

Evaluation of Mitral Annular Plane Systolic Excursion Derived Ejection Fraction to Determine Left Ventricular Systolic Function

by

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A dissertation

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*To Zavian
for being our bright light in the darkest times*

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Declaration of Independent Work

I, Hendré van Rensburg, do hereby declare that this research project submitted to the Central University of Technology for the degree **MASTER OF HEALTH SCIENCES IN CLINICAL TECHNOLOGY** is my own independent work that has not been submitted to any institution by me or any other person in fulfilment of the requirements for the attainment of any qualification.

March 2024

Signature

Date

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Firstly, I want to say thank you to the almighty Lord and Saviour for guiding me during this process. With You everything is possible and without You, everything is impossible, and this I have realised more and more each day. I thank You, Lord for everything You have done, are doing, and are going to do for me.

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List of Abbreviations

Acronym

25 th %	Lower 25 th percentile
75 th %	Upper 75 th percentile
2D	Two-dimensional
3D	Three-dimensional
a' velocity	Late diastolic velocity
AP2CH	Apical two chamber
AP4CH	Apical four chamber
ASE	American Society of Echocardiography
AVPD	Atrioventricular plane displacement
BMI	Body mass index
CCF	Congestive cardiac failure
CT	Computed tomography
CVD	Cardiovascular disease
D1	Length
D2	Width
ET	Ejection time
e' velocity	Early diastolic velocity
ECG	Electrocardiogram
EDV	End-diastolic volume
EF	Ejection fraction
ESV	End-systolic volume

F	Female
GLS	Global longitudinal strain
h	Height
HFmrEF	Heart failure mid-range ejection fraction
HFpEF	Heart failure preserved ejection fraction
HFrEF	Heart failure reduced ejection fraction
HICs	High-income countries
ICD	Implantable cardioverter-defibrillator
IHD	Ischemic heart disease
IVCT	Isovolumetric contraction time
IVRT	Isovolumetric relaxation time
Lat	Lateral
LMIC	Low- and middle-income countries
LV	Left ventricle
LV MPI	Left ventricular myocardial performance index
LVEDD	Left ventricular end diastolic dimension
LVEDV	Left ventricular end diastolic volume
LVEF	Left ventricular ejection fraction
LVESD	Left ventricular end-systolic dimension
LVESV	Left ventricular end systolic volume
M	Male
MA $\pm$ Std	Median age with standard deviation

MAE	Mitral annulus excursion
MAPSE	Mitral annular plane systolic excursion
MAPSE EF	Mitral annular plane systolic excursion derived ejection fraction
Med	Medial
mm	millimetre
M-mode	Motion mode
MPI	Myocardial performance index
MRI	Magnetic resonance imaging
MUGA	Multigated acquisition
n	Each disk
N	Total patients
NYHA	New York Heart Association
PET	Positron emission tomography
p-value	Probability value
ROI	Region of interest
S'	Mitral annular systolic velocity
SAS	Statistical Analysis System
SPECT	Single-photon emission computed tomography
SV	Stroke volume
TDI	Tissue Doppler imaging
TTE	Transthoracic echocardiogram
V	Volume
v	Ventricle

List of Symbols

$=$	Equal
$\geq$	Greater than or equal to
$\times$	Multiply
$'$	Omission of letters
$\%$	Percentage/ Percentile
π	Pi equal to 3.14159
$+$	Plus
$\pm$	Plus, minus
$\rightarrow$	Result
$-$	Subtract

Glossary

Term	Definition
Angiogenesis	The physiological process through which new blood vessels form from pre-existing vessels (Kurz <i>et al.</i> , 2003).
Aortic stenosis	Obstruction of blood flow across the aortic valve due to aortic valve fibrosis and calcification (Nkomo <i>et al.</i> , 2006).
Atrial fibrillation	A cardiac arrhythmia due to abnormal electrical activity within the atria of the heart, causing them to fibrillate (Markides <i>et al.</i> , 2003).
Biomarkers	A defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes or responses to an exposure or intervention (Califf, 2018).
Cardiac remodelling	A group of molecular, cellular, and interstitial changes that manifest clinically as changes in size, mass, geometry, and function of the heart after injury (Azevedo <i>et al.</i> , 2016).
Cardiotoxic	Medication or treatment leading to left ventricular function or failure (Pardo <i>et al.</i> , 2020).
Cardiovascular diseases	Refers to any disorder of the heart and vascular system (Benjamin <i>et al.</i> , 2018).
Cardioverter-defibrillator device	A device that treats arrhythmias specifically those of ventricular origin (Bardy <i>et al.</i> , 2005).
Congenital heart defect	Abnormalities in heart structure that occur before birth (Sun <i>et al.</i> , 2015).
Computer tomography scan	A radiological imaging study (Petrik <i>et al.</i> , 2006).
Coronary artery disease	A condition characterised by an inadequate supply of blood and oxygen to the myocardium (Dalen <i>et al.</i> , 2014).
Diastolic dysfunction	The disturbance in ventricular relaxation, distensibility, or filling (Gaasch <i>et al.</i> , 2004).
dp/dt	Represents the ratio of pressure change in

	the ventricular cavity during the isovolumetric contraction period (Morimont <i>et al.</i> , 2012).
Eccentric hypertrophy	Volume overload-induced cardiac hypertrophy (Mihl <i>et al.</i> , 2008).
Effusion	Fluid accumulation between structures (Lepus <i>et al.</i> , 2018).
Electrocardiogram	Diagnostic test which records from the body surface and registers the differences in electrical potential generated by the heart (Krikler, 1987).
Isovolumetric contraction	The phase of systole when both valves are closed (Sinanis <i>et al.</i> , 2023).
Isovolumetric relaxation	The period immediately after ventricular contraction when the aortic valve has closed, but the mitral valve has not yet opened (Yothi Prakash <i>et al.</i> , 2019).
Left ventricular aneurysms	The bulging or outpouching of the weakened muscle wall (Aquerque <i>et al.</i> , 2018).
Left ventricular dyssynchrony	Asynchronous ventricular contraction and relaxation, which may or may not be associated with electrical conduction delay (Yu <i>et al.</i> , 2003).
Magnetic resonance imaging	Diagnostic scan, which uses a strong magnetic field and radio waves to create detailed images of the organs and tissues within the body (Haralson & Zuckerman, 2009).
Multigated acquisition	Nuclear medicine imaging modality that aids healthcare providers to evaluate the heart's structural and dynamic properties (Aul & Nabi, 2004).
Murmur	A series of vibrations of variable duration, audible with a stethoscope at the chest wall, that emanates from the heart or great vessels (Mineo <i>et al.</i> , 2001).
Myocardial deformation	Quantifies how two different points of the myocardium change position with regard to each other over a certain period of time (Bijnens <i>et al.</i> , 2012).

Myocardial infarction	A condition in which there is decreased or complete cessation of blood flow to a portion of the myocardium (Thygesen <i>et al.</i> , 2007).
Pericardium	Fibrous sac that encloses the heart and great vessels (Saxton <i>et al.</i> , 2023).
Positron emission tomography	A technique that measures physiological function by looking at blood flow, metabolism, neurotransmitters, and radiolabelled drug (Berger, 2003).
Pulsed wave Doppler	An ultrasound modality which sends short pulses of ultrasound and analyses reflected sound waves between the pulses (Moorthy, 2002).
Regurgitation	Leakage of blood backward through the valve each time the left ventricle contracts or relaxes (Bekeredjian & Grayburn, 2005).
Single-photon emission computed tomography	A nuclear imaging modality (Israel <i>et al.</i> , 2012).
Spatial resolution	The scale or size of the smallest unit of an image capable of distinguishing objects, or a measure of the smallest angular or linear distance to identify adjacent objects in an image (Watts, 2019).
Temporal resolutions	The extent to which an ultrasound system is able to distinguish changes between successive image frames over time (Alexander & Swanevelter, 2011).
Tissue Doppler Imaging	An echocardiography mode that detects low-velocity, high-amplitude myocardial velocity rather than the blood cells that are high velocity, and low amplitude (Pellerin <i>et al.</i> , 2003).
Ventriculography	A manner of assessing ventricular function and intracardiac hemodynamics (Lapińska <i>et al.</i> , 2012).

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Executive Summary

Introduction

Left ventricular ejection fraction (LVEF) is an essential measurement in echocardiography used to diagnose, treat, and manage patients. Two dimensional (2D) echocardiography is the most common imaging modality used to determine LVEF.

Mitral annular plane systolic excursion (MAPSE) is considered a useful surrogate of 2D longitudinal function and can be converted to an ejection fraction through the formula $\text{MAPSE EF} = (4.8 \times \text{MAPSE}) + 5.8$. MAPSE EF has been proven to be a valid method to determine ejection fraction in adult males with impaired LV systolic function. Currently, no research has been conducted to determine if this equation could be used in the daily setting. Therefore, the aim of the study was to evaluate mitral annular plane systolic excursion formula for determining ejection fraction in daily practice.

Methods

This prospective descriptive-analytical study was conducted in central South Africa, including 475 male or female adult participants aged 18 and above. Ethical approval (Appendix A) and informed consent (Appendix C) were obtained, and participants were provided with an information guide (Appendix D). The patients were further subdivided according to their primary clinical condition: systemic hypertension, diabetes mellitus type 2, congestive cardiac failure, and ischemic heart disease.

Systolic parameters were measured by transthoracic echocardiography. MAPSE was measured and converted to MAPSE EF and correlated with Teichholz EF, modified Simpson's apical four chamber (AP4CH) and apical two chamber (AP2CH) EF, global longitudinal strain-derived EF, systolic (S') tissue Doppler imaging of the medial and lateral mitral valve annuli, and LV myocardial performance index (MPI). A correlation value of ≥ 0.70 was considered a strong clinical correlation.

Participants were excluded if they had had aortic-and/or mitral valve replacement surgeries, had mitral valve annular dysfunction, pericardial diseases,

tachyarrhythmias, malignant- or uncontrolled hypertension, new or uncontrolled diabetes mellitus type 2, acute ischemic events, or inadequate imaging views.

Results

Patients presented at a mean age of 61 ± 14.9 years with no gender dominance. Most of the patients were from the Bethlehem region, since the private practice where the study was conducted is situated in Bethlehem (Appendix E). Furthermore, 70% of the patients had mild symptoms and were in New York Heart Association (NYHA) class 1 and 2 at presentation (Appendix F).

Normal to mildly impaired systolic measurements were noted in the total population with a mean EF: $50.2 \pm 0.3\%$ (Appendix G). A noteworthy impairment of all systolic parameters was present in the congestive cardiac failure (CCF) group (EF < 30%). Normal to mild impairment was noted in the ischemic group, while normal systolic parameters were found in the hypertension and diabetes mellitus groups.

Correlation coefficients for the total study group are illustrated in Appendix H1. Overall, a strong positive correlation was observed between MAPSE EF and all the other systolic parameters ($r > 0.82$), while LV MPI had a strong negative correlation with MAPSE EF ($r = -0.74$). MAPSE EF also correlated strongly with the systolic parameters in both genders ($r > \pm 0.73$) (Appendix H2 and H3).

MAPSE EF and the systolic parameters correlated the best ($r > 0.80$) in the congestive cardiac failure group. Similarly, in both genders, a strong close correlation was noted between MAPSE EF and the systolic parameters ($r > \pm 0.70$), with only LV MPI in the female group, which had low clinical correlation ($r = -0.65$) (Appendix H4 and H5). In the diabetes mellitus type 2, hypertension, and ischemic heart disease groups, no clinical correlation was noted between MAPSE EF and the systolic parameters. However, a low correlation ($r < 0.62$) was noted between MAPSE EF and S' in the hypertension group, and S' was the only systolic parameter which had a strong, positive correlation ($r > 0.74$) with MAPSE EF in the ischemic heart disease group.

Patients with grade one diastolic dysfunction also demonstrated poor correlations between MAPSE EF and all the systolic parameters (Appendix H6). This improved in grade two diastolic dysfunction (Appendix H7), while patients with grade three

diastolic dysfunction had an excellent correlation ($r:\geq\pm 0.84$) between MAPSE EF and the other systolic parameters (Appendix H8).

Strain-derived EF had a strong, positive correlation ($r:>0.81$) with modified Simpson's AP4CH EF in the total population, as well as in all the subgroups (Appendix H9). Strong, negative correlation ($r:>-0.76$) was observed between LV MPI and Simpson's AP4CH EF in the total population, while low to weak clinical correlation between these two systolic variables was noted in the subgroups (Appendix H10).

Discussion

Our patients presented at a mean age of 61 ± 14.9 years with normal or minimally impaired systolic echocardiographic parameters. However, in patients with congestive cardiac failure, echocardiographic parameters were exclusively impaired.

Although strong correlations were noted in the total population, subgroup analyses demonstrated several differences between MAPSE EF, and the other methods used to determine systolic LV function. In the congestive cardiac failure group, MAPSE EF correlated superbly with all the systolic parameters, irrespective of gender. It should be noted that this is the first time that MAPSE EF in both genders with CCF was determined.

In the hypertension, diabetes mellitus, and ischemic heart disease groups, less favourable correlations were observed between MAPSE EF and the other systolic parameters. MAPSE EF correlated moderately only with S' in the hypertension group, and strongly in the ischemic heart disease group. We predict that basal segment function was most likely preserved in our patient population study since MAPSE and S' were normal, although left ventriculography was not obtained.

Conclusion

Results demonstrated that MAPSE EF is a valid method to determine ejection fraction in patients with significantly impaired systolic function, irrespective of gender.

CHAPTER 1: Introduction

1.1 Background

Cardiovascular diseases result in a major burden to healthcare globally and are a leading cause of death in industrialised countries. The prevalence of cardiovascular disease (CVD) is increasing, and the age-specific mortality rates are decreasing (Chan *et al.*, 2020). CVD mortality rates have been declining globally by 14.5% between 2006 and 2016, but the burden remains larger in low- and middle-income countries (LMICs) like South Africa compared to high-income countries (HICs), as more than 80% of CVD deaths occur in LMICs. In Sub-Saharan Africa half of cardiovascular deaths occur in the 30–69 years age group, at least ten years earlier than in HICs (Gheorghe *et al.*, 2018).

Patients with CVD are increasingly likely to present at primary care physicians as their first point of care or for a follow-up examination. The treatment of patients with cardiovascular diseases almost invariably involves the use of echocardiography as a means of initial and follow-up investigation. The most widely used and accepted echocardiographic parameter of left ventricle (LV) systolic function has been ejection fraction (EF), with this parameter having a unique position in cardiology and featured as a selection criterion for almost all landmark therapeutic trials of heart failure. As a result, references to EF are incorporated in clinical guidelines (Chan *et al.*, 2020; Kjaeboe and Edvardsen, 2019).

Left ventricular ejection fraction (LVEF) is a vital and established measurement of left ventricular systolic function (Karlsen *et al.*, 2019). The accurate measurement of LVEF is significant, as it is used to manage patient outcomes presenting with various cardiovascular diseases. This measurement also has a prognostic value in predicting undesirable outcomes (Bonhorst *et al.*, 2019). This is especially important for patients admitted with acute coronary syndrome and those who need coronary artery intervention as the risk of complications such as heart failure and cardiac arrhythmias increases in patients with an impaired LVEF (Perelshtein-Brezinov *et al.*, 2017). An increase in operative and postoperative complications are also associated with reduced LVEF values, despite the type of operation (Lindenfeld *et al.*, 2010).

There are several established methods to calculate ejection fraction. However, most of these imaging modalities and procedures require visualisation of two or more left ventricular wall segments to estimate LVEF (Ponikowski *et al.*, 2016). Poor image quality can lead to inaccuracies when measuring LVEF (Plana *et al.*, 2014). Poor visualisation of the left ventricular endocardial border is associated with considerable inconsistencies among sonographers (Hoffmann *et al.*, 2014). Unsatisfactory image quality occurs in approximately 10-15 % of routine echocardiograms with interobserver agreement as low as 43% (Nagata *et al.*, 2018). Echocardiography image quality can be further compromised by abnormal patient anatomy, patients on ventilators in the intensive care unit or emergency room and undesirable patient position (Flegal *et al.*, 2005).

High error rates with limited images and several methods using more than a few left ventricular wall segments to calculate LVEF is a challenge for a sonographer in practice. Due to these limitations, new methods were developed to quantify EF. According to Matos *et al.* (2012) the use of a single left ventricular wall segment to derive an ejection fraction is possible. Adel *et al.* (2016) also reported that the MAPSE derived EF equation is a valid technique in adult males with impaired LV systolic function. However, gender specific differences in MAPSE measurements or to validate the equation for EF prediction in females was a significant limitation in this study as only men were included in the study. Currently, no research has been done to evaluate if this equation could be used in females with impaired LV systolic function. Irrespective of these limitations, MAPSE-derived EF using the equation $EF = 4.8 \times MAPSE \text{ (mm)} + 5.8$ is a valid method to calculate LVEF in adult males with severely impaired LVEF.

Therefore, the aim of the study was to evaluate mitral annular plane systolic excursion formula to determine ejection fraction in daily practice because the need for another systolic LVEF measurement is of immense importance.

1.2 Aim

The study aimed to determine how well MAPSE derived EF correlated with other left ventricular systolic parameters and to determine if this method could be used as a substitute systolic measurement.

1.3 Objectives

The objectives for this study were:

- To correlate MAPSE derived EF with M-mode EF, Simpson's method EF, strain derived EF, LV MPI, and tissue Doppler annular systolic velocities.
- To determine if MAPSE derived EF could be used as a substitute systolic measurement compared to standardised EF measurement.
- To serve as a pilot study for future research on MAPSE derived EF in subgroups.

CHAPTER 2: Literature review

2.1 Heart failure

Heart failure is defined as a clinical syndrome with typical symptoms and signs, which are triggered by a functional and/or structural cardiac abnormality resulting in reduced cardiac output and/or elevated intracardiac pressures at rest or during stress (Ponikowski *et al.*, 2016). Currently, there are no population-based studies that have evaluated the incidence of heart failure in South Africa. In South Africa, heart failure is predominantly found in adults, usually in the 30-40's (Agbor *et al.*, 2018). In the United States and Canada, a prevalence rate of 1.5-1.9% was estimated, compared to Europe with a rate of 1-2% (Ponikowski *et al.*, 2014). The survival rates for heart failure in 1 month, 1, 2, 5, and 10 years were 95.7%, 86.5%, 72.6%, 56.7% and 34.9% respectively (Jones *et al.*, 2019).

Heart failure has been categorised into three subgroups based on LVEF. These subgroups are:

- Heart failure with reduced ejection fraction (HFrEF),
- Heart failure with mid-range ejection fraction (HFmrEF),
- Heart failure with preserved ejection fraction (HFpEF) (Ponikowski *et al.*, 2016).

2.1.1 Heart failure with reduced ejection fraction

HFrEF accounts for 30% of the heart failure subgroup and is defined by LVEF measured at 40% or less, and is associated with progressive LV dilation and adverse cardiac remodelling as shown in Figure 2.1 (Abraham *et al.*, 2008).

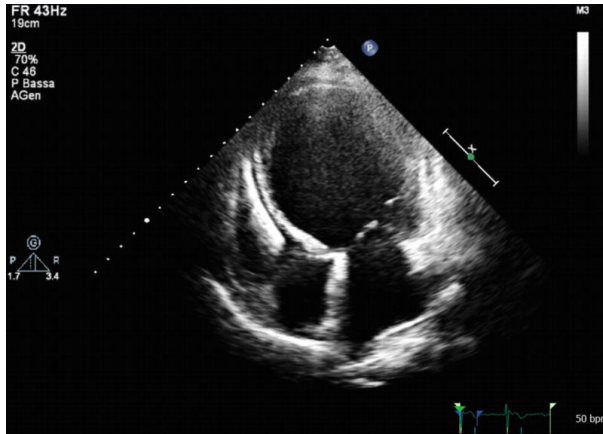


Figure 2.1 *Apical four chamber view shows a dilated LV cavity with a spherical appearance (Adapted from Kleijn et al., 2009).*

HFrEF is characterised by dilation of the LV with impaired global/segmental contractility. Atrial dilation, right ventricular enlargement, functional mitral and tricuspid valve regurgitations, and LV dyssynchrony are often linked with HFrEF (Murphy *et al.*, 2020). The primary causes of HFrEF include coronary artery disease, hypertension, aortic stenosis, mitral regurgitation, and viral infections (Abraham *et al.*, 2008).

HFrEF shares the same pathophysiological processes as HFmrEF and HFpEF but does not increase ventricular stiffness as seen with HFpEF, resulting in eccentric LV hypertrophy. Around 40-60% of individuals with HFrEF have accompanying diastolic dysfunction; in contrast, diastolic dysfunction may occur in the absence of systolic dysfunction. The prognosis of patients with HFrEF and HFmrEF is 42% worse compared to HFpEF. The mortality rate is higher in HFrEF than HFmrEF and HFpEF, according to the OPTIMIZE-HF trial that showed a mortality rate of 3.9% for HFrEF, 3% for HFmrEF, and 2.9% for HFpEF, respectively (Tsuji *et al.*, 2017).

2.1.2 Heart failure with mid-range ejection fraction

HFmrEF accounts for 13-24% of the heart failure subgroup and is defined by LVEF measured between 40-49%. The term HFmrEF was first proposed in 2014 (Lam & Solomon, 2014) and in 2016, the European Society of Cardiology Guidelines replaced the term “grey area”, which was previously referred to patients in this LVEF group with the term HFmrEF (Ponikowski *et al.*, 2016).

HFmrEF is usually seen in younger individuals, and more likely to present in men compared to the HFpEF group. HFmeEF and HFrEF share a higher prevalence of coronary artery disease and ischemic events than HFpEF (Tsuji *et al.*, 2017). In contrast, HFmeEF and HFpEF share a higher prevalence in atrial fibrillation and LV hypertrophic formation, and diabetic and hypertensive patients are more common in these groups (Chioncel *et al.*, 2017).

Limited evidence is currently available with regard to the pathophysiology; however, biomarkers demonstrated an intermediate biomarker profile. Myocardial stretch, angiogenesis etc. was noted, as observed with HFrEF, as well as inflammation, typically seen with HFpEF (Tromp *et al.*, 2017).

2.1.3 Heart failure with preserved ejection fraction

HFpEF accounts for more than 50% of the heart failure subgroup and is characterised by an LVEF of more than 50%. LV hypertrophy, left atrial enlargement and diastolic dysfunction are the key findings associated with HFpEF as shown in Figure 2.2 (Chioncel *et al.*, 2017).

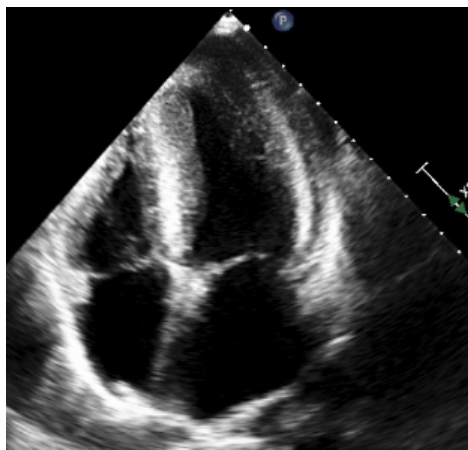


Figure 2.2 *Apical four chamber view shows significant hypertrophy of the LV cavity with accompanying LA dilation (Adapted from Devereux., 2009).*

The primary conditions associated with HFpEF include hypertension, diabetes, obesity, coronary artery disease and atrial fibrillation. The prevalence of HFpEF is

increasing, and it is expected that by 2020, 65% of patients hospitalised for HF will have HFpEF (Chioncel *et al.*, 2017).

The pathophysiology for HFpEF is consistent with impairment of intraventricular pressure gradients, mitral annular longitudinal motion, early diastolic LV untwisting, and the elastic recoil in the previous contraction cycle. Consequences of these conditions result in a normal systolic LV performance with diastolic LV dysfunction, which consists of prolonged isovolumetric LV relaxation, slow LV filling, and increased diastolic LV stiffness (Tsuji *et al.*, 2017).

2.2 Cardiac function measurement using echocardiography

Echocardiography is a procedure that uses sound waves to generate live images of the heart. This can either be done non-invasive (transthoracic echocardiogram) or invasive (transesophageal echocardiogram) (Mohammed *et al.*, 2010).

An echocardiogram can be performed for several reasons. The most common include discovery of a heart murmur, chest pain, chronic diseases affecting the heart, congenital heart defect, or other test showing signs of heart problems such as an electrocardiogram (ECG) (Wood *et al.*, 2014).

The images produced of the heart can be used to evaluate the heart chambers' sizes and functions, the pericardium and presence of pericardial effusion, size of the aorta and pulmonary artery, structure, and function of the cardiac valves etc. (Mohammed *et al.*, 2010).

2.3 Left ventricular ejection fraction

LVEF is defined as the fraction of left ventricular chamber volume ejected in systole in relation to the volume of the blood in the ventricle at the end of diastole. Normal LVEF is considered 50-70% (Behnoush *et al.*, 2023). Stroke volume (SV) is considered as the difference between end-diastolic volume (EDV) and end-systolic volume (ESV). LVEF is calculated as $LVEF: (SV/EDV) \times 100$ (Lang *et al.*, 2015).

LVEF is arguably the most important measurement performed during echocardiography, as it is the central measurement to determine left ventricular systolic function. The clinical significance of determining LVEF cannot be underestimated, as it is a vital measurement in echocardiography used to diagnose, manage, and predict various stages of cardiac pathologies. It is also a powerful predictor of cardiac mortality. LVEF is the primary criterion for the placement of a cardioverter-defibrillator device (ICD) among patients with ischemic heart disease with reduced LVEF (Melo *et al.*, 2019), also used to predict the diagnosis, management, and prognosis of patients in heart failure (Alushi *et al.*, 2019).

LVEF is an important parameter for monitoring LV function in the management of cardiotoxic chemotherapy. LVEF is the method of choice to evaluate patients before, during, and after cancer therapy. An LVEF less than 53% at baseline requires an early cardiology consultation to discuss the risk and benefits ratio (Plana *et al.*, 2014). LVEF is also one of the criteria to manage patients with valvular heart disease. Aortic valve replacement is recommended for asymptomatic patients with severe aortic stenosis or chronic severe aortic regurgitation and LVEF less than 50%. Mitral valve surgery is considered for asymptomatic patients with LVEF $\leq 60\%$ (Bonow *et al.*, 2018).

2.4 Left ventricular systolic function measuring methods

LVEF can be calculated using various modalities by either using subjective visual estimation or objective quantitative methods. The preferred methods are to utilise quantitative measures to assess LVEF to diminish variability and favour more precision and accuracy in the measurement. Various invasive and non-invasive modalities with different methods can be used to calculate LVEF. Invasive modalities include LV contrast ventriculography during cardiac catheterisation, whereas non-invasive include transthoracic-and transesophageal echocardiogram, magnetic resonance imaging (MRI), computer tomography (CT), multigated acquisition (MUGA) scan, and gated myocardial perfusion imaging with either single-photon emission computed tomography (SPECT) or positron emission tomography (PET) (Hoffman *et al.*, 2014). In echocardiography alone, various methods can be used to determine LVEF. These include motion mode, two-dimensional (2D), or three-

dimensional (3D), and the equations used to determine LV volumes. These methods also differ based on the echocardiographic images obtained. These measurements can be linear (one-dimensional), area (two-dimensional), or volume (three-dimensional) measurements (Plana *et al.*, 2014). Several methods are available to determine the systolic function of the left ventricle. 2D echocardiography, 2D-guided M-mode echocardiography, and Doppler echocardiography can be used to calculate the dimensions and volume of the LV cavity (Chegonde, 2016).

2.4.1 Motion mode

Motion mode (M-mode) is a modality from which ejection fraction (EF) is estimated as a percentage derived from the mid-left ventricular volumes measured in end-diastole and end-systole (Cacciapuoti, 2008). These are derived volumes, which are computed based on the “cubed” or Teichholz equations. The Teichholz method calculates LV volumes from LV linear dimensions from which an ejection fraction is derived, as noted in Figure 2.3 (Plana *et al.*, 2014).

The Teichholz formula states:

$$\text{LVEDV} = [7 / (2.4 + \text{LVEDD})] \times \text{LVEDD}^3$$

$$\text{LVESV} = [7 / (2.4 + \text{LVESD})] \times \text{LVESD}^3$$

$$\text{LVEF} = (\text{LVEDV} - \text{LVESV}) / \text{LVEDV},$$

where:

LVEDV → Left ventricular end diastolic volume,

LVEDD → Left ventricular end diastolic diameter,

LVESV → Left ventricular end systolic volume,

LVESD → Left ventricular end systolic diameter (Arora *et al.*, 2010).

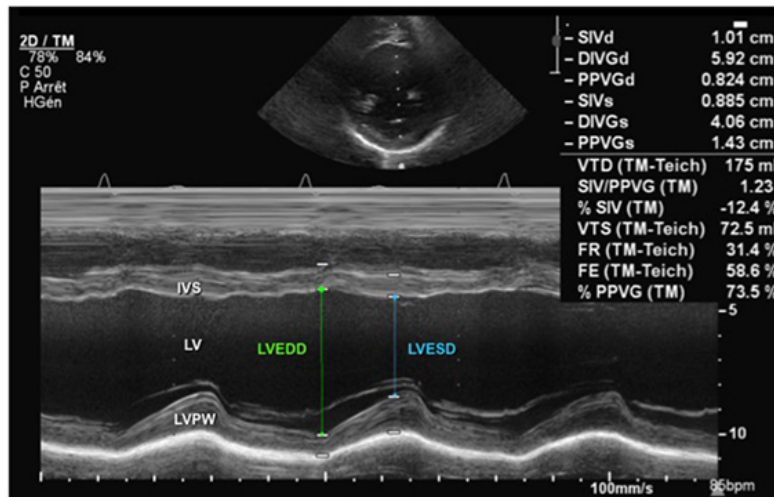


Figure 2.3 M-mode measurement of the LVEDD and LVESD dimensions from which LVEDV and LVESV is derived (Adapted from Benfari G., 2019).

2.4.1.1 Advantages of M-mode derived LVEF

The advantages using this method include reproducibility of 74%, high frame rates, a considerable amount of data accumulated, and a considerable improvement of the accuracy of LV volume measurements. This technique enhances accurate determination of linear dimensions and improves quantitation of chamber size and wall thickness (Darasz *et al.*, 2002; Lang *et al.*, 2005; Thorstensen *et al.*, 2010).

2.4.1.2 Limitations of M-Mode derived LVEF

Limitations of this method are that it only represents a single wall measurement, and the beam orientation is frequently off axis. This method cannot be used in patients with abnormal cardiac morphology seen with congenital heart defects, ischemic heart disease, left ventricular aneurysms, etc. Volume calculations derived from linear measurements may be inaccurate, because they rely on the assumption of a fixed geometric LV shape such as a prolate ellipsoid, which does not apply in a variety of cardiac pathologies. The Quinones method for calculating LV volume from LV linear dimensions is no longer recommended for clinical use (Darasz *et al.*, 2002; Lang *et al.*, 2005).

2.4.2 Modified Simpson's method

Modified Simpson's method is a modality requiring area tracings of the LV cavity. This is the method recommended by the American Society of Echocardiography to measure LVEF (Lang *et al.*, 2015). This method requires tracing of the endocardial border in both the apical four chamber (AP4CH) and apical two chamber (AP2CH) views in end-systole and end-diastole. These tracings ultimately divide the LV cavity into a determined number of disks of equal height (usually 20) (Plana *et al.*, 2014). The volume (V) of each disk (n) is calculated using the length (D1) and width (D2). The height (h) of each disk is calculated from the total length of the LV divided by the number of disks within the chamber. The volume of each disk is then calculated and formulated into the system calculation package to provide the EDV and ESV of the LV, as illustrated in Figure 2.4.

The formula states:

$$\text{Volume} = \pi (D1/2) \times (D2/2) \times h$$

Where π $\rightarrow$ Pi equal to 3.14159
D1 $\rightarrow$ Length
D2 $\rightarrow$ Width
h $\rightarrow$ Height (Lang *et al.*, 2015).

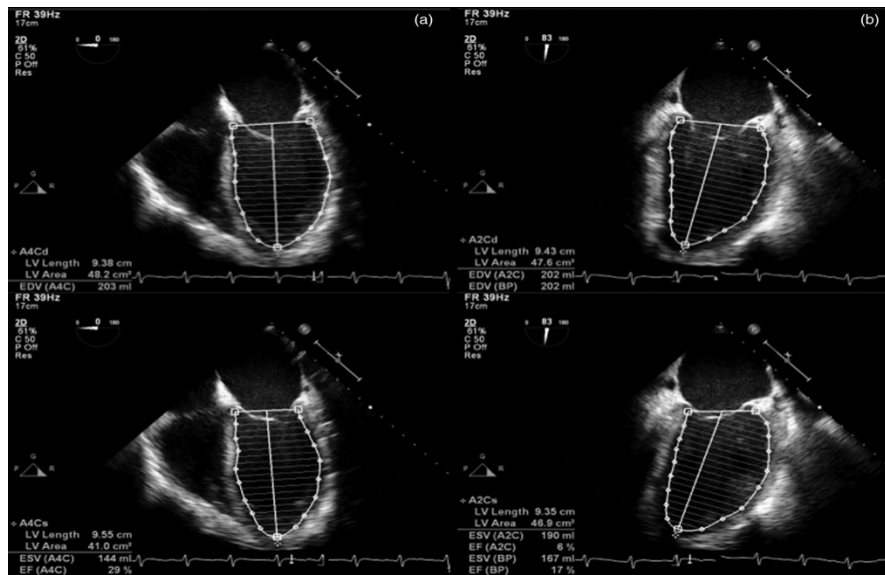


Figure 2.4 Tracing of the left ventricle using the Simpson method. Images left top and bottom are used to determine EF using the AP4CH. Images right top and bottom are used to determine EF using AP2CH (Adapted from Valchanov *et al.*, 2018).

2.4.2.1 Advantages of Simpson's method derived LVEF

Advantages of this method include correcting LV distortions and less geometrical assumptions can be made (Lang *et al.*, 2005).

2.4.2.2 Limitations of Simpson's method derived LVEF

Disadvantages are primarily image quality associated, and includes endocardial dropout and apex foreshortening (Lang *et al.*, 2005).

2.4.3 Global longitudinal strain

Global longitudinal strain (GLS) by speckle tracking echocardiography is an additional method to evaluate LV function, as it evaluates both global and regional function of the left ventricle. Strain is defined as the degree of myocardial deformation, which is calculated by the extent of shortening or lengthening of the myocardial fibres during a cardiac cycle. The speed at which this occurs is known as strain rate (Karlsen *et al.*, 2019).

GLS is performed by obtaining 3 standard apical views (AP4CH, AP2CH, and apical long axis) by utilising 2-dimensional grey scale images. These images are used to directly measure segmental myocardial deformation of the LV in a 16-segment model, which is then expressed as GLS (Grenne *et al.*, 2010; Dahlslett *et al.*, 2014). After the region of interest (ROI) is set in strain measurement, speckle tracking is performed automatically by the system software from which an EF is calculated. The strain measurements of the 16 LV wall segments are displayed in a bull's eye analysis as demonstrated in Figure 2.5 (Gjesdal *et al.*, 2008).

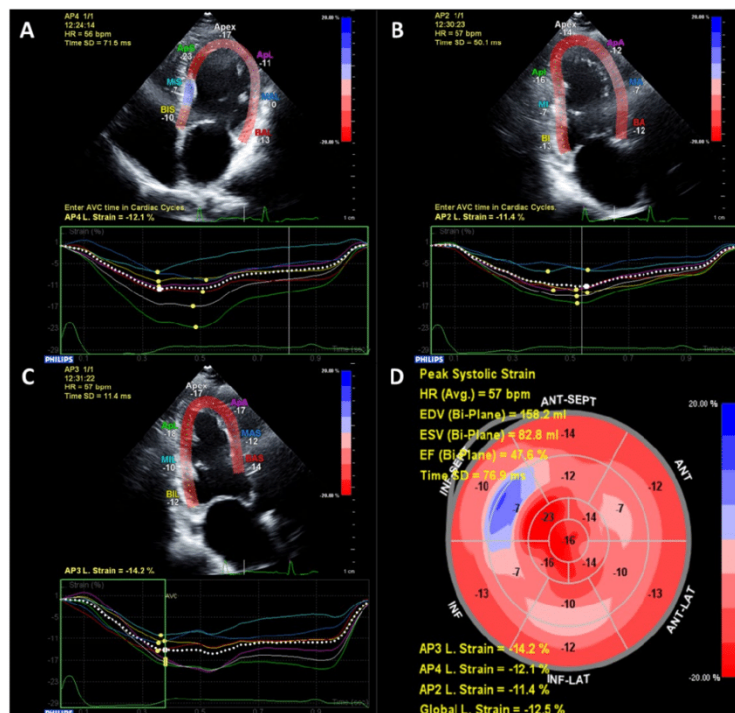


Figure 2.5 The standard apical views (A, B and C)) from which GLS and EF are calculated. The bull's eye analysis (D) displays the strain measurements of each of the LV wall segments (Adopted from Mordi, 2019).

2.4.3.1 Advantages of global longitudinal strain derived LVEF

This method has better intra- and inter-observer reproducibility regardless of echocardiographic training (Kalam *et al.*, 2014; Karlsen *et al.*, 2019). In addition, GLS may be used in a majority of patients with good image quality, does not rely on geometric assumptions, and is as timely as conventional LVEF methods. GLS can also be used to identify reduced regional LV wall function in patients with acute

coronary syndrome (Staton *et al.*, 2009) and the detection of cardiotoxicity during chemotherapy (Zamorano *et al.*, 2016).

2.4.3.2 Limitations of global longitudinal strain derived LVEF

Limitations of this method include poor temporal resolution, lack of reproducibility, oversimplification due to software processing algorithms, and 2D imaging limitations such as image dropout (Fabiani *et al.*, 2016).

2.4.4 Tissue Doppler imaging

Tissue Doppler imaging (TDI) is an echocardiographic method that uses Doppler principles to measure the velocity of myocardial motion. TDI can be used to assess LV systolic and diastolic function. The systolic velocity (S') of the lateral mitral annulus is a measurement of longitudinal systolic function and correlates with LV ejection fraction measurements and peak dp/dt. The assessment, using TDI for diastolic function is less load dependent compared to standard Doppler techniques and validated against invasive hemodynamic measurements and TDI can be used to calculate the isovolumetric relaxation phase (Ho & Solomon, 2006).

The mitral annulus velocities can be calculated by performing pulsed wave Doppler in TDI over the medial and lateral annulus of the mitral valve in the AP4CH view (Isaaz *et al.*, 1989). The mitral annulus has three distinct waves: S', early diastolic velocity (e' velocity), and late diastolic velocity (a' velocity) as presented in Figure 2.6. A significant correlation between S' and LVEF have been reported in previous studies (Gulati *et al.*, 1996). Normal mean value for S' is 9 cm/s (septal: 8 cm/s and lateral: 10 cm/s) (Chahal *et al.*, 2013). A strong positive correlation has been noted between MAPSE and S', with the correlation being as high as $r: 0.90$ (Ballo *et al.*, 2008).

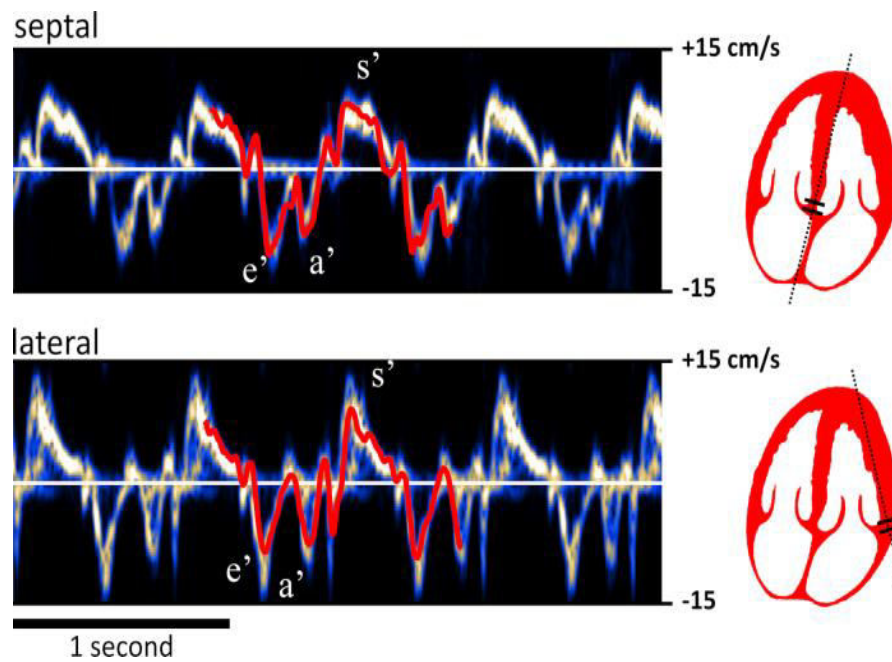


Figure 2.6 Septal and lateral mitral annulus velocities measured by pulsed wave TDI with S' , e' and a' displayed (Adapted from Porée *et al.*, 2016).

2.4.4.1 Advantages of tissue Doppler imaging

Advantages include it being easy to perform with low inter- and intra-observer variability. Furthermore, these measurements are not influenced by the volume states of the LV (Park *et al.*, 2010) and can determine both systolic and diastolic LV function (Morka *et al.*, 2016).

2.4.4.2 Limitations of tissue Doppler imaging

TDI limitations include it measuring only absolute tissue velocity and is not able to discriminate between passive and active motions. TDI also only measures the vector in motion that is parallel to the direction of the ultrasound beam (Ho & Solomon, 2006).

2.4.5 Left ventricular myocardial performance index

Myocardial performance index (MPI) or Tei index is a fairly new Doppler derived time interval index that can evaluate both systolic and diastolic function. MPI is defined as the sum of isovolumetric contraction time (IVCT) and isovolumetric relaxation time (IVRT) divided by ejection time (ET) as shown in Figure 2.7. Normal value for LV MPI is 0.39 ± 0.05 (Tei *et al.*, 1995).

MPI is a reliable parameter of global left ventricular systolic function; however, MPI measured by pulsed wave Doppler was considered not to be a reliable parameter for the assessment of LV diastolic function (Fernandes *et al.*, 2019). The Tei index can also provide prognostic information about morbidity and mortality in patients with cardiac amyloidosis, ischemic heart disease, dilated cardiomyopathy, and primary pulmonary hypertension (Pattoneri *et al.*, 2007).

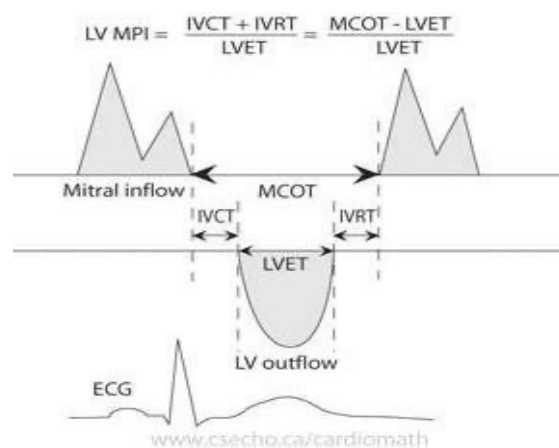


Figure 2.7 Doppler inflow and outflows of the ventricle (v) demonstrated with corresponding electrocardiogram (ECG) tracing. Measurements for IVCT, IVRT and ET are shown with the MPI formula (Adapted from Packard *et al.*, 2017).

2.4.5.1 Advantages of left ventricular myocardial performance index

Advantages using MPI include good reproducibility and being independent from LV geometry and heart rate. The index is easily obtained from trans-mitral flow and LV outflow velocity time intervals. MPI also correlates strongly with systolic and diastolic LV function (Tei *et al.*, 1995).

2.4.5.2 Limitations of left ventricular myocardial performance index

MPI intervals are based on flow-velocity curves and are performed in different cardiac cycles, which is a significant limitation. This method requires several measurements to reduce beat-to-beat variation (Gaibazzi *et al.*, 2005).

2.4.6 Three-dimensional Echocardiography

Three-dimensional (3D) echocardiography captures three-dimensional views of the heart, which allows for better evaluation of chambers and valves, and more accuracy with cardiac measurements. 2D echocardiography is the widespread technique used for evaluation of LVEF; however, 2D echocardiography techniques are based on geometric assumptions. The accurate measurement of LV volume and function requires the true reconstruction of the LV geometry, especially in patients with distorted LV geometries and impaired LV functions (Cacciapuoti, 2008).

3D echocardiography uses direct volumetric analysis measuring LV volumes throughout the cardiac cycle from the surface of the LV cavity. The end-diastolic and end-systolic volumes are measured, and the stroke volume and LVEF is calculated as illustrated in Figure 2.8. This is a very promising technique to calculate LVEF as it allows measurements without geometric assumptions (Lang *et al.*, 2012).

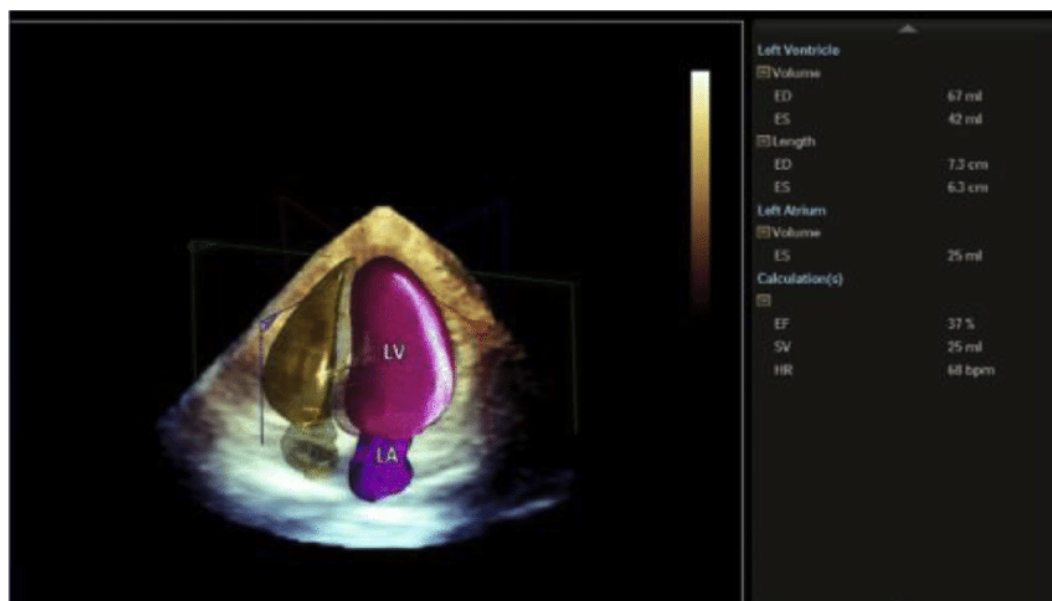


Figure 2.8 3D apical four chamber view of a patient with heart failure. Evaluation of the LV volumes and LVEF was done by 3D echocardiography using an automated adaptive analytics algorithm for quantification. LVEF was 37% (Adapted from Acquatella *et al.*, 2018).

2.4.6.1 Advantages of three-dimensional echocardiography

3D echocardiography is considered more accurate than 2D echocardiography in quantifying LV volumes, especially in patients with an abnormal LV shape or

regional wall abnormality. There is also a higher reproducibility rate in 3D echocardiography compared to 2D echocardiography (Lang *et al.*, 2012).

2.4.6.2 Limitations of three-dimensional echocardiography

3D echocardiography is not routinely used, as it remains time consuming and resource intensive. Low temporal and spatial resolutions are a common disadvantage associated with 3D echocardiography. The quality of the 3D datasets is determined by patient factors including the acoustic window, sinus rhythm, and adequate breath hold. 3D echocardiography also requires in-depth knowledge of echocardiography settings during image acquisition, which is not routine in every echocardiography laboratory (Lang *et al.*, 2012).

2.4.7 Mitral annular plane systolic excursion

Mitral annular plane systolic excursion (MAPSE) is an M-mode derived echocardiographic marker of LV longitudinal function. Also known as left atrioventricular plane displacement (AVPD), mitral annulus excursion (MAE) or mitral ring displacement, this parameter correlates well with other systolic LV function measurements (Hu *et al.*, 2013). This measurement has been suggested as a surrogate for LVEF (Bergenzaun *et al.*, 2011). In a cohort study involving 600 patients, it was found that MAPSE measurement by an untrained observer was considered to be a highly accurate predictor of EF. Sensitivity for this study was 73-92%, specificity 81-100%, and accuracy as high as 82-86% (Matos *et al.*, 2012). It also found that MAPSE measured in critically ill mechanically ventilated patients also correlated well with LVEF (Shad *et al.*, 2019). It has also been proved that there is a strong correlation between MAPSE and LVEF by visual assessment and also between MAPSE and Simpson's biplane technique (Bergenzaun *et al.*, 2011).

A reduced MAPSE correlates with patients who have reduced LV function due to myocardial infarction, atrial fibrillation, and heart failure. MAPSE is also more sensitive than conventional echocardiographic markers in detecting abnormalities in LV systolic function at an early stage (Emilsson *et al.*, 2000). A prognostic

importance for major cardiac occurrences and mortality has also observed seen (Rydberg *et al.*, 2003).

MAPSE can be measured from four areas of the atrioventricular plane, which corresponds to the lateral, septal, posterior, and anterior walls using AP4CH and AP2CH views by M-mode (Taşolar *et al.*, 2015). The lateral (lat) and medial (med) walls are generally used, where the lateral value is higher than the medial value in normal hearts. The M-mode cursor should always be aligned parallel to the LV walls and the excursion is measured from the lowest point at end-diastole to the highest point, as noted in Figure 2.9. Normal value for MAPSE is considered 10-15 mm (Elnoamany & Abdelhameed, 2006; Cindolo *et al.*, 2005).

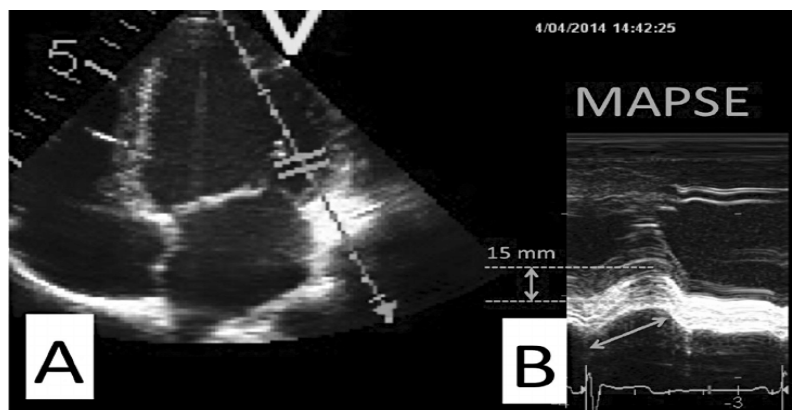


Figure 2.9 Panel A demonstrates the cursor line over the lateral annulus of the mitral valve from which M-mode will be performed. Panel B demonstrates the M-mode image and how MAPSE is measured (Adapted from Vermeiren *et al.*, 2015).

2.4.7.1 Advantages of MAPSE

Advantages of performing MAPSE are that it is easy to perform, with a 70-95% reproducibility, that is exhibits high temporal resolution, is less dependent on 2 D imaging quality, and correlates well with left ventricular ejection fraction (Kai *et al.*, 2013).

2.4.7.2 Limitations of MAPSE

Limitations are that it is pre-and afterload dependent, angle dependent, that is exhibits variation due to cardiac size, and is unable to detect regional myocardial abnormalities. MAPSE also only reflects longitudinal LV function (Kai *et al.*, 2013).

2.5 Mitral annular plane systolic excursion derived ejection fraction

Matos *et al.* (2012) first used MAPSE as a substitute for LVEF by formulating the formula: $\text{MAPSE EF} = (4.8 \times \text{MAPSE}) + 5.8$. This cohort study focused on MAPSE measurements by a trained and untrained observer and to compare these measurements. The study involved 600 patients to establish this algorithm and also to verify the test accuracy of this established algorithm. It was found that the MAPSE measurements were a highly accurate predictor of EF.

Adel *et al.* (2016) further investigated this formula by reporting that the MAPSE derived EF (MAPSE EF) equation is a valid technique in adult males with severely impaired LV systolic function. However, gender specific differences in MAPSE measurements or to validate the equation for EF prediction in females was a significant limitation in this study as only men were included in the study. No investigation was done to evaluate the formula in females who present with impaired LV systolic function.

CHAPTER 3: Article

Article was prepared according to the author instructions for submission to the SA Heart Journal.

Evaluation of mitral annular plane systolic excursion derived ejection fraction to determine left ventricular systolic function

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Abstract

Introduction

Left ventricular (LV) ejection fraction (EF) is an essential measurement in echocardiography. Mitral annular plane systolic excursion (MAPSE) is an easy systolic longitudinal function measurement, which can be used as a surrogate measurement for LVEF and can be converted into an ejection fraction using the formula $EF = (4.8 \times MAPSE) + 5.8$. The aim of this study was to investigate if MAPSE EF can be used in the daily clinical setting.

Methods

A prospective descriptive-analytical study was conducted by correlating MAPSE EF with Teichholz EF, Modified Simpson's apical four-chamber and apical-two chamber EF, global longitudinal strain-derived EF, peak systolic velocity of the mitral valve annuli, and LV myocardial performance index (MPI). A correlation value of ≥ 0.70 was considered a strong clinical correlation.

Results

The study population consisted of 475 patients presenting at a mean age of 61 ± 14.9 years. MAPSE EF and the systolic parameters correlated the best in the congestive cardiac failure group ($r > 0.80$) and gender had no influence. No clinical correlation was observed between MAPSE EF and the systolic parameters in the diabetes mellitus type 2, hypertension, and ischemic heart disease groups.

Conclusion

MAPSE EF is a valid technique to measure systolic function in patients with impaired LV function.

Introduction

Patients with cardiovascular disease (CVD) are increasingly likely to present at primary care physicians as their first point of care or for a follow-up examination. Treatment of patients with CVD almost invariably involves the use of echocardiography as a means of initial diagnosis and follow-up investigations. The most widely used and accepted echocardiographic parameter of left ventricular (LV) systolic function is the ejection fraction (EF). Ejection fraction has a unique position in cardiology since it serves as a selection criterion for almost all landmark therapeutic trials of heart failure and is incorporated in clinical guidelines.^{1,2}

Left ventricular ejection fraction (LVEF) is an established measurement of left ventricular systolic function.³ Accurate measurement of LVEF is essential since it is used to manage patient outcomes. LVEF also has prognostic value in predicting undesirable outcomes and mortality rates, especially in patients with cardiac failure and acute coronary disease, aiding in deciding which course of treatment would benefit the most.⁴ There are several methods available to calculate ejection fraction. However, most of these imaging modalities and procedures require visualisation of two or more left ventricular wall segments to estimate LVEF.⁵

Existing methods exhibit inherent limitations relating to LV cavity border tracing and geometric assumptions.⁶ In both M-mode and two-dimensional (2-D) echocardiography, longitudinal contraction is directly measured. However, since the entire LV border is not traced, some geometric assumptions must be made when using such methods. With the modified Simpson's rule, assumptions of the sum of a cylinder-shaped LV have to be made, assuming that the three sections that make up the cylinder are all equal in height. Poor image quality can lead to inaccurate echocardiographic measured LVEF.⁷ Inadequate visualisation of the left ventricular endocardial border may give rise to inconsistent measurements among sonographers.⁸ Poor image quality occurs in approximately 10-15% of routine echocardiographic examinations, with interobserver agreement as low as 43%.⁹

Mitral annular plane systolic excursion (MAPSE) was first introduced in the late 1980's¹⁰ and is considered a relatively new and valuable surrogate of LV longitudinal

function.¹¹ The advantages of using MAPSE include: (i) it is easy to perform with high reproducibility (ii) has a high temporal resolution, (iii) is less dependent on 2D imaging quality, and (iv) correlates well with left ventricular ejection fraction.¹²

Matos et al.¹³ endorsed the use of a single left ventricular wall segment to derive an ejection fraction by using the formula $\text{MAPSE EF} = (4.8 \times \text{MAPSE}) + 5.8$. MAPSE has been suggested as a substitute measurement for LVEF.¹⁴ Converting MAPSE to EF is easier for clinicians to comprehend and compare with other EF measurements during an echocardiographic examination.

The aim of the study was to evaluate the MAPSE EF formula for determining EF in daily practice and how it compares to other methods of EF determination.

Methods

This prospective descriptive-analytical study was conducted in central South Africa at the private practice of a specialist physician in the wards of Hoogland Medi-Clinic, Bethlehem. Before the study commenced, ethical clearance was obtained from the Health Sciences Research Ethics Committee (HSREC) of the University of the Free State (UFS-HSD2022/1176). Informed consent was obtained from all subjects.

Study population

The study included four hundred and seventy-five ($n=475$) male and female participants aged 18 and above. The patients were divided according to their primary clinical condition, which consisted of systemic hypertension, diabetes mellitus type 2, congestive cardiac failure (CCF), and ischemic heart disease.

Participants were excluded if they had had aortic and/or mitral valve replacement surgeries, had mitral valve annular dysfunction, new or diagnosed pericardial diseases, tachyarrhythmias, malignant- or uncontrolled hypertension, new or uncontrolled diabetes mellitus type 2, acute ischemic events, or inadequate imaging views. Recruited patients with hypertension, diabetes, and congestive cardiac failure had no other pre-existing conditions.

Definitions

Systemic hypertension: patients who previously had, on average, two or more readings and on two or more occasions presented with a systolic blood pressure of ≥ 140 mmHg and/or diastolic blood pressure of ≥ 90 mmHg, in the absence of any known precipitating cause.

Diabetes mellitus type 2: patients who previously had a fasting glucose above 7.0mmol/L (126 mg/dL) and were diagnosed with diabetes mellitus type 2 and placed on the appropriate management.

Congestive cardiac failure: patients with a confirmed clinical diagnosis of CCF and an LVEF below 50%.

Ischemic heart disease: patients with a history of confirmed ischemic cardiac events. All patients had pre-existing conditions such as hypertension or diabetes mellitus type 2; thus, some overlapping was noted in this group.

Data collection

Demographic and clinical data were recorded during the recruitment visit. The same qualified sonographer performed all transthoracic echocardiograms (TTE) tests. Clinical data included (i) medical history and (ii) a TTE. TTE was performed on a Philips Affiniti 70 C diagnostic ultrasound system, utilising the S5-1 cardiac probe. All echocardiographic procedures and measurements were performed according to the guidelines of the American Society of Echocardiography (ASE).¹⁵ Each systolic parameter was measured five times and averaged.¹⁶

LVEF was determined using the Teichholz method, Modified Simpson's method in the apical two (AP2CH) and four-chamber (AP4CH) views, and by global longitudinal strain-derived ejection fraction. Strain percentage and strain rate were automatically calculated by performing speckle tracking.

Peak systolic (S') tissue velocities of the medial and lateral mitral valve annuli were performed and averaged using tissue Doppler imaging.

Left ventricular myocardial performance index (LV MPI) was performed by pulsed wave Doppler of the mitral and left ventricular outflow tract. Isovolumetric relaxation time (IVRT) and isovolumetric contraction time (IVCT) were measured by the mitral valve Doppler, and the ejection time was measured by the left ventricular outflow tract Doppler.¹⁷

MAPSE of the medial and lateral mitral valve annuli were performed by M-mode echocardiography and averaged. MAPSE EF was calculated using the formula $\text{MAPSE EF} = (4.8 \times \text{MAPSE}) + 5.8$ for each annulus.¹³

Statistical analysis

Continuous variables were described using mean and median, and categories were described using counts and percentages. Blom's transformation was applied to improve data normality and to rescale the variables to a common numerical range.

Pearson correlation coefficients with 95% confidence limits were performed to describe the correlation of mean MAPSE EF with mean Teichholz EF, mean Simpson's apical four and two chambers EF, mean Strain EF, mean S' and mean LV MPI.

Correlations were determined for the overall sample and by diagnosis. A correlation value of ≥ 0.70 was considered a strong clinical correlation. Correlation values between 0.5-0.69 were considered low clinical correlation, while correlation values ≤ 0.49 were considered weak clinical correlation.

All statistical two-tailed tests were performed with a type-I error rate of 5% ($\alpha = 0.05$). The statistical analyses were conducted using SAS (Statistical Analysis System) version 9.04.

Results

Demographic data

Total population

The study population consisted of 475 patients presenting at a mean age of 61 ± 14.9 years; there were 255 (54%) females and 220 (46%) males. Most of the patients were from the Bethlehem region, since the private practice where the study was conducted is situated in Bethlehem. The majority of patients were in New York Heart Association (NYHA) class 1 (50.3%) and 2 (32.6%) at presentation. Overall, 75% of all patients were either overweight or obese, with a third of the patients with a body mass index (BMI) $> 30 \text{ kg/m}^2$ (Table I).

Subgroups according to clinical presentation

Table I depicts the patients' clinical conditions at presentation. Females with congestive cardiac failure were, on average, two years younger than their male counterparts (mean: 59.9 ± 15.5 vs 61.7 ± 12.6). In the diabetes mellitus group, men were two years younger (55.7 ± 13.3 vs 57.1 ± 16.4) than females, while in the hypertension and ischemic heart disease groups, men were older by one (mean: 58.1 ± 13.7 vs 57.8 ± 17.1) and three years (mean: 70.3 ± 10.8 vs 67.9 ± 10.3), respectively.

Table I: Age and BMI summary of the total population, as well as the subgroups according to clinical presentation and total population.

Condition	n	F n (%)	M n (%)	Age (mean $\pm$ SD)	BMI (kg/m ²) n (%)		
					Normal 18.5-24.9	Overweight 25.0-29.9	Obese >30
Congestive cardiac failure	118 (24.8%)	68 (57.6%)	50 (42.4%)	60.1 ± 14.3	24 (20.3%)	46 (39%)	48 (40.7%)
Diabetes mellitus type 2	117 (24.6%)	59 (50.4%)	58 (49.6%)	56.4 ± 14.9	33 (28.2%)	42 (35.9%)	4 (35.9%)
Hypertension	127 (26.7%)	78 (61.4%)	49 (38.5%)	57.9 ± 15.9	30 (23.6%)	57 (44.9%)	40 (31.5%)
Ischemic heart disease	113 (23.8%)	50 (44.3%)	63 (55.8%)	69.1 ± 10.7	33 (22%)	60 (40%)	20 (13.3%)
Total	475	255 (54%)	220 (46%)	60.8 ± 14.9	120 (25.2%)	205 (43.2%)	150 (31.6%)

n: total patients, F: female, M: male, SD: standard deviation, BMI: body mass index.

Echocardiographic findings

Diastolic dysfunction

Virtually all patients had some degree of diastolic dysfunction, and grade two diastolic dysfunction was present in half of the population, most frequently observed in the congestive cardiac failure and ischemic heart disease groups. Severe diastolic dysfunction (grade three) was almost exclusively found in the CCF group. The findings on diastolic dysfunction are summarised in Table II.

Table II: *Diastolic dysfunction grade of each subgroup and total population.*

Grade	Congestive cardiac failure n (%)	Diabetes mellitus type 2 n (%)	Hypertension n (%)	Ischemic heart disease n (%)	Total n (%)
0	0 (0%)	3 (2.5%)	0 (0%)	0 (0%)	3 (0.6%)
1	7 (5.9 %)	84 (71.8%)	59 (46.5%)	18 (15.9%)	168 (35.4%)
2	62 (52.6 %)	30 (25.7%)	64 (50.4%)	89 (78.8%)	245 (51.6%)
3	49 (41.5 %)	0 (0%)	4 (3.1%)	6 (5.2%)	59 (12.4%)
Total	118 (25%)	117 (25%)	127 (27%)	113 (24%)	475

n: number of patients.

Systolic echocardiography parameters

Normal to mildly affected systolic functions were noted in the total population with a mean EF of $50.2 \pm 0.3\%$. However, a noteworthy impairment of all systolic parameters was present in the congestive cardiac failure group (EF < 30%) (Table III)). Normal to mild impairment was noted in the ischemic group, while normal systolic parameters were found in the hypertension and diabetes mellitus groups. MAPSE was normal in the hypertension and diabetes groups, while impairment was found in the congestive cardiac failure and ischemic heart disease groups (Table III).

Table III: *Echocardiographic systolic parameters of each subgroup.*

Variable	Mean	Standard deviation	Median	25 th %	75 th %
<i>Congestive cardiac failure</i>					
Teichholz EF (%)	26.5	9.3	25.9	19.6	33.6
Simpson's AP4CH EF (%)	26.1	9.0	25.8	20.0	33.2
Simpson's AP2CH EF (%)	26.3	8.9	25.6	20.8	32.6
Strain EF (%)	25.9	9.3	25.9	19.8	33.0
S' (cm/s)	4.1	1.4	3.9	3.1	5.6
LV MPI	0.7	0.1	0.7	0.6	0.7

MAPSE (mm)	4.1	1.8	3.6	2.9	5.3
MAPSE EF (%)	25.4	8.6	23.1	19.7	30.8
<i>Diabetes mellitus type 2</i>					
Teichholz EF (%)	60.9	4.2	61.2	58.0	62.8
Simpson's AP4CH EF (%)	60.9	4.3	61.4	58.8	63.0
Simpson's AP2CH EF (%)	60.3	4.3	61.4	58.6	63.2
Strain EF (%)	60.5	6.6	60.8	58.2	62.8
S'(cm/s)	10.1	0.9	10.2	9.5	10.8
LV MPI	0.3	0.1	0.3	0.3	0.3
MAPSE (mm)	11.8	0.9	11.8	11.2	12.3
MAPSE EF (%)	62.4	4.1	62.4	59.6	64.4
<i>Hypertension</i>					
Teichholz EF (%)	61.3	4.4	61.6	58.2	64.2
Simpson's AP4CH EF (%)	61.7	4.2	62.2	59.0	64.6
Simpson's AP2CH EF (%)	61.5	4.2	61.6	59.0	64.2
Strain EF (%)	61.3	4.3	61.2	58.6	64.4
S'(cm/s)	10.1	1.3	10.1	9.1	10.8
LV MPI	0.3	0.1	0.3	0.3	0.4
MASPE (mm)	11.7	0.9	11.8	11.0	12.5
MAPSE EF (%)	62.2	4.7	62.4	58.6	65.8
<i>Ischemic heart disease</i>					
Teichholz EF (%)	52.5	8.0	53.2	51.2	55.8
Simpson's AP4CH EF (%)	49.9	7.3	52.0	46.8	53.4
Simpson's AP2CH EF (%)	49.7	7.5	52.0	46.6	53.4
Strain EF (%)	54.1	44.9	51.2	46.2	53.0
S'(cm/s)	7.2	1.4	7.3	6.3	8.2
LV MPI	0.5	0.1	0.5	0.4	0.5
MAPSE (mm)	9.1	1.8	9.8	7.9	10.4
MAPSE EF (%)	49.6	8.6	52.8	43.7	55.7

EF: ejection fraction, AP4CH: apical four chamber, AP2CH: apical two chamber, S': peak systolic tissue value, LV MPI: left ventricular myocardial performance index, MAPSE: mitral annular plane systolic excursion, mm: millimetres.

Regression and correlation

Subgroups according to clinical presentation

MAPSE EF and the systolic parameters correlated the best in the congestive cardiac failure group. In this group, a strong correlation ($r > 0.80$) was noted between MAPSE EF and all the systolic parameters. Importantly, this strong correlation was maintained and basically identical between MAPSE EF and all the pure systolic parameters ($r > \pm 0.70$) when separately analysed for males and females. LV MPI was the only parameter with a low negative correlation ($r: -0.69$) with MAPSE EF in this group, as

well as with MAPSE EF ($r:-0.65$) in females with congestive cardiac failure when analysed separately.

In the diabetes mellitus type 2 group, a low clinical correlation ($r:<0.56$) was observed between MAPSE EF and the systolic parameters, while LV MPI demonstrated no correlation ($r:0.0004$) (Table IV). A low correlation ($r:<0.62$) was noted between MAPSE EF and S' in the hypertension group, while a weak correlation was found between MAPSE EF and the other parameters (Table IV).

The worst correlations were found in the ischemic group. In this group, S' was the only systolic parameter that had a strong, positive correlation ($r:>0.74$) with MAPSE EF, while a weak clinical correlation ($r:<0.21$) was observed between MAPSE EF and the other systolic parameters (Table IV).

Patients with grade one demonstrated low to weak correlations between MAPSE EF and all the systolic parameters ($r:<0.69$). All patients with grade two and three diastolic dysfunction had an excellent correlation ($r:\geq\pm 0.78$) between MAPSE EF and the other systolic parameters.

Table IV: Correlation between MAPSE EF and systolic variables in the subgroups.

<i>with Variable</i>	<i>n</i>	<i>Correlation</i>	<i>Fisher's z</i>	<i>Confidence limits</i>	<i>p-value</i>
<i>Congestive cardiac failure</i>					
Teichholz EF (%)	118	0.88	1.37	0.83 – 0.91	<0.0001
Simpson's AP4CH EF (%)	118	0.87	1.34	0.82 – 0.91	<0.0001
Simpson's AP2CH EF (%)	118	0.84	1.22	0.77 – 0.88	<0.0001
Strain EF (%)	118	0.84	1.22	0.78 – 0.86	<0.0001
S'(cm/s)	118	0.81	1.12	0.73 – 0.86	<0.0001
LV MPI	118	-0.69	-0.84	-0.77 – -0.58	<0.0001
<i>Diabetes mellitus type 2</i>					
Teichholz EF (%)	117	0.54	0.60	0.39 – 0.65	<0.0001
Simpson's AP4CH EF (%)	117	0.56	0.63	0.42 – 0.67	<0.0001
Simpson's AP2CH EF (%)	117	0.55	0.62	0.41 – 0.66	<0.0001
Strain EF (%)	117	0.53	0.60	0.39 – 0.65	<0.0001
S'(cm/s)	117	0.53	0.57	0.37 – 0.64	<0.0001
LV MPI	117	0.0004	0.0004	-0.18 – 0.18	0.9967
<i>Hypertension</i>					
Teichholz EF (%)	127	0.33	0.34	0.16 – 0.47	0.0002

Simpson's AP4CH EF (%)	127	0.33	0.34	0.17 – 0.48	0.0001
Simpson's AP2CH EF (%)	127	0.40	0.42	0.24 – 0.54	<0.0001
Strain EF (%)	127	0.37	0.36	0.21 – 0.51	<0.0001
S'(cm/s)	127	0.62	0.73	0.50 – 0.72	<0.0001
LV MPI	127	0.02	0.02	-0.16 – 0.19	0.8377
<i>Ischemic heart disease</i>					
Teichholz EF (%)	113	0.21	0.21	0.03 – 0.38	0.0247
Simpson's AP4CH EF (%)	113	0.07	0.07	-0.12 – 0.25	0.4540
Simpson's AP2CH EF (%)	113	0.09	0.09	-0.10 – 0.27	0.3635
Strain EF (%)	113	0.07	0.07	-0.11 – 0.25	0.4729
S'(cm/s)	113	0.74	0.94	0.63 – 0.81	<0.0001
LV MPI	113	-0.40	-0.42	-0.54 – -0.23	<0.001

EF: ejection fraction, AP4CH: apical four chamber, AP2CH: apical two chamber, S': peak systolic tissue value, LV MPI: left ventricular myocardial performance index, MAPSE: mitral annular plane systolic excursion, mm: millimetres, n: number of patients.

Sub-analysis of other parameters

Strain-derived EF had a strong, positive correlation ($r>0.81$) with modified Simpson's AP4CH EF in the total population and in all the subgroups ($r>0.70$). A strong, negative correlation ($r>-0.76$) was observed between LV MPI and Simpson's AP4CH EF in the total population. Within the subgroup analysis between LV MPI and Simpson's AP4CH EF, a weak to low negative correlation was noted in the ischemic heart disease and congestive cardiac failure groups, while a weak correlation was found in hypertension and diabetes mellitus groups.

Discussion

This study aimed to evaluate and compare MAPSE EF to other echocardiographic methods of measuring ejection fraction. Limited data regarding the use of MAPSE to EF conversion is available. Our results show that MAPSE EF is a valid method to determine ejection fraction in patients with CCF and those with grade three diastolic dysfunction but not diabetes, hypertension, or ischemic heart disease. Gender had no influence on the determination of MAPSE EF.

The advantage of using MAPSE lies in the simplicity of performing the measurement. MAPSE is fast and easy to perform, even by inexperienced sonographers.¹⁵ It consists of a one-dimensional measurement, is less dependent on endocardial border resolution

and can be accurately reproduced.¹³ MAPSE is associated with low intra- and inter-observer variability, 4.4% and 5.3%, respectively^{13,14}. The need for additional systolic measurements in daily practice is vital, as difficult image quality can thwart accurate measurements. As a single wall measurement, MAPSE is less affected by poor image quality compared to other methods.¹⁸ Conversion to EF makes it easier to interpret for clinicians.

Patients were divided into four sub-groups based on their initial clinical presentation. Of concern was that almost three-quarters of the patients were either overweight or obese according to their BMI classification. Systolic parameters were normal to mildly impaired in all groups, with meaningful systolic impairment (EF less than 30%) occurring exclusively in patients with congestive cardiac failure.

In the congestive cardiac failure group, MAPSE EF correlated superbly with all the systolic parameters, only LV MPI had a low clinical correlation. This finding is in agreement with the findings of Adel et al.¹⁹, who demonstrated that MAPSE-derived EF is a valid technique in adult males with markedly impaired LVEF. Compared to Adel et al.¹⁹, the correlations in our study were significantly stronger. The correlation coefficient (r) values in this study for MAPSE EF versus Teichholz EF and Simpson's AP4CH EF were 0.88 and 0.87, while in Adel et al.¹⁹, it was 0.55 and 0.58, respectively. The lower correlation coefficient values in Adel et al.¹⁹ may be attributed to the lower numbers (n=66) included in their subgroup, compared to 118 in this study. Not only did MAPSE EF correlate strongly with the other systolic parameters in the congestive cardiac failure group, but it also demonstrated that the strong correlation was maintained and was similar when used in males and females. Our results show that the MAPSE-derived EF formula is a valid method to determine ejection fraction in patients with congestive cardiac failure and that gender does not affect the measurement. It should be noted that this is the first time that MAPSE EF in both genders with CCF were determined, as Adel et al.¹⁹ only included males in their study.

In the hypertensive and diabetes mellitus groups, less favourable correlations were observed. MAPSE EF had a low correlation with S' in the hypertension group, while the other systolic modalities overall demonstrated weak clinical correlations with

MAPSE EF in this group. A low correlation was noted between MAPSE EF and most of the systolic parameters in the diabetes mellitus group, with only LV MPI correlating weakly with MAPSE EF. Interestingly, in both the hypertension and diabetes mellitus groups, MAPSE itself was preserved. It is noteworthy that the association between MAPSE and EF is only valid in the case of normal or dilated left ventricle²⁰, while the correlation is rather poor in patients with LV hypertrophy.²¹ A reduced MAPSE was documented in patients with concentric hypertrophy despite normal EF.²² Thus, one can speculate that some degree of hypertrophy may have been present in our groups, as MAPSE was normal, and correlations were weak to low despite having a normal LVEF. Therefore, it is not advisable to use MAPSE EF as a single determinant of EF in patients with hypertension and diabetes mellitus.

The worst correlations of MAPSE EF with the other systolic parameters were seen in the ischemic heart disease group. In this group, only S' had a strong correlation with MAPSE EF. In contrast to Adel et al.¹⁹, our study found weak to low correlations (r : 0.21 and 0.07 versus 0.6 and 0.63) between MAPSE versus Teichholz EF and Simpson's AP4CH EF. Although left ventriculography was not obtained, basal segment function was most likely preserved in our patient population study since MAPSE and S' were normal. Patients in our study had preserved EF, compared to severely impaired LVEF in the group of Adel et al.¹⁹. The use of MAPSE in ischemic heart disease is still relevant, as a decreased MAPSE could still serve as an echocardiographic functional sign for myocardial abnormalities, especially subendocardial dysfunction.²³

Strain-derived EF and modified Simpson's AP4CH EF correlated strongly in the total population, as well as in the subgroups. This finding is in agreement with Bayram et al.²⁴ and Delgado et al.²⁵, who demonstrated a good correlation between patients with ischemic heart disease and heart failure, respectively. Noticeable systolic and diastolic dysfunction were present in patients with ischemic heart disease and congestive cardiac failure. A low to weak negative correlation was noted between Simpson's AP4CH EF and LV MPI in these subgroups. This finding is in agreement with Malladi²⁶, who demonstrated that LV MPI increases in patients with heart failure due to both systolic and diastolic dysfunction. Benjamin²⁷ reported similar findings in

patients with ischemic heart disease where a significant correlation was observed between LVEF and LV MPI: the lower the LVEF, the higher the MPI. This study, however, correlated LV MPI with Teichholz EF and not Simpson's method as in our study.

Some degree of diastolic dysfunction was present in the entire study population. Grade three diastolic dysfunction almost exclusively occurred in those with congestive cardiac failure. Kosmala et al.²⁸ reported that the greater the degree of diastolic dysfunction, the more impaired systolic function was. Contradicting results were noted in healthy patients, with no relationship between LV systolic and diastolic function. De Simone et al.²⁹ concluded that changes in systolic and diastolic function may occur simultaneously, however, some degree of diastolic abnormalities could occur in the absence of systolic dysfunction. Similar results were obtained in our study, where patients with a mild to moderate degree of diastolic dysfunction had weak correlations between the systolic parameters, whereas, in the more outspoken degrees of diastolic dysfunction, the correlation between MAPSE EF and the systolic parameters became stronger.

Although MAPSE and LVEF are related, they are not identical.³⁰ MAPSE is representative of subendocardial, longitudinally oriented, myocardial fibres compared to the subepicardial, circumferential fibres measured by LVEF through Simpson's methods and strain echocardiography. LVEF is known to detect more subtle abnormalities of LV function compared to MAPSE.³⁰ This has been described in patients with increasing age, myocardial hypertrophy, or diastolic dysfunction with preserved ejection fraction where the longitudinal-axial function of the heart may be impaired while the radial function can be preserved or even increased. However, using methods such as Doppler LV MPI and Teichholz to evaluate LV systolic function, the longitudinal function of the heart is not necessarily considered.³¹

The heart is a 3-dimensional organ with longitudinal, radial and circumferential contraction. Therefore, it stands to reason that a single method cannot adequately describe global systolic function. Although each method has its advantages and disadvantages, certain methods should be used in certain conditions.³² The modified Simpson's method is a modality consisting of area tracings of the LV cavity and is

considered the golden standard of systolic EF measurement.³³ Newer methods, such as strain echocardiography, incorporate multiple wall segments to measure global systolic function and not only regional function.⁶ Certain systolic methods (Teichholz) can also not be used in abnormal LV geometry (ischemic heart disease or LV aneurysms), thus limiting the possible modalities that can be used in a particular patient.⁷

MAPSE EF can be used as an additional systolic function measurement parameter to compare and evaluate longitudinal left ventricular function, especially in poor image quality or technically difficult echocardiograms. MAPSE EF and S' had low to strong correlations; thus, incorporating both MAPSE EF and S' in systolic functional assessments will improve global LV systolic function determination. Various systolic functional assessment methods are available, each measuring either the longitudinal, radial or circumferential function of the left ventricle. No single method can determine holistic LV function; thus, the use of more than one geometric assessment is suggested to improve the accuracy of LV systolic function determination.

Limitations

A limited number of patients and disease groups were included, which only represents a small section of the disease population in South-Africa. Only type two diabetes mellitus patients were included, not type one. Since the pathophysiology and effect on the heart in type one and two diabetes mellitus differ, the associated systolic measurements might also differ.³⁴ Patients with ischemic heart disease had pre-existing conditions such as hypertension and diabetes, since it is impossible to have ischemic heart disease as an isolate condition with no pre-existing conditions as risk factors. Because angiography was not performed in this study to identify the region of ischemia, measurements may have been under- or overestimated. More research should be done to evaluate how MAPSE EF is affected by ischemic heart disease. The MAPSE EF formula is not a standardised formula incorporated in modern echocardiography machines. The authors suggest that more research should be done on MAPSE EF and perhaps this formula can be included in sonography machines in the future.

Conclusion

Results of this study show that MAPSE EF correlated best with the systolic parameters in patients with congestive cardiac failure and those with severe diastolic dysfunction. Gender has no influence on the determination of MAPSE-derived EF. The use of multiple geometric systolic measurements may improve the assessment of global LVEF measurement.

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CHAPTER 4: General Conclusion

This is the first study in our region (Eastern Free State) that aimed to evaluate and compare MAPSE EF and the use of MAPSE EF with other echocardiographic systolic methods. Limited research has been done on MAPSE EF and the applications where this function can be used. This study served as a pilot study with more research to be hopefully done, including a larger range of pathologies. As the MAPSE EF is not standard in echocardiography protocol practises and available on sonography machines, we hope future research might change this. The study investigated the use of MAPSE EF in various conditions, not only in congestive cardiac failure, as previously done.

The aim of this study was to convert a longitudinal systolic measurement to an EF. EF is well known and the most important measurement in transthoracic echocardiography. By converting MAPSE to an EF, we aimed to make it easier for healthcare professionals to understand, as EF is much more recognised in the healthcare community than MAPSE and to compare the MAPSE EF measurement with other EF measurements, rather than to compare MAPSE with an EF.

The majority of the patients in our study were either overweight or obese, highlighting the unhealthy nature of patients included in this study. Systolic parameters were either normal or minimally impaired in all groups with meaningful systolic impairment occurring exclusively in patients with congestive cardiac failure. Although strong correlations were noted in the total population, subgroup analyses demonstrated several differences between MAPSE EF, and the other methods used to determine systolic LV function.

The study found that MAPSE EF correlated strongly in both genders and provided an additional systolic measurement to be done in patients with CCF. MAPSE EF can be used to compare with other systolic echocardiographic measurements and assest in limited imaging settings. The excellent correlation within the congestive cardiac failure group was already discovered in previous studies, however, not in both genders.

In pathologies such as hypertension, diabetes mellitus type 2 and ischemic heart disease no significant correlation was found between MAPSE EF and the systolic echocardiographic parameters. Therefore, it would not be advisable to use MAPSE and MAPSE EF as a solo systolic measurement to determine the LV function. MAPSE EF could still be used to assist as an additional parameter to compare with, in conjunction with established systolic echocardiographic EF methods. This can be done to provide additional systolic function support and LV information, especially in the setting of limited image quality.

Some degree of diastolic dysfunction was present in the full study population with grade two diastolic dysfunction occurring mostly in patients with congestive cardiac failure or ischemic heart disease. Grade three diastolic dysfunction almost exclusively occurred in those with congestive cardiac failure.

LV geometric changes pose a challenge for LVEF measurement. In conditions such as ischemic heart disease and congestive cardiac failure, LV geometric changes such as eccentric hypertrophy, fibrotic wall changes, and regional wall abnormalities including hypo/akinesia can occur. Reduced contractility of the LV in these conditions must also be taken into consideration when global LVEF is measured. Left ventricular hypertrophy is strongly associated with systemic hypertension, and the presence of diabetes mellitus type two increases the risk of LVH. These geometric changes affect the methods that should be selected to determine LVEF accurately.

Various systolic left ventricular measurements are available, each method either measuring radial and/or circumferential and/or longitudinal LV function. Methods such as MAPSE EF and Teichholz only incorporate single or two LV wall segments to determine EF and can only measure regional wall function and not global LV function. Methods such as global strain-derived EF and Simpson's methods include multiple LV wall segments to provide a more accurate LVEF measurement and provide information about multiple LV wall segments.

MAPSE is an easy systolic modality to perform with the mitral annulus frequently seen, even in poor image quality. The use of MAPSE and MAPSE EF in limited images might serve as a rapid method to determine EF, but if transthoracic images are

limited, supporting modalities such as transoesophageal echocardiogram, CT or MRI should be considered.

We do not recommend the use of MAPSE EF as a solo systolic measurement, as it is not the gold standard and significant research still has to be done regarding its application. However, incorporating MAPSE in each echocardiogram can assist in systolic function measurement and by converting MAPSE to MAPSE EF, an additional EF measurement is available to compare with.

CHAPTER 5: References

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CHAPTER 6: Appendices

- A. HSREC Approval letter
- B. Detailed Methodology
- C. Informed consent
- D. Information guide
- E. Patient location
- F. NYHA classification
- G. Systolic parameters values of the total population
- H. Correlation parameters between MAPSE EF and the systolic parameters

Appendix A

HSREC Approval letter

UNIVERSITY OF THE
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FREISTATA



UFS·UV
HEALTH SCIENCES
GESONDHEIDSWETenskappe

Health Sciences Research Ethics Committee

06-Feb-2023

Dear Mr Hendre Van Rensburg

Ethics Clearance: **Evaluation of mitral annular plane systolic excursion derived ejection fraction to determine left ventricular systolic function.**

Principal Investigator: **Mr Hendre Van Rensburg**

Department: **Clinical Technology - CUT**

[Submission Page](#)

APPLICATION APPROVED

Please ensure that you read the whole document

With reference to your application for ethical clearance with the Faculty of Health Sciences, I am pleased to inform you on behalf of the Health Sciences Research Ethics Committee that you have been granted ethical clearance for your project.

Your ethical clearance number, to be used in all correspondence is **UFS-HSD2022/1176**

The ethical clearance number is valid for research conducted for one year from issuance. Should you require more time to complete this research, please apply for an extension.

We request that any changes that may take place during the course of your research project be submitted to the HSREC for approval to ensure we are kept up to date with your progress and any ethical implications that may arise. This includes any serious adverse events and/or termination of the study.

A progress report should be submitted within one year of approval, and annually for long term studies. A final report should be submitted at the completion of the study.

Research conducted in any Department of Health facility: Researchers are required to sign and return the HSREC approval letters to the provincial Department of Health where they applied. It is also a requirement for researchers to submit electronic copies of their final research findings, and/or make a presentation of their findings and recommendations at departmental research days when and where indicated.

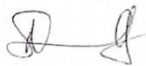
The HSREC functions in compliance with, but not limited to, the following documents and guidelines: The SA National Health Act No. 61 of 2003; Ethics in Health Research: Principles, Structures and Processes (2015); SA GCP(2020); Declaration of Helsinki; The Belmont Report; The US Office of Human Research Protections 45 CFR 461 (for non-exempt research with human participants conducted or supported by the US Department of Health and Human Services- (HHS), 21 CFR 50, 21 CFR 56; CIOMS; ICH-GCP- E6 Sections 1-4; International Council for Harmonisation (ICH) Harmonised Guideline, Integrated Addendum to ICH E6(R1), Guideline for Good Clinical Practice (GCP) E6(R2), 2016, SAHPRA Guidelines as well as Laws and Regulations with regard to the Control of Medicines, Constitution of the HSREC of the Faculty of Health Sciences.

The Principal Investigator (PI) bears final responsibility for the RIMS application. In the event of any misconduct or improper activities perpetrated by a third party, the PI will be held vicariously liable. The HSREC will bear no responsibility or liability for any actions of a PI and/or third party or breach of confidentiality caused by the PI and/or third party.

For any questions or concerns, please feel free to contact HSREC Administration: 051-4017794/5 or email EthicsFHS@ufs.ac.za.

Thank you for submitting this proposal for ethical clearance and we wish you every success with your research.

Yours Sincerely



Prof. A. Sherriff
Chairperson: Health Sciences Research Ethics Committee

Health Sciences Research Ethics Committee
Office of the Dean: Health Sciences
T: +27 (0)51 401 7795/7794 | E: ethicsfhs@ufs.ac.za
IRB 00011992, REC 230408-011, IORG 0010096, FWA 00027947
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www.ufs.ac.za



Appendix B

Detailed Methodology

B1 Study location

The study will be conducted at Hoogland Medi-Clinic, Bethlehem, South Africa within the private practice of Dr Jaco Coetzee and patients admitted/referred to him in ward A (Gynaecology and Obstetrics), ward B (Medical), ward C (Surgical) and ward J (Intensive and high care).

B2 Study design

The study will be a prospective, descriptive analytical study.

B3 Study population and sampling

Patients from central South Africa will be included.

The study population will include at least one hundred adult participants aged eighteen and above.

Recruitment of patients will commence as soon as ethical approval from the HSREC. After ethical clearance, recruitment will commence for a period of 4 months.

B3.1 Study group

This study was open-ended, and participants male or female aged 18 and above were recruited to participate in the research project. One hundred patients were recruited during a 4-month period.

B3.1.1 Inclusion and exclusion criteria

To address the objectives of the study, the selection criteria for the patients were based on two main variables namely (1) male or female (2) aged 18 and above. The specific requirements for the inclusion and exclusion of patients are outlined in the inclusion and exclusion criteria below:

B3.1.1.1 Inclusion criteria for study group

- Male and female patients
- Aged eighteen and above

B3.1.1.2 Exclusion criteria group

- Previous aortic –and/or mitral valve replacement surgeries
- Mitral valve annular dysfunction
- New or diagnosed pericardial diseases
- Tachyarrhythmias
- Patients with inadequate imaging views

B4 Subject identification

Patient confidentiality will be maintained throughout the study and at no time will confidentiality be breached. Patient details including patient names will only be known by the research team anchoring this study. Patients will be identified by a study number, which will be allocated to each participant (P1-).

B5 Conceptual framework for data collection

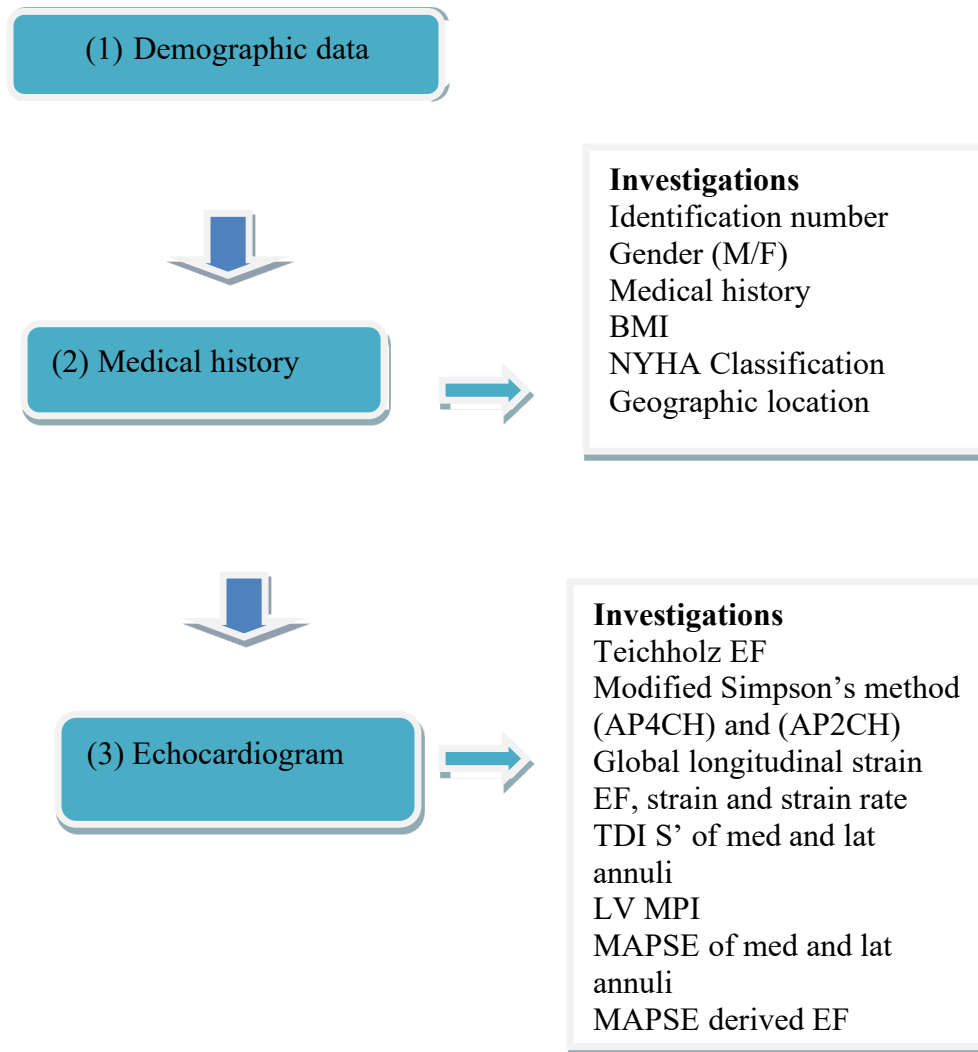


Figure 3.1 *Conceptual framework for data collection.*

B6 Special investigations

All the special investigations that form part of this study are routine investigations for patients who meet the inclusion criteria. No additional investigations will be carried out on patients that are willing to participate in this research study.

Demographic, anthropometric and clinical data (medical history) will be recorded by Dr J. Coetzee during the medical examination.

These analyses will be performed during the initial identification of the patient.

(a) Participants will undergo the following routine clinical investigations:

- Medical history (demographic data)
- Transthoracic echocardiogram

B6.1 Demographic data

The following demographic data will be recorded for each participant:

- Identification number
- Gender (male/female)
- Geographic location
- Medical history
- NYHA classification
- BMI

B6.2 Transthoracic echocardiogram

An experienced echocardiographer (Mr H. van Rensburg) will perform a routine transthoracic echocardiographic examination according to the guidelines of the American Society of Echocardiography (Lang *et al.*, 2005). Note that echocardiography is a routine procedure for patients in the inclusion criteria and no additional procedures or tests will be performed.

Images will be obtained from the left lateral decubitus position using a Philips Affiniti 70 C Diagnostic Ultrasound System, equipped with a S5-1 ultrasound transducer. Three ECG electrodes will be placed on the patients' chest to obtain an ECG on the ultrasound machine. Views obtained will consist of standard parasternal long- and short axis and apical four- and two chamber views. M-mode, pulsed wave, colour Doppler, tissue Doppler and speckle tracking will be obtained in all views. Care will be taken with 2-dimensional and gain settings to ensure and concise measurements. Multiple measurements will be performed (at least five) and an average will be calculated.

The following parameters will be recorded:

(A) Ejection fraction by M-mode

- M-mode echocardiography will be used to calculate the ejection fraction.
- A parasternal long-axis view will be obtained.
- M-mode cursor will be aligned at the tip of mitral leaflets or exactly perpendicular to the inferior wall and passing through the centre of the left ventricular cavity, resulting in an M-mode tracing.
- The left ventricular end diastolic dimension is measured when the time cursor is placed before the peak R-wave in the QRS complex. The dimension of the LV at this time is the widest.
- The left ventricular end systolic dimension is measured when the time cursor is placed at the end of the T-wave in the ECG. The dimension of the LV at this time is the narrowest.
- Left ventricular end diastolic- and systolic dimensions are converted into volumes by the ultrasound system from which the Teichholz formula calculates an ejection fraction (Chengode, 2016).

(B) Ejection fraction by Modified Simpson's method

- An apical four chamber view will be obtained.
- The left ventricular end diastolic volume is traced when the time cursor is placed at the peak of the R-wave in the QRS complex. The left ventricle at this timing has the largest volume. The endocardial border of the left ventricle is traced, producing the end diastolic volume.
- The left ventricular end systolic volume is traced when the time cursor is placed at the end of the T-wave in the ECG. The left ventricle at this timing has the smallest volume. The endocardial border of the left ventricle is traced, producing the end systolic volume.

- The ejection fraction is calculated by the ultrasound system, which deducts the systolic volume from the diastolic volume, which is then divided by the diastolic volume (Chengode, 2016).

(C) Ejection fraction by global longitudinal strain

- Apical four, two and three chamber views will be obtained with the frame rate of 40-80 fps.
- A good quality image will be acquired, avoiding foreshortening and artefacts.
- Contour of the myocardium will be according to the procedure of the vendor and bright pericardium inclusion will be avoided.
- Careful tracing of the myocardium will be done in each of the above-mentioned views and suboptimal traced segments will be retraced.
- The ejection fraction, strain and strain rate are automatically calculated by the ultrasound system (Mada *et al.*, 2012).

(D) Tissue Doppler Imaging

- An apical four chamber view will be obtained.
- The sample volume is placed over one of the mitral valve annuli.
- Pulsed wave in Doppler is performed and a waveform is produced.
- Systolic velocity (S') is identified and by using the calliper line, the S' value is measured.
- This is performed on both the medial and lateral annulus (Ho & Solomon., 2006).

(E) Left ventricular myocardial performance index

- An apical four chamber view will be obtained.
- The sample volume will be placed at the tips of the mitral valve and a pulsed wave in Doppler will be recorded.
- The time between two consecutive mitral valve inflows will be measured, which produces the mitral valve closure to opening time, which contains both the IVRT and IVCT.

- An apical five chamber will be obtained.
- The sample volume will be placed at the left ventricular outflow track and a pulsed wave in Doppler will be recorded.
- The left ventricular ejection time is measured.
- The ultrasound software automatically calculates the LV MPI value.

(F) Mitral annular plane systolic excursion

- An apical four chamber view will be obtained.
- The M-mode cursor is aligned parallel to the lateral wall (for the lateral annulus) or medial wall (for the medial annulus) over the annulus.
- M-mode is pressed on the ultrasound system and a two-dimensional M-mode waveform is produced.
- The longitudinal excursion between end diastole and peak systole for each annulus is measured (Lang *et al.*, 2005).

(G) Mitral annular plane systolic excursion derived ejection fraction

- An apical four chamber view will be obtained.
- The M-mode cursor is aligned parallel to the lateral wall (for the lateral annulus) or medial wall (for the medial annulus) over the annulus.
- M-mode is pressed on the ultrasound system and a two-dimensional M-mode waveform is produced.
- The longitudinal excursion between end diastole and peak systole for each annulus is measured (Lang *et al.*, 2005).
- The MAPSE measurement is converted using the formula $EF = (4.8 \times \text{MAPSE}) + 5.8$ and an EF is calculated (Matos *et al.*, 2016).
- MAPSE EF for the medial and lateral annulus will be calculated and then averaged.

B7 Statistical analysis

All the results generated from the study will be captured in Microsoft ® Excel ® 2007 datasheet from Appendix D.

Position and dispersion indexes such as arithmetic mean and standard deviation or median and interquartile range will be performed according to variables' skewness. Pearson or Spearman correlation coefficient will be performed to determine the strength of the association between the MAPSE EF and other systolic parameters. Univariate comparisons between groups will be performed according to variables' skewness for continuous outcomes (t-test and ANOVA or U-test and Kruskal test for normally distributed and skewed outcomes, respectively), Chi-squared and the Fisher exact tests will be performed for categorical outcomes. Parametric and non-parametric regression analysis along with generalised linear models will be performed to investigate multivariate regression and to perform adjusted comparisons between groups. All statistical tests will be two-tailed, and type-I error rate will be set at 5% ($\alpha = 0.05$). The SAS software version 9.4 and the R software version 4.0.2 will be used for the statistical analysis.

Post hoc and a priori power calculation were performed, considering a type-II error rate of 20% ($1 - \beta = 0.2$) or a type II error rate below 80% considering the standardised effect size according to Cohen's definition (F for ANOVA) and related methods, correlation coefficients and d for two group comparisons as for the t or U tests.

According to the above calculation and a possible rate of missing value of 10%, we will assume that an overall sample size of 20-30 individuals could be considered at least as sufficient to detect large, standardised effect sizes ($F \geq 0.5$, $d \geq 0.8$, $r \geq 0.5$).

Post hoc power analysis will be conducted to investigate border line non-significant results ($0.05 < P\text{value} < 0.10$) using the observed data.

Sample size adequacy was assessed using G*Power software version 3.1, the power procedure of the SAS software version 9.4 and the pwr package of the R-software version 4.0.2.

B8 Ethical aspects and good clinical practice

B8.1 Ethical clearance

Recruitment of patients will only commence when the HSREC grants ethical approval. Approval will also be obtained by Dr Jaco Coetzee and the hospital manager of Hoogland Medi-Clinic.

B8.2 Patient's safety

The research project will not subject the patient to any additional risk over and above that of routine echocardiography. Patients participating in this study will be monitored by Dr J Coetzee and may discontinue participation in the study at any time.

B8.3 Discontinuation and withdrawal criteria

Discontinuation of the study will take place in the case of any unethical procedures. Participation is completely voluntary. Patients will have the right to withdraw from the study at any time, for any reason, and without any prejudice.

B8.4 Good Clinical Practice

All clinical work conducted during this research project will be subjected to the Good Clinical Practice guidelines. The Declaration of Helsinki's basic principle number 3, states that research should be conducted only by scientifically qualified people and under the supervision of adequately qualified personnel involved (South African Good Clinical Practice guidelines, 2006; World Medical Association Declaration of Helsinki, 2013). Fundamentally GCP requires oversight of the local ethics committee, verification of the investigator's qualifications, a study protocol, informed consent and essential documentation needed to undertake the study, monitoring, submission of reports, and maintenance of records. By applying the GCP guidelines in this research study provides public assurance that the rights, safety and wellbeing of the participants will be protected and that the research data will be credible.

B8.5 Financial implications to the patient

All the research performed will be routine practice. No financial remuneration will be claimed from the patients if they consent to participate in the study.

B8.6 Subject information and Informed Consent

All the patients will be informed about the purpose and necessity of the research project (Appendix C), the financial implications and the consequences as well as the adverse effects, and their right to withdraw without any effects on them or their doctor-patient relationship. They will sign an informed consent form (Appendix A) and receive an information sheet that they may retain. The Ethical Committee will also approve the consent form. Both the information sheet and the consent form will be available in English, Afrikaans and SeSotho.

B9 Research team

Principle Investigator:

Mr H van Rensburg

Supervisors:

Ms MJ Mofokeng

Prof. SC Brown

Appendix C and D

Informed consent

English

Informed consent

CONSENT PROVIDED BY PARTICIPANT IN RESEARCH PROJECT

Title of study: Evaluation of mitral annular plane systolic excursion derived ejection fraction to determine left ventricular systolic function.

You hereby grant permission (Name & Surname) _____ to participate in the research study mentioned above.

You have been informed about the study by The study was explained to you in detail and all your questions have been addressed.

(Where applicable): You have been informed about any available compensation or medical treatment available if you experience injury resulting from study-related procedures.

You may contact Mr H. van Rensburg or Ms M.J. Mofokeng at any time if you have questions about the research project.

You may contact the Secretariat of the HSREC, UFS at telephone number (051) 4052812 if you have questions about your rights as a research subject.

Your participation in this research study is voluntary and you will not be penalised or lose benefits if you refuse or withdraw from the study at any time.

If you agree to participate in the study, you will be given a signed copy of this document as well as an information sheet explaining the study to you.

The research study that I participate in has been verbally described to me. I understand what my involvement in the study will be and I voluntarily agree to participate in this research study.

Signature of Participant

Date

Signature of Witness *

Date

Signature of Translator *

Date

* Where applicable

Information guide

INFORMATION DOCUMENT

Title of study: Evaluation of mitral annular plane systolic excursion derived ejection fraction to determine left ventricular systolic function.

Introduction:

I wish to investigate if a one wall systolic measurement converted to a function can be used regardless of gender in daily practice. This will aid sonographers to determine a more accurate function of the heart and further the diagnoses, management, and prognosis of patient care.

Invitation to participate:

I am asking your permission to participate in this research study.

What the study involves:

The study will include routine standardised medical practices as you would normally receive in the physicians' practice/admission. The results and data from all the patients will be kept confidential at all times. No additional tests will be performed that do not form part of the planned treatment.

The following test will be performed on the participant:

- Transthoracic echocardiogram (non-invasive).

Risks:

There are no risks involved with transthoracic echocardiogram and it is a standardised medical procedure for your medical condition.

Benefits:

There will be no remuneration or added benefits for patients to participate in the research, but their participation will help improve patient care in the future.

The participant will be given pertinent information on the study while involved in the project and after the results are available.

Participation is voluntary, and refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled; the subject may discontinue

participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

Reimbursements:

Not applicable as all investigations are done when they visit/are admitted for Dr Jaco Coetzee.

Confidentiality:

Personal information will be kept confidential. Patients who enter the study will be assigned numbers, which will be used to report all results.

Organisations that may inspect and/or copy your research records for quality assurance and data analysis include groups such as the Ethics Committee for Medical Research and the Medicines Control Council (*where appropriate*).

Contact details of researcher(s)

Prof. S Brown/ Ms M.J. Mofokeng/ Mr H. van Renburg.
gnpdsch@ufs.ac.za/ mapulengmofokeng@cut.ac.za/ Hendrevanrensburg@gmail.com
051 405 3214/3577

Contact details of REC Secretariat and Chair – for reporting of complaints/problems.

Prof. A. Sherriff
For Attention: Mrs M Marais
Block D, Room 104,
Francois Retief Building

Appendix C and D

Afrikaans

Ingeligte Toestemming

TOESTEMMING VERSKAF DEUR DIE DEELNEMER AAN NAVORINGSSTUDIE

Titel van studie: Evaluasie van mitraal annulus-vlak sistoliese ekskursie afgeleide uitwerpfraksie om linker-ventrikulêre sistoliese funksie te bepaal.

U gee hiermee toestemming (Naam en Van) _____ om deel te neem aan die bogenoemde navorsingsstudie.

U is oor die studie deur Die besonderhede van die studie was is u verduidelik en al u vrae aangaande die studie is beantwoord.

(Van toespasing): U is oor enige beskikbare vergoeding of mediese behandeling ingelig sou 'n besering as gevolg van studieverwante prosedures plaasvind.

U kan ter enige tyd vir Mnr. H van Rensburg of Me. MJ Mofokeng kontak indien u enige vrae oor die navorsingstudie het.

U kan die Sekretariaat van HSREC, UV by telefoonnommer (051) 4052812 skakel indien u enige vrae oor u regte as 'n deelnemer aan 'n navorsingsstudie het.

U deelname aan die navorsingsstudie is vrywilliglik en u sal nie gepenaliseer word nie of voordele verbeur indien u deelname sou weier of uit van die navorsingsstudie onttrek nie.

Indien u sou instem om aan die navorsingsstudie, deel te neem, sal u 'n getekende afskrif van die dokument ontvang, sowel as die deelnemerinligtingsblad, wat 'n geskrewe opsomming van die navorsing is.

Die navorsingsstudie is verbaal aan my verduidelik. Ek verstaan wat my betrokkenheid by die studie beteken en ek stem vrywilliglik in om aan hierdie studie deel te neem.

Handtekening van deelnemer

Datum

Handtekening van getuie*

Datum

Handtekening van vertaler *

Datum

* Waar van toespasing

Information guide

INFORMASIE DOKUMENT

Titel: Evaluasie van mitraal annulus-vlak sistoliese ekskursie afgeleide uitwerpfraaksie om linker-ventrikulêre sistoliese funksie te bepaal.

Inleiding:

Ek will graag bepaal of 'n eenwand-sistoliese meting wat omgeskakel word na 'n funksie in die daaglikse praktyk gebruik kan word. Dit sal sonograwe help om 'n meer akkurate funksie van die hart te meet en bevorder die diagnose, bestuur en prognose van pasiëntsorg.

Uitnodiging om deel te neem:

Hiermee vra ek u toestemming om deel te neem aan die navoringsstudie.

Wat behels die studie:

Die studie sluit roetine, gestandaardiseerde, mediese praktyke in wat u normaalweg sou ontvang by die internis se praktyk/opname. Die resultate en data van die pasiënt sal anonim bly en vertroulikheid sal ten alle tye gewaarborg word. Geen addisionele toetse wat nie deel uitmaak van u beplande behandeling sal op u gedoen word nie.

Die volgende toetse sal op u gedoen word:

- Transtorokale eggokardiogram (nie-indringend).

Risiko's:

Daar is geen risiko's by 'n transtorokale eggokardiogram betrokke nie en dis 'n gestandaardiseerde, mediese prosedure vir u mediese kondisie.

Voordele:

Daar sal geen monetêre of behandelingsvoordele vir deelnemers aan die studie wees nie, maar deelname sal toekomstige pasiëntesorg verbeter.

Relevante inligting oor die studies al aan die deelnemer verskaf word tydens sy/haar deelname aan die studie, asook nadat die resultate bekend gemaak is.

Deelname is vrywilliglik, en weiering om deel te neem sal geensins lei tot penalisering of verlies van voordele wat die pasiënt normaalweg sou ontvang nie. Die deelnemer is vry om op enige tydstip uit die studie te onttrek, sonder enige benadeling of verlies van voordele wat die pasiënt normaalweg sou ontvang.

Vergoeding:

Is nie van toepassing nie, want al die ondersoeke word tydens die pasiënt se normale besoek/opname aan Dr Jaco Coetzee gedoen.

Vertroulikheid:

Persoonlike inligting sal vertroulik gehou word. Pasiënte wat aan die studie deelneem sal unieke nommers ontvang wat gebruik sal word om enige en alle resultate te rapporteer.

Organisasies wat jou/ons rekords of data vir kwaliteitsversekerings- en data-analise-doeleindes mag inspekteer sluit groepe soos die Etiese Komitee vir Mediese Navorsing en alle Medisyne Kontrole raad in (*waar van toepassing*).

Kontakbesonderhede van navorser(s)

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Prof. A. Sherriff
Vir aandag: Mev. M. Marais
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Francois Retief Gebou

Appendix C and D

Sesotho

Tumello ka kutlwisiso

TUMELO YA HOBA MONKA-KAROLO DIPATLISISONG

Sehlooho: Evaluation of mitral annular plane systolic excursion derived ejection fraction to determine left ventricular systolic function.

**O fana ka tumelo (Name & Surname) _____ ho nka
karolo dipatlisising tse boletsweng ka hodimo.**

O hlaloseditswe ka dipatlisiso ke.....ke hlaoseditswe
dipatlisiso ka botlalo mme le dipotso tsaka di arabuwe.

(Moo ho kgonehang) O hlaloseditswe ka moputso kapa kalafo e leng teng, ha ngwana wa hao
a ka iphumana a lemetse ka lebaka la dipatlisiso tsena.

O ka letsetsa MJ Mofokeng kapa H Van Rensburg nako enngwe le enngwe ha ona le dipotso
ka dipatlisiso , kapa ha ngwana a lemetse ka lebaka la dipatlisiso

O ka letsetsa mongodi wa HSREC, UFS mohaleng wa 051 405 2812 ha ona le dipotso ka
ditokelo tsa ngwana wa hao jwalo ka monka-karolo.

Ho nka karolo hwa ngwana wa hao dipatlisising tsena ho boitahopong ,ngwana wa hao akeke
a fuwa kotlo kapa ho se thole se melemo ha o hana kapa o kgetha hore e se be karolo ya
dipatlisiso kapa ha o ka montsha dipatlisising nako enngwe le enngwe.

Ha o dumella jwalo ka motswadi/mohlokomedi hore ngwana wa hao a nke karolo o tla fuwa
tokomane ena e tekennweng le pampiri ya tlhakisetsa ya banka karolo, e ngotsweng
kgutsufatsong ya patlisiso e hlalosang dipatlisiso ka bobatsi.

Dipatlisiso tsena tseo nna jwalo ka motswadi/mohlokomedi ke dumellang ngwana wa ka e be
karolo ya tsona, ke di hlaloseditswe ka molomo, le ngwana wa ka o di hlaloseditswe. Ke
utlwisisa bonka-karolo ba ngwana wa ka patlisising ena, mme ke ya dumela ka boithaopo
hore ngwana wa ka a nke karolo.

Ho tekene monka-karolo

Letsatsi

Ho tekene Paki

Letsatsi

Ho tekene Toloko*

Letsatsi

Tokomane ya thliso-leseding

TOKOMANE YA TLHAISO LESEDING

Sehooaho: Evaluation of mitral annular plane systolic excursion derived ejection fraction to determine left ventricular systolic function.

Selelekela:

Ke batla ho etsa dipatlisiso tsa ho fuputsa hore na reka kgona ho etsa teko ya lehlakore le le leng feela la pelo hore le sebetsa jwang, ebe rre tseba ka ho sebetsa hwa pelo kaofela na, phuputso ena ke batla ho tseba hore na teko ena eka sebediswa ho sa kgathalatshe bong ba motho, le tsatsi ka letsatsi na.. Phuputso ena etla thusa bahlahlubi ba bitwang disonographer to fana ka karabo yah o sebetsa hwa pelo e nepahetseng ho thusa ho hlaloba, ho alafa le ho phekola bakudi.

Memo ya honka karolo:

Ke kopa tuemllo ya hao ho o mema obe monka-karolo dipatlisisong tsena.

Ho etsahalang dipatlisisong tsena:

Dipatlisiso di tlo kenyeletsa diketsahalo tse tlwaeleileng tsa booki jwalo ka ha o tlwaetse ho bofumana kliniking ya tsa pelo/o robaditswe sepetlele. Diphetho tsa bakodi di tlo ngolwa ho sa bitswe mabitso a batho o netefaletswa le sephiri. Ditnho tsohle tse etswang ngakeng di tlo etswa ho bakudi bohle, ha hona diteko tse ding tseo monka karolo atlang ho tlameya ho di etsa ha ese karolo ya kalafo ya lefu la hae.

Diteko tse latelang di tla etswa ho banka-karolo:

- Transthoracic echocardiogram (Ha e behe monka-karolo kotsing).

Kotsi:

Jwalo ka booki bo bong le bo bong ho kaba le dikotsi tse etsahalang, empa ka ha diteko le di patlisiso ele dintho tse tlwaetseng ho etsahala ketelong ya ngaka, ha hona kotsi tse ntjha tse ka hlalolang banka-karolo.

Melemo:

Ha hona tjhelete kapa booki bo ikgethileng bo tla fuwa banka karolo, empa bakudi bankileng karolo dipatlisisong tsena ba ka thusa ho ntlafatsa booki foreisetata le kapa leboya bakeng la bakudi beo hosing bonolo ho tseba ka hore pelo tsa bona di sebetsa hantle na..

Monka-karolo o tlo fuwa tlhakisetso e mo loketseng ka dipatlisiso nakong eo antseng anka karolo le ha sephetho se sefumanehile

Ho nka karolo ho boithaoping ba mokodi, ha mokodi a sa batle ho nka karolo ho ka sebe le kotlo kapa ho se fuwe booki bo loketseng, monka-karolo aka tlohela ho nka karolo nako enngwe le enngwe asa lahlehelwe ke melemo e mo loketseng.

Patala:

Ha hona tjelete kapa tefo e tlo fuwa banka-karolo ka ha dipatlisiso di tlo etsahala ha mokodi a tlile ngakeng ya hae ya pelo nakong eo a e behetsweng.

Lekunutu:

Mabitso a mokodi a tlo bolokwa jwalo ka lekunutu. Mokodi a nkang karolo o tlo fuwwa nomoro e tlang ho sebediswa ho tlaheha sephetho.

Mekgatlo e ka lekolang ditlaleho tsa dipatlisiso tsena bakeng sa netefaletso ya boleng ke mekgatlo e kang ethics committee for medical research le medicines control council (ha ho hlokeha).

Dintlha tsa bafuputsi

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051 405 3214/3577

Dintlha tsa mongodi le modula-setulo wa rec -ho tlaleha ditlalebo/mathata

Prof. A. Sherriff
Bakeng sa tlhokomelo: Mrs M Marais
Karolo D, Kamore 104,
Francois Retief Maoho

Appendix E

Patient location

<i>Town</i>	<i>n</i>	<i>Percentage (%)</i>
<i>Bethlehem</i>	170	35.8
<i>QwaQwa</i>	64	13.5
<i>Reitz</i>	31	6.5
<i>Harrismith</i>	26	5.5
<i>Phuthaditjhaba</i>	24	5.0
<i>Clarens, Senekal</i>	21	4.4
<i>Vrede</i>	14	2.9
<i>Ficksburg</i>	13	2.7
<i>Witsieshoek</i>	12	2.5
<i>Fouriesburg</i>	11	2.3
<i>Lindley</i>	9	1.9
<i>Petrus Steyn</i>	8	1.7
<i>Kestell, Warden</i>	6	1.3
<i>Marquard, Paul Roux</i>	5	1.1
<i>Frankfort, Heilbron</i>	4	0.8
<i>Sasolburg, Tweeling</i>	3	0.6
<i>Kroonstad, Arlington, Steynsrus</i>	2	0.4
<i>Bloemfontein, Clocolan, Van Reenen, Koppies, Ladybrand, Philippolis, Villiers, Welkom, Rosendal</i>	1	0.2

n: number of patients.

Appendix F

NYHA classification

		<i>Congestive cardiac failure</i>	<i>Diabetes mellitus type 2</i>	<i>Hypertension</i>	<i>Ischemic heart disease</i>	<i>Total</i>
NYHA CLASS	1	1 (0.8%)	107 (91.5%)	100 (78.7%)	31 (20.6%)	239 (50.3%)
	2	40 (33.9%)	10 (8.6%)	27 (21.3%)	78 (52.0%)	155 (32.6%)
	3	58 (49.2%)	0 (0 %)	0 (0%)	4 (2.6%)	62 (13.0%)
	4	19 (16.1%)	0 (0 %)	0 (0%)	0 (0%)	19 (4.0%)
		118	117	127	150	475

NYHA: New York Heart Association.

Appendix G

Systolic parameters' values of the total population

<i>Variable</i>	<i>Mean</i>	<i>Standard deviation</i>	<i>Median</i>	<i>25th %</i>	<i>75th %</i>
Teichholz EF (%)	50.5	15.8	55.8	41.0	61.8
Simpson's AP4CH EF (%)	49.9	15.8	55.0	39.2	62.0
Simpson's AP2CH EF (%)	49.8	15.7	55.0	40.0	61.8
Strain EF (%)	50.6	26.9	55.0	39.6	61.2
S' (cm/s)	7.9	2.8	8.6	5.6	10.2
LV MPI	0.5	0.2	0.4	0.3	0.6
MAPSE (mm)	9.2	3.4	10.6	6.7	11.8
MAPSE EF (%)	50.1	16.3	57.2	37.9	62.4

EF: ejection fraction, AP4CH: apical four chamber, AP2CH: apical two chamber, S': peak systolic tissue value, LV MPI: left ventricular myocardial performance index, MAPSE: mitral annular plane systolic excursion, mm: millimetres.

Appendix H

Correlation between MAPSE EF and the systolic parameters

H1 Correlation between MAPSE EF and systolic variables in the total study population

<i>Variable</i>	<i>with Variable</i>	<i>n</i>	<i>Correlation</i>	<i>Fisher's z</i>	<i>Confidence limits</i>	<i>p-value</i>
<i>Average MAPSE EF (%)</i>	<i>Teichholz EF (%)</i>	475	0.82	1.15	0.79 – 0.85	<0.0001
<i>Average MAPSE EF (%)</i>	<i>Simpson's AP4CH EF (%)</i>	475	0.84	1.222	0.81 – 0.86	<0.0001
<i>Average MAPSE EF (%)</i>	<i>Simpson's AP2CH EF (%)</i>	475	0.84	1.23	0.81 – 0.87	<0.0001
<i>Average MAPSE EF (%)</i>	<i>Strain EF (%)</i>	475	0.83	1.16	0.79 – 0.85	<0.0001
<i>Average MAPSE EF (%)</i>	<i>S' (cm/s)</i>	475	0.89	1.41	0.86 – 0.91	<0.0001
<i>Average MAPSE EF (%)</i>	<i>LV MPI</i>	475	-0.74	-0.95	-0.77 – -0.69	<0.0001

EF: ejection fraction, AP4CH: apical four chamber, AP2CH: apical two chamber, S': peak systolic tissue value, LV MPI: left ventricular myocardial performance index, MAPSE: mitral annular plane systolic excursion, mm: millimetres, n: number of patients.

H2 Correlation between MAPSE EF and systolic variables in females in the total population

<i>Variable</i>	<i>with Variable</i>	<i>n</i>	<i>Correlation</i>	<i>Fisher's z</i>	<i>Confidence limits</i>	<i>p-value</i>
<i>Average MAPSE EF (%)</i>	<i>Teichholz EF (%)</i>	225	0.83	1.82	0.78 – 0.86	<0.001
<i>Average MAPSE EF (%)</i>	<i>Simpson's AP4CH EF (%)</i>	225	0.84	1.22	0.79 – 0.87	<0.001
<i>Average MAPSE EF (%)</i>	<i>Simpson's AP2CH EF (%)</i>	225	0.84	1.22	0.80 – 0.87	<0.001
<i>Average MAPSE EF (%)</i>	<i>Strain EF (%)</i>	225	0.81	1.11	0.76 – 0.84	<0.001
<i>Average MAPSE EF (%)</i>	<i>S' (cm/s)</i>	225	0.89	1.41	0.86 – 0.91	<0.001
<i>Average MAPSE EF (%)</i>	<i>LV MPI</i>	225	-0.73	-0.93	-0.78 – -0.66	<0.001

EF: ejection fraction, AP4CH: apical four chamber, AP2CH: apical two chamber, S': peak systolic tissue value, LV MPI: left ventricular myocardial performance index, MAPSE: mitral annular plane systolic excursion, mm: millimetres, n: number of patients.

H3 Correlation between MAPSE EF and systolic variables in men in the total population

<i>Variable</i>	<i>with Variable</i>	<i>n</i>	<i>Correlation</i>	<i>Fisher's z</i>	<i>Confidence limits</i>	<i>p-value</i>
<i>Average MAPSE EF (%)</i>	<i>Teichholz EF (%)</i>	220	0.81	1.13	0.76 – 0.85	<0.001
<i>Average MAPSE EF (%)</i>	<i>Simpson's AP4CH EF (%)</i>	220	0.85	1.24	0.80 – 0.88	<0.001
<i>Average MAPSE EF (%)</i>	<i>Simpson's AP2CH EF (%)</i>	220	0.85	1.27	0.81 – 0.86	<0.001
<i>Average MAPSE EF (%)</i>	<i>Strain EF (%)</i>	220	0.85	1.26	0.81 – 0.88	<0.001
<i>Average MAPSE EF (%)</i>	<i>S' (cm/s)</i>	220	0.89	1.43	0.86 – 0.92	<0.001
<i>Average MAPSE EF (%)</i>	<i>LV MPI</i>	220	-0.76	-1.00	-0.76 – -0.70	<0.001

EF: ejection fraction, AP4CH: apical four chamber, AP2CH: apical two chamber, S': peak systolic tissue value, LV MPI: left ventricular myocardial performance index, MAPSE: mitral annular plane systolic excursion, mm: millimetres, n: number of patients.

H4 Correlation between MAPSE EF and systolic variables in females with congestive cardiac failure

<i>Variable</i>	<i>with Variable</i>	<i>n</i>	<i>Correlation</i>	<i>Fisher's z</i>	<i>Confidence limits</i>	<i>p-value</i>
<i>Average MAPSE EF (%)</i>	<i>Teichholz EF (%)</i>	68	0.89	1.44	0.83 – 0.93	<0.0001
<i>Average MAPSE EF (%)</i>	<i>Simpson's AP4CH EF (%)</i>	68	0.88	1.35	0.80 – 0.92	<0.0001
<i>Average MAPSE EF (%)</i>	<i>Simpson's AP2CH EF (%)</i>	68	0.84	1.23	0.75 – 0.90	<0.0001
<i>Average MAPSE EF (%)</i>	<i>Strain EF (%)</i>	68	0.85	1.26	0.77 – 0.90	<0.0001
<i>Average MAPSE EF (%)</i>	<i>S' (cm/s)</i>	68	0.77	1.02	0.65 – 0.85	<0.0001
<i>Average MAPSE EF (%)</i>	<i>LV MPI</i>	68	-0.65	-0.78	-0.77 – -0.49	<0.0001

EF: ejection fraction, AP4CH: apical four chamber, AP2CH: apical two chamber, S': peak systolic tissue value, LV MPI: left ventricular myocardial performance index, MAPSE: mitral annular plane systolic excursion, mm: millimetres, n: number of patients.

H5 Correlation between MAPSE EF and systolic variables in men with congestive cardiac failure

<i>Variable</i>	<i>with Variable</i>	<i>n</i>	<i>Correlation</i>	<i>Fisher's z</i>	<i>Confidence limits</i>	<i>p-value</i>
<i>Average MAPSE EF (%)</i>	<i>Teichholz EF (%)</i>	50	0.88	1.40	0.80 – 0.93	<0.0001
<i>Average MAPSE EF (%)</i>	<i>Simpson's AP4CH EF (%)</i>	50	0.87	1.35	0.78 – 0.93	<0.0001
<i>Average MAPSE EF (%)</i>	<i>Simpson's AP2CH EF (%)</i>	50	0.86	1.29	0.76 – 0.92	<0.0001
<i>Average MAPSE EF (%)</i>	<i>Strain EF (%)</i>	50	0.85	1.25	0.74 – 0.91	<0.0001
<i>Average MAPSE EF (%)</i>	<i>S' (cm/s)</i>	50	0.85	1.26	0.75 – 0.91	<0.0001
<i>Average MAPSE EF (%)</i>	<i>LV MPI</i>	50	-0.74	-0.95	-0.84 – -0.58	<0.0001

EF: ejection fraction, AP4CH: apical four chamber, AP2CH: apical two chamber, S': peak systolic tissue value, LV MPI: left ventricular myocardial performance index, MAPSE: mitral annular plane systolic excursion, mm: millimetres, n: number of patients.

H6 Correlation between MAPSE EF and systolic variables in patients with grade 1 diastolic dysfunction

<i>Variable</i>	<i>with Variable</i>	<i>n</i>	<i>Correlation</i>	<i>Fisher's z</i>	<i>Confidence limits</i>	<i>p-value</i>
<i>Average MAPSE EF (%)</i>	<i>Teichholz EF (%)</i>	168	0.42	0.45	0.29 – 0.53	<0.001
<i>Average MAPSE EF (%)</i>	<i>Simpson's AP4CH EF (%)</i>	168	0.50	0.55	0.38 – 0.61	<0.001
<i>Average MAPSE EF (%)</i>	<i>Simpson's AP2CH EF (%)</i>	168	0.52	0.58	0.40 – 0.62	<0.001
<i>Average MAPSE EF (%)</i>	<i>Strain EF (%)</i>	168	0.49	0.53	0.36 – 0.59	<0.001
<i>Average MAPSE EF (%)</i>	<i>S' (cm/s)</i>	168	0.69	0.85	0.60 – 0.76	<0.001
<i>Average MAPSE EF (%)</i>	<i>LV MPI</i>	168	-0.22	-0.22	-0.36 – 0.70	0.0041

EF: ejection fraction, AP4CH: apical four chamber, AP2CH: apical two chamber, S': peak systolic tissue value, LV MPI: left ventricular myocardial performance index, MAPSE: mitral annular plane systolic excursion, mm: millimetres, n: number of patients.

H7 Correlation between MAPSE EF and systolic variables in patients with grade 2 diastolic dysfunction

<i>Variable</i>	<i>with Variable</i>	<i>n</i>	<i>Correlation</i>	<i>Fisher's z</i>	<i>Confidence limits</i>	<i>p-value</i>
<i>Average MAPSE EF (%)</i>	<i>Teichholz EF (%)</i>	245	0.86	1.28	0.82 – 0.89	<0.001
<i>Average MAPSE EF (%)</i>	<i>Simpson's AP4CH EF (%)</i>	245	0.86	1.30	0.82 – 0.89	<0.001
<i>Average MAPSE EF (%)</i>	<i>Simpson's AP2CH EF (%)</i>	245	0.87	1.33	0.83 – 0.90	<0.001
<i>Average MAPSE EF (%)</i>	<i>Strain EF (%)</i>	245	0.84	1.21	0.79 – 0.87	<0.001
<i>Average MAPSE EF (%)</i>	<i>S' (cm/s)</i>	245	0.88	1.40	0.85 – 0.91	<0.001
<i>Average MAPSE EF (%)</i>	<i>LV MPI</i>	245	-0.78	-1.04	-0.82 – -0.72	0.0041

EF: ejection fraction, AP4CH: apical four chamber, AP2CH: apical two chamber, S': peak systolic tissue value, LV MPI: left ventricular myocardial performance index, MAPSE: mitral annular plane systolic excursion, mm: millimetres, n: number of patients.

H8 Correlation between MAPSE EF and systolic variables in patients with grade 3 diastolic dysfunction.

<i>Variable</i>	<i>with Variable</i>	<i>n</i>	<i>Correlation</i>	<i>Fisher's z</i>	<i>Confidence limits</i>	<i>p-value</i>
<i>Average MAPSE EF (%)</i>	<i>Teichholz EF (%)</i>	59	0.93	1.64	0.87 – 0.95	<0.001
<i>Average MAPSE EF (%)</i>	<i>Simpson's AP4CH EF (%)</i>	59	0.92	1.58	0.86 – 0.95	<0.001
<i>Average MAPSE EF (%)</i>	<i>Simpson's AP2CH EF (%)</i>	59	0.90	1.48	0.83 – 0.94	<0.001
<i>Average MAPSE EF (%)</i>	<i>Strain EF (%)</i>	59	0.90	1.47	0.83 – 0.93	<0.001
<i>Average MAPSE EF (%)</i>	<i>S' (cm/s)</i>	59	0.93	1.63	0.88 – 0.96	<0.001
<i>Average MAPSE EF (%)</i>	<i>LV MPI</i>	59	-0.84	-1.23	-0.90 – -0.74	0.0041

EF: ejection fraction, AP4CH: apical four chamber, AP2CH: apical two chamber, S': peak systolic tissue value, LV MPI: left ventricular myocardial performance index, MAPSE: mitral annular plane systolic excursion, mm: millimetres, n: number of patients.

H9 Correlation between Simpson's AP4CH EF and strain derived EF

<i>Variable</i>	<i>with Variable</i>	<i>Group</i>	<i>n</i>	<i>Correlation</i>	<i>Fisher's z</i>	<i>Confidence limits</i>	<i>p-value</i>
<i>Simpson's AP4CH EF (%)</i>	<i>Strain EF (%)</i>	Total population	475	0.96	1.91	0.95 – 0.96	<0.001
<i>Simpson's AP4CH EF (%)</i>	<i>Strain EF (%)</i>	Congestive cardiac failure	118	0.97	2.03	0.00 – 0.97	<0.001
<i>Simpson's AP4CH EF (%)</i>	<i>Strain EF (%)</i>	Hypertension	127	0.93	1.65	0.00 – 0.93	<0.001
<i>Simpson's AP4CH EF (%)</i>	<i>Strain EF (%)</i>	Diabetes mellitus type 2	117	0.81	1.12	0.81 – 0.73	<0.001
<i>Simpson's AP4CH EF (%)</i>	<i>Strain EF (%)</i>	Ischemic heart disease	113	0.82	1.16	0.75 – 0.87	<0.0001

EF: ejection fraction, AP4CH: apical four chamber, n: number of patients.

H10 Correlation between Simpson's AP4CH EF and LV MPI

<i>Variable</i>	<i>with Variable</i>	<i>Group</i>	<i>n</i>	<i>Correlation</i>	<i>Fisher's z</i>	<i>Confidence limits</i>	<i>p-value</i>
<i>Simpson's AP4CH EF (%)</i>	<i>LV MPI</i>	Total population	475	- 0.76	-0.99	-0.79 – -0.72	<0.001
<i>Simpson's AP4CH EF (%)</i>	<i>LV MPI</i>	Congestive cardiac failure	118	-0.65	-0.77	-0.74 – -0.52	<0.001
<i>Simpson's AP4CH EF (%)</i>	<i>LV MPI</i>	Hypertension	127	-0.17	-0.17	-0.33 – 0.002	0.05
<i>Simpson's AP4CH EF (%)</i>	<i>LV MPI</i>	Diabetes mellitus type 2	117	0.05	0.05	-0.13 – 0.23	0.59
<i>Simpson's AP4CH EF (%)</i>	<i>LV MPI</i>	Ischemic heart disease	113	-0.45	-0.49	-0.59 – -0.29	<0.0001

EF: ejection fraction, AP4CH: apical four chamber, LV MPI: left ventricular myocardial performance index, n: number of patients.