEPTUM SYST(MM)
1,1	LV POST SYSTOLE(MM)
5,9	LV POST DIASTOLE(MM)

4,7	LV EF (%)
2,3	LV FS(%)
5,5	LAD(MM)
4,8	RAD(MM)
3,0	TAD(MM)
2,4	RV FAC(%)
1,3	TAPSE(MM)
2,3	A0 ROOT