UNDERSTANDING DIASTOLIC HEART FAILURE

by

DR YU TING TAN

A thesis submitted to
The University of Birmingham
for the degree of
DOCTOR OF PHILOSOPHY

Department of Cardiovascular Medicine
School of Clinical & Experimental Medicine
The University of Birmingham
November 2012

Abstract

Many patients who present with symptoms of heart failure are found to have a normal left ventricular ejection fraction and therefore were labelled as having “diastolic heart failure” implying that the underlying pathophysiology is due to diastolic dysfunction alone. However, using a combination of echocardiographical techniques, a variety of abnormalities were found including reduced longitudinal function, impaired left ventricular twist and torsional dyssynchrony in systole leading to reduced and delayed untwisting, impaired suction and reduced early diastolic left ventricular filling not fully compensated for in late diastole due to left atrial dysfunction. Furthermore in a group of subjects with treated hypertension, the most common risk factor for this form of heart failure, despite a normal resting echocardiogram, there were already substantial abnormalities of both systolic and diastolic function which were only apparent on exercise. Thus these studies have demonstrated that in heart failure with a normal ejection fraction, there are major abnormalities of systolic function especially torsion or twist, which impact on diastolic filling and that the condition is not due to diastolic dysfunction alone. In addition, these findings emphasise the importance of exercise echocardiography for diagnosis and detecting early left ventricular dysfunction before patients progress to developing heart failure.

To my grandfather

ACKNOWLEDGEMENTS

This research was conducted under the direct supervision of Profession John Sanderson, initially at the University Hospital of North Staffordshire and then at the University of Birmingham. I am indebted to Professor Sanderson for his endless patience, priceless advice and immense support throughout the period of this research and beyond. His guidance and reassurance have strengthened my determination to complete my research and enable the production of this thesis. I am most grateful for his trust in me to undertake this project. In addition to being a resourceful and supportive supervisor, he is someone I have the highest admiration and respect for.

Many thanks to my co-supervisor Dr Francisco Leyva who has been most supportive in all aspects of my research. Whether it was a funding issue or an extension of research ideas, Dr Leyva's contributions have been priceless. His persistence and enthusiasm are insurmountable. His good sense of humour and friendship is invaluable.

My most sincere thanks go to Dr Frauke Wenzelburger, particularly for her help and effort in painstakingly entering our data from handwritten hard copies into the electronic database. She is not only a colleague, but also a dear friend.

I would like to acknowledge the British Heart Foundation for funding and supporting this research through the award of a Project Grant (PG/06/006/106/21472). I would also like to extend my gratitude to the North Staffordshire Heart Committee for a

generous contribution to an equipment grant which we used to purchase the tilting bicycle ergometer and the echocardiogram couch, which were the two essential pieces of equipment for the project. In addition, part of the equipment grant was put to good use in turning a storage room into a fully functional research area.

I would like to thank Mr Stuart Wragg and Miss Rebekah Weaver for their help in performing and analysing the cardiopulmonary exercise tests. Special thanks go to Miss Julie Machin for her tireless help and support in the ethics application for the project and various logistic issues pertaining to the project. Thanks also to Dr Eveline Lee for her help in the echocardiography scanning of study subjects especially on exercise, and Dr Peter Nightingale for his invaluable statistical input and advice.

Thank you to the patients and healthy controls for their participation. This project would have been impossible without your precious time and your belief in our project. I would also like to thank my colleagues at the University Hospital of North Staffordshire and the University Hospital Birmingham for their help in referring patients for this project.

Finally, I must thank my family, close friends and especially Michael, who had to put up with me throughout the journey of my research. Your understanding, encouragement and emotional support, particularly during the writing of this thesis, have enforced my ambition to obtain this PhD degree.

EXTENT OF PERSONAL CONTRIBUTION

The original research hypothesis and British Heart Foundation (BHF) grant application were obtained by Professor Sanderson.

At the start of the project, I was responsible for the writing of the information leaflets and consent forms, the application of ethics approval and submission of ethics committee amendments, the ordering of research equipment, designing and setting up of the research room, and the writing of the study and echogradiographical protocols.

I screened and recruited all potential patients from the Heart Failure Clinic at the University Hospital of North Staffordshire between May 2007and December 2008. I also recruited potential patients from the cardiology clinic at the University Hospital Birmingham between September 2007 and December 2008. I screened for potential healthy controls from two large general practices in Birmingham.

Assisted by Dr Wenzelburger, I took full medical history, performed physical examination and consented all study subjects. Either myself or Dr Wenzelburger was present during all the cardiopulmonary exercise testing. I was responsible for organising, scheduling and sending out appointments of various tests for all study subjects.

Assisted by Dr Lee and / or Dr Wenzelburger, I performed echocardiography at rest and on exercise for all recruited subjects. I analysed echocardiography data with Dr Wenzelburger. Statistical analysis was performed with the assistance of statistician Dr Nightingale. I was also responsible for the maintenance of all regulatory documents.

Under the supervision of Professor Sanderson and later, Dr Leyva, I was the author of all published manuscripts. I was the presenter for all accepted abstracts at conferences in the United Kingdom (British Cardiovascular Society, British Society of Echocardiography and British Society of Hypertension), Europe (European Society of Cardiology Congress, European Society of Heart Failure and European Society of Echocardiography) and the United States of America (American College of Cardiology and American Heart Association conferences).

PUBLICATIONS

This PhD thesis is based on the following publications:

Original research

- Tan YT, Wenzelburger F, Lee E, Heatlie G, Leyva F, Patel K, Frenneaux M, Sanderson JE. The pathophysiology of heart failure with normal ejection fraction: exercise echocardiography reveals complex abnormalities of both systolic and diastolic ventricular function involving torsion, untwist and longitudinal motion. J Am Coll Cardiol 2009;54(1):36-46.

- Tan YT, Wenzelburger F, Lee E, Heatlie G, Frenneaux M, Sanderson JE. Abnormal left ventricular function occurs on exercise in well-treated hypertensive subjects with normal resting echocardiography. Heart 2010;96(12):948-55.

- Tan YT, Wenzelburger F, Lee E, Nightingale P, Heatlie G, Leyva F, Sanderson JE. Reduced left atrial function on exercise in patients with heart failure and normal ejection fraction. Heart 2010;96(13):1017-23.

- Wenzelburger FW, Tan YT, Choudhary FJ, Lee ES, Leyva F, Sanderson JE. Mitral annular plane systolic excursion on exercise: a simple diagnostic tool for heart failure with preserved ejection fraction. Eur J Heart Fail 2011;13(9):953-60.

- Tan YT, Wenzelburger F, Sanderson JE, Leyva F. Exercise-induced torsional dyssynchrony relates to impaired functional capacity in patients with heart failure and normal ejection fraction. Heart 2013;99(4):259-66

Related publications

- Yip GW, Fung JW, Tan YT, Sanderson JE. Hypertension and heart failure: a dysfunction of systole, diastole or both? J Hum Hypertens 2009;23(5):295-306.

- Sanderson JE, Tan YT, Heart Failure with Normal Ejection Fraction. In: Henein MY, editor. Heart Failure in Clinical Practice. London: Springer;2010.p.123-137.

- Tan YT, Sanderson JE. Forgotten atrial: driver of symptoms in heart failure with normal ejection fraction? Heart 2012;98(17):1261-2.

ABTRACTS

Award winning abstracts

- YT Tan, FWG Wenzelburger, ESP Lee, G Heatlie, G Mahadavan, LK William, F Leyva, MP Frenneaux, JE Sanderson. Abnormal left ventricular systolic and diastolic function on exercise in patients with heart failure and normal ejection fraction. Moderated poster presentation at European Society of Cardiology Congress 2008 Munich, Germany (winner of the moderated poster award).

- YT Tan, ESP Lee, FWG Wenzelburger, G Heatlie, F Leyva, MP Frenneaux, JE Sanderson. Impaired left ventricular rotation and rotational dyssynchrony in heart failure. Oral presentation at British Society of Echocardiography 2008 Harrogate, United Kingdom (young investigator runner up).

- YT Tan, ESP Lee, FWG Wenzelburger, G Heatlie, F Leyva, MP Frenneaux, JE Sanderson. Impaired left ventricular twist in heart failure with normal ejection fraction. Moderated poster presentation at Euroecho 2008 Lyon, France (travel grant award).

- YT Tan, FWG Wenzelburger, JE Sanderson, F Leyva. Dyssynchrronous three plane motion and impaired left ventricular twist in patients with heart failure and normal ejection fraction. Poster presentation at British Cardiovascular Society 2011 Manchester, United Kingdom (highest scoring abstract).

Also presented as poster presentation at the 2nd International Conference on Heart Failure with Preserved Ejection Fraction, Heart Failure Association, European Society of Cardiology, Budapest, Hungary (2011).

Abstract shortlisted for Young Investigator Prize

- YT Tan, ESP Lee, FWG Wenzelburger, G Heatlie, MP Frenneaux, JE Sanderson. Reduced longitudinal functional reserve on exercise in hypertensive patients with exertional dyspnoea and normal echocardiography at rest. Moderated poster presentation at British Hypertension Society 2008 Cambridge, United Kingdom.

Oral presentations

- YT Tan, FWG Wenzelburger, ESP Lee, G Mahadevan, L Williams, G Heatlie, F Leyva, JE Sanderson. Reduced left ventricular early diastolic suction on exercise in breathless patients with normal ejection fraction. European Society of Cardiology 2008 Munich, Germany.

- YT Tan, F Wenzelburger, E Lee, G Heatlie, M Frenneaux, JE Sanderson. Reduced longitudinal functional reserve on exercise in hypertensive patients with breathlessness on exertion in the absence of left ventricular hypertrophy. British Society of Hypertension 2008 Cambridge, United Kingdom.

- YT Tan, ESP Lee, FWG Wenzelburger, G Heatlie, M Frenneaux, JE Sanderson. Treated hypertensives with normal standard echocardiography at rest have marked left ventricular dysfunction on exercise. European Society of Cardiology 2009 Barcelona, Spain.

Plenary session

- Assessment of left ventricular torsion. British Cardiovascular Society 2010 – British Society of Echocardiography plenary session.

Moderated poster presentations

- YT Tan, F Wenzelburger, E Lee, G Heatlie, K Patel, F Leyva, M Frenneaux, JE Sanderson. Impaired left ventricular twist and untwist in heart failure and normal ejection fraction is associated with reduced ventricular suction. British Cardiovascular Society 2009 London, United Kingdom.
  Also poster presentation at European Society of Cardiology 2009, Barcelona, Spain and the 13th Asia Pacific Congress of Echocardiography, Brisbane, Australia (2009).

- YT Tan, F Wenzelburger, E Lee, G Heatlie, F Leyva, K Patel, M Frenneaux, JE Sanderson. Reduced exercise capacity is associated with impaired left ventricular longitudinal function in patients with heart failure and normal ejection fraction. British Cardiovascular Society 2009, London, United Kingdom.
  Also poster presentation at the 13th Asia Pacific Congress of Echocardiography, Brisbane, Australia (2009).

- YT Tan, F Wenzelburger, E Lee, G Heatlie, F Leyva, JE Sanderson. Impaired apical and basal rotation lead to a reduction in twist on exercise in patients with heart failure and normal ejection fraction. British Cardiovascular Society 2010 Manchester, United Kingdom.

  Also, poster presentation at European Society of Cardiology 2010, Stockholm, Sweden.

Poster presentations

- YT Tan, F Wenzelburger, E Lee, G Mahadevan, G Heatlie, F Leyva, MP Frenneaux, JE Sanderson. The breathless patient with normal echocardiography at rest : occult ventricular functional abnormalities are revealed by exercise echocardiography. Euroecho 2008 Lyon, France.

- YT Tan, ESP Lee, FWG Wenzelburger, G Heatlie, MP Frenneaux, JE Sanderson. Reduced longitudinal functional reserve on exercise in hypertensive patients with exertional dyspnoea and normal echocardiography at rest. Euroecho 2008 Lyon, France and American Heart Association 2008, New Orleans, United States of America.

- YT Tan, F Wenzelburger, E Lee, G Heatlie, F Leyva, M Frenneaux, JE Sanderson. Reduced left atrial function and normal ejection fraction in hypertensive patients with dyspnoea. European Society of Cardiology 2009 Barcelona, Spain and British Cardiovascular Society 2009 London, United Kingdom.

- YT Tan, FWG Wenzelburger, ESP Lee, G Heatlie, K Patel, F Leyva, M Frenneaux, JE Sanderson. Systolic ventricular deformation and rotation are reduced at rest and on exercise in patients with heart failure and normal ejection fraction. European Society of Cardiology 2009 Barcelona, Spain; British Cardiovascular Society 2009 London, United Kingdom and American College of Cardiology 2009, Orlando, United States of America.

- YT Tan, E Lee, F Wenzelburger, G Heatlie, S Davies, M Frenneaux, JE Sanderson. Reduced longitudinal and radial strain in patients with hypertension without left ventricular hypertrophy. The 13th Asia Pacific Congress of Echocardiography, Brisbane, Australia (2009).

List of abbreviations

The main abbreviations used are shown below.

DHF	Diastolic heart failure
E/e’	ratio of early mitral diastolic inflow velocity to early diastolic mitral annular velocity
EF	Ejection fraction
HFNEF	Heart failure with a normal ejection fraction
HFREF	Heart failure with a reduced ejection fraction
LV	Left ventricle / ventricular
LVEF	Left ventricular ejection fraction
SHF	Systolic heart failure

A full list of abbreviations is contained in Appendix 1.

Table of contents

Table of contents - continued

Table of contents - continued

Table of contents - continued

List of Figures

List of Figures continued

List of Figures continued

List of Figures continued

List of Figures continued

List of Tables

List of Tables continued

List of Tables continued

CHAPTER 1

INTRODUCTION

Contributory publications:

Yip GW, Fung JW, Tan YT, Sanderson JE. Hypertension and heart failure: a dysfunction of systole, diastole or both? J Hum Hypertens 2009;23(5):295-306.

Sanderson JE, Tan YT, Heart Failure with Normal Ejection Fraction. In: Henein MY, editor. Heart Failure in Clinical Practice. London: Springer;2010.p.123-137.

1. INTRODUCTION

1.1 DEFINING HEART FAILURE WITH NORMAL EJECTION FRACTION

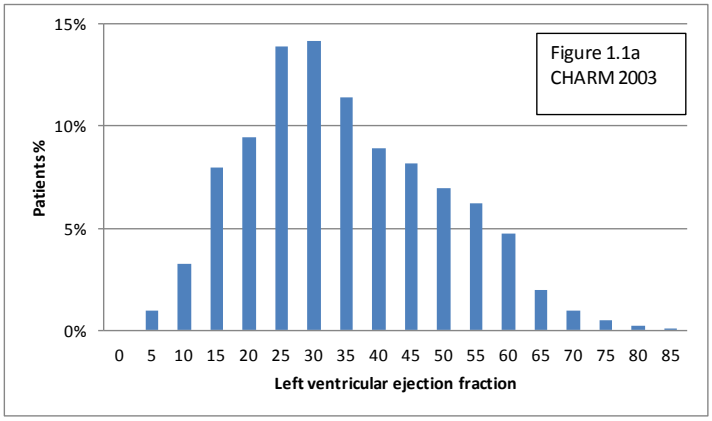
It has been known for over 70 years that heart failure can occur in patients in whom left ventricular systolic contractile function appears to be normal when measured by the ejection fraction. Since systolic function was presumed to be normal in these patients, this form of heart failure was thought to be due to diastolic dysfunction or abnormal filling and hence was labelled as diastolic heart failure (DHF). However, there has been increasing evidence that systolic function is not entirely normal in these patients and therefore the terms 'heart failure with a normal ejection fraction' (HFNEF) and 'heart failure with a preserved ejection fraction' (HFPEF) have been used as the preferred terms to diastolic heart failure, as they are more descriptive terms which do not make assumptions about the causation of the condition, nor imply that the primary abnormality lies solely in diastole. For these reasons, the term HFNEF is used throughout this thesis.

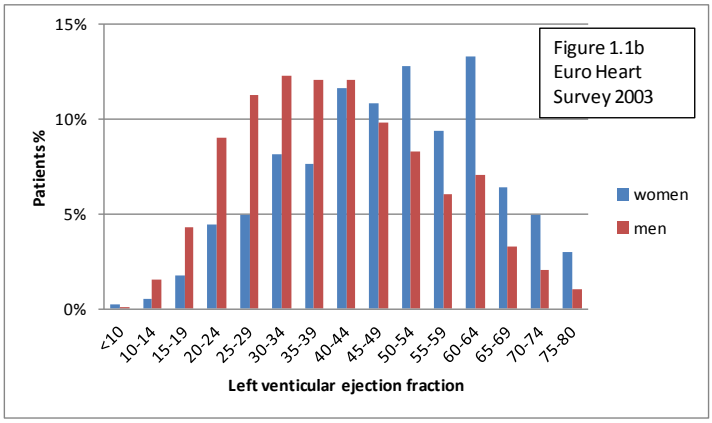
The term HFNEF is descriptive of a syndrome which has been shown to involve a collection of cardiovascular abnormalities each contributing to the genesis of symptoms. These include vascular and ventricular stiffening (1;2), diastolic dysfunction requiring elevated filling pressure to enable adequate left ventricular filling, increased heart volume and epicardial constraints (2).

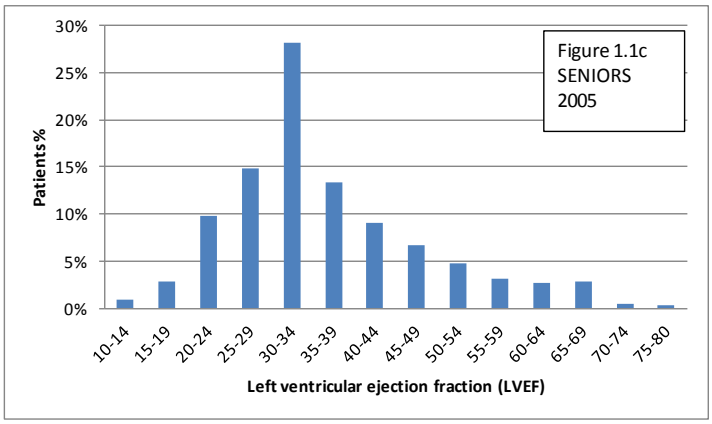
Over the past decade, there has been an apparently steady rise in the prevalence of HFNEF (3). Despite this, there has been considerable controversy with regards to the existence of the condition, its terminology, the characteristics of the condition and the diagnostic criteria for HFNEF. The confusion has arisen as some authors suggested that systolic function is normal in HFNEF patients (4;5), while others questioned if the two entities exist as a continuum of heart failure or whether they are distinct entities (6).

In view of the unimodal distribution of left ventricular ejection fraction illustrated by observational studies (7-9) (Figure 1.1), it was thought that chronic heart failure is a pathophysiological identity which encompasses a continuous spectrum of related phenotypes and should not be dichotomised into two separate entities based on the left ventricular ejection fraction (LVEF) alone (10).

Figure 1.1 Illustrating the unimodular distribution of left ventricular ejection fraction in patients with heart failure







1.1a, the CHARM study (7). 1.1b, the Euro Heart Survey (8). 1.1c, the SENIOR study (7-9).

Adapted from Brutsaert DL (10).

Furthermore, several studies have shown that left ventricular systolic function is not entirely normal despite a seemingly normal global systolic performance, hence suggesting that diastolic heart failure and systolic heart failure reflect two ends of the spectrum of heart failure syndrome, and that diastolic heart failure progresses to systolic heart failure with time (11-16). In contrary, there are studies which showed that there are significant structural, functional and molecular differences between those patients with diastolic heart failure and those patients with systolic heart failure, and it has been suggested therefore that these two conditions are different entities and exist as two separate syndromes (17).

For example, van Heerebeek et al. found morphological differences between systolic and diastolic heart failure (18), but this study did not reflect a true comparison between HFNEF and heart failure with a reduced ejection fraction (HFREF) as it compared hypertensive patients with a normal ejection fraction and non-hypertensive non-ischaemic cardiomyopathy patients. There are differences in microscopic and neuroendocrine features which consequently lead to differences in left ventricular structure and echocardiographic characteristics between HFNEF and HFREF. These differences are attributed by underlying or contributing factors such as ageing, diabetes and hypertension. Yip et al. comprehensively summarised the phenotypic differences between HFNEF and HFREF and the close similarities of exercise response in both conditions (Table 1.1) (19). However, diastolic dysfunction which has been shown to be a strong predictor of exercise intolerance (20), is present in both conditions and is not unique to HFNEF.

Table 1.1 Summary of the similarities and differences between HFNEF and HFREF

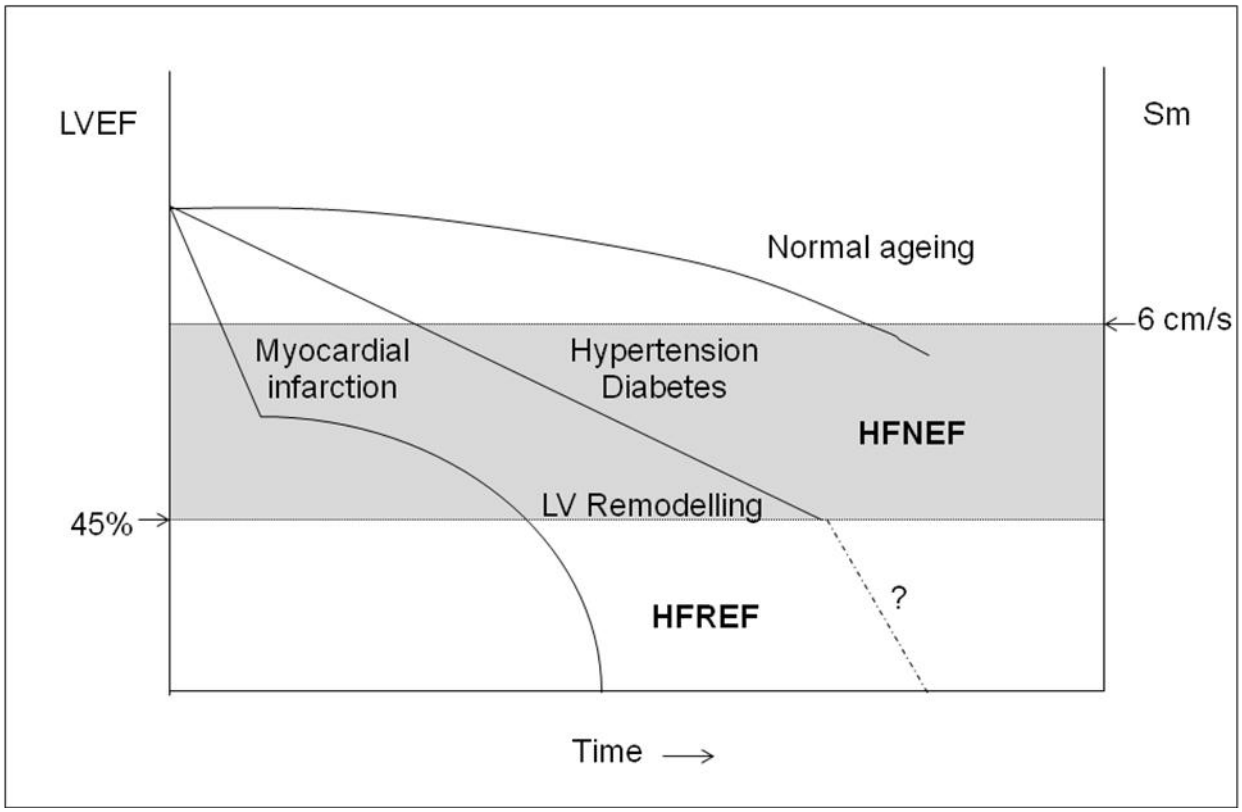
Parameters	HFNEF	HFREF
Microscopic and neuroendocrine features		
Cardiac cell hypertrophy	Increased	Minimal
Cardiomyocytes resting tension	Increased	Decreased
Myofilament density	Preserved	Decreased
Titin N2B/N2BA ratio	Increased	Decreased
Interstitial collagen	Increased	Decreased
MMP-1 / TIMP-1 ratio	Minimal change	Decreased
B-receptor down regulation	Present	Present
Myocardial β-adrenergic receptor desensitisation	Present	Present
Norepinephrine	Increased	Increased
B-type natriuretic peptide	Increased	More increased
Resting echocardiographic parameters		
LV cavity size	Normal/decreased	Increased
LV shape and geometry	Minimal change	Spherical
LV mass index	Increased	Increased
LV mass to cavity ratio	Increased	Normal/decreased
Relative wall thickness	Increased	Normal
End-diastolic volume / wall stress	Normal/decreased	Increased
End-systolic volume / wall stress	Normal	Increased
LV ejection fraction	Normal	Decreased
Longitudinal velocity / strain	Decreased	More decreased
Radial strain	Decreased	More decreased
LV twist / torsion	Normal/decreased	Decreased
LV twist / untwist rate	Normal/decreased	Decreased
Exercise response		
Peak oxygen consumption	Reduced	Reduced
Ventilatory anaerobic thresholds	Reduced	Reduced
Heart rate response	Blunted	Blunted
Stroke volume / cardiac output	Decreased	More decreased
Contractile reserve	Decreased	Decreased
Systemic vascular resistance	Normal/increased	Increased
Longitudinal velocity / strain	Decreased	More decreased
Radial strain	Decreased	More decreased
Circumferential strain	Decreased	More decreased
LV twist / torsion	Decreased	More decreased
LV untwisting	Delayed	Delayed

Adapted from Yip G et al. (19).

The neuroendocrine, gross and microscopic structural differences between the two conditions (18;21;22) are likely a reflection of the aetiology of the conditions and this determines the phenotype and the progression of the disease. Ultimately, the primary difference is whether left ventricular remodelling has occurred or not (Figure 1.2) (21).

In HFREF, myocardial infarction is the more usual cause and this is a powerful stimulus of ventricular remodelling and there is rapid progression of systolic dysfunction with ventricular dilatation, the more typical and recognisable form of heart failure. Patients who develop HFREF following a myocardial ischaemic event usually pass through an early or initial HFNEF phase (Figure 1.2). In contrast, hypertension in conjunction with diabetes and ageing are the more common causes of HFNEF, is commonly associated with left ventricular hypertrophy (LVH) in the absence of left ventricular dilatation. It appears that HFNEF does progress to HFREF with time (21). Table 1.2 summarises the comparison of clinical features of HFNEF and HFREF.

Figure 1.2 Phenotype of heart failure relates to degree of remodelling and aetiology



Adapted from Sanderson JE (21).

LVEF, left ventricular ejection fraction; Sm, peak systolic myocardial mitral annular velocity by colour tissue Doppler; LV, left ventricular; HFREF, heart failure with a reduced ejection fraction; HFNEF, heart failure with a normal ejection fraction.

Table 1.2 Comparison of clinical features of HFNEF and HFREF

Clinical features	HFNEF	HFREF
Gender	Females > Males	Males > Females
Age	60-80	50-70
Aetiology	Hypertension Diabetes Atrial fibrillation Transient ischaemia	Myocardial infarction Idiopathic dilated cardiomyopathy
Clinical progress	Often episodic heart failure	Persistent heart failure
Ventricular remodelling (increased volume)	None	Present
LV hypertrophy	Increased	Increased / decreased
Peak mitral inflow velocity pattern	Abnormal relaxation pattern (ARP)	Restrictive filling pattern (RFP)
Peak mitral annular velocity	Moderately reduced	Markedly reduced
LA volume index	Increased	Increased

Adapted from Sanderson JE (21).

HFNEF, heart failure with a normal ejection; HFREF, heart failure with a reduced ejection fraction; LV, left ventricular; LA, left atrial.

The exact pathophysiology of HFNEF is still debated. There is unlikely to be one pathophysiology common to all HFNEF subjects. The challenge of studying and understanding HFNEF arises from the heterogenous aetiologies (ageing, hypertension, diabetes, renal dysfunction, obesity and atrial fibrillation) (23), which are all confounders of diagnosis and are known disease modifiers with direct causal effect in the prevalence of HFNEF, and the complex mechanisms related to the condition, some of which have been demonstrated in the following chapters of this thesis, such as left ventricular systolic and diastolic impairment, left ventricular torsional abnormality, left ventricular dyssynchrony, ventricular-arterial coupling (2) and impaired chronotropic response (24).

Traditional measurements of global systolic function such as left ventricular ejection fraction, stroke work and peak dP/dt (left ventricular pressure change) do not account for the non-uniformity of regional myocardial function as global compensation is likely to mask regional impairment. A common example is radial compensation for longitudinal or long axis dysfunction seen particularly in many patients with HFNEF. In addition, there is currently no robust and accurate method to discriminate between pure systolic and diastolic dysfunction. This is not surprising as systolic and diastolic functions are intimately linked.

1.2 EPIDEMIOLOGY OF HFNEF

Patients with HFNEF are typically older females and frequently have a history of hypertension and other comorbidities such as atrial fibrillation, diabetes mellitus, obesity, renal impairment, anaemia and mild coronary artery disease (23). Clinically, the presenting symptoms and signs of patients with HFNEF are similar to those with HFREF (25). While it is much easier to recognise patients with HFREF given their classic history and presentation, patients with HFNEF do not always present with typical diagnostic history, symptoms and signs. Patients with HFNEF often complain of breathlessness on exertion or reduced exercise tolerance, which is confounded by many other common factors such as underlying pulmonary disease, anaemia or obesity. Hence, they are often not referred for further investigations due to the non-specific symptom of breathlessness. Consequently, the prevalence of HFNEF could be under-estimated and may lead to adverse clinical consequence, as the prognosis of HFNEF has been shown to be comparable to that of HFREF (3;25;26).

The mortality of HFNEF one year post hospital discharge was 22-29%, similar to that of HFREF, and the five year mortality was as high as 65% (3;25). The poor prognosis of HFNEF was also reflected in another follow up study which found comparable five year survival rates between HFNEF (43%) and HFREF (46%) (26).

A cross-sectional echocardiographic survey of randomly selected subjects over the age of 60 years found 35% of the study population had diastolic dysfunction which was associated with poorer quality of life despite the absence of signs of heart

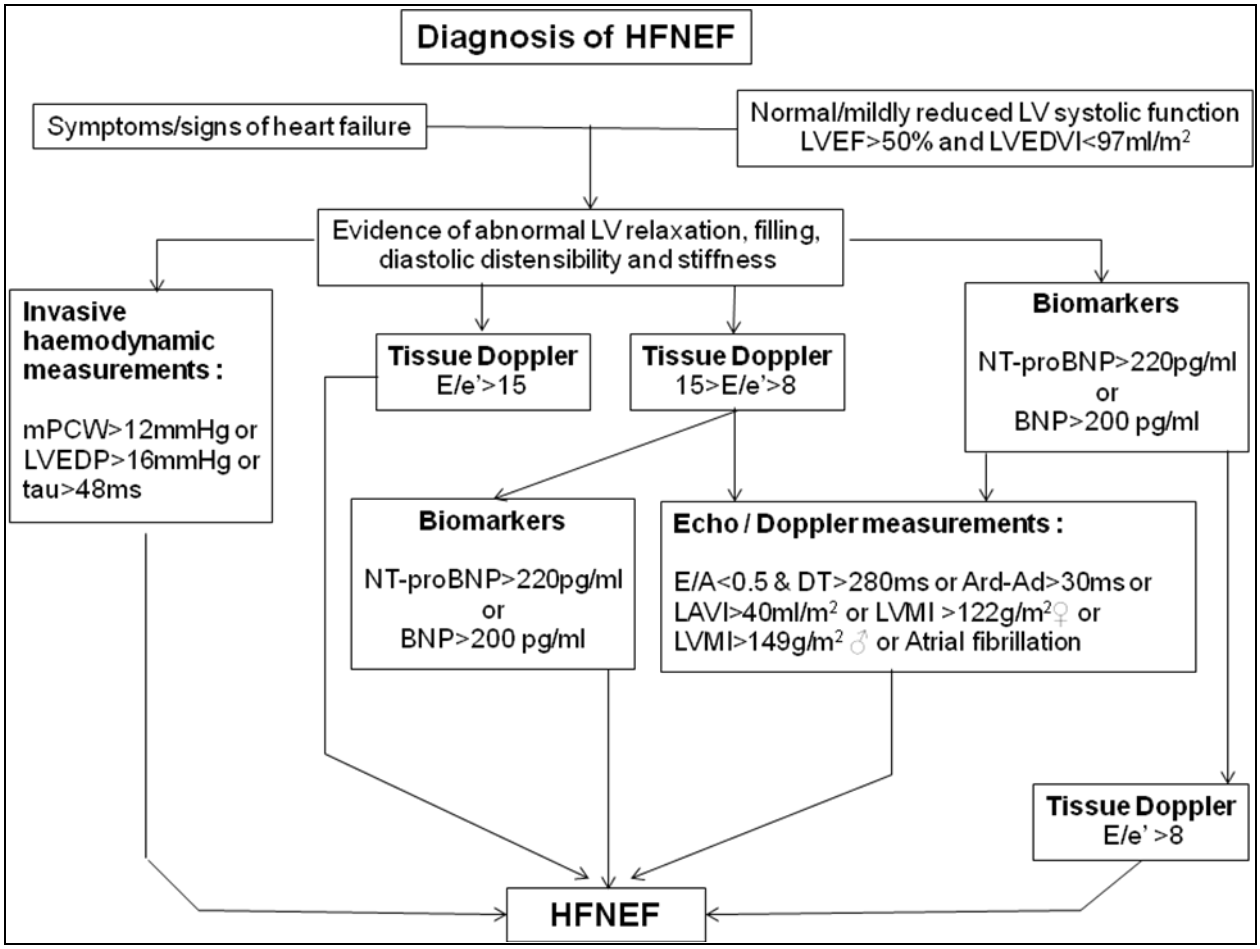
failure (27). This study assessed diastolic function by Doppler evaluation of the mitral and pulmonary venous inflow and tissue Doppler imaging. The abnormal relaxation pattern (ARP) of the mitral inflow velocity is very common in the elderly and therefore it is difficult to assess the true prevalence of diastolic dysfunction in the elderly population over and above that due to ageing (28). Similarly, diastolic dysfunction is associated with obesity (29), which is commonly seen in patients with HFNEF. A study of patients with HFNEF with similar symptoms and 6-minute walk test (6-MWT) performance as patients with HFREF, has found normal levels of N-terminal pro B-type natriuretic peptide (NT-proBNP) at rest in HFNEF patients implying that these patients did not have heart failure (30). Ultimately, the diagnosis challenge of HFNEF could lie in the fact that patients with HFNEF are mainly symptomatic on exertion and thus abnormalities are only apparent when tests are performed on exercise.

1.3 GUIDELINES FOR DIAGNOSING HFNEF

A recent report (2007) from the European Society of Cardiology (ESC) attempted to provide some guidelines for the diagnosis of HFNEF based on the presence of four conditions (Figure 1.3) (31):

- the presence of clinical symptoms or signs of heart failure;
- left ventricular ejection fraction of more than 50%;
- a non-dilated left ventricle; and
- the demonstration of abnormalities in left ventricular diastolic function.

Figure 1.3 European Society of Cardiology recommendation for diagnosing HFNEF



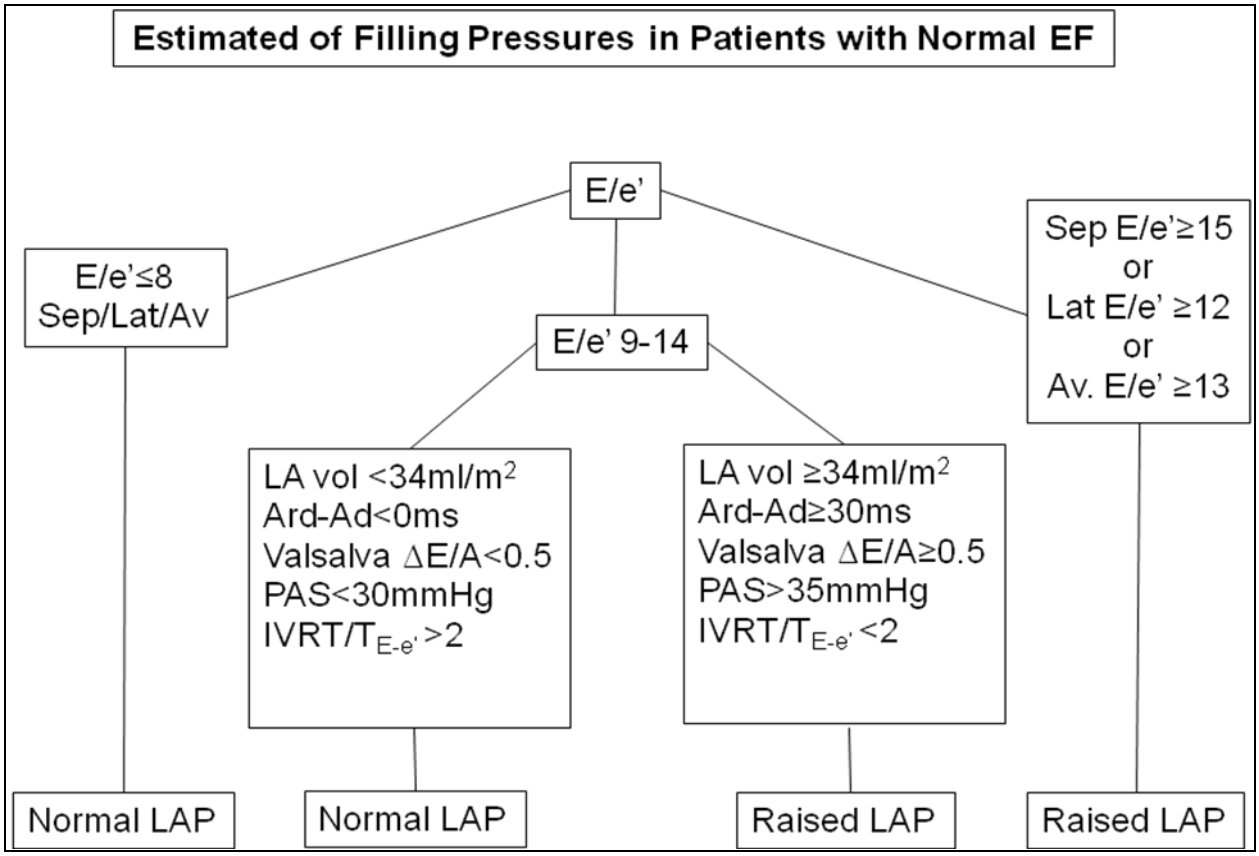
Adapted from Paulus W.J. et al. (31).

HFNEF, heart failure with a normal ejection; LV, left ventricular; LVEF, left ventricular ejection fraction; LVEDVI, left ventricular end diastolic volume index; mPCW, mean pulmonary capillary wedge pressure; LVEDP, left ventricular end diastolic pressure; E/e', ratio of early mitral diastolic inflow velocity to early diastolic mitral annular velocity; NT-proBNP, N-terminal pro B-type natriuretic peptide; BNP, B-type natriuretic peptide; E/A, ratio of early to late diastolic mitral inflow velocity; DT, deceleration time of early mitral inflow velocity; Ard - Ad, difference between duration of reversed pulmonary vein atrial systolic flow (Ard) and duration of late diastole mitral inflow (Ad); LAVI, left atrial volume index; LVMI, left ventricular mass index.

The assessment of diastolic function is not easy and has been a subject of much debate as it cannot be done by a single method and there is no obvious ‘gold standard’. The latest recommendation published by the American Society of Echocardiography (ASE) for the evaluation of diastolic function uses similar parameters as the European Society of Cardiology and outlined an approach to grade diastolic dysfunction (32) (Figures 1.4 and 1.5).

Based on both these updated guidelines and recommendations, it appears that imaging, particularly echocardiography, is the cornerstone of diagnosis and remains the most widely available and versatile assessment tool for the evaluation of left ventricular function and the diagnosis of HFNEF.

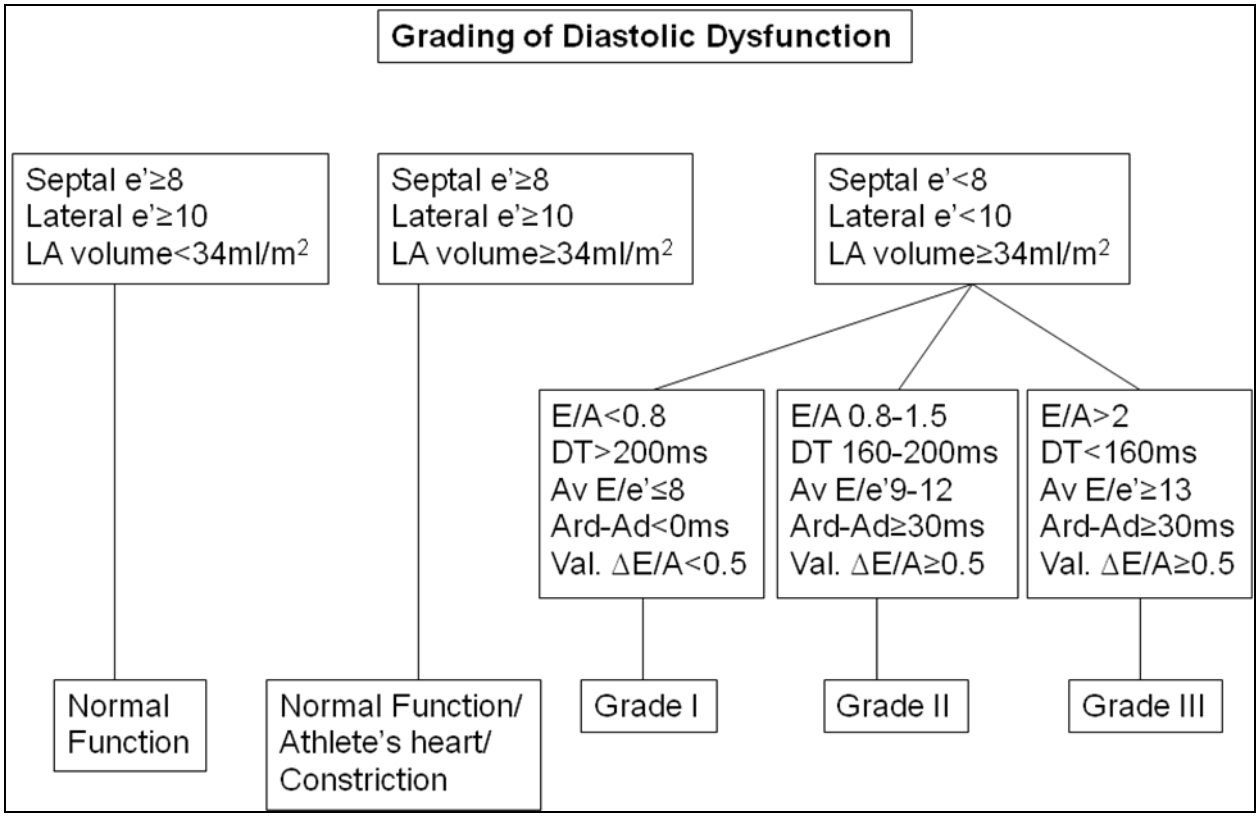
Figure 1.4 Scheme for diagnosing diastolic dysfunction



Adapted from American Society of Echocardiography recommendation (32).

EF, ejection fraction; E/e', ratio of early mitral diastolic inflow velocity to early diastolic mitral annular velocity; Sep, septal wall ; Lat, lateral wall ; Av, average of septal and lateral walls; LAP, left atrial pressure; LA vol, left atrial volume; Ard - Ad, difference between duration of reversed pulmonary vein atrial systolic flow (Ard) and duration of late diastole mitral inflow (Ad); Δ, change in (delta); E/A, ratio of early to late diastolic mitral inflow velocity; PAS, pulmonary arterial systolic pressure; IVRT, isovolumic relaxation time; T, time; E-e', early mitral diastolic inflow velocity less early diastolic mitral annular velocity.

Figure 1.5 Scheme for grading diastolic dysfunction



Adapted from American Society of Echocardiography recommendation (32).

LA, left atrial; e', peak early diastolic myocardial mitral annular velocity by pulse wave Doppler imaging; E/A, ratio of early to late diastolic mitral inflow velocity; DT, deceleration time of early mitral inflow velocity; AV, average; E/e', ratio of early mitral diastolic inflow velocity to early diastolic mitral annular velocity; Ard - Ad, difference between duration of reversed pulmonary vein atrial systolic flow (Ard) and duration of late diastole mitral inflow (Ad); Δ, change (delta); E/A, ratio of early to late diastolic mitral inflow velocity; Val, Valsalva.

Prior to these guidelines, Vasan and Levy proposed the criteria for diagnosing "Diastolic Heart Failure". The proposed criteria for definite, probable and possible diagnosis of diastolic heart failure were based on clinical, echocardiographical and cardiac catheterisation findings (Table 1.3) (33). The short coming of this is the requirement of invasive measurement and confirmation of a raised left ventricular end diastolic pressure (LVEDP) which is not always feasible in daily clinical practice.

Table 1.3 Vasan and Levy criteria for definite diastolic heart failure

Criteria for definite diastolic heart failure
1. Evidence of congestive heart failure (Framingham or Boston Criteria).
2. Objective evidence of normal left ventricular ejection fraction (ejection fraction more than 50% more than 72 hours after presentation with congestive heart failure).
3. Evidence of left ventricular diastolic dysfunction by cardiac catheterisation.

Adapted from Vasan and Levy (33).

- Framingham Criteria for congestive heart failure requires at least two major or one major and two minor criteria.
- Boston Criteria for congestive heart failure involves scoring system of which the composite score has a maximum of 12 points. A diagnosis of definite heart failure requires a score of eight or more points.

Yturralde and Gaasch suggested that the diagnosis of definite diastolic heart failure should fulfill two major criteria and one item of the confirmatory evidences; and a probable diagnosis of diastolic heart failure could be made in those without confirmatory evidence (Table 1.4) (34).

Table 1.4 Yturralde and Gaasch criteria for diagnosing diastolic heart failure

Major criteria:	
1.	Clinical evidence of heart failure (Framingham or Boston criteria), plasma B-type natriuretic peptide or chest x-ray, cardiopulmonary exercise testing.
2.	Normal left ventricular ejection fraction and chamber size.
Confirmatory evidence:	
1.	Left ventricular hypertrophy or concentric remodelling.
2.	Left atrial enlargement (in absence of atrial fibrillation).
3.	Echocardiographic or catheterisation evidence of diastolic dysfunction.

Adapted from Yturralde and Gaasch (34).

The measurement of left ventricular ejection fraction remains one of the crucial criteria for the diagnosis of HFNEF in all the guidelines and this is not without problems. The guidelines do not include tissue Doppler imaging and speckle tracking imaging measurements of left ventricular twist, strain or strain rate which may give further insight into the mechanics of HFNEF. The guidelines also include invasive measurement of left ventricular diastolic function which is not without its pitfalls and is not routinely performed. More importantly, none of the current available guidelines include exercise measurement of left ventricular function which is when patients are most symptomatic. All these guidelines for diagnosis are based on measurements made at rest while HFNEF is essentially an exercise related condition.

1.3.1 MEASUREMENT OF LEFT VENTRICULAR EJECTION FRACTION

It is difficult to define a “normal” range of left ventricular ejection fraction. Left ventricular ejection fraction of more than 45-50% has been considered to reflect normal systolic function in many studies on HFNEF. The measurement of ejection fraction has been widely used as a convenient and readily available index in clinical practice even though it is recognised as a poor and non-specific measurement of left ventricular function, as it merely reflects the change in left ventricular volume and therefore only provides a crude guide to distinguish good and poor overall pump function. The measurement of left ventricular ejection fraction does not provide any information about myocardial contractile function, and fails to account for any compensatory mechanisms.

All the guidelines involve measurement of left ventricular ejection fraction which requires measurement of left ventricular end-diastolic and end-systolic volumes by echocardiography. There are two commonly used methods of measuring left ventricular ejection fraction by echocardiography. Firstly, using Simpson’s biplane technique by applying the method of discs, the left ventricular volumes and ejection fraction are calculated after measuring the left ventricular end-diastolic and end-systolic contours by planimetry of the apical images. This method relies on clear delineation of endocardial edges for accurate measurements with acceptable reproducibility. The measurements should be averaged from both four-chamber and two-chamber views which are not significantly foreshortened, preferably from two or three beats.

Secondly, the estimation of left ventricular ejection fraction can also be made from radial end-diastolic and end-systolic diameter measurements obtained by M-mode echocardiography from a parasternal window. There are several pitfalls of using this method. Firstly, measurements of the left ventricular diameter are made along a single scan line which involves assumptions about the left ventricular cavity size and shape. Secondly, this method is dependent on measurements taken at the correct time points (end diastole and systole), on-axis images and correct identification of the endocardium as applied in the Simpson's biplane method. Although commonly used in clinical practice, it is not an accurate method for the measurement of left ventricular ejection fraction (35). Furthermore, although ejection fraction has some prognostic value it is affected by preload, afterload, heart rate and dyssynchrony as well as myocardial contractility. It reflects radial function more than longitudinal function, and is not, therefore, to be a true measure of systolic function (36).

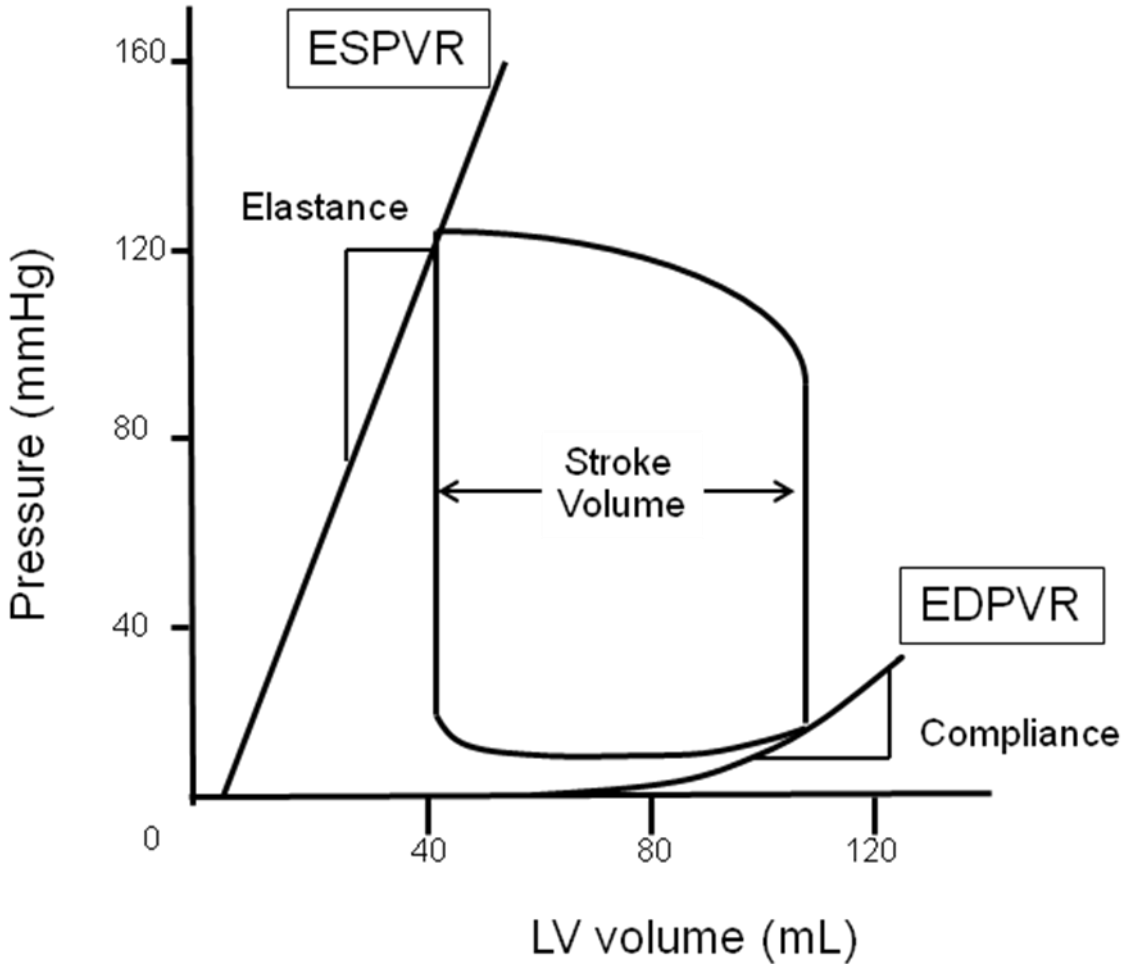
For example, Maciver and Townsend have demonstrated that the left ventricular ejection fraction is mathematically increased in the presence of left ventricular hypertrophy and a normal left ventricular volume (37). This creates a false impression of normal systolic function. Using a model, they illustrated that there may be a reduction in stroke volume and impaired left ventricular long axis function despite a normal left ventricular ejection fraction. The preservation of ejection fraction is directly related to the presence of increased left ventricular mass. Myocardial radial thickening occurs when the myocardial long-axis shortens, therefore an increase in myocardial mass leads to an additional increase in

endocardial displacement radially. Consequently, an increase in ejection fraction is observed if myocardial shortening remains unchanged. This explains the preservation of ejection fraction in the presence of left ventricular hypertrophy which is present in many patients with HFNEF, even when there is a significant reduction in long-axis function and stroke volume.

1.3.2 ASSESSMENT OF DIASTOLIC FUNCTION AND LEFT VENTRICULAR FILLING PRESSURES

Classically, diastolic dysfunction is assessed from pressure-volume loops measured at cardiac catheterisation (38). The end diastolic pressure-volume relationship (EDPVR) is thought to represent the passive mechanical properties of the left ventricle. Changes in the left ventricular pressure-volume relationship reflect changes in ventricular elastance and compliance. Compliance is the slope of the end diastolic pressure-volume relationship, while the slope of end systolic pressure-volume relationship (ESPVR) is a measure of end systolic elastance (Ees) (38) (Figure 1.6).

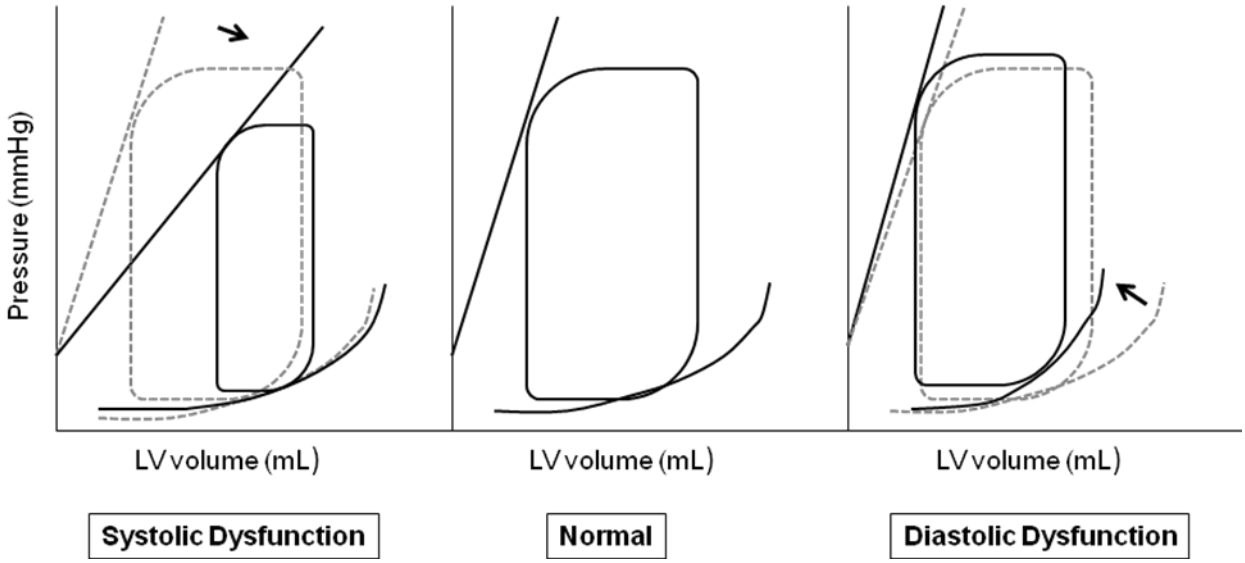
Figure 1.6 Left ventricular pressure-volume relationship



ESPVR, end systolic pressure-volume relationship; EDPVR, end diastolic pressure-volume relationship; LV, left ventricular.

Classically, in systolic heart failure, the end systolic pressure-volume relationship is displaced to the right and downwards associated with reduced left ventricular ejection capacity while end diastolic pressure remains normal. In diastolic dysfunction, the end-diastolic pressure-volume relationship is displaced to the left and upwards associated with reduced left ventricular capacity to fill and raised end diastolic pressure (39) (Figure 1.7).

Figure 1.7 Left ventricular pressure-volume loops in systolic and diastolic dysfunction

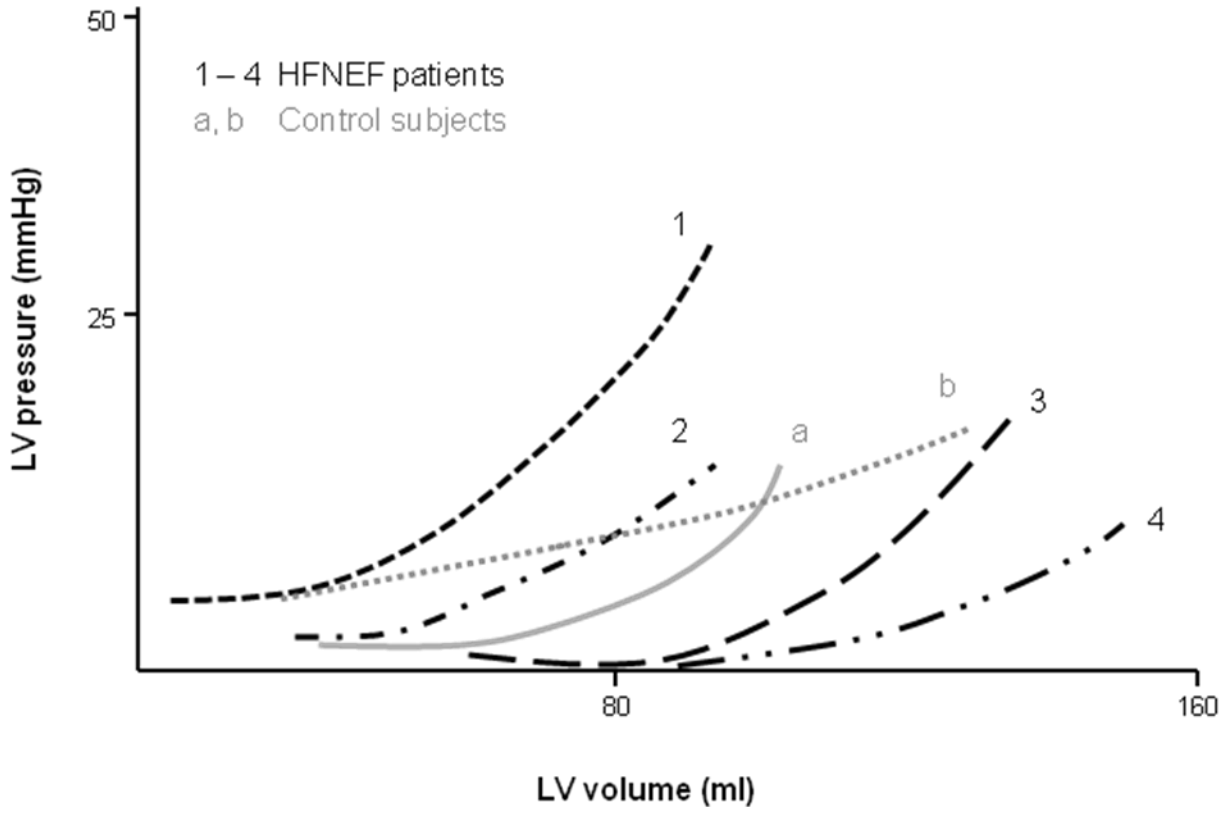


Adapted from Maeder T. et al. (23).

LV, left ventricular.

Data from patients with HFNEF has shown that end diastolic pressure-volume relationship curves are highly variable and may be shifted towards lower, normal and higher volumes. The heterogeneous results of pressure-volume analysis in patients with HFNEF highlighted by Maurer et al. suggest that different pathophysiological mechanisms exist in individual patients (38) (Figure 1.8).

Figure 1.8 Variations of end diastolic pressure-volume relationship of patients with HFNEF



Adapted from Maurer M.S. et al. (38).

LV, left ventricular.

A normal left ventricle will become less compliant consequent to an abnormal increase in left ventricular volume such as in renal failure. Therefore, the end diastolic pressure-volume relationship is actually not a measure of stiffness but the extent to which stiffness depends on volume (40). Consequently, the measurement of end diastolic pressure-volume relationship is not particularly useful in daily practice and cannot be considered a 'gold' standard as is commonly claimed.

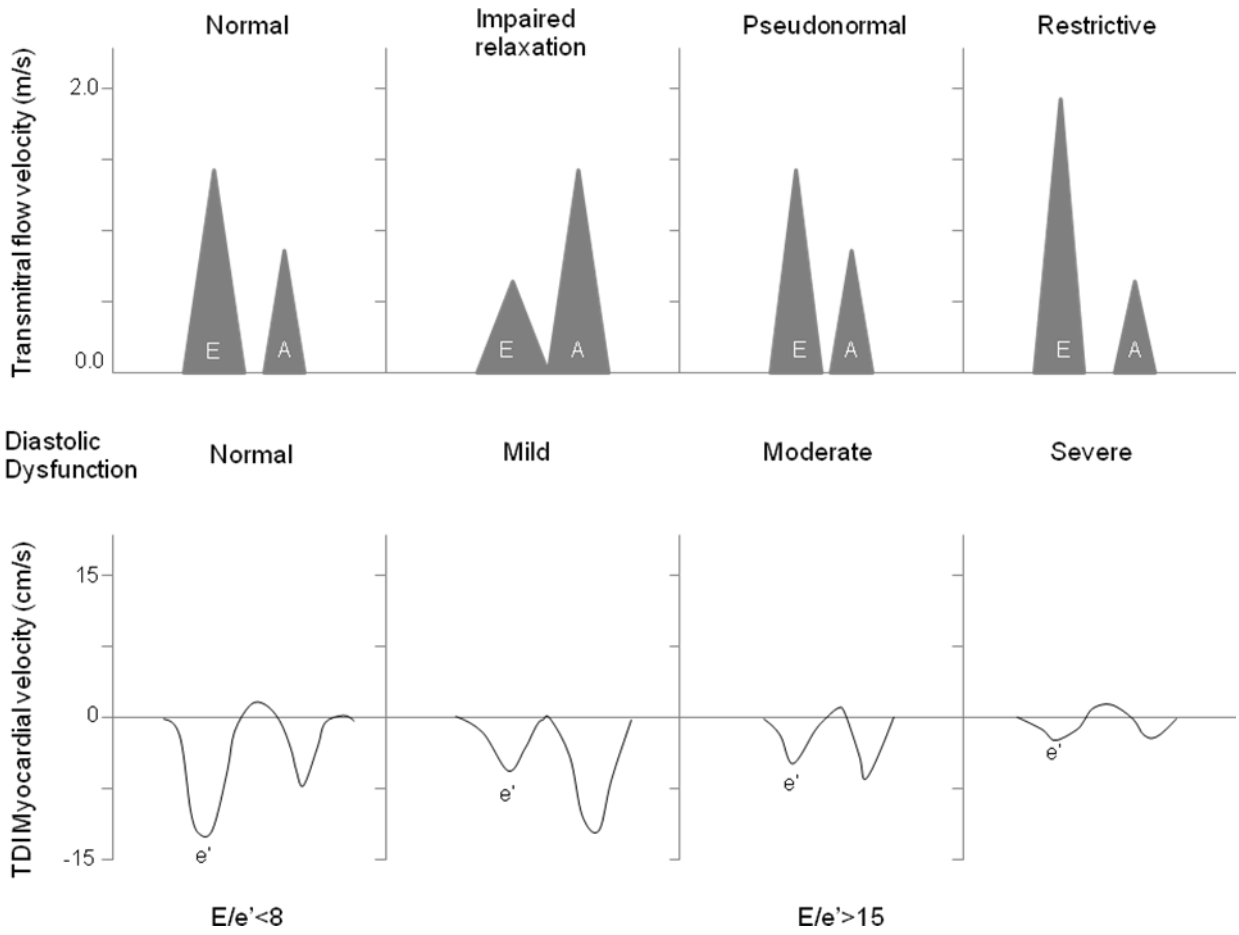
Mitral inflow velocities in contrast are easy to obtain and represents the overall diastolic filling characteristics of the heart and thus provide a rough assessment of diastolic function and left ventricular filling pressures. The limitations of this measurement include age, heart rate, preload and afterload dependency. Measurements have to be adjusted for age (31;41;42). However, the preload dependence of the peak early diastolic mitral inflow velocity (E) can be useful given that it reflects the driving force across the mitral valve.

When pulse wave sample is placed at the tip of the mitral valve leaflets when the valve is opened, the peak velocity measured represents the change in pressure between the left atrium and the left ventricle. In normal subjects, the left ventricular pressure decreases rapidly during left ventricular relaxation, soon after the completion of left ventricular contraction. A driving force is created when the left ventricular pressure becomes lower than the left atrial pressure. The blood flow velocity from the left atrium to the left ventricle across the mitral valve is measured as the mitral inflow velocity. The peak velocity is measured as the early diastolic mitral

inflow velocity E wave (Figure 1.9). In late diastole, left atrial pressure exceeds left ventricular pressure during atrial contraction, creating the late diastolic mitral inflow velocity (A) wave.

Diastolic function can be graded into four broad categories, namely normal, mild, moderate and severe diastolic dysfunction based on mitral inflow Doppler patterns. Mild diastolic dysfunction is associated with abnormal left ventricular relaxation leading to reduced driving force to fill the left ventricle, hence a reduced velocity across the mitral valve. This is reflected as a smaller early diastolic mitral inflow velocity E wave. Reduced early diastolic filling is compensated by increased late diastolic filling during atrial contraction and hence a bigger late diastolic mitral inflow velocity A wave, resulting in a lower ratio of early to late diastolic mitral inflow velocity (E/A). As disease progresses from mild to moderate diastolic dysfunction, left atrial pressure is raised leading to an increase in driving pressure in early diastole resulting in pseudonormalisation when the E wave and E/A ratio are similar to the normal pattern. In more advanced disease associated with abnormal left ventricle compliance (severe diastolic dysfunction), the left atrial pressure becomes even higher resulting in higher transmitral pressure gradient, hence a marked increase in early diastolic mitral inflow velocity. This results in a restrictive mitral Doppler inflow pattern (Figure 1.9).

Figure 1.9 Doppler echocardiographic left ventricular diastolic filling patterns



E, early diastolic mitral inflow velocity; A, late diastolic mitral inflow velocity; e', early diastolic mitral annular velocity; TDI, tissue Doppler imaging.

Tissue Doppler imaging has introduced new indices which can give additional help in the assessment of left ventricular function. Given that the apex is relatively fixed, the movement of the mitral valve annulus is a direct measure of left ventricular longitudinal function also known as the long axis movement or the mitral annular motion or the atrioventricular plane displacement. The same holds true for the tricuspid valve annulus and the right ventricle. Therefore, the application of tissue Doppler to the mitral annulus is used as a measure of long axis function.

Rushmer et al. showed that long axis shortening was greater than that of the short axis during early systole, causing a geometrical change in the left ventricle to become more spherical in shape (43). They also showed that there was a greater change in volume per unit change in the short axis fibre length during systole when the left ventricle is more spherical. As pointed out by Henein and Gibson, this change occurs due to the motion of discreet long axis fibres separate from fibres supporting the short axis, and not due to a homogenous set of oblique fibres (44).

During ejection, the two axes are effectively in phase with one another although peak long axis shortening occurs at aortic valve closure, while the short axis continues to reduce reaching its minimum at the time of mitral valve opening. In diastole, the mitral annular motion starts at the same time as mitral inflow when the left ventricular pressure has fallen. Therefore, the mitral annular motion can be considered primarily as a measure of left ventricular recoil and has been shown to correlate with tau, the exponential decay of left ventricular pressure, during isovolumic relaxation (45).

In the literature, Em is also represented as E' or e', all of which are abbreviations used to describe early diastolic mitral annular velocity. Usually now the term e' refers to the measurement by pulse wave Doppler (PWD) while Em is by continuous wave Doppler (CWD), detailed in Chapter 4.

Myocardial velocity is a relatively load independent measure. In an experimental model of heart failure in dogs, the early diastolic mitral annular velocity (Em) was impaired early, and progressive decline of Em with worsening heart failure was associated with increased left atrial pressures (46). Furthermore, early diastolic (Em) and systolic mitral annular velocities (Sm) are powerful predictors of prognosis in a variety of cardiac conditions including heart failure (47-49), and add incremental value to standard clinical and echocardiographical measures.

Wang et al. found that Em <3 cm/s was the best prognostic index in long-term follow-up of heart failure patients (48). Taking into account of measurements of Sm, E/e' and deceleration time (DT), they showed that Em is the strongest predictor of cardiac mortality in patients with heart failure. In addition to DT≤140ms and E/e'>15, Em <3cm/s improved the power of heart failure survival prediction. Similar results were found by the same investigators in a group of hypertensive subjects with left ventricular hypertrophy, where again a low Em (<3.5cm/s) was the strongest prognostic indicator after adjusting for increased septal thickness and moderate to severe diastolic dysfunction assessed by mitral inflow patterns (pseudonormalisation and restrictive filling pattern) (49). In a group of patients with idiopathic dilated

cardiomyopathy, Em was significantly lower in those who had pulmonary oedema compared to those who were clinically stable (17). These studies confirmed that decreased Em is one of the earliest markers for diastolic dysfunction and is present in all stages of diastolic dysfunction (Figure 1.9).

Since Em or e' remains reduced and early diastolic mitral inflow velocity E increases with higher filling pressure (Figure 1.9), the ratio between transmitral E and e', E/e', is considered a good surrogate marker for left ventricular filling pressure and has been shown to correlate with pulmonary capillary wedge pressure (45;50). Ommen et al. demonstrated that E/e'>15 predicts an elevated left ventricular filling pressure of more than 15mmHg, while E/e' <8 is associated with normal left ventricular filling pressure (45). Thus the preload dependence of the mitral inflow velocities can be put to good use as a clinical guide, even more so when used in combination with e'.

An increased left atrial volume is a marker of a chronically elevated left atrial pressure. In a population based study, left atrial volume indexed to body surface area (LAVI) is strongly associated with cardiovascular disease including hypertension, atrial fibrillation and congestive heart failure (51). In another study, LAVI was shown to be a strong predictor of diastolic dysfunction in a group of suspected heart failure patients with normal left ventricular ejection fraction, given that parameters which predict raised left atrial pressure used for assessing diastolic function such as left ventricular wall thickness, left ventricular mass index,

deceleration time of E wave, and age are all predictors of left atrial volume index (52).

Therefore, using a combination of e' and the ratio E/e' with left atrial volume index, a reasonable diagnosis of increased left ventricular filling pressure or raised left atrial pressure and probable diastolic dysfunction can be reliably made (53). However, early diastolic filling is very dependent on the previous systole. Any reduction in systolic function, co-ordination or dyssynchrony (discussed later) will have a profound impact on the ability of the left ventricle to fill adequately at normal pressures during diastole. But in practice, the presence of left ventricular hypertrophy and an increased left atrial volume index on echocardiography in the absence of valvular heart disease in a breathless patient, strongly supports a clinical diagnosis of HFNEF.

1.4 PATHOPHYSIOLOGY OF HFNEF

The classical explanations for HFNEF include the following, all of which were based on measurements acquired at rest.

- An increase in intrinsic myocardial stiffness and impaired relaxation in diastole requires higher left atrial pressures for filling in late diastole, predisposing these patients to pulmonary venous congestion and dyspnoea especially on exertion (4).
- Deranged ventricular-arterial coupling secondary to systolic ventricular and arterial stiffening which exaggerates hypertensive response when systolic pressure load is increased during exercise or stress, consequently inducing load-dependent diastolic dysfunction (2).
- Enhanced sensitivity to volume overload in relation to volume-dependent elevation of filling pressures seen in renal impairment. This was observed in a subgroup of hypertensive HFNEF patients who had renal impairment and increased left ventricular volumes but normal systolic ventricular and vascular stiffness (54).

These concepts underestimate the impact of the previous systole on early diastolic filling, particularly inco-ordination or dyssynchrony, reduced longitudinal function and left ventricular torsion. Furthermore, heart failure is essentially a disease on exercise, therefore studies performed at rest might not unmask the underlying abnormalities.

1.4.1 SYSTOLIC FUNCTION IN HFNEF

In an early study Yip et al. studied 68 patients with heart failure, 29 with a LVEF>45% and 39 with a LVEF<45% compared to age-matched controls (12). They found that systolic mitral annular velocity (Sm) was significantly lower in those with HFNEF (4.81 ± 0.23 cm/s) compared to controls (6.10 ± 0.14 cm/s), but was higher than those with HFREF. A similar finding was seen using early diastolic mitral annular velocity (Em). In this study, the left ventricular ejection fraction in the HFNEF group was statistically lower than age-matched controls although still within the accepted normal limits. They concluded that there was evidence of abnormal systolic function in many patients with HFNEF and that true 'isolated' diastolic dysfunction is probably rare. These findings have now been confirmed by several other studies (11;13-16;55).

In a thorough assessment of regional myocardial function, Yu et al. studied 339 subjects, 92 with systolic heart failure or HFREF (ejection fraction <50%), 73 with diastolic heart failure or HFNEF (ejection fraction >50% with diastolic abnormalities on Doppler echocardiography), 68 had isolated diastolic dysfunction (DD) without symptoms of heart failure and 106 were normal subjects (11). They assessed myocardial velocities of 12 segments (6 basal and 6 mid segments) and found significantly lower Sm and Em in patients with systolic heart failure, diastolic heart failure and diastolic dysfunction, compared to control subjects (systolic heart failure < diastolic heart failure < diastolic dysfunction < controls). This concluded that despite a normal ejection fraction, systolic function is not normal in HFNEF. This is not

surprising as systolic function is probably affected by left ventricular hypertrophy and the accompanying fibrosis as much as diastolic function.

Shan et al. found that Sm and Em are related to the percentage of interstitial fibrosis within the myocardium as both measurements are reduced with increased fibrosis (56). In another study involving a large number of subjects with a wide range of left ventricular ejection fraction, a close relationship between systolic and diastolic velocities was demonstrated (57). Vinereau et al. similarly found a strong correlation between the Sm and Em (16). These studies suggest that left ventricular systole and diastole are closely intertwined.

In reality, systole and diastole constitute one cycle and the major determinant of diastolic filling is the strength and coordination of the previous systole. Early diastolic suction is dependent on the force of the previous systolic contraction (58). In addition, incoordinated systolic contraction, as seen in left ventricular dyssynchrony, will prolong isovolumic relaxation and impair diastolic function (59). The motion of the ventricular base (mitral annulus) during early diastole reflects both systolic and diastolic function of the subendocardial fibres which because of their position, are more susceptible to the effects of fibrosis, hypertrophy and ischaemia. This may explain why the measurement of mitral annular velocities is a powerful predictor of prognosis in a variety of cardiac diseases including heart failure (48). Furthermore, all the precursors of HFNEF such as hypertension, left ventricular hypertrophy, ageing and diabetes alter global myocardial architecture and fibre orientation which

have important effects on left ventricular torsion in systole and left ventricular untwisting in diastole (60).

1.4.2 DIASTOLIC FUNCTION IN HFNEF

Diastolic function is known as the ability of the heart to fill while maintaining normal pressure to enable subsequent systolic ejection applying the Frank-Starling mechanism. Diastole consists of four phases as outlined below.

- Phase 1 is the onset of left ventricular relaxation which begins before aortic valve closure. This is associated with a rapid fall in intraventricular pressure during isovolumic relaxation period. This process is influenced by both active (adenosine triphosphate hydrolysis to facilitate calcium reuptake and to release actin-myosin bonds) and passive (elastic recoil derived from the release of stored elastic energy during systole) components.

- Phase 2 starts at the opening of the mitral valve when rapid filling takes place. This process is dependent on the generation of atrial-ventricular pressure gradient which is driven by the ability of the left ventricle to relax in order to create and maintain a low intraventricular pressure. This transmitral pressure gradient acts as a suction mechanism to draw blood into the ventricle for early rapid filling which contributes approximately 80% of normal ventricular filling.

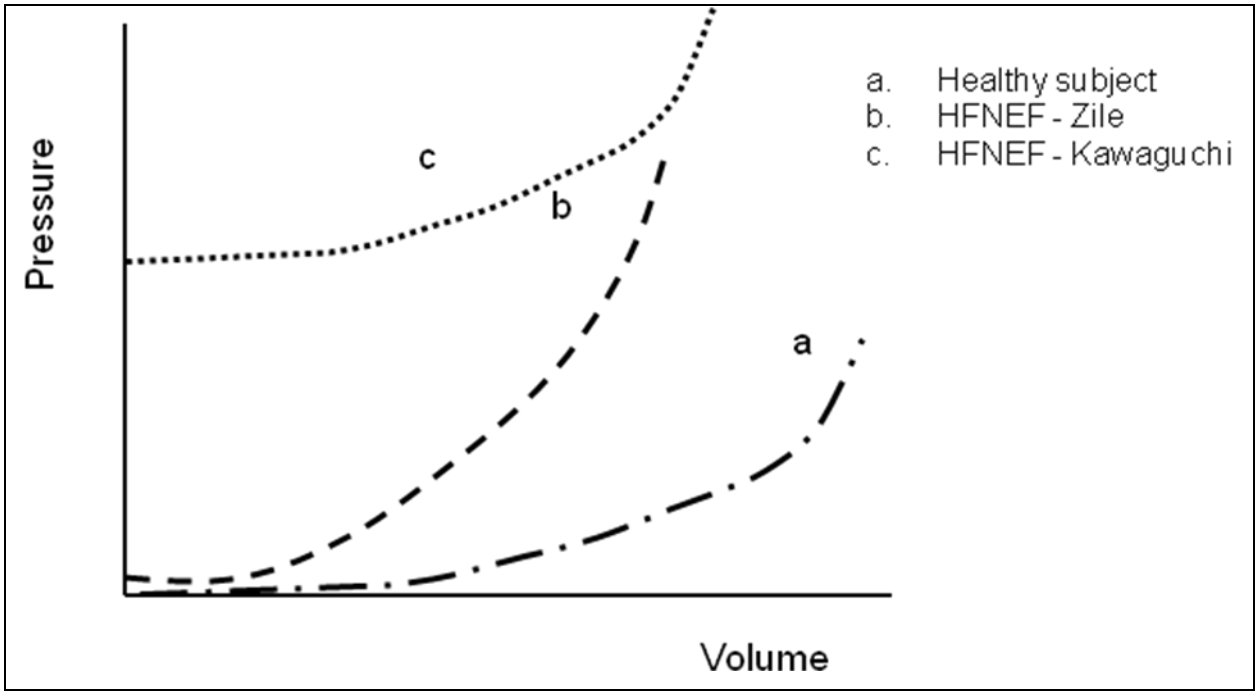
- Phase 3 is diastasis when the atrial-ventricular pressure equilibrates. When this phase is studied using pressure-volume loops, it represents the passive mechanical properties of the left ventricle and left ventricular compliance can be derived (discussed in section 1.3.2).

- Phase 4 is atrial contraction or late diastolic filling which contributes approximately 20% of normal ventricular filling. This process is dependent on the left ventricular end diastolic pressure and left atrial function (detailed in section 1.4.3).

Many studies of diastolic dysfunction in HFNEF were performed using pressure-volume analysis focusing on the EDPVR (phase 1-3). Zile et al. showed increased diastolic stiffness and abnormal left ventricular relaxation in patients with diastolic dysfunction by pressure-volume analysis (5). They demonstrated a shift in the EDPVR upwards and to the left suggesting increased left ventricular stiffness or reduced compliance (Figure 1.10). The same group of investigators also found a prolonged time constant of relaxation in a majority of HFNEF patients, implying reduced left ventricular relaxation rate (61).

In the contrary, Kawaguchi et al. found an upward parallel shift of the EDPVR in HFNEF compared to controls, suggesting that systolic ventricular and arterial stiffness, but not left ventricular diastolic stiffness, are raised in HFNEF (2) (Figure 1.10). Nevertheless, these studies showed that there is an increase in left ventricular end diastolic pressure in HFNEF.

Figure 1.10 End diastolic pressure-volume relationships in diastolic dysfunction



Adapted from Borlaug & Kass (62).

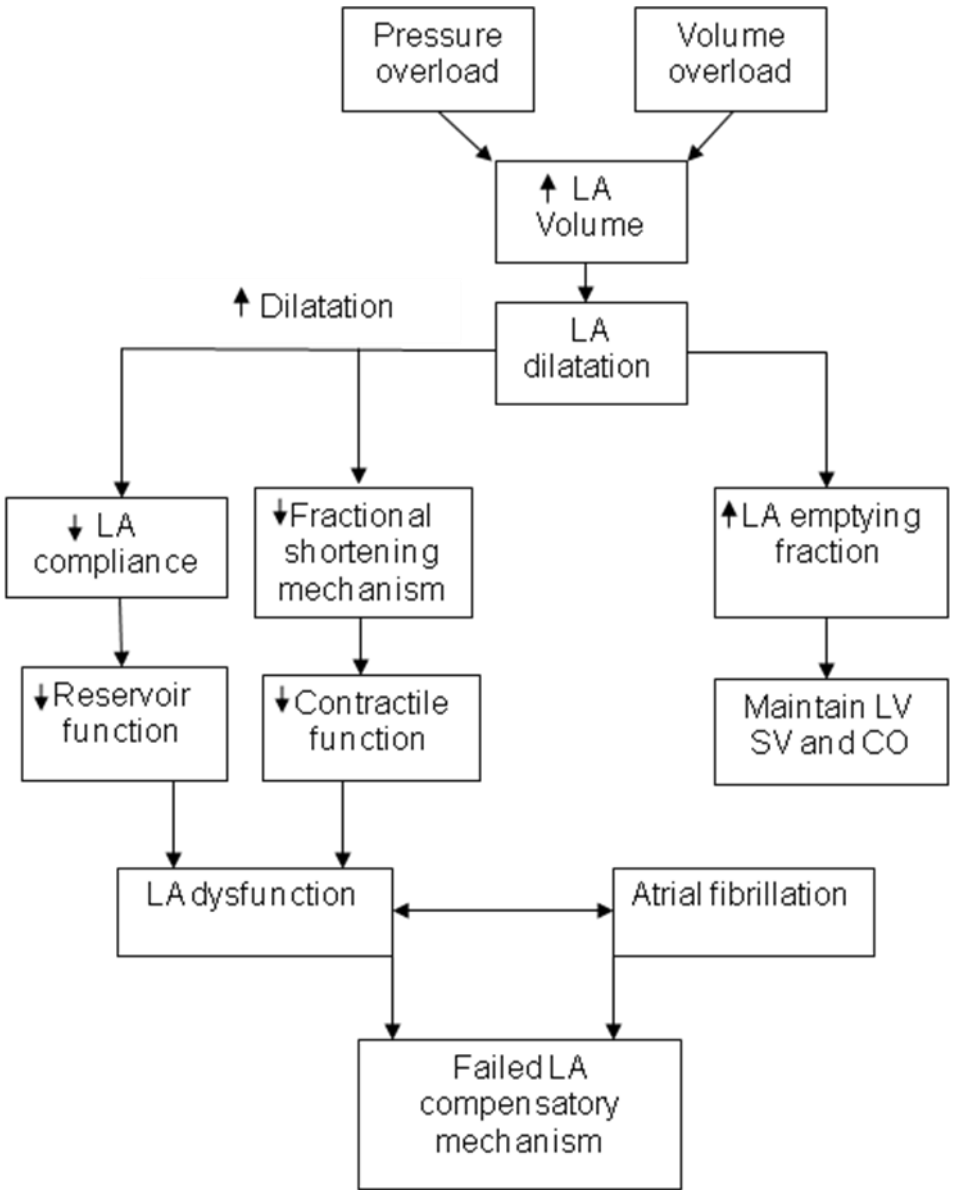
1.4.3 LEFT ATRIAL FUNCTION IN HFNEF

Left atrial contraction constitutes to late diastolic filling in phase 4 of diastole. The left atrium plays three main mechanical roles throughout the different phases of the cardiac cycle. It acts as a reservoir from pulmonary venous filling during ventricular systole and then as a conduit during early diastole before it contracts in late diastole (63). It has been shown that atrial contraction contributes 29% of total left ventricular stroke volume and thus plays a significant role in heart failure (64). Active atrial contraction acts as a booster to augment left ventricular filling particularly in compensation of decreased early diastolic filling due to diastolic dysfunction, for example in left ventricular hypertrophy seen in hypertensive heart disease which is one of the common precursors of HFNEF.

The loss of atrial contraction in atrial fibrillation (AF), also a common condition associated with HFNEF, results in up to 20% of cardiac output reduction which can lead to presentation of heart failure symptoms (63). Fung et al. reported that HFNEF patients with AF had a dilated left atrium and reported poorer quality of life and reduced exercise capacity (65). It is recognised that an increase in left atrial size is a strong predictor of adverse cardiovascular outcome and is associated with worse diastolic dysfunction (66;67). Increase in left ventricular filling pressure causes left atrial pressure overload leading to left atrial dilatation hence increase in left atrial volume as discussed in section 1.3.2. This is considered an adaptive response to maintain left ventricular stroke volume and cardiac output. Sustained and prolonged increase in left ventricular filling pressure causes further left atrial dilatation

exceeding the limits of Frank-Starling relationship resulting in left atrial dysfunction (68), as illustrated in Figure 1.11.

Figure 1.11 Mechanisms of left atrial dysfunction



CO, cardiac output; LA, left atrium; LV, left ventricle; SV, stroke volume.

Using tissue Doppler imaging, Wang et al. found that the hazard ratio of cardiac death was significantly increased when late diastolic myocardial velocity, Am was ≤4cm/s (47). Measurements of left atrial function were found to be predictive of exercise capacity in chronic heart failure in two other studies (69;70). Melenovsky et al. found that left atrial volume was higher in HFNEF patients compared to hypertensive subjects with left ventricular hypertrophy, and that left atrial total, passive and active emptying fractions were reduced in HFNEF subjects (71). They also demonstrated that the Am rose in the hypertensive subjects with handgrip exercise but remained unchanged in HFNEF patients. It has been shown in another study that left atrial dilatation and dysfunction are present in systolic heart failure or HFREF and can predict outcome (72). This finding was also supported by Kurt et al. in addition to their finding of impaired left atrial function in subjects with diastolic dysfunction and those with “diastolic heart failure” (73).

Most of these studies were performed at rest or during isometric handgrip exercise when patients were asymptomatic but demonstrated a wider abnormality in the pathophysiology of HFNEF.

1.4.4 DYSSYNCHRONY IN HFNEF

The contraction and relaxation of a normal left ventricle are synchronous. The movement of the ventricular walls are coordinated in systole to enable maximum systolic ejection, while coordinated relaxation in diastole allows optimal filling. The loss of coordinated cardiac movement results in cardiac dyssynchrony. Essentially, the term dyssynchrony describes the abnormal and discoordinated timing of cardiac motions, particularly the timing of contraction or relaxation of different myocardial segments known as systolic or diastolic dyssynchrony respectively. Disturbances of regional myocardial function have been recognised to occur in a variety of cardiac diseases (74;75). The relationship between electrical activation of the left ventricle and the mechanical contraction of the left ventricle is known as the electro-mechanical synchrony. The disturbance of electrical propagation such as those seen in bundle brunch block, leads to delayed activation of affected myocardial segments, hence a change in activation sequence of various left ventricular segments. This is known as electro-mechanical dyssynchrony or intraventricular dyssynchrony, which is recognised to be an important contributing factor of left ventricular remodelling and systolic dysfunction (76). Recently, it has been shown that electro-mechanical dyssynchrony is present in patients with heart failure even with narrow QRS complexes (77).

Tissue Doppler imaging provides good temporal resolution and is most commonly used to detect dyssynchronous contraction and relaxation. The myocardial velocity-time curve provides information about the magnitude and the timing of left ventricular

segmental contraction and relaxation. Two recent studies applying tissue Doppler imaging technique have demonstrated that dyssynchrony can occur in both systole and diastole in patients with HFNEF (78;79). Wang et al. compared 60 patients with DHF (LVEF>50%), 60 with SHF and 35 controls (78). Systolic dyssynchrony was taken as the maximum time difference between 4 basal segments of the time to either peak or onset of the systolic myocardial velocity. The maximum time difference to the onset of the peak early diastolic velocity was used as a measurement for diastolic dyssynchrony. Left ventricular intraventricular delay was abnormal in patients with DHF, 58% in diastole and 33% also in systole. These results were very similar to those with SHF (60% with diastolic dyssynchrony and 40% with systolic dyssynchrony). In a second study by Yu et al., by applying the technique of standard deviation of time to peak systolic and early diastolic velocities derived from 12 segments, they found the prevalence of diastolic and systolic dyssynchrony in 92 patients with HFNEF was 36% and 39% respectively, and 43% and 57% respectively in 281 patients with SHF (79). Despite the close relationship between peak systolic and early diastolic myocardial velocities shown by Yip et al. (57), the correlation between systolic and diastolic dyssynchrony was weak although statistically significant. Yu et al. found 57% of SHF patients had systolic dyssynchrony but reported that only 26% of SHF patients had co-existing systolic and diastolic dyssynchrony. Only 14% of DHF patients had co-existing systolic and diastolic dyssynchrony.

In contrast to the well described systolic dyssynchrony commonly seen in patients with systolic heart failure or HFREF which is associated with wide QRS complexes, the presence of diastolic and / or systolic dyssynchrony in HFNEF patients was associated with narrow QRS complexes. This suggests that electro-mechanical dissociation is not the main explanation of left ventricular dyssynchrony seen in HFNEF. The nature of dyssynchrony in HFNEF is likely to be different from that in HFREF and this abnormality could arise from the myocardium itself, given that the geometrical difference between the two conditions, which is regional wall motion abnormalities in the presence of left ventricular dilatation and the presence of electro-mechanical discoordination seen in HFREF, compared to left ventricular hypertrophy in the absence of left ventricular dilatation and lack of apparent electro-mechanical discoordination in HFNEF.

Of note, these studies assessed dyssynchrony in a single myocardial plane (longitudinal plane) using tissue Doppler imaging which reflects segmental dyssynchrony. However, myocardial mechanics involve a combination of radial, circumferential and oblique motions in addition to longitudinal motion. Assessing multi-plane motion coordination or left ventricular torsional synchrony may provide more insight into these complex left ventricular mechanics and may be more applicable in HFNEF. In addition, these studies were performed at rest and the impact of left ventricular dyssynchrony on exercise remains unknown.

CHAPTER 2

LEFT VENTRICULAR

TWIST AND TORSION

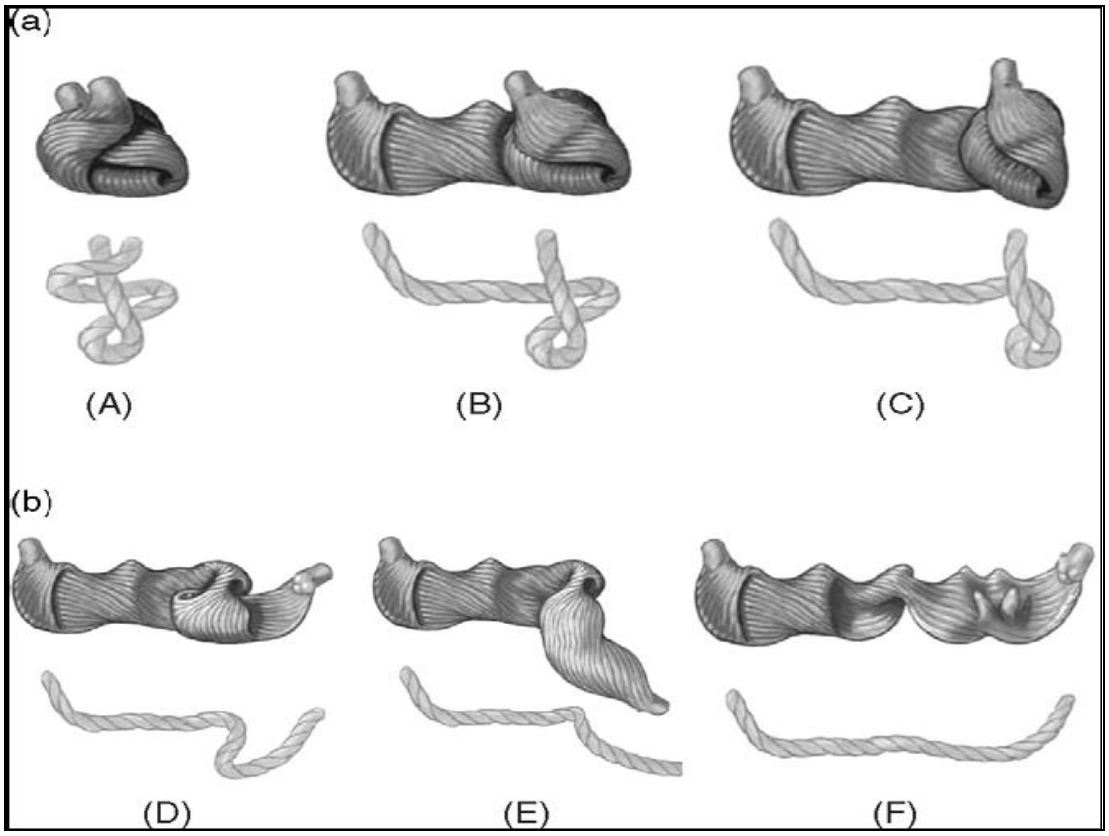
2. LEFT VENTRICULAR TWIST AND TORSION

2.1 LEFT VENTRICULAR MUSCLE FIBRE

Left ventricular twist and torsion has intrigued many since its first description by William Harvey in 1628 when the twisting motion of the left ventricle was observed and described. The anatomical arrangement and the architecture of the myocardium underlying this motion have caused much fascination amongst anatomists and physiologists. Knowledge of the myocardial fibre orientation helps in the understanding of the function of the heart and its efficiency as a pumping chamber. The knowledge of myofibre geometry of the left ventricle is important in the understanding of torsion mechanics which contribute significantly to the overall atrioventricular plane displacement or long axis function.

There is still ongoing debate amongst cardiac anatomists with regards to the true left ventricular architecture. Descriptions of the myocardial architecture range from layered myofibre sheets, aggregated myocyte mesh to myocardial band (80-82). The proposal of the myocardial band theory by Torrent-Guasp et al. which described a continuum of myocardial band wrapping around itself to form the helical structure containing two distinct arms of the left ventricle (Figure 2.1), has been a subject of much debate, but explains the overall left ventricular mechanics, particularly torsion mechanics (82).

Figure 2.1 The myocardial band theory



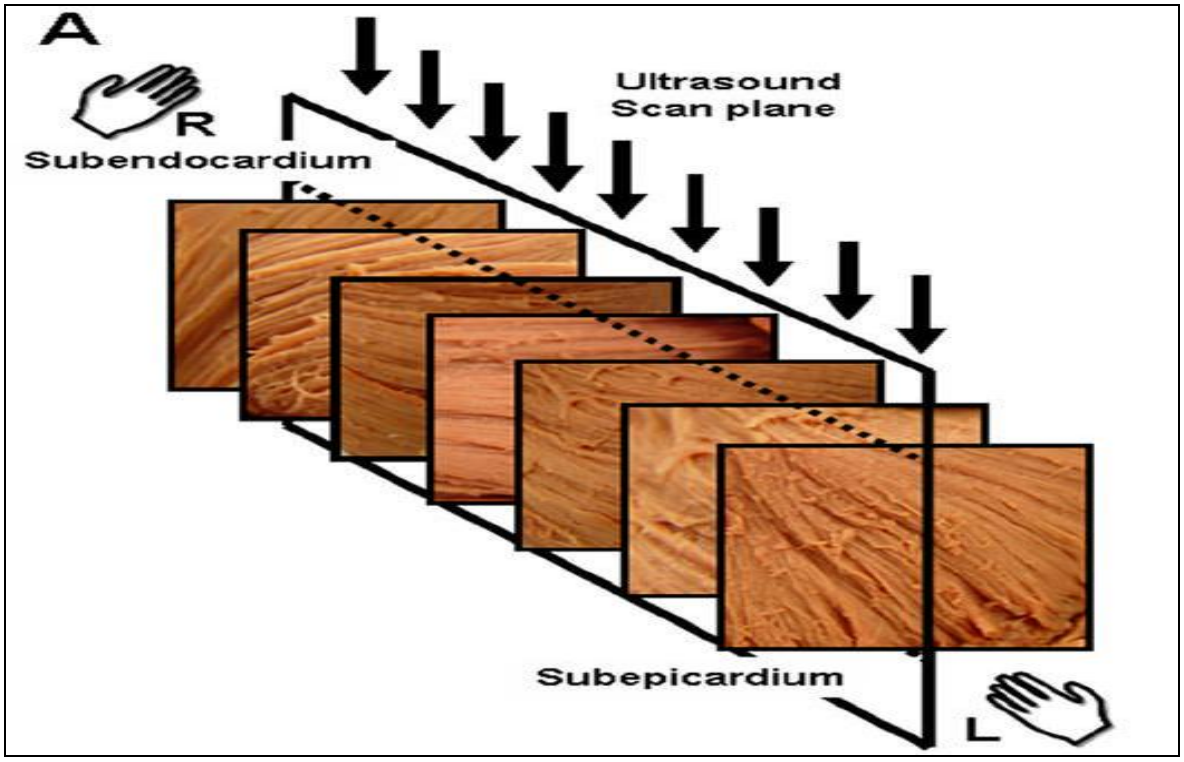
Extracted from Buckberg GD et al. (83).

Histological studies established that there is a transmural transition of fibre direction from the endocardium to the epicardium (80;84). Streeter et al. used a rapid fixation method to analyse canine hearts set in various stages of the cardiac cycle, and found that fibre angles, in relation to the circumferential fibres, increase during systole compared to diastole and concluded the presence of ventricular twist motion (80). The predominantly longitudinal endocardial fibre becomes circumferentially orientated in the midwall which then orientates longitudinally again in the epicardium. These different planes of myofibres have been described as myocardial sheets which contribute to the different plane of motion of the myocardium. In addition to the

longitudinal and circumferential fibres, the left ventricle also has a helical muscle fibre arrangement which contributes significantly in the efficiency of left ventricular ejection, storage and release of potential energy leading to relaxation and left ventricular suction in diastole.

The helical myofibre consists of subendocardial and subepicardial fibres orientated in an opposing oblique fashion. The subendocardium is orientated in an ascending direction and has been described to adopt a right-handed helix similar to the finger orientation of a superimposed human hand. Conversely, the subepicardium is orientated in a descending direction and has been described to adopt a left-handed helix (85)(Figure 2.2).

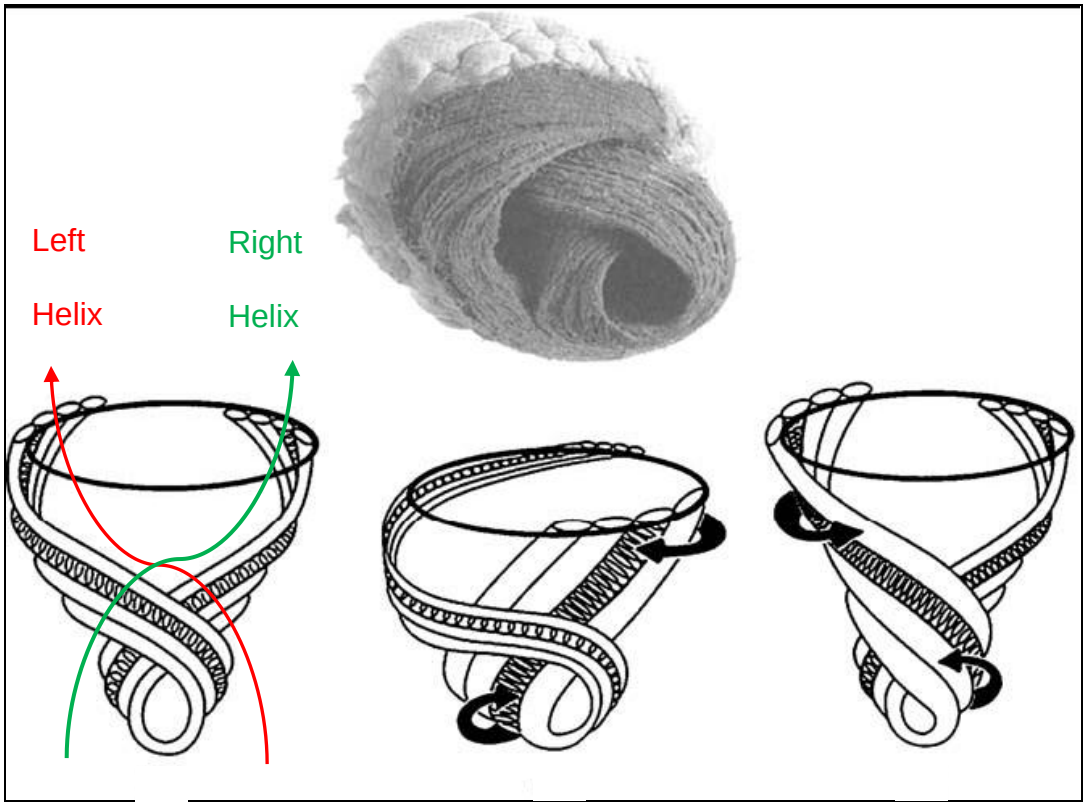
Figure 2.2 The opposing helixes of subendocardium and subepicardium



Modified from Sengupta PP et al. (85).

This transition of the helical myofibre from the right-handed helix in the subendocardium to the left-handed helix in the subepicardium (86;87) results in a significant increase in myocardial thickening and structural rearrangement throughout the cardiac cycle (88). This finding fits the description of myocardial band by Torrent-Guasp (82;86) and was further elaborated in the study by Buckberg et al. (83) as illustrated in Figure 2.3.

Figure 2.3 **Illustration of left ventricular torsion due to opposing helical myocardium**



Modified from Buckberg GD et al. (83).

2.2 LEFT VENTRICULAR TORSION MECHANICS

The helical geometry of the ventricle and the oblique fibre orientation of the myocardial fibre in opposing direction results in rotational movement of the ventricle. During isovolumic contraction, the electrical activation starts in the subendocardium from the apex towards the base leading to the shortening of the subendocardial fibres while the subepicardial fibres lengthen, resulting in a biphasic deformation between the two muscle layers (87). The opposing muscle deformation allows muscular force adjustment to maintain isovolumic mechanics. The contraction of the subepicardium and all other muscles occurs during systolic ejection, resulting in maximum myocardial shortening in the apex compared to the base (89). The apical-basal strain gradient allows the mitral annulus to be pulled towards the apex to produce the longitudinal mitral annular systolic motion.

In addition, contraction of the subepicardial fibres results in a predominant counterclockwise rotation of the left ventricular apex in view of the longer arm and hence a bigger lever of the subepicardial fibre. At the same time, the opposing direction of myocardial fibre orientation, results in the clockwise rotation of the left ventricular base to produce a wringing motion in aid of systolic ejection and left ventricular emptying. This wringing mechanism of the left ventricle enables potential energy to be stored during systole and later released to aid diastolic filling.

In early diastole, the left ventricular pressure starts to decline even before the mitral valve opens and this is associated with the change of shape of the ventricle also

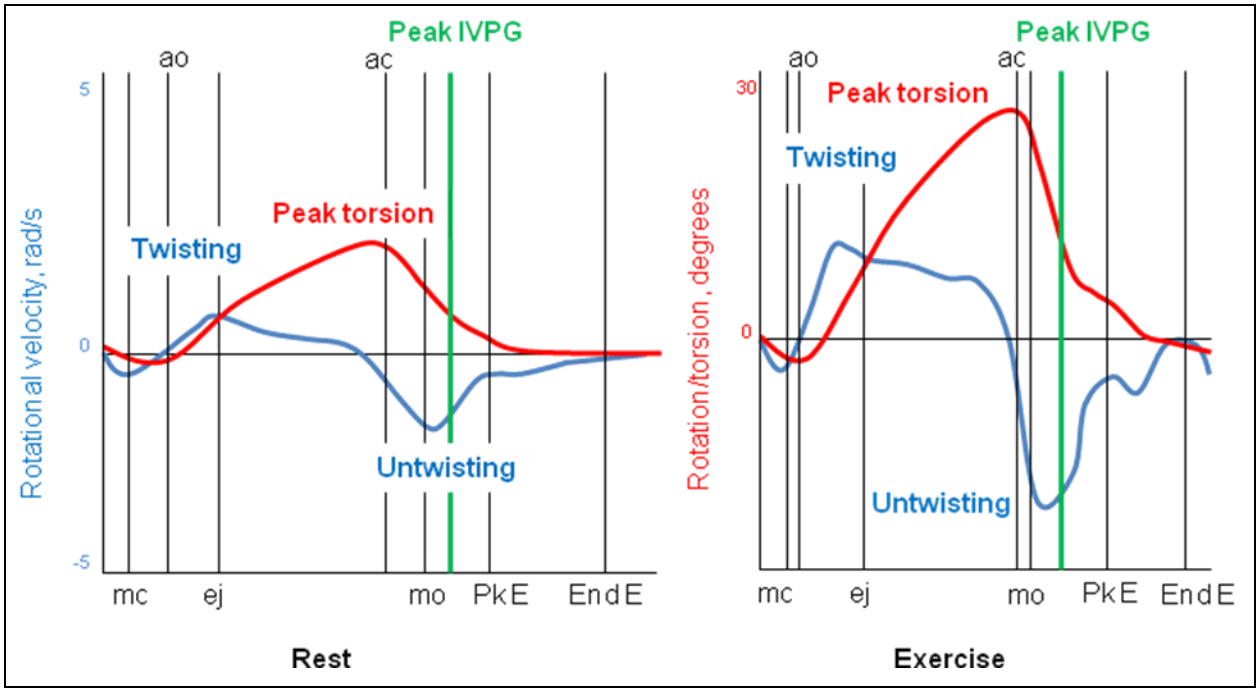
known as the ellipticalisation of the ventricle (90;91). Early diastole encompasses the period of isovolumic relaxation and pressure decay extending into the period of rapid ventricular filling. The twisted subendocardial and subepicardial fibres behave like fully compressed springs which uncoil with the release of stored potential energy turning the left ventricle in the opposite direction (92).

Diastolic untwist starts in the subendocardium in the apical-basal direction and in the subepicardium in the basal-apical direction. Subendocardial fibres start to relax before the subepicardial fibres and the direction of relaxation is of an opposite direction. This results in a transmural apical-basal gradient of relaxation to produce a lower ventricular pressure in the apex compared to the base to facilitate base-to-apex diastolic suction (83;93), contributing to rapid early diastolic filling (94;95).

In normal hearts, about 40% of the left ventricular untwisting is completed during the isovolumic relaxation period (96). Further untwisting continues beyond mitral valve opening to facilitate additional left ventricular filling. Notomi et al. demonstrated that left ventricular untwist occurs at the beginning of left ventricular relaxation and preceded the generation of intraventricular pressure gradient (IVPG) which reflects ventricular suction and showed a close correlation between the left ventricular untwisting rate with tau, the time constant of left ventricular pressure decay, and IVPG (96). They also found a strong correlation between peak left ventricular twist and peak left ventricular untwisting rate, illustrating the inseparable mechanism connecting systole to diastole.

In another study involving healthy subjects and patients with hypertrophic cardiomyopathy, Notomi et al. demonstrated the temporal link between torsion and cardiac events at rest and on exercise (97). In resting normal subjects, left ventricular torsion starts soon after mitral valve closure and peak torsion takes place just before aortic valve closure. The left ventricle starts to untwist just before aortic valve closure and maximum untwisting occurs after mitral valve opening. This is followed by the generation of peak intraventricular pressure gradient which precedes the peak E wave detected on pulse wave Doppler of the mitral inflow. On exercise, the sequence of events is similar, albeit the magnitude of twist and untwisting are increased (97) (Figure 2.4).

Figure 2.4 Left ventricular torsion at rest and on exercise in normal subjects

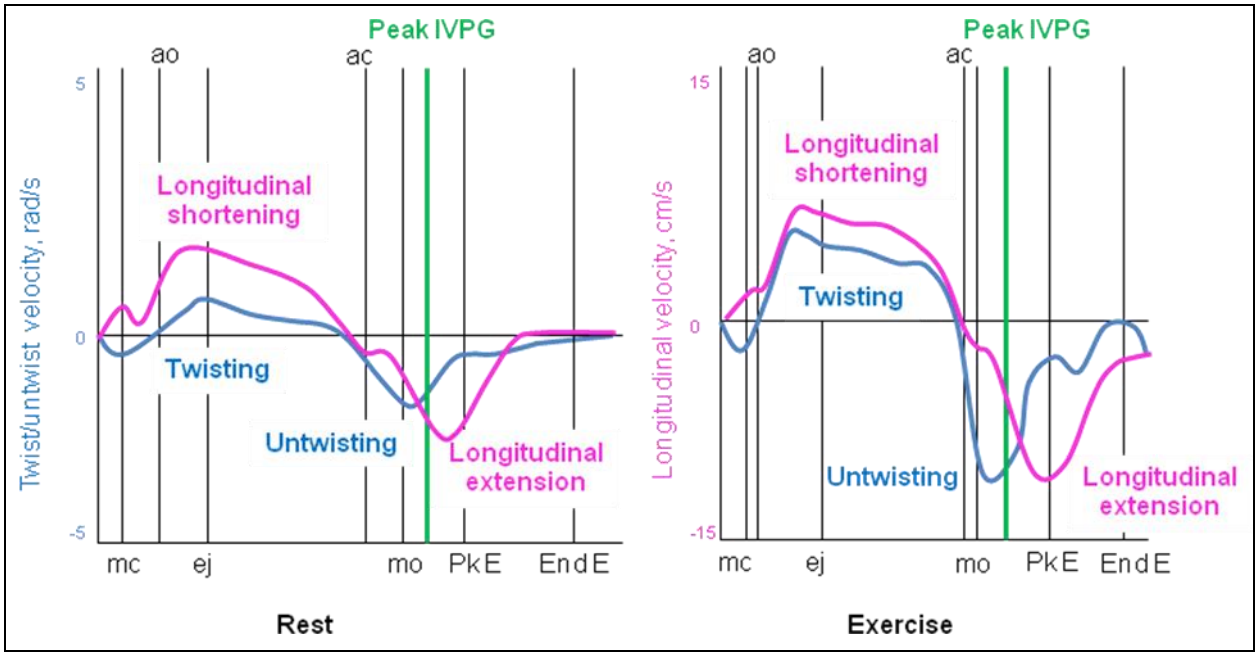


Adapted from Notomi Y et al. (97).

mc, mitral valve closure; ao,aortic valve opening; ej, left ventricular ejection; ac,aortic valve closure; mo, mitral valve opening; Peak IVPG, peak intraventricular pressure gradient; Pk E, peak mitral inflow E wave; End E, end of mitral inflow E wave.

Notomi et al. also showed that longitudinal fibres contract simultaneously during left ventricular twisting in systole but peak untwisting precedes peak longitudinal fibre relaxation in diastole. This temporal sequence of events is maintained on exercise (97) (Figure 2.5).

Figure 2.5 Myocardial velocity of two left ventricular components at rest and on exercise in normal subjects



Adapted from Notomi Y et al. (97).

Annotations as per Figure 2.4.

In addition to the apex-to-base gradient, there is also a transmural subepicardial-subendocardial gradient (93). Sengupta et al. has found evidence of delayed subepicardial circumferential apex-to-base lengthening which correlated with the isovolumic relaxation time and duration required for the left ventricle to reach the lowest pressure (93). They explained that this is due to the late repolarisation of the apical subepicardium. Their study also showed that the subepicardial circumferential fibres continued to shorten beyond aortic valve closure and isovolumic relaxation.

2.3 MEASUREMENT OF TORSION

The study of left ventricular torsion had been most challenging until the development of sophisticated imaging techniques and analytical software such as cardiac magnetic resonance imaging (CMRI) and 2D speckle tracking.

Using an invasive technique, Ingels et al. studied the motion of the heart by implanting tantalum wire clippings and found the left ventricular base and apex rotate in an opposing direction in systole creating a wringing effect (98). Such invasive studies were limited by the surgical accessibility of the epicardium and results may be affected by tissue inflammation, fibrosis and haemorrhage.

Mirro et al. explored the use of 2D echocardiography in the assessment of left ventricular torsion (99). The study was limited as the technique was dependent on identifying papillary muscles as landmarks, which were presumed to be relatively consistent in position for motion study. Their technique limited the study of the overall left ventricular torsion as they were unable to reliably locate landmarks at the left ventricular base and apex to study the opposing rotational motions which result in the overall torsion. It was not until 1990 that cardiac magnetic resonance imaging (MRI) was first used to study left ventricular torsion. Tagging technique was used to mark a specific area of the myocardium prior to image acquisition. This technique allowed detailed assessment of the myocardial motion (100). While the availability and accessibility of cardiac MRI with tagging is sparse, the advancement of 2D echocardiography continued.

In 2002, Garot et al. used tissue Doppler imaging (TDI) to assess left ventricular torsion (101). This method was validated against standard cardiac MRI and was found to correlate well. However, the angular-dependency of TDI limits the study of multiplane movement of the left ventricle (102). The breakthrough came from the development and application of speckle tracking imaging (STI) which allowed accurate tracking of the left ventricular motion without the limitation of angle-dependency (103). The use of STI to assess left ventricular torsion was validated against TDI and cardiac MRI tagging by Notomi et al. (104). With these modern non-invasive techniques, measurements of myocardial movement can be undertaken reliably and results are reproducible.

The ellipsoid shape of the left ventricle has a long axis which is directed from apex to base. The left ventricular rotation, twist and torsion are terms frequently used interchangeably in published literature to describe the wringing motion of the left ventricle. The more accurate and concise definition of these terms are outlined as below.

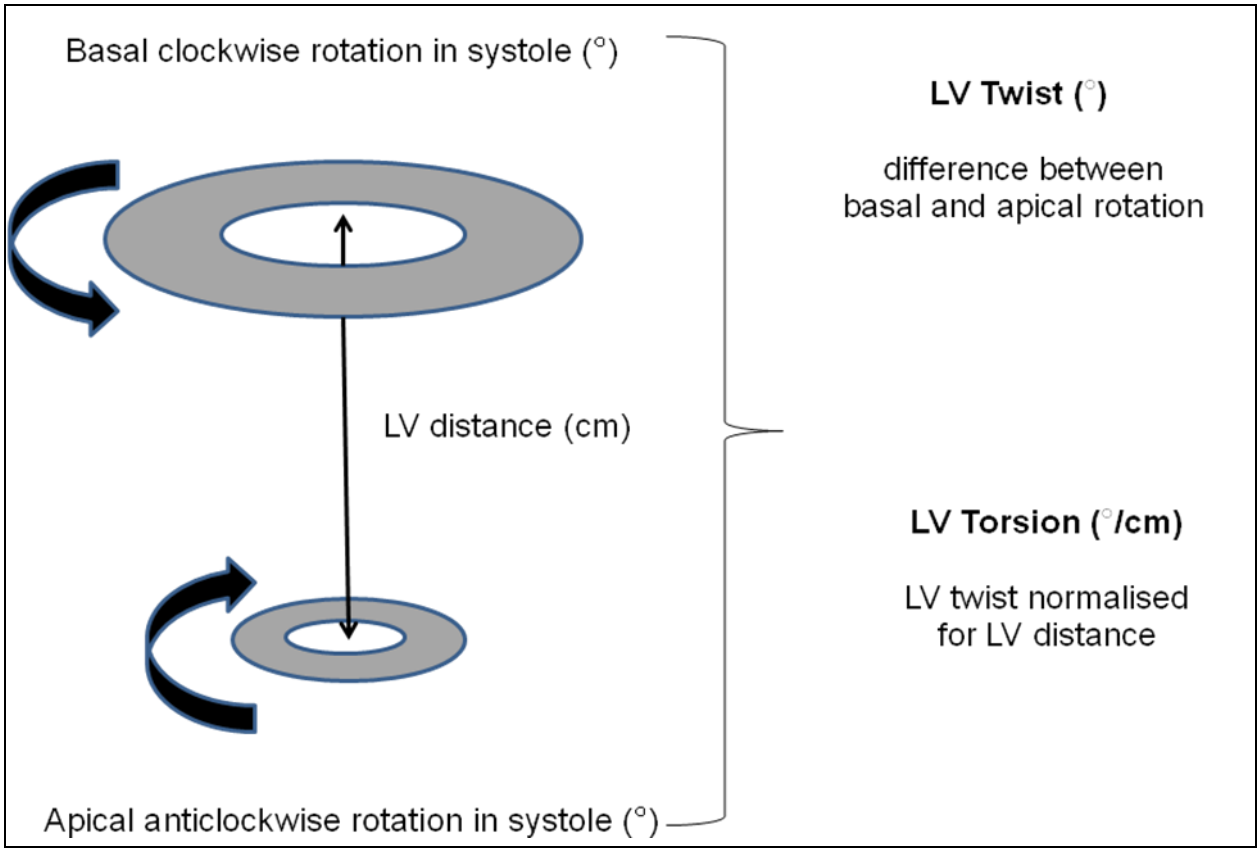
The left ventricular rotation is referred to as the two dimensional rotational motion of a section of the left ventricular short axis as viewed from the apex. The base and apex of the left ventricle rotate in opposite directions throughout the cardiac cycle. During systole, the apex rotates in a counter-clockwise direction while the base

rotates in a clockwise direction when viewed from the apex, and vice versa during diastole.

Left ventricular twist is the net difference between the rotational angles from apex to base along the central long axis, or simply the difference between the opposite rotational motions. Rotation and twist are measured in degrees.

Torsion is the difference in apical rotation and basal rotation with respect to left ventricular length and is a measurement of gradient of the rotational angle from the base to the apex of the left ventricle along the long axis. It is also regarded as left ventricular twist corrected to left ventricular length and is expressed as degrees per centimetre (Figure 2.6).

Figure 2.6 Definitions of left ventricular rotation, twist and torsion



Adapted from van Dalen BM et al. (105).

LV, left ventricular.

CHAPTER 3

HYPOTHESIS

3. HYPOTHESIS

We hypothesised that there are combined complex abnormalities in both systolic and diastolic left ventricular function in HFNEF. These abnormalities are more apparent on exercise and contribute to the generation of exertional symptoms in patients.

We hypothesised that abnormalities in systole, such as impaired long axis function and reduced left ventricular twist, lead to impaired diastolic function particularly on exercise when left ventricular filling time is shortened. There is a delay in left ventricular untwisting and mitral annular recoil, leading to reduced left ventricular suction causing impaired early diastolic filling.

We hypothesised that left atrial function is also impaired, hence the reduced compensatory late diastolic filling further contributes to the genesis of symptoms in HFNEF.

Furthermore, we hypothesised that there is systolic and diastolic dyssynchrony attributed by the lack of cohesive movements of different myocardial planes, particularly on exercise, which further impacts on the left ventricular mechanics. Impaired mitral annular motion is caused by the uncoupling of longitudinal motion and twist during systole and the separation of longitudinal lengthening and untwist in diastole.

We hypothesised that left ventricular assessment performed on exercise which is when patients are symptomatic, is key to elucidate mechanism.

Aim of study:

- To assess the overall left ventricular systolic and diastolic function at rest and on exercise in patients with HFNEF.
- To assess the role of left ventricular twist and torsion on exercise in patients with HFNEF.
- To assess the coordination of left ventricular twist and longitudinal motion on exercise in patients with HFNEF.
- To assess left ventricular torsional dyssynchrony on exercise in patients with HFNEF.
- To assess left atrial function in patients with HFNEF.
- To study the overall left ventricular systolic and diastolic function in patients with and without symptoms of heart failure.
- To provide a coherent explanation and schema of the mechanisms involved in the genesis of symptoms on exercise in patients with HFNEF and patients with hypertension without overt heart failure.

CHAPTER 4

METHODS

4. METHODS

4.1 PATIENTS

A total of 90 patients were recruited from the two university hospital heart failure specialist clinics (University Hospital of North Staffordshire and University Hospital Birmingham). A full medical history was taken from all patients and a complete clinical examination was performed, including 12-lead electrocardiogram (ECG), initial screening echocardiogram to rule out significant structural abnormalities, pulmonary function test and cardiopulmonary exercise testing. These patients had:

- signs or symptoms of heart failure;
- normal left ventricular ejection fraction and chamber size;
- objective evidence of exercise limitation on cardiopulmonary exercise testing; and
- absence of pulmonary disease on pulmonary function test.

All patients had symptoms of heart failure with New York Heart Association (NYHA) class II or more and met the criteria of Vasan and Levy for probable diastolic heart failure (33).

Thirty had previous coronary angiography which did not find any obstructive coronary lesions and there were no ECG changes on cardiopulmonary exercise on reaching a respiratory exchange ratio (RER) >1 to suggest ischaemia in any of the study subjects.

Exclusion criteria were moderate to severe pulmonary disease, significant congenital or valvular heart disease, electrical pacemakers or implantable cardiac defibrillators, and established history of ischaemic heart disease. Exclusion criteria specific to each study are outlined in each chapter.

Overall, eighteen patients were excluded (seven had evidence of respiratory restriction, one had significant coronary artery disease, two were unable to exercise, one had normal peak oxygen consumption on cardiopulmonary exercise testing, two failed to increase their heart rate on exercise and five did not have adequate images for analysis). The remaining 72 patients subsequently underwent detailed resting and exercise echocardiography studies.

4.2 HEALTHY CONTROLS

A total of 58 healthy subjects with comparable mean age to the patients were recruited. These healthy subjects were volunteers from local general practitioner surgeries. They had no past medical history and were not on any medications. All healthy subjects had a full clinical examination, 12-lead electrocardiogram, initial screening echocardiogram when they participated in a community screening programme at the surgery, pulmonary function test and cardiopulmonary exercise testing.

Overall, three healthy subjects were excluded from the study (one was tachycardic at rest due to anxiety, one had reduced peak oxygen consumption on cardiopulmonary exercise testing and one had echocardiographic findings fulfilling some of the criteria for diagnosing HFNEF). Seventeen completely asymptomatic volunteers were found to have elevated blood pressure which had not been previously diagnosed. Two of these subjects did not have adequate images for analysis therefore were excluded. The remaining 15 asymptomatic hypertensive volunteers underwent similar investigations and assessments as the healthy controls, and their data was used for a substudy (see Chapter 6).

Thirty eight remaining healthy subjects who were found to have no abnormal findings in the initial assessment were regarded as age-matched healthy controls and underwent detailed resting and exercise echocardiography study. Data of these healthy controls was used as comparison for all the studies in this thesis.

All patients and healthy subjects (including the asymptomatic hypertensive volunteers) gave written informed consent prior to their participation and the study was approved by the National Research Ethics Service (Research Ethics Committee reference: 06/Q2706/69).

4.3 CARDIOPULMONARY EXERCISE TEST

The age, height, weight and calculated body mass index (BMI) of all subjects were recorded. Subjects had standard spirometry (forced expiratory volume in one second and forced vital capacity) before they underwent incremental treadmill exercise testing using a modified Bruce protocol (106;107) with metabolic gas exchange and simultaneous heart rate and rhythm, systolic and diastolic blood pressure and oxygen saturation by pulse oximetry monitoring. The exercise testing was performed using a Schiller CS-200 Ergo-Spiro exercise machine which was calibrated by a trained physiologist prior to every study. Exercise data was collected continuously and expressed as 30-second means and analysed by the physiologist who was blinded to the clinical details of each subject. Peak oxygen consumption (peak VO_2) was defined as the highest value of oxygen consumption during exercise and expressed as ml/min/kg. A respiratory exchange ratio (RER) of >1 was taken to indicate maximal effort (108). All subjects achieved a RER >1. The tests were performed and results interpreted by two qualified physiologists, blinded to subject groups.

4.4 IMAGE ACQUISITION AND ANALYSIS

4.4.1 TWO-DIMENSIONAL ECHOCARDIOGRAPHY

All subjects underwent full echocardiography examination using a GE Vingmed Vivid Seven scanner (Horton, Norway) at rest and on exercise. All echocardiographic measurements and analyses were done in duplicate by two independent observers blinded to each other's results.

Exercise echocardiography was performed on a semi-recumbent and tilting bicycle ergometer (Lode BV, Netherlands). The position of the subjects on the bicycle ergometer was adjusted to enable optimal image acquisition. All subjects paddled at a constant speed of 60 revolutions per minute (rpm) starting at a workload of five watts. The load of the ergometer was increased by five watts every three minutes. At the onset of symptoms of breathlessness, patients were advised to continue paddling while the load of the ergometer was fixed and image acquisitions made. Image acquisition was made when healthy controls reached a maximum heart rate of 100bpm while paddling (sub-maximal exercise to maximise frame rates).

The heart rate, symptom status, brachial blood pressure and heart rhythm were monitored continuously during exercise. Image acquisition was performed with the same pre-determined protocol for all subjects.

Two-dimensional (2D) images and colour-coded tissue Doppler images (TDI) from the parasternal (long axis and short axis at basal, mid ventricular and apical levels) and apex (two, three and four chamber views) were obtained and stored digitally. The sector width and depth were optimised to maintain a frame rate of >50 frames/second for the 2D images which were later used for speckle tracking. At least three sets of images with loops consisting of at least three consecutive cardiac cycles each were stored. Three sets of images with loops consisting of five consecutive cardiac cycles each were stored if the patient was in atrial fibrillation. Cardiac cycles before and after ectopic beat were excluded. Images were analysed offline using a customised software package (EchoPac, GE).

Left ventricular (LV) dimensions and wall thickness were measured according to the recommendation of the American Society of Echocardiography (109). LV volume and ejection fraction (EF) were measured using the modified biplane Simpson's method from the apical four and two chamber views. Left ventricular mass was calculated according to the Devereux formula (110). Left atrial (LA) volume was calculated using the biplane area-length method from the apical four and two chamber views, and was indexed to body surface area to derive the LA volume index (LAVI) (52). The early filling (E) and atrial filling (A) peak velocities, E/A ratio, deceleration time (DT) of early filling and isovolumic relaxation time (IVRT) were measured from transmitral flow.

4.4.2 COLOUR DOPPLER M-MODE PROPAGATION VELOCITY

Courtois et al showed that the intraventricular pressure gradient generated during early left ventricular relaxation contributes to left ventricular suction (111). Colour Doppler M-mode propagation velocity ,Vp, has been shown to relate closely to the intraventricular pressure gradient (58) and can be used as an index of left ventricular filling due to its relative preload-independence (112). Vp has also been shown to be decreased in myocardial ischaemia (113) and heart failure (114).

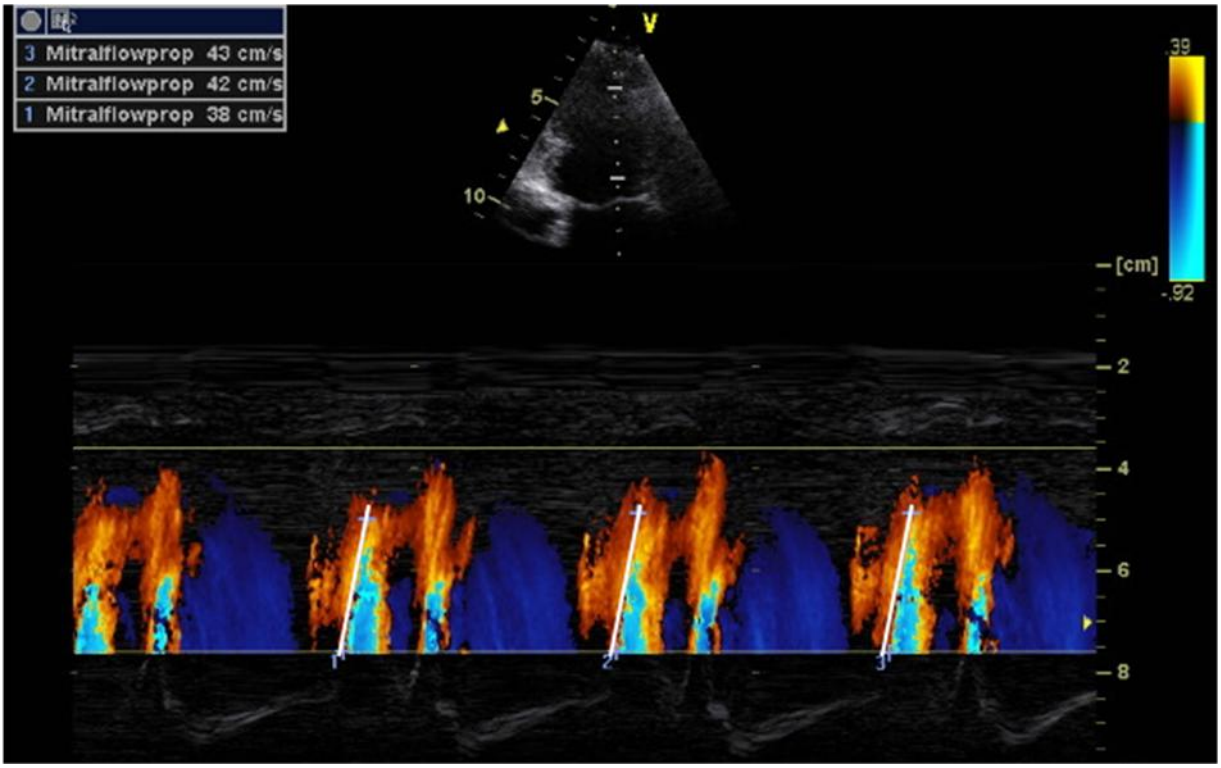
There has been no agreement in the method of measuring Vp and each method is associated with pitfalls and advantages. The major limitation is a large variation in Vp values with small deviation of slope measurement. Sessoms et al. compared Vp measured by difference methods and found that the measurement of Vp can vary up to 250% using different methods (115). They concluded that the method of Vp measurement applied by Garcia et al. (112) had the lowest variability and hence more reliable.

The Garcia method of Vp measurement (112) was adopted in the studies in this thesis as it produces a more consistent measurement particularly in the analyses of exercise images.

Colour M-mode Doppler was obtained by positioning the scan line through the mitral valve in the four chamber view using colour flow imaging with the Nyquist limit and the colour baseline adjusted to obtain the best spatial resolution. The colour M-Mode

signal was recorded using a narrow sector with minimum depth to include only the annulus and 4cm into the ventricular cavity with an aliasing velocity of 0.5-0.7 m/s. The colour M-mode profile was recorded at a sweep speed of 100mm/s. The slope of the line along the edge of the colour Doppler flow as it moves from the mitral annulus to the ventricular apex in early diastole, was taken as the propagation velocity (Vp). Vp was measured by the slope of the first aliasing isovelocity line (along the yellow or blue isovelocity line) in early diastole as described by Garcia et al. (112) (Figure 4.1). The average of five measurements was taken in view of the large variability in numerical value with slight change of the slope even when measurements were made on the same image.

Figure 4.1 Measurement of mitral flow propagation velocity



4.4.3 TISSUE DOPPLER IMAGING

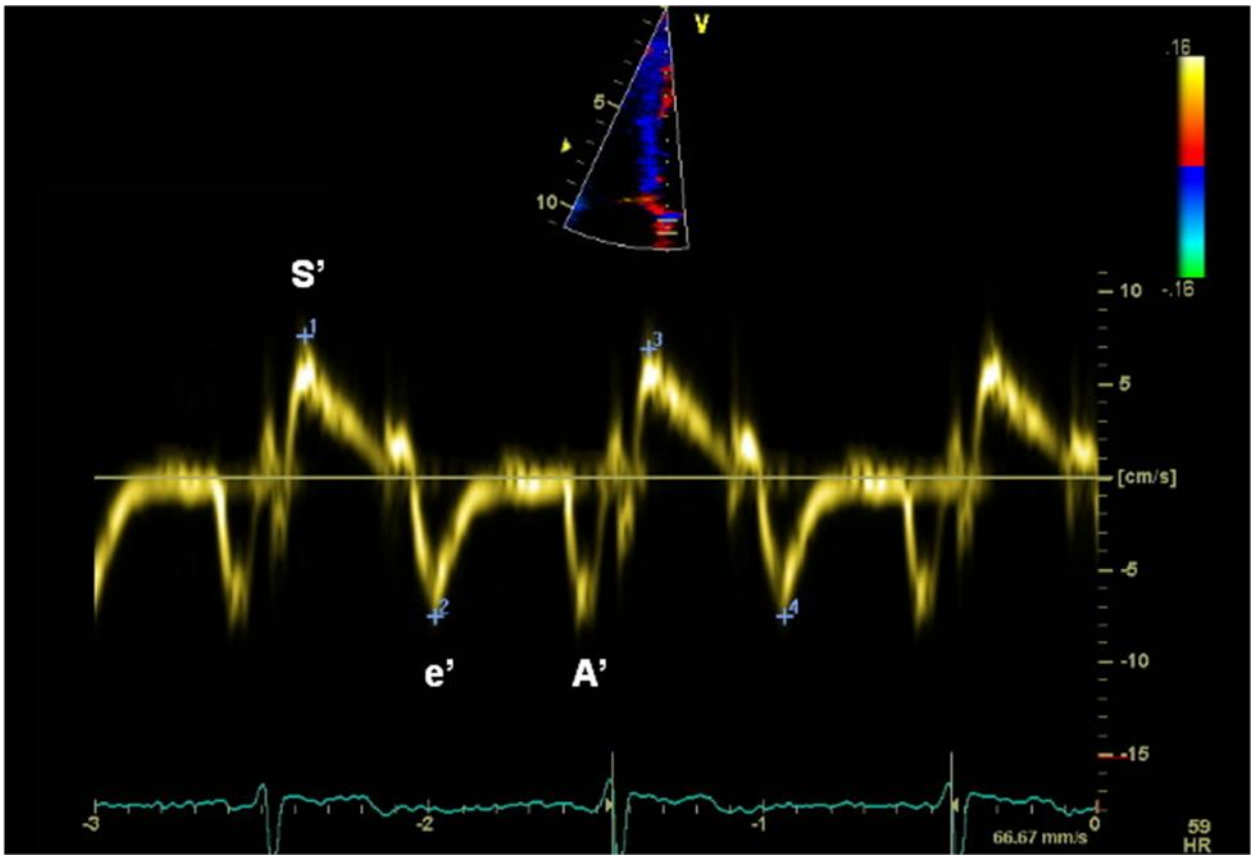
Tissue Doppler imaging (TDI) provides excellent temporal resolution and enables measurement of instantaneous quantitative information on myocardial velocity along an image line. Pulse wave TDI provides Doppler frequency at a given time whereby the peak of each frequency is linearly related to tissue velocity therefore representing the tissue velocity at the given time and position. This enables accurate timing and velocity measurements.

On the other hand, colour TDI provides the mean Doppler frequency estimated from several Doppler frequencies per time unit, with each pixel colour coded according to its velocity. The added advantage of colour TDI is that it allows analysis of tissue velocity from various regions at a given time. Displacement is the integration of velocity over time. Strain describes the deformation or the change in length of an object from one state to another and is commonly expressed as a percentage. Strain rate is the rate of deformation and is derived from the differentiation of strain with time, expressed sec^{-1}.

The derivatives of tissue velocity provide information on tissue displacement, strain and strain rate which are incorporated into most of the commercially available analysis software, such as Echopac by GE, and are calculated automatically. The main limitation of TDI is its angle dependency but it has the advantage of feasibility, high reproducibility and is relatively pre-load independent.

The peak mitral annular myocardial velocity of all the four walls of the left ventricle (septal, lateral, inferior and anterior) was recorded with real time pulse wave tissue Doppler method as previously described (116). At least three consecutive beats of Doppler tissue images of each ventricular wall were stored digitally. The sample volume and gain were optimised and the Nyquist limit was set to 15-20 cm/s. The peak systolic (S'), early diastolic (e') and late diastolic (A') velocities were measured (Figure 4.2) and E/e', an index of left ventricular filling pressure, was calculated (50).

Figure 4.2 Measurement of mitral annular myocardial velocities using pulse wave Doppler

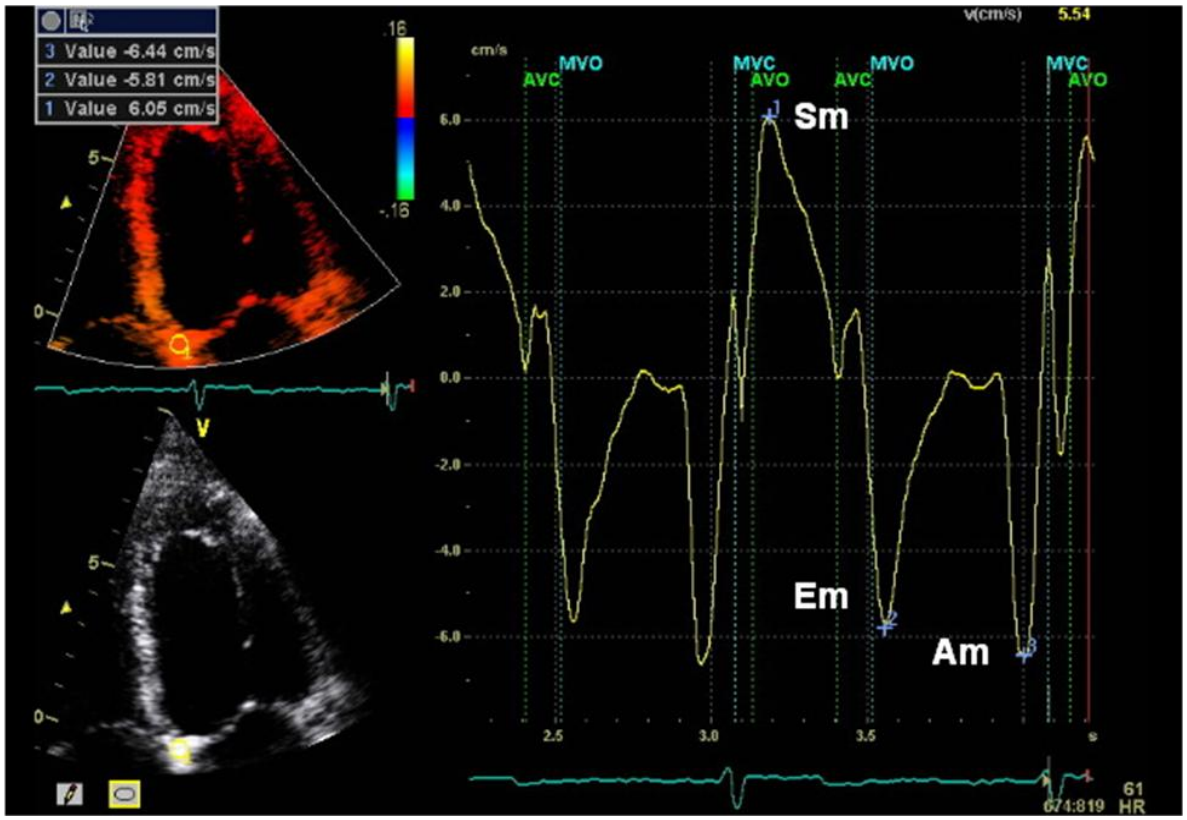


Example of measurement of mitral annular velocities of left ventricular septal wall using pulse wave Doppler.

S', peak systolic myocardial mitral annular velocity; e', early diastolic myocardial mitral annular velocity; A', late diastolic myocardial mitral annular velocity.

Colour coded tissue Doppler images were also acquired over three consecutive cardiac cycles for each of the four myocardial walls and analysed offline as previously described (47;48). Mean systolic (Sm), early diastolic (Em) and late diastolic (Am) velocities were measured by placing a 4×4 mm region of interest in the midmyocardial area of each wall (Figure 4.3). Measurements were performed manually by post-processing of data using Echopac software. All data was transferred to spreadsheets for further calculations and analyses.

Figure 4.3 Measurement of mitral annular myocardial velocities using colour tissue Doppler



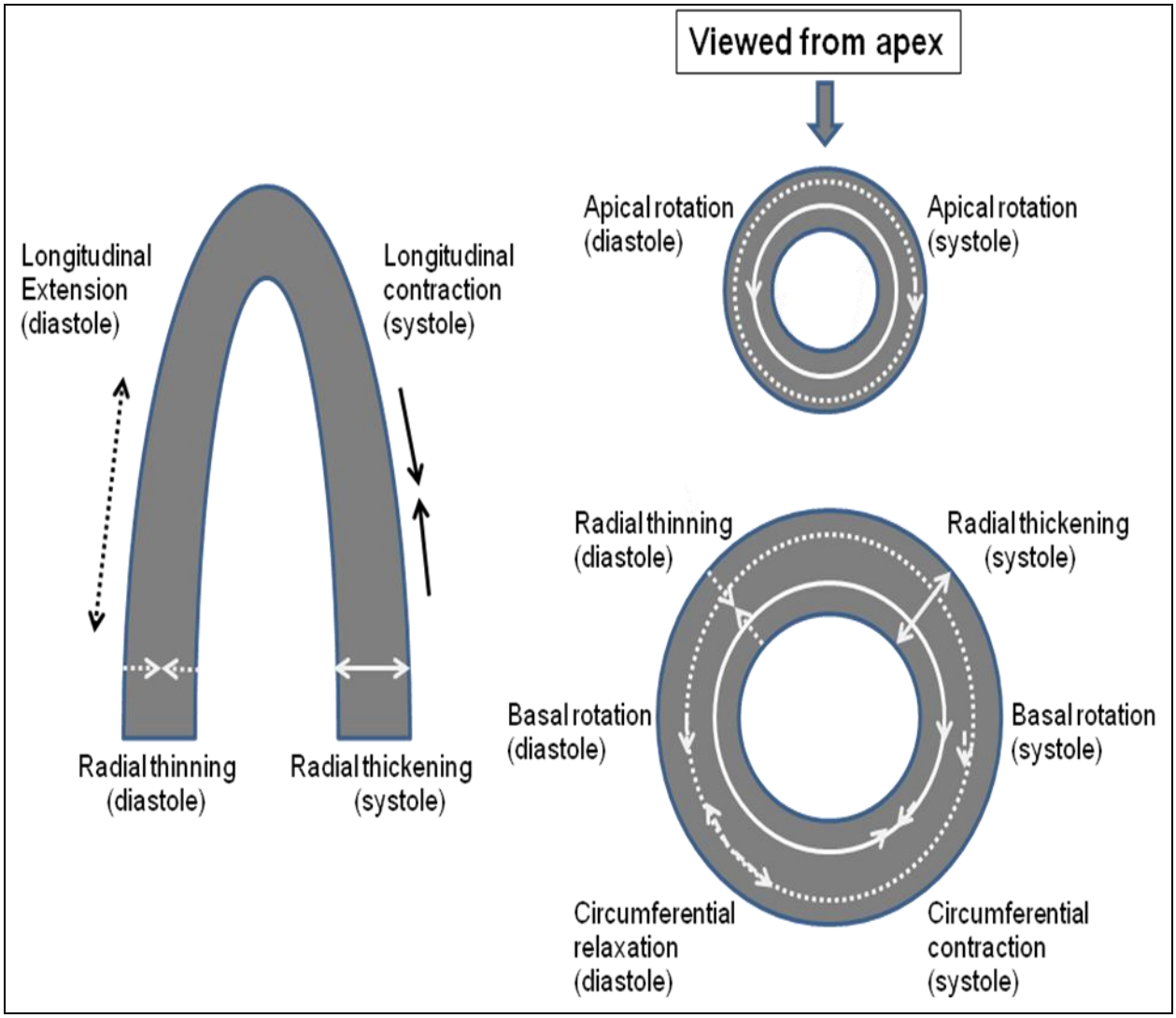
Example of measurement of mitral annular velocities of left ventricular septal wall using colour coded tissue Doppler.

Sm, systolic myocardial mitral annular velocity; Em, early diastolic myocardial mitral annular velocity; Am, late diastolic myocardial mitral annular velocity; AVO, aortic valve opening; AVC, aortic valve closure; MVO, mitral valve opening; MVC, mitral valve closure.

4.4.4 SPECKLE TRACKING

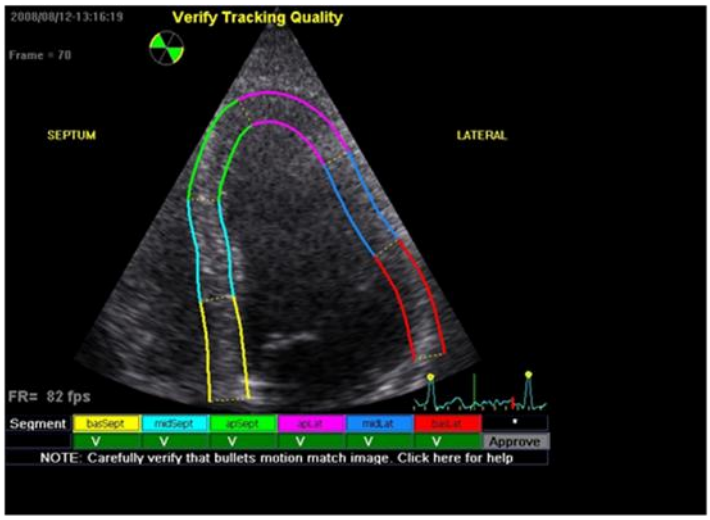
The use of speckle tracking imaging (STI) overcomes the issue of angle dependency in TDI. The fundamental principle of STI is based on the spatial distribution of characteristic myocardial tissue acoustic assumed to be unique for each myocardial segment, known as speckle pattern, attributed by the constructive and destructive interference of radiofrequency reflections from the myocardium. Tracking of the speckle pattern throughout the cardiac cycle allows one to follow the movement of the myocardium (117). Two-dimensional deformation can be measured with each plane of image as illustrated in Figure 4.4.

Figure 4.4 Two-dimensional left ventricular deformation

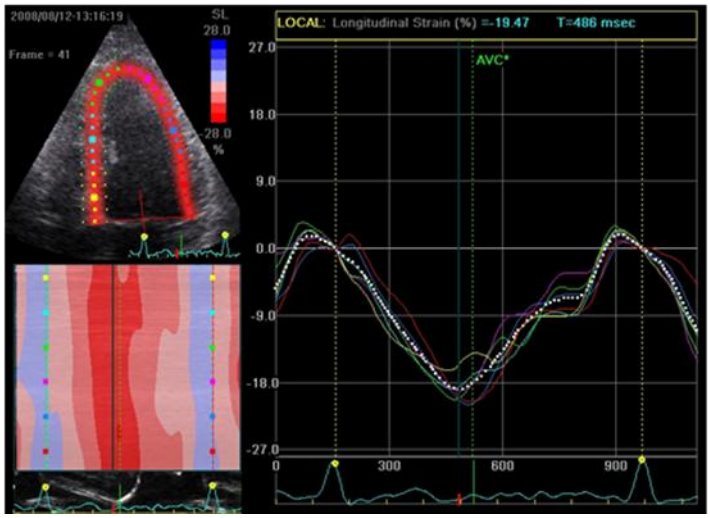


2D images of the apical long axis views (apical four chamber and two chamber) and parasternal short axis views at three levels (base, papillary and apex) were obtained at a frame rate of >60 Hz. Left ventricular longitudinal strain, radial strain, circumferential strain and rotation were assessed using the speckle tracking method using offline analysis of the long and short axis images as illustrated in Figure 4.4, by tracing the endocardium on end-diastolic frame and the thickness of the region of interest adjusted to include the entire myocardium. Each R-R internal was taken as a cardiac cycle and was used to correct for differences in heart rate (Figures 4.5 and 4.6).

Figure 4.5 Example of longitudinal strain analysis by speckle tracking



Satisfactory speckle tracking and appropriate adjustment of region of interest in 4 chamber view.

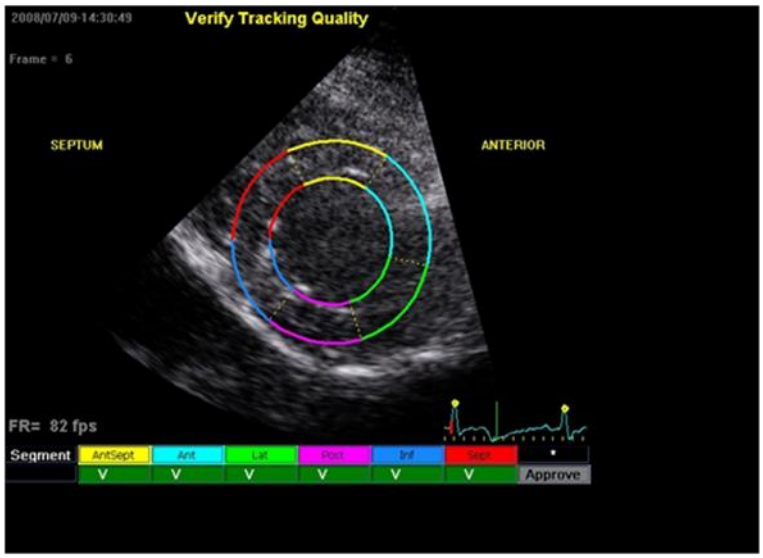


Longitudinal strain by speckle tracking

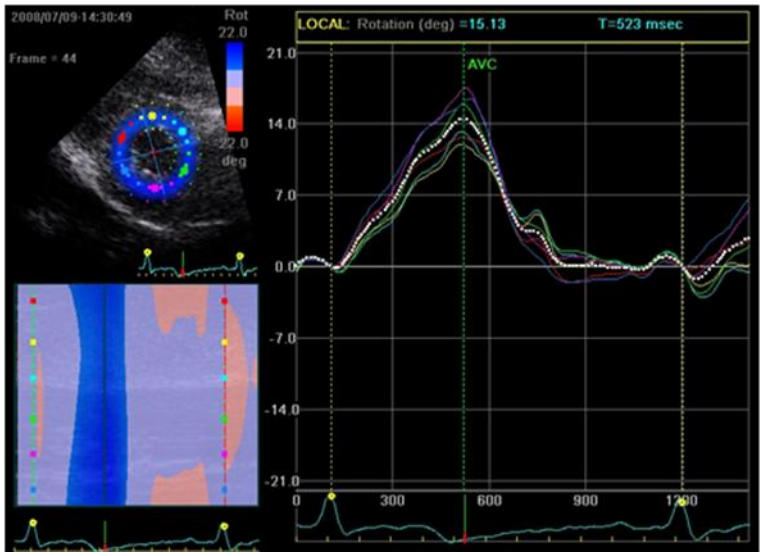
Colour of each longitudinal strain curve corresponds to each colour-coded myocardial segment. White curve represents average longitudinal strain of the six segments.

AVC, aortic valve closure.

Figure 4.6 Example of rotation analysis by speckle tracking



Satisfactory speckle tracking and appropriate adjustment of region of interest in apical short axis view.



Rotation by speckle tracking

Colour of each rotation curve corresponds to each colour-coded myocardial segment.

White curve represents average rotation of the six segments.

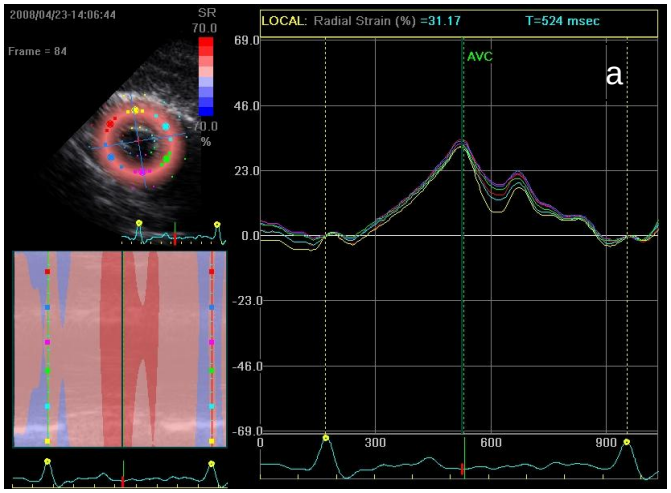
AVC, aortic valve closure.

In this study, the thickness of the region of interest (ROI) was adjusted so that the tracking border traces the endocardium and the outer border of the region of interest traces the inner edge of the epicardium. This is particularly crucial when applying speckle tracking in the short axis views for the analysis of left ventricular rotation, radial and circumflex strain.

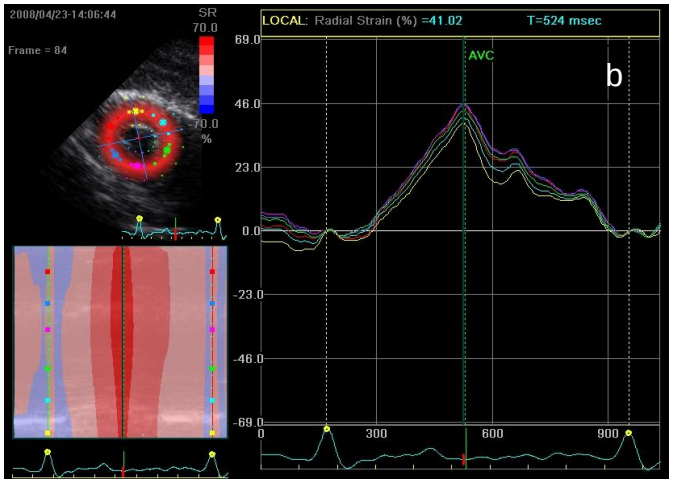
The setting of the ROI affects the magnitude of these results significantly. If the ROI extends beyond the epicardium, the magnitude of measurement is significantly lower. Conversely, if the ROI is set too small the magnitude of measurement is significantly higher as illustrated in Figure 4.7. Once the ROI is set, the EchoPac software automatically tracks the myocardial motion on the subsequent frame and results are displayed graphically.

In view of the significant difference in measurement, particularly when analysing short axis images, the observers agreed to select the thickness of the region of interest described above in all speckle tracking analyses.

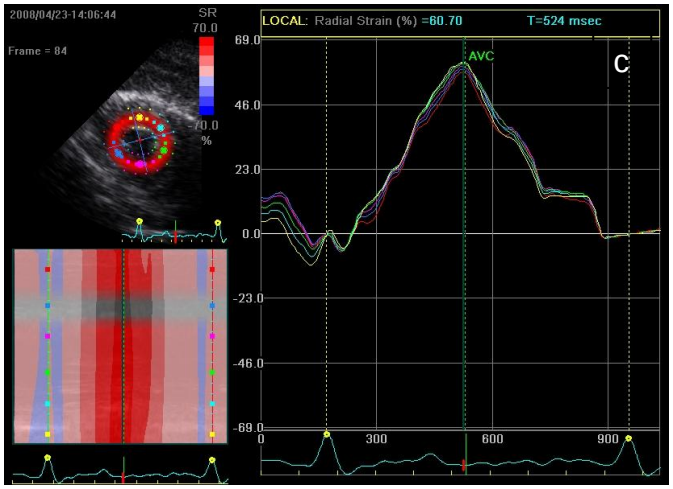
Figure 4.7 Region of interest selection using speckle tracking analysis



Maximum thickness of region of interest resulting in radial strain < 41%



Moderate thickness of region of interest resulting in radial strain = 41%



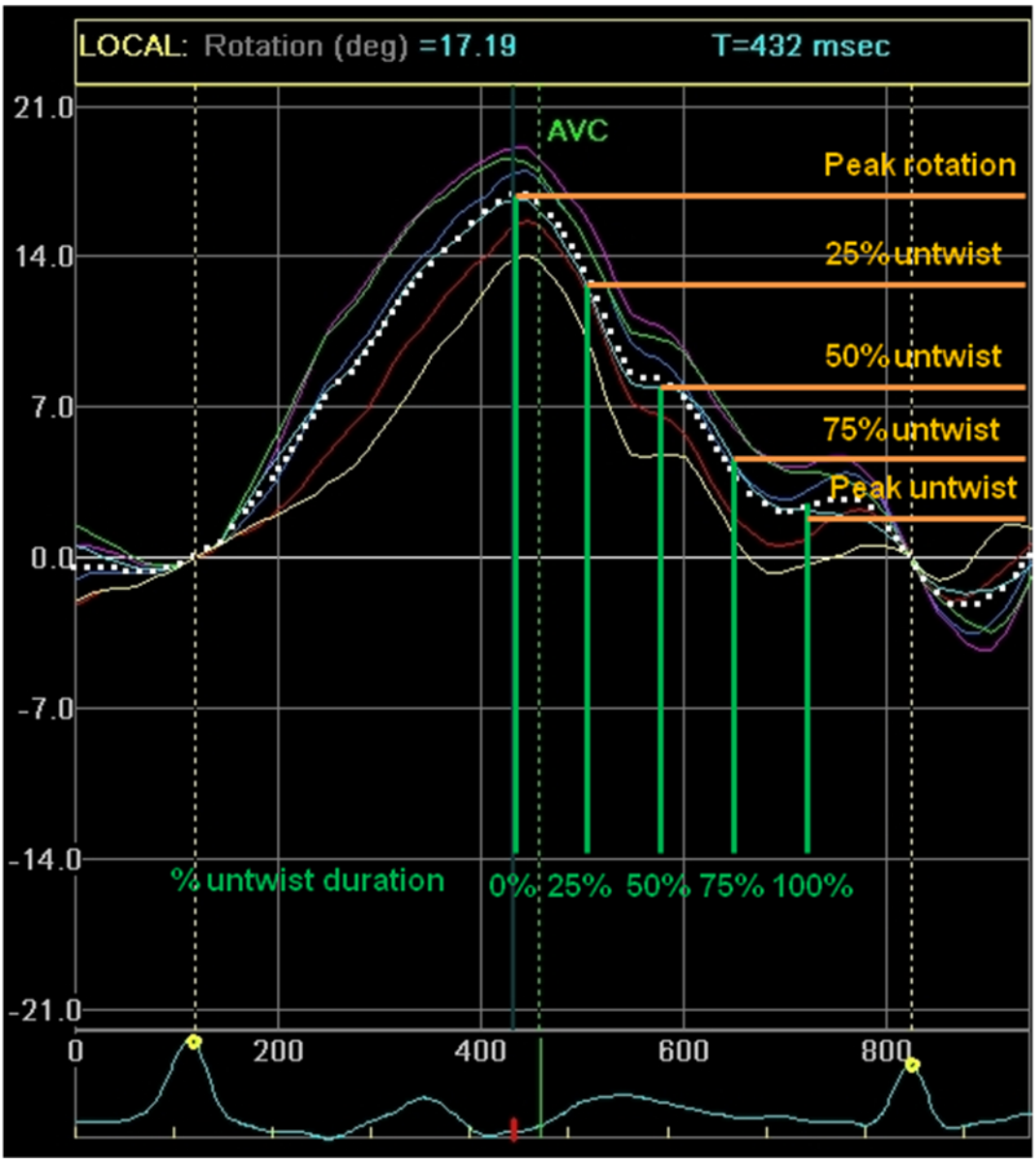
Minimum thickness of region of interest resulting in radial strain > 41%

Annotations as per Figure 4.6.

Rotation and strain in the radial, longitudinal and circumferential planes were measured as previously described (103;104;118). The thickness of the region of interest was adjusted as detailed above. Three sets of strain values for each segment (six segments from both apical long axis views and six segments from each short axis views at three levels) were measured manually and recorded. The average longitudinal, radial and circumferential strain was manually calculated from the three data sets. The global longitudinal, radial and circumferential strain data automatically generated by the Echopac software was also recorded.

Takeuchi et al. defined left ventricular untwist as a percentage of systolic twist and normalised untwist rate with isovolumic relaxation time (119). This only assesses early untwist mechanism albeit this is the significant proportion of the entire event. In this thesis, the left ventricular untwisting and untwisting rate were assessed by using data from speckle tracking. The degree of untwisting was taken as the reverse direction of twist in diastole. The time of peak twist and peak untwist were recorded and the duration between the two events was noted as the total duration of untwisting. The total duration of untwist was taken as 100%. Early untwist was taken as the magnitude of untwist at 25% of the total untwisting duration. The left ventricular untwisting at 50% (mid untwisting) and 75% (late untwisting) of the total duration of untwisting were also calculated (Figure 4.8).

Figure 4.8 Measurement of left ventricular untwist



Annotations as per Figure 4.6.

4.5 STATISTICAL METHODS

SPSS version 16 software (SPSS Inc,Chicago, Illinois, USA) was used for statistical analyses. The following methods were applied to examine data in all chapters. Additional statistical analyses specific to individual studies are outlined in each chapter.

Power analysis was performed for the first study in this thesis (Chapter 5). Sample size was estimated using pilot data. For systolic longitudinal function with anticipated difference in mean of 1.5 and standard deviation (SD) of 2, the achieved sample sizes of 56 patients and 27 controls provide 89% power for an unpaired t-test with α=0.05 (two tail). For rotation an anticipated difference in mean of 3 degrees and SD of 4, the achieved sample sizes of 56 patients and 27 controls provide 89% power for an unpaired t-test with α=0.05 (two tail).

Continuous variables were expressed as mean ± standard deviation (SD). Fisher's exact test was conducted for nominal variables. Normality was assessed by visualising P-P plot and Q-Q plots.

Comparisons of normally distributed data between HFNEF patients and controls were performed using an unpaired t-test and Mann-Whitney U test was used for non-normally distributed data. Comparisons of rest and exercise data for HFNEF patients and controls were performed using a paired t-test. The paired and unpaired t-tests were applied in all chapters except Chapter 6.

The Pearson correlation coefficient, r, was used to examine the association and the strength of the relationship between variables. Scatterplots were generated and linear regressions were performed to assess the relationship between two continuous variables.

Inter-observer and intra-observer agreements were performed using readings of 10 randomly selected subjects and calculated using alpha model reliability analysis and reported as interclass correlation coefficient (ICC) with 95% confidence interval (CI).

A p value of <0.05 was considered statistically significant.

CHAPTER 5

SYSTOLIC AND DIASTOLIC DYSFUNCTION ON EXERCISE

Contributory publication:

Tan YT, Wenzelburger F, Lee E, Heatlie G, Leyva F, Patel K, Frenneaux M, Sanderson JE. The pathophysiology of heart failure with normal ejection fraction: exercise echocardiography reveals complex abnormalities of both systolic and diastolic ventricular function involving torsion, untwist and longitudinal motion. J Am Coll Cardiol 2009;54(1):36-46.

5. SYSTOLIC AND DIASTOLIC DYSFUNCTION ON EXERCISE

5.1 SUMMARY

This study was to test the hypothesis that in HFNEF, exercise limitation is due to combined systolic and diastolic abnormalities particularly involving ventricular twist and deformation leading to reduced left ventricular suction, delayed untwisting and impaired early diastolic filling.

Fifty six patients and 27 age-matched healthy controls had rest and exercise images of sufficient quality for analysis. At rest, systolic longitudinal and radial strain, systolic mitral annular velocities and apical rotation were lower in patients and all failed to rise normally on exercise. Systolic longitudinal functional reserve was also significantly lower in patients . In diastole, patients had reduced and delayed untwisting, reduced left ventricular suction at rest and on exercise, and higher end-diastolic pressures. Mean mitral annular systolic and diastolic velocities, systolic left ventricular rotation and early diastolic untwist on exercise all correlated with peak VO_2.

This study concluded that in HFNEF, there are widespread abnormalities of both systolic and diastolic function which become more apparent on exercise and hence HFNEF is not an isolated disorder of diastole.

5.2 INTRODUCTION

Some studies suggested that systolic function is normal in HFNEF(4;5). This study was to test the hypotheses that systolic function is not normal in HFNEF and that complex abnormalities in systolic and diastolic left ventricular function are more apparent on exercise and contribute to the generation of exertional symptoms in HFNEF patients. These abnormalities include impaired long axis function and reduced left ventricular twist in systole, leading to delayed left ventricular untwist and mitral annular recoil, reduced left ventricular suction and impaired early diastolic filling.

New developments in echocardiography particularly speckle-tracking imaging enable a much fuller assessment of left ventricular systolic and diastolic functions including the measurement of myocardial deformation or strain in three planes, ventricular twist and untwist, and left ventricular suction which is a vital mechanism in early diastolic ventricular filling. As outlined earlier in Chapter 4, these advanced echocardiography techniques were applied to assess global and regional left ventricular function at rest and more importantly on exercise. This study forms the major part of this thesis.

5.3 METHODS

Patients and age-matched controls were recruited as described in Chapter 4. All patients had symptoms of heart failure with New York Heart Association (NYHA) class II or more and met the criteria of Vasan and Levy for probable diastolic heart failure (33).

All study subjects underwent cardiopulmonary exercise testing and full echocardiography at rest and on semi-recumbent exercise on a tilting bicycle ergometer as described in Chapter 4.

Two-dimensional echocardiography, tissue Doppler and speckle tracking imaging and analyses were performed as described in Chapter 4.

In addition, derived parameters for assessing systolic and diastolic function were calculated. Stroke volume was calculated using the aortic valve pulse wave Doppler method, whereby the velocity time integral of aortic annular flow was obtained by tracing the pulsed Doppler profile and multiplied by the area of the aortic annulus as previously described (120). Preload recruitable stroke work index, peak power index, single beat estimated end-systolic elastance, arterial elastance (121;122), chamber stiffness (123), pressure volume ratio (124) and longitudinal reserve indices (125) were calculated.

Calculation of derived parameters:

Stroke work index	=	mean blood pressure (BP) * stroke volume (SV) / end diastolic volume (EDV)
Mean blood pressure (BP)	=	BP diastole + 1/3 (BP systole-BP diastole)
Cardiac output (CO)	=	heart rate (HR) * stroke volume (SV)
Arterial elastance (Ea)	=	0.9 * BP systole / stroke volume
End systolic elastance (Ees)	=	0.9 * BP systole / end systolic volume (ESV)
Peak power index (PPI)	=	peak ejection rate (LVOT peak velocity) * BP systole / EDV
Pressure / volume ratio	=	(E/e') / EDV
Chamber stiffness (K)	=	$70 / (DT-20)^2$
Systolic longitudinal function reserve index	=	$\Delta S' * [1 - (1/S'_{rest})]$
Diastolic longitudinal function reserve index	=	$\Delta E' * [1 - (1/E'_{rest})]$

LVOT, left ventricular outflow tract; DT, deceleration time.

5.4 STATISTICS

Statistical analyses were performed as described in Chapter 4.

Comparisons between HFNEF patients and controls were performed using an unpaired t-test for normally distributed data and the Mann-Whitney U-test for non-normally distributed data. Comparisons within HFNEF patients and controls were performed using a paired t-test only as all data was normally distributed. Linear regression was performed to test correlations.

Inter-observer and intra-observer agreements were performed using readings of 10 randomly selected subjects. Variability of tissue Doppler analysis, speckle tracking analysis and mitral flow propagation velocity were assessed at rest and on exercise.

5.5 RESULTS

In this study, a total of 121 subjects (74 patients and 47 controls) were recruited. Eighteen patients were excluded (seven were found to have respiratory limitation on cardiopulmonary exercise test and did not achieve a respiratory exchange ratio of >1, six were unable to exercise and had poor picture quality for analysis, two had no increase in heart rate on exercise, one was found to have evidence of ischaemia on cardiopulmonary exercise test, one had normal peak VO_2 on cardiopulmonary exercise testing, and one had entirely normal echocardiography). Only 27 completely healthy controls without past medical history and on no medications were included. Twenty subjects were excluded (seventeen of the control subjects had evidence of hypertension at rest which was not previously diagnosed, one had a reduced peak VO_2 on cardiopulmonary exercise test, one had echocardiographic findings which fulfilled the criteria for HFNEF although completely asymptomatic, and one had sinus tachycardia at rest due to anxiety).

The mean age of the patients was 72 ± 7 years and 70% were female. Control subjects were of comparable age (70 ± 7 years, p= not significant) and also 70% were female. The past medical history and drug history of patients are summarised in Table 5.1. All patients were on treatment and had symptoms of heart failure with New York Heart Association (NYHA) class II or III. Patients had a significantly higher body mass index (BMI) compared to controls but peak VO_2, which was indexed to BMI and age, was significantly lower in patients compared to controls (Table 5.1). The left ventricular ejection fraction and left ventricular dimensions were comparable

between patients and controls. Left atrial volume index (LAVI), mitral inflow E and A waves, and E/e' were significantly higher in patients (Table 5.2).

Table 5.1 Clinical characteristics – left ventricular function study

	Patients	Controls	p-value
Number of subjects	56	27	
Age	72±7	70±7	0.195
Gender	39♀ / 17♂	19♀ / 8♂	0.579 *
BMI	30±5	24±4	<0.001
NYHA	class II = 41 class III = 15	n/a	
NT-proBNP (pg/ml)	131±153	46±23.4	
Peak VO_2 (ml/min/kg) (percent of predicted)	17.9±4.0 (78±16%)	30.9±.4.3 (135±18%)	<0.001
Hypertension	45/56 (80%)	0 (0%)	
Years of hypertension	8.3±10.0	0	<0.001 ‡
Diabetes mellitus	12 (21%)	0 (0%)	
Atrial fibrillation	3 (5%)	0 (0%)	
Coronary artery disease	6 (11%)	0 (0%)	
ACE-inhibitor	18 (32%)	0 (0%)	
AR1-blocker	16 (29%)	0 (0%)	
α-blocker	11 (20%)	0 (0%)	
β-blocker	20 (36%)	0 (0%)	
Calcium-channel-blocker	13 (23%)	0 (0%)	
Diuretic	28 (50%)	0 (0%)	
Statin	19 (34%)	0 (0%)	

Data is presented as number (and %) or mean ± standard deviation.

p-value: unpaired t-test between patients and controls except * Fisher exact test between patients and controls and ‡ Mann-Whitney U test between patients and controls.

BMI, body mass index; NYHA, New York Heart Association classification for heart failure; Peak VO_2, peak oxygen consumption; ACE, angiotension-converting enzyme; AR1, angiotensin 1 receptor; NT-proBNP,N-terminal pro B-type natriuretic peptide.

Table 5.2 Standard echocardiographic parameters – left ventricular function study

	Patients	Controls	p-value
LVEDD (cm)	4.7±0.7	4.6±0.5	0.275
Biplane LVEF (%)	61±6	62±8	0.306
FS (%)	40±10	39±7	0.558
IVSd (cm)	1.1±0.3	1.0±0.2	0.092
LVMI (g/m^2)	96±34	82±22	0.081
LAVI (ml/m^2)	32±11	24±9	0.002
E-Wave (cm/s)	0.69±0.19	0.57±0.11	0.003
A-Wave (cm/s)	0.85±0.19	0.70±0.14	0.001
E/A	0.83±0.26	0.84±0.19	0.877
DT (ms)	250±58	258±46	0.515
IVRT (ms)	96±27	100±22	0.569
E/e’	11.4±4.3	8.2±2.0	0.001

Data is presented as mean ± standard deviation.

p-value: unpaired t-test between patients and controls.

LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; FS, fractional shortening; IVSd, diastolic interventricular septal thickness; LVMI, left ventricular mass index; LAVI, left atrial volume index; E,early diastolic mitral inflow velocity; A late diastolic mitral inflow velocity; E/A ratio of E to A; DT, deceleration time; IVRT, isovolumic relaxation time; e’ peak early diastolic myocardial mitral annular velocity; E/ e’; ratio of E to e’.

5.5.1 HAEMODYNAMIC CHANGES

The resting and exercise heart rate and blood pressure were comparable between patients and controls (Table 5.3). The increase in aortic outflow velocity time integral (VTI), peak left ventricular outflow track (LVOT) velocity, stroke volume and cardiac output on exercise were significantly higher in controls. Even though controls had a slightly lower initial aortic outflow VTI, stroke volume and cardiac output, they were able to achieve a significant increase on exercise compared to patients (Table 5.3).

Table 5.3 Haemodynamic measurements at rest and on exercise – left ventricular function study

	Patients rest	Patients exercise	Patients p-value (paired t-test)	Controls rest	Controls exercise	Controls p-value (paired t-test)	Patients / controls p-value (unpaired t-test)
BP systolic (mmHg)	146±16	168±18	<0.001	140±15	163±15	<0.001	0.114 * 0.298 #
BP diastolic (mmHg)	75±10	86±13	<0.001	78±8	87±9	<0.001	0.166 * 0.687 #
Heart rate (beats per minute)	69±11	89±10	<0.001	67±9	92±5	<0.001	0.484 * 0.157 #
VTI (cm)	21.5±4.8	22.8±5.3	0.066	19.3±3.9	23.3±3.4	<0.001	0.045 * 0.743 #
Δ VTI (cm)		1.3±4.2			4.3±1.9		0.003 #
Stroke volume (ml)	73±20	74±23	0.239	62±13	79±20	0.004	0.015 * 0.364 #
Δ Stroke volume (ml)		4±24			18±24		0.039 #
Cardiac output (l/min)	4.8±1.5	6.4±2.0	<0.001	4.2±0.9	7.4±2.0	<0.001	0.059 * 0.097 #
Δ Cardiac output (l/min)		1.6±2.2			3.1±2.4		0.027 #
Peak LVOT velocity (m/s)	1.1±0.2	1.2±0.3	0.004	1.0±0.2	1.2±0.1	<0.001	0.044 * 0.682 #
Δ Peak LVOT velocity (m/s)		0.1±.2			0.2±0.1		0.007 #

Data is presented as mean ± standard deviation.

p-value (paired t-test): paired t-test of patients (or controls) at rest and on exercise.

p-value (unpaired t-test): * unpaired t-test between patients and controls at rest and

unpaired t-test between patients and controls on exercise.

BP, blood pressure; VTI, velocity time integral; LVOT, left ventricular outflow tract.

5.5.2 LONGITUDINAL FUNCTION - TISSUE DOPPLER

The mitral annular velocities in systole (S'), early diastole (e') and late diastole (A') at rest were significantly lower in patients compared to controls. There was a significant increase in S' and e' in patients on exercise, but the differences in S' and e' between patients and controls became highly significant on exercise(Table 5.4). This reflected a reduction in left ventricular reserve which was then calculated using the changes in S' and e' from rest to exercise to determine the systolic and diastolic longitudinal function reserve indexes respectively. HFNEF patients had a significantly lower systolic (0.64 ± 0.51 versus 1.54 ± 0.51, $p<0.001$) and diastolic (1.49 ± 0.77 versus 2.32 ± 1.24, $p=0.011$) longitudinal reserve compared to controls (Table 5.4) (Figure 5.1).

Table 5.4 Rest and exercise results of tissue Doppler imaging – left ventricular function study

	Patients rest	Patients exercise	Patients p-value (paired t-test)	Controls rest	Controls exercise	Controls p-value (paired t-test)	Patients / controls p-value (unpaired t-test)
S' (cm/s)	5.1±1.0	6.0±1.0	<0.001	5.7±0.9	7.7±1.0	0.001	0.025 * 0.001 #
e'(cm/s)	4.4±1.2	6.4±1.5	<0.001	5.4±1.1	8.3±1.2	<0.001	0.004 * 0.001 #
A'(cm/s)	6.8±1.5	8.7±1.6	<0.001	7.8±1.4	9.7±1.7	<0.001	0.012 * 0.063 #
E/e'	11.4±4.3	11.4±4.5	0.298	8.2±2.0	8.8±1.8	0.384	0.001 * 0.009 #
Systolic reserve index		0.6±0.5			1.5±0.7		<0.001 #
Diastolic reserve index		1.5±0.8			2.3±1.2		0.011 #

Data is presented as mean ± standard deviation.

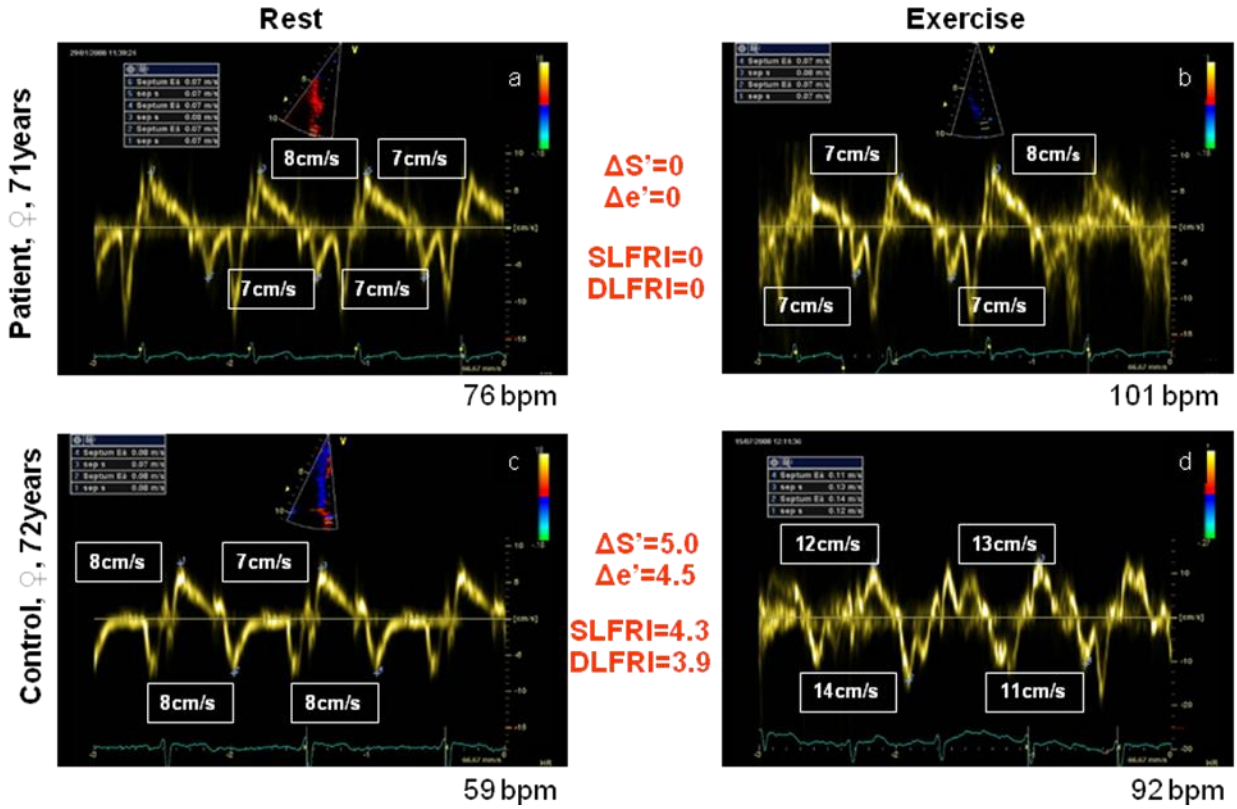
p-value (paired t-test): paired t-test of patients (or controls) at rest and on exercise.

p-value (unpaired t-test):* t-test between patients and controls at rest and

t-test between patients and controls on exercise.

S', peak systolic myocardial mitral annular velocity; e', peak early diastolic myocardial mitral annular velocity; A' peak late diastolic myocardial mitral annular velocity; E/e' ratio of E to e'.

Figure 5.1 Illustration of systolic and diastolic longitudinal function reserve



a. TDI of patient at rest; b. TDI of patient on exercise; c. TDI of control at rest; d. TDI of control on exercise.

This example illustrates that both patient and control had appropriate increase in heart rate on exercise. There was a significant increase in systolic and diastolic mitral annular velocity on exercise in the control subject which was not seen in the patient. Hence, this patient showed a lack of systolic and diastolic longitudinal function reserve.

Δ, change in (delta); S', peak systolic myocardial mitral annular velocity; e', peak early diastolic myocardial mitral annular velocity; SLFRI, systolic longitudinal function reserve index; DLFRI, diastolic longitudinal function reserve index.

5.5.3 LONGITUDINAL FUNCTION - SPECKLE TRACKING

Using 2D speckle tracking technique, longitudinal strain at rest and on exercise was assessed using the apical four chamber and apical two chamber images. Longitudinal strain of 12 segments were studied (apical, mid and basal segments of the septal, lateral, inferior and anterior walls). Patients had significantly lower longitudinal strain at rest regardless of the left ventricular wall used for assessment. Calculation of the average longitudinal strain using six segments of the septal and lateral walls (apical four chamber view), or the average from the six segments of the inferior and the anterior walls (apical two chamber view), or the average of all 12 segments of all four walls (taken as global strain) yielded similar results. This indicated a reduction in global longitudinal function in patients (Table 5.5). Even though patients had a significant increase in longitudinal strain on exercise, the magnitude of longitudinal strain on exercise only approximated to the magnitude of longitudinal strain in controls at rest. The longitudinal strain on exercise was significantly lower in patients compared to controls (Table 5.5).

Table 5.5 Longitudinal strain – left ventricular function study

	Patients rest	Patients exercise	Patients p-value (paired t-test)	Controls rest	Controls exercise	Controls p-value (paired t-test)	Patients / controls p-value (unpaired t-test)
Long strain SepLat (%)	-19.4±3.8	-20.4±4.2	0.082	-21.5±3.0	-24.4±2.6	<0.001	0.018 * <0.001 #
Δ Long strain SepLat (%)		-1.2±3.9			-3.1±2.8		0.051
Long strain InfAnt (%)	-18.4±3.8	-20.1±4.5	0.012	-20.4±3.7	-23.2±3.2	0.004	0.042 * 0.008 #
Δ Long strain InfAnt (%)		-2.1±4.2			2.8±3.9		0.592
Global long strain (%)	-18.9±3.5	-20.1±4.1	0.005	-20.9±3.0	-23.8±2.5	<0.001	0.018 * <0.001 #
Δ Global long strain (%)		-1.9±3.3			-2.8±2.7		0.315

Data is presented as mean ± standard deviation.

p-value (paired t-test): paired t-test of patients (or controls) at rest and on exercise.

p-value (unpaired t-test): * unpaired t-test between patients and controls at rest and

unpaired t-test between patients and controls on exercise.

SepLat, septal and lateral walls; InfAnt, inferior and anterior walls; Δ, change in (delta).

5.5.4 RADIAL FUNCTION – SPECKLE TRACKING

Radial strain was assessed by speckle tracking of the mid-ventricular short axis view. This was also significantly reduced in patients at rest, more so on exercise compared to healthy controls (Table 5.6). Interestingly, similar to the findings in longitudinal strain, there was a significant increase in radial strain on exercise in patients but the mean radial strain on exercise in patients only equated to the resting radial strain in controls.

Table 5.6 Radial strain – left ventricular function study

	Patients rest	**Patients exercise**	**Patients p-value (paired t-test)**	**Controls rest**	**Controls exercise**	**Controls p-value (paired t-test)**	**Patients / controls p-value (unpaired t-test)**
Radial strain (%)	41.8±13.5	49.1±15.4	0.020	49.2±12.9	61.9±12.8	0.001	0.030 * 0.002 #
Δ Radial strain (%)		6.6±15.6			12.4±12.3		0.154

Data is presented as mean ± standard deviation.

p-value (paired t-test): paired t-test of patients (or controls) at rest and on exercise.

p-value (unpaired t-test): * unpaired t-test between patients and controls at rest and

unpaired t-test between patients and controls on exercise.

Δ, change in (delta).

5.5.5 LEFT VENTRICULAR ROTATION AND UNTWIST

As discussed in Chapter 2, left ventricular torsion plays an important role in the overall left ventricular function. In this study, rotation and untwisting of the left ventricle were studied by speckle tracking of the apical short axis images (full study of left ventricular torsion is discussed in the Chapter 7). This study showed that the ability of the left ventricle to rotate in systole and untwist in diastole was significantly less in patients compared to controls both at rest and on exercise. As described in Chapter 4, the left ventricular untwisting was taken as the magnitude of untwist at 25%, 50% and 75% of the total untwisting duration to represent early, mid and late diastolic untwisting of the left ventricle (Figure 4.8). The percentages of left ventricular untwist in early diastole (25% of untwist duration) and late diastole (75% of untwist duration) at rest were found to be significantly lower in patients compared to controls. However, on exercise, the percentages of untwist in early and mid diastole (50% untwist duration) were significantly lower in patients, and the percentage of untwist in late diastole showed a trend to being significant. The Echopac software generated speckle tracking result of left ventricular untwist rate was not significantly different at rest but became significantly different on exercise with controls having a significantly higher untwist rate compared to patients (Table 5.7) (Figure 5.2).

Similar to the findings for longitudinal and radial strain, the magnitude of apical rotation, untwist rate and percentage of untwist in late diastole on exercise in patients increased only to a level comparable to controls at rest. However, the percentage of

early untwist, which is the more crucial portion of the untwisting mechanics, is significantly lower in patients on exercise compared to the resting result of the controls. Similar finding was seen for mid-diastolic untwisting (Table 5.7).

Table 5.7 Left ventricular rotation and untwist – left ventricular function study

	Patients rest	Patients exercise	Patients p-value (paired t-test)	Controls rest	Controls exercise	Controls p-value (paired t-test)	Patients / controls p-value (unpaired t-test)
Apical Rotation (º)	10.4±4.0	13.5±4.7	0.008	13.0±2.8	17.7±3.6	0.003	0.015 * 0.005 #
Δ Apical Rotation (º)		3.0±4.9			4.9±4.1		0.216
Untwist rate (º/s)	-80±34	-105±32	<0.001	-96±30	-129±32	0.007	0.069 * 0.013 #
Δ Untwist rate (º/s)		-33±35			-29±39		0.722
25% Untwist	23.7±9.3	21.2±8.5	0.465	30.9±9.7	29.2±7.7	0.477	0.006 * 0.002 #
Δ 25% Untwist		-2.0±13.1			-2.4±14.1		0.922
50% Untwist	53.9±12.6	50.5±12.3	0.371	58.8±8.4	61.7±8.2	0.384	0.101 * 0.001 #
Δ 50% Untwist		-3.3±17.7			3.0±14.2		0.223
75% Untwist	77.3±6.4	80.3±9.8	0.477	81.8±7.1	85.0±4.7	0.126	0.016 * 0.057 #
Δ 75% Untwist		1.8±12.1			3.3±8.7		0.652

Data is presented as mean ± standard deviation.

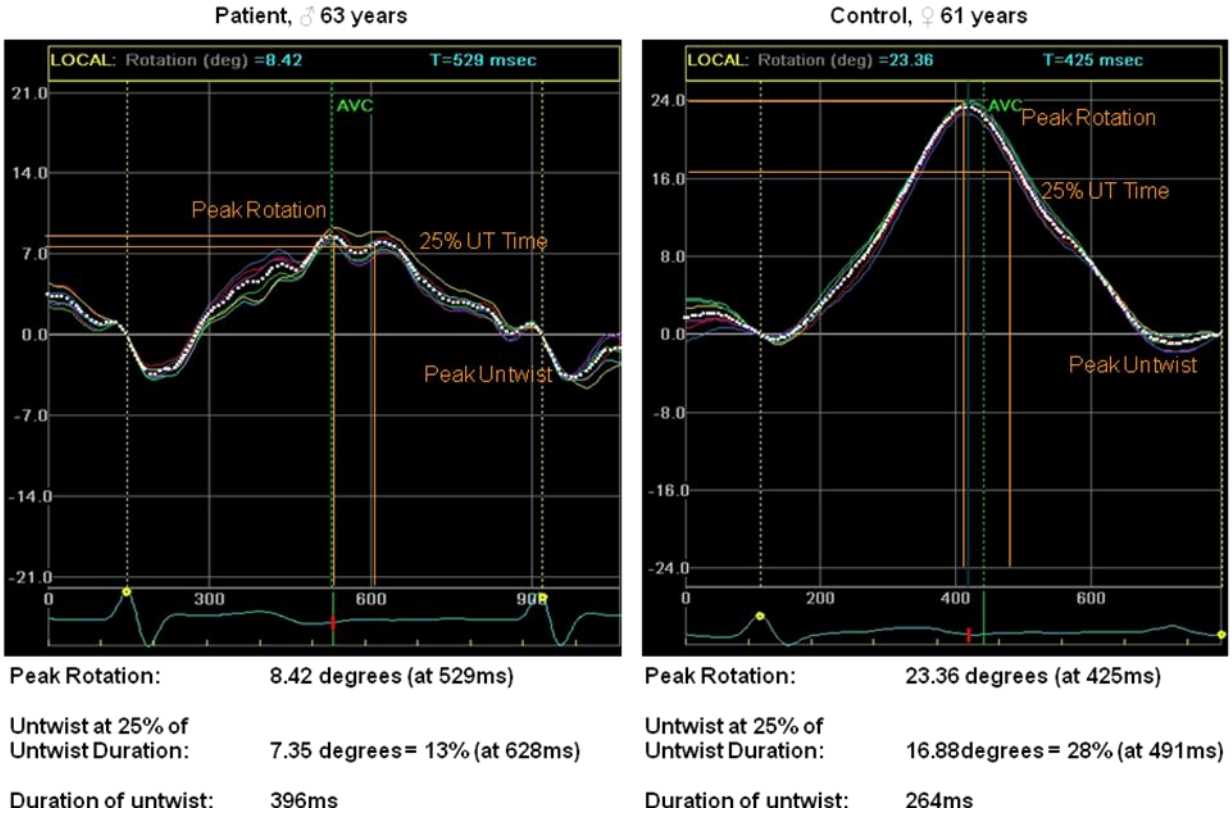
p-value (paired t-test): paired t-test of patients (or controls) at rest and on exercise.

p-value (unpaired t-test): * unpaired t-test between patients and controls at rest and

unpaired t-test between patients and controls on exercise.

25% (50%, 75%) Untwist, percentage untwist at 25% (50%, 75%) of total untwist duration; Δ, change in (delta).

Figure 5.2 Illustration of left ventricular rotation and untwist in patient with HFNEF and control



This example illustrates the significantly lower magnitude of systolic rotation and early diastolic untwist in patient compared to control. The duration of untwist in patient with HFNEF is significantly longer despite a lower peak rotation.

AVC, aortic valve closure; UT,untwist.

5.5.6 MITRAL FLOW PROPAGATION VELOCITY

Mitral flow propagation velocity (Vp) was used as an approximation to the intraventricular pressure gradient, reflecting ventricular suction. Vp was comparable between the two groups at rest but became significantly different on exercise with the controls having a higher increase in Vp on exercise compared to patients. Patients had a significant increase in Vp on exercise, but the magnitude of the increase was significantly less than controls (Table 5.8) (Figures 5.3 and 5.4). Vp on exercise correlated with S' on exercise (r=0.47, p=0.005) suggesting a mechanistic link between systole and diastolic suction.

Table 5.8 Mitral flow propagation velocity

	Patients rest	**Patients exercise**	**Patients p-value (paired t-test)**	**Controls rest**	**Controls exercise**	**Controls p-value (paired t-test)**	**Patients / controls p-value (unpaired t-test)**
Vp (m/s)	40±10	49±11	<0.001	39±7	61±14	<0.001	0.516 * <0.001 #
ΔVp (m/s)		11±13			22±14		0.001

Data is presented as mean ± standard deviation.

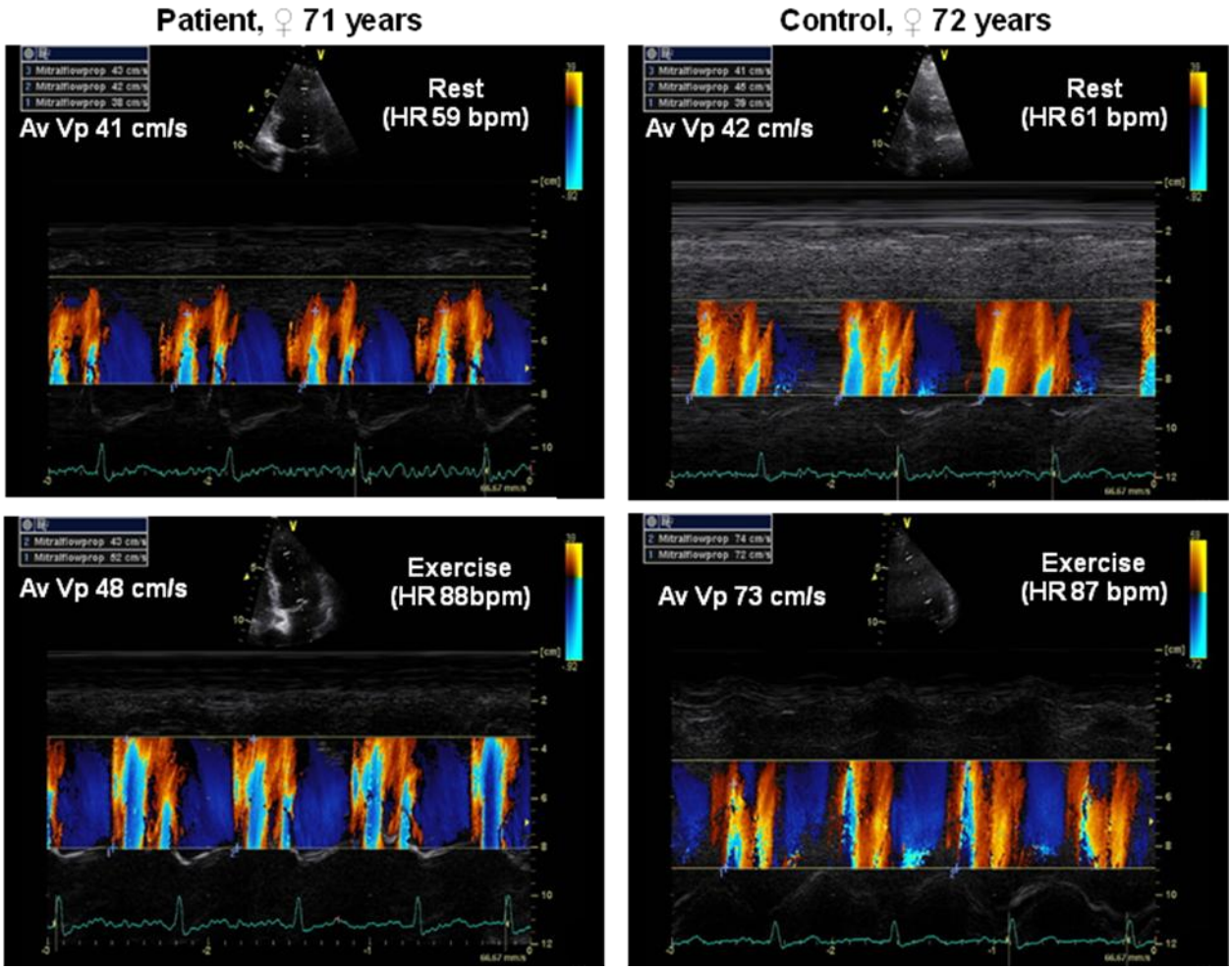
p-value (paired t-test): paired t-test of patients (or controls) at rest and on exercise.

p-value (unpaired t-test): * unpaired t-test between patients and controls at rest and

unpaired t-test between patients and controls on exercise.

Vp, mitral flow propagation velocity; Δ, change in (delta).

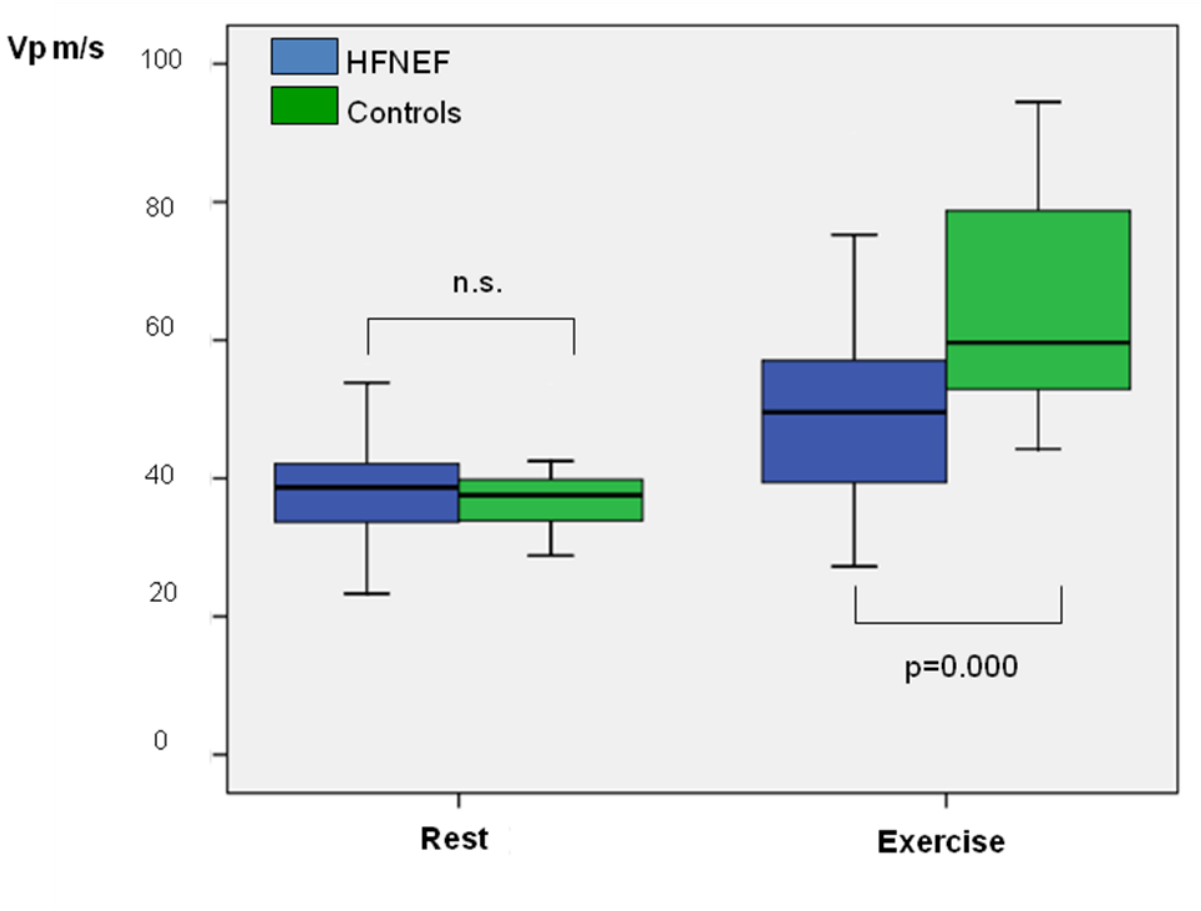
Figure 5.3 Illustration of mitral flow propagation velocity at rest and on exercise in patient with HFNEF and control



This example illustrates that there was only a 17% increase in mitral flow propagation velocity in the patient with HFNEF despite a similar increase in heart rate on exercise, compared to the control who achieved a 74% increase in mitral flow propagation velocity on exercise.

Av Vp, average mitral flow propagation velocity; HR, heart rate.

Figure 5.4 Boxplot of mitral flow propagation velocity at rest and on exercise



Boxplot shows minimum, first quartile, median, third quartile and maximum.

Vp, mitral flow propagation velocity; p, probability; n.s., not significant.

5.5.7 CORRELATIONS BETWEEN PEAK VO_2 ON EXERCISE AND ECHOCARDIOGRAPHIC PARAMETERS

The aim of this study was to relate the symptoms of patients to echocardiographic findings. All patients were breathless at the time of image acquisition during exercise echocardiography on the ergometer. This study found significant correlation of left ventricular systolic and diastolic parameters on exercise with peak VO_2. Peak VO_2 correlated with the following echocardiographic parameters on exercise: Sm (r=0.61, p=0.003), Em (r=0.417, p=0.038), apical rotation (r=0.44,p=0.026), E/e' (r=-0.34, p=0.04), Vp (r=0.35, p=0.03) and early diastolic (25%) untwisting (r=0.53, p=0.007). There were no significant correlations of echocardiographical parameters at rest with peak VO_2.

5.5.8 DERIVED MEASUREMENTS

There was no significant difference in arterial elastance or end-systolic elastance (a measure of systolic function and end-systolic stiffness) at rest. However, there was an increase, although not statistically significant, in arterial elastance in patients on exercise while controls had a reduced arterial elastance on exercise, resulting in a significant difference in the change in arterial elastance on exercise (Table 5.9). Stroke work index was similar between patients and controls at rest and on exercise, rising in both groups to the same degree. Estimated 'chamber stiffness' was also comparable in both groups.

Table 5.9 Derived measurements

	Patients rest	Patients exercise	Patients p-value (paired t-test)	Controls rest	Controls exercise	Controls p-value (paired t-test)	Patients / controls p-value (unpaired t-test)
Pressure / Volume (1/ml)	0.17±0.80	0.17±0.70	0.135	0.13±0.50	0.14±0.44	0.543	0.035 * 0.039 #
Δ P / V (1/ml)		0.01±0.05			0.01±0.06		0.744
Arterial elastance (mmHg/ml)	2.0±0.7	2.2±0.9	0.083	2.1±0.5	1.9±0.4	0.227	0.403 * 0.145 #
Δ Ea (mmHg/ml)		0.2±0.7			-0.2±0.7		0.044
Chamber stiffness (K) (mmHg/ml)	1.6±0.7	3.4±1.6	<0.001	1.4±0.6	3.8±1.4	<0.001	0.200 * 0.380 #
Δ K (mmHg/ml)		1.9±1.7			2.4±1.7		0.249
Power peak index (mmHg/s)	2.2±0.7	3.1±1.1	<0.001	2.2±0.7	3.1±0.8	<0.001	0.793 * 0.947 #
Δ PPI (mmHg/s)		1.0±1.0			0.9±0.8		0.702
End-systolic elastance (mmHg/ml)	4.9±1.9	7.4±2.7	<0.001	5.6±2.2	6.9±1.7	<0.001	0.206 * 0.461 #
Δ Ees (mmHg/ml)		2.5±2.6			1.4±2.3		0.138
Stroke work index (mmHg)	94±26	132±49	0.001	101±36	140±46	0.02	0.405 * 0.579 #
Δ SWI (mmHg)		39.4±52.9			36.6±56.2		0.872

Data is presented as mean ± standard deviation.

p-value (paired t-test): paired t-test of patients (or controls) at rest and on exercise.
p-value (unpaired t-test): * unpaired t-test between patients and controls at rest and
unpaired t-test between patients and controls on exercise.

P / V, pressure volume ratio; Ea, arterial elastance; K, chamber stiffness; PPI, peak power index; Ees, end-systolic elastance; SWI, stroke work index; Δ, change in (delta).

5.5.9 INTER-OBSERVER AND INTRA-OBSERVER VARIABILITY

Inter-observer and intra-observer agreements for parameters measured by different modalities, both at rest and on exercise, were performed using readings of 10 randomly selected subjects and calculated using Alpha model reliability analysis and reported as interclass correlation coefficient (ICC) with 95% confidence interval (CI) as described in Chapter 4.

In this study, three methods of echocardiography were used to generate the raw data (tissue Doppler, speckle tracking and colour M-mode Doppler) at rest and on exercise. The variability of these methods is listed below.

The inter-observer variability for parameters measured at rest were:

- TDI measurement of Sm, ICC=0.88, 95% CI=0.52-0.97;
- TDI measurement of Em, ICC=0.96, 95% CI=0.83-0.99;
- Speckle tracking of long axis images, ICC=0.92, 95% CI=0.68-0.98;
- Speckle tracking of short axis images, ICC=0.90, 95% CI=0.57-0.98; and
- Colour M-mode Doppler measurement of Vp, ICC=0.82, 95% CI=0.43-0.94.

The inter-observer variability for parameters measured on exercise were:

- TDI measurement of Sm, ICC=0.99, 95% CI=0.97-0.99;
- TDI measurement of Em, ICC=0.99, 95% CI=0.78-0.99;
- Speckle tracking of long axis images, ICC=0.75, 95% CI=0.01-0.94;
- Speckle tracking of short axis images, ICC=0.80, 95% CI=0.13-0.96; and
- Colour M-mode Doppler measurement of Vp, ICC=0.79, 95% CI=0.42-0.94.

The intra-observer variability for parameters measured at rest were:

- TDI measurement of Sm, ICC=0.91, 95% CI=0.65-0.98;
- TDI measurement of Em, ICC=0.95, 95% CI=0.80-0.99;
- Speckle tracking of long axis images, ICC=0.90, 95% CI=0.61-0.98;
- Speckle tracking of short axis images, ICC=0.98, 95% CI=0.90-0.99; and
- Colour M-mode Doppler measurement of Vp, ICC=0.88, 95% CI=0.70-0.95.

The intra-observer variability for parameters measured on exercise were:

- TDI measurement of Sm, ICC=0.91, 95% CI=0.62-0.98;
- TDI measurement of Em, ICC=0.97, 95% CI=0.86-0.99;
- Speckle tracking of long axis images, ICC=0.97, 95% CI=0.89-0.99;
- Speckle tracking of short axis images, ICC=0.98, 95% CI=0.91-0.99; and
- Colour M-mode Doppler measurement of Vp, ICC=0.66, 95% CI= 0.49-0.89.

5.6 DISCUSSION

In this study a comprehensive assessment of systolic and diastolic ventricular function was performed using non-invasive techniques at rest and on exercise, and demonstrated that breathlessness on exercise in HFNEF patients is associated with a variety of abnormalities of both systolic and diastolic function. These include reduced radial and longitudinal myocardial systolic strain both at rest and on exercise, reduced systolic and diastolic longitudinal functional reserve, reduced left ventricular rotation at rest which fails to increase normally on exercise, and delayed ventricular untwisting which became worse on exercise. These abnormalities were associated with reduced left ventricular suction consequently leading to failure of stroke volume to rise on exercise.

These results are consistent with previous studies (96;97) using similar echocardiographic techniques which have demonstrated the close temporal, functional and tightly coordinated relationships between left ventricular twist during systole, the mitral annular motion towards the apex during systole, and in early diastole, how the untwisting process and recoil generates the negative intraventricular pressure gradient or left ventricular suction coinciding with the rapid motion of the mitral annulus back towards the base of the heart which aids left ventricular filling by enveloping the incoming column of blood (44). As discussed in Chapter 2, left ventricular torsion or twist is a mechanism for generating stored energy during systole which is released during early diastole to produce ventricular recoil, upward annular motion and generation of intraventricular pressure gradient to

facilitate left ventricular suction. This mechanism occurs to complete a cardiac cycle and confirms the close relationship between systole and early diastole (57).

All these aspects of left ventricular function increase on exercise in the normal heart to aid rapid ejection and more importantly, to enable efficient filling of the left ventricle during a shortened diastole period, associated with increased heart rate, while maintaining a normal filling pressure. Notomi et al. showed that when this mechanism is disrupted, such as in hypertrophic cardiomyopathy, there is an associated rise in left ventricular end-diastolic and left atrial pressures (97). Their findings confirmed early studies which also linked diastolic dysfunction with regional inhomogeniety of contraction and relaxation in similar condition (74).

The findings in this chapter are similar to the results reported by Notomi et al. in hypertrophic cardiomyopathy (97). It is likely that these fundamental abnormalities of both systolic and diastolic left ventricular function are more relevant to the genesis of the symptoms of breathlessness than the increased passive myocardial stiffness measured at end-diastole at rest, as previously suggested (4;5).

This study only reported the left ventricular apical rotation because it has been shown that the apical rotation represents the dominant contribution to the overall left ventricular twist over a range of haemodynamic conditions (126;127). As outlined in Chapter 2, the left ventricular twisting motion is a consequence of myocardial fibre orientation, which changes from an approximately longitudinal but slightly oblique

orientation in the subendocardium, to a circumferential orientation in the mid-wall and to an oblique orientation in the subepicardium (84;128). Thus, the subendocardial and subepicardial fibres represent two oppositely directed spirals. Due to their larger radii, the torque of the subepicardial fibres dominates and accounts for the counterclockwise rotation of the left ventricular apex.

Previous studies have found that in left ventricular hypertrophy or those with diastolic dysfunction, apical twist and untwisting may be augmented or reduced (119;129). Similarly, torsion is increased in patients with mild diastolic dysfunction, but reduced in those with more severe degrees of diastolic dysfunction (130). These variable findings could be a consequence of the anatomical arrangement of the myocardial fibres. In the early stage of myocardial insult, such as ischaemia or fibrosis, the more vulnerable subendocardial longitudinal fibres are primarily affected early so that unopposed epicardial torque will increase the apical twist. When the disease progresses, more widespread fibrosis or damage will affect global function and lead to the overall reduced left ventricular twist with delayed untwisting. This also explains the findings of reduced myocardial annular velocities, which were seen in HFNEF patients particularly on exercise as shown in the results of this chapter, given that the left ventricular longitudinal dysfunction primarily reflects subendocardial fibres damage, hence making them sensitive measures of left ventricular function (131). All previous studies of torsion and untwisting in HFNEF were done at rest and this is the first study which has assessed both longitudinal function and apical rotation on exercise. Reduced and delayed untwisting on exercise will undoubtedly impede left

ventricular suction in early diastole and delay rapid filling, so that more filling will occur in late diastole during atrial systole. This explains the common finding of the delayed relaxation pattern (reduced early but increased atrial velocity) of the mitral inflow velocities associated with ageing and left ventricular hypertrophy (119;132). Late diastolic compensation depends on left atrial function, which is assessed in the next study reported in Chapter 6.

The derived measurements of stiffness, arterial stiffness and ventricular systolic compliance did not show any major differences between patients and controls, at rest or on exercise. In part, this may be because these measurements are often derived from single beats and have many assumptions involved in their calculations. Left ventricular chamber stiffness is derived from the E-wave deceleration time (DT) but is probably only accurate in those with a short DT, whereas some of the HFNEF patients had a delayed DT and there is no data on the effects of exercise. Furthermore, DT has been shown to be a function of both chamber stiffness and chamber relaxation viscoelasticity hence applying DT alone may not estimate chamber stiffness accurately(133). Pressure-volume index was higher in patients as expected. Although in the study by Westerman et al., stiffness was different between groups at baseline and did not change significantly in HFNEF patients during handgrip exercise (4), it is likely that there are other non-cardiac factors involved in the symptom generation. Apart from ventricular-arterial interactions, some investigators have reported that a significant number of HFNEF patients have attenuated heart rate response to exercise, similar to patients with HFREF (24;134).

Furthermore, those with such chronotropic incompetence have even more severe exercise intolerance than those without it.

Exercise echocardiographic studies were deliberately done during sub-maximal exercise to optimise image quality. However, the end results of arterial compliance and ventricular interactions will be to impair ventricular function on exercise. Interestingly, the other derived measures of global systolic function (end-systolic elastance, stroke work index and peak power index) were not significantly different from the control group. This may reflect the methodology or the fact that the abnormalities of systolic function are more subtle and are not affecting pump function to any great degree but have a profound influence on early diastolic filling.

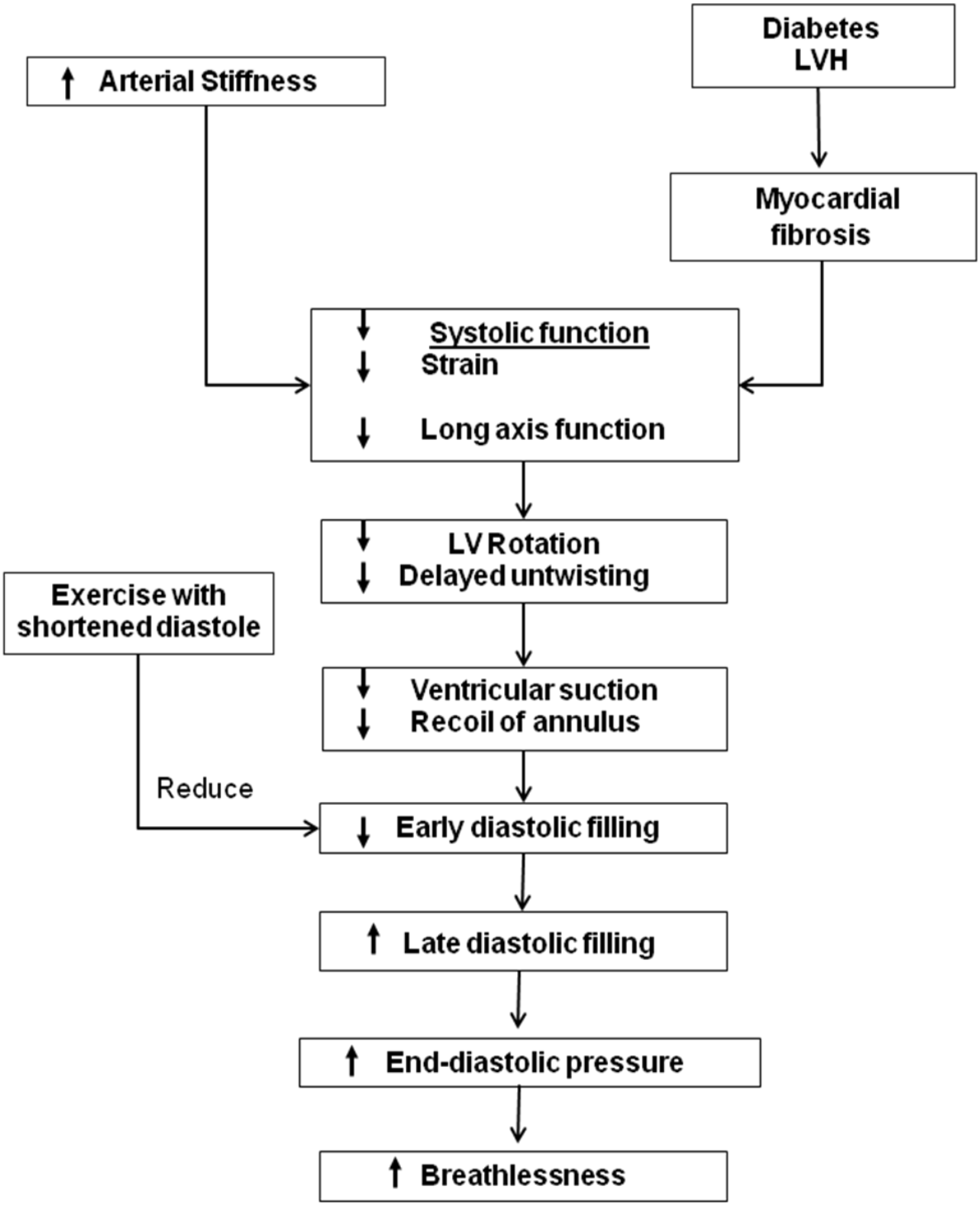
5.7 LIMITATIONS

This study has potential limitations. Firstly, all patients were taking medications as it was considered unethical to stop treatment entirely and it was important that blood pressure did not rise excessively on exercise compared to controls as this would have made interpretation of the results difficult. However, it is difficult to know exactly what effect the drug therapy has on twist and longitudinal function. Diuretics reduce symptoms and there is a suggestion that angiotensin converting enzyme inhibitors or angiotensin-1 antagonists may improve longitudinal function (135). Despite being on medications, all patients remained symptomatic on exercise. Secondly, exercise was sub-maximal, but all the patients were breathless at this level, therefore allowing correlation between symptoms and echocardiographic findings. Also, in a more elderly population, sub-maximal exercise is more relevant and comparable to daily activities than exercising to exhaustion which is probably done very rarely in life. Thirdly, the diagnostic criteria for HFNEF patients on treatment are not available and the NT pro-BNP results were very variable but these were taken on treatment. Nevertheless, cardiopulmonary exercise testing was used to confirm that the symptoms of breathlessness in all patients were cardiac in origin.

5.8 CONCLUSION

This study demonstrated that HFNEF patients have a combination of systolic and diastolic abnormalities of the left ventricular function which are more obvious on exercise than at rest. These include reduced myocardial systolic strain, rotation, left ventricular suction, longitudinal function and delayed untwisting (Figure 5.5). This is not a condition of isolated diastolic dysfunction or a problem of ventricular stiffness alone. A variety of aetiologies commonly seen in HFNEF including ageing, hypertension, left ventricular hypertrophy, fibrosis and diabetes could all induce changes in the myocardial tissue which affect the architecture of the heart and its global function. Treatments which only reverse myocardial tissue changes without restoring the architectural function of the heart are unlikely to improve symptoms.

Figure 5.5 Schema illustrating the pathophysiology of HFNEF



LVH, left ventricular hypertrophy; LV left ventricular.

CHAPTER 6:

LEFT ATRIAL DYSFUNCTION

ON EXERCISE

Contributory publications:

Tan YT, Wenzelburger F, Lee E, Nightingale P, Heatlie G, Leyva F, Sanderson JE. Reduced left atrial function on exercise in patients with heart failure and normal ejection fraction. Heart 2010;96(13):1017-23.

Tan YT, Sanderson JE. Forgotten atrial: driver of symptoms in heart failure with nomal ejection fraction? Heart 2012;98(17):1261-2.

6. LEFT ATRIAL DYSFUNCTION ON EXERCISE

6.1 SUMMARY

This study tested the hypothesis that failure of left atrial compensatory mechanism particularly on exercise, contributes to the genesis of symptoms in HFNEF patients.

Fifty HFNEF patients, 15 asymptomatic hypertensive subjects and 30 healthy controls underwent rest and sub-maximal exercise echocardiography to assess systolic (Sm), early diastolic (Em) and late diastolic (Am) mitral annular velocities. Left atrial functional reserve index (LAFRI) was used as an index of left atrial function.

Left atrial volume index was significantly higher in HFNEF patients. Am at rest was comparable between all three groups but exercise Am was significantly lower in HFNEF patients compared to both hypertensive subjects and healthy controls resulting in a lower LAFRI. There was a significant correlation between Am on exercise with peak VO_2 and E/e' on exercise. The area under the receiver operator curve for Am on exercise to differentiate HFNEF patients from controls was 0.768 (95% CI = 0.660-0.877).

These results demonstrate that HFNEF patients have reduced left atrial function on exercise in addition to left ventricular systolic and diastolic dysfunction shown in

Chapter 5. Reduced left atrial function probably contributes significantly to exercise intolerance and breathlessness in HFNEF patients.

6.2 INTRODUCTION

There are a variety of abnormalities of systolic and diastolic function in patients with HFNEF, all of which failed to increase normally on exercise as shown in Chapter 5 (136). These abnormalities of systolic function were associated with subsequent reduced early diastolic filling. Given that the left atrium is in direct communication with the left ventricle when the mitral valve opens in early diastole, any increase in the left ventricular filing pressure would lead to raised left atrial pressure. There is a greater dependence on late diastolic filling contributed by left atrial contraction to compensate for reduced early diastolic filling. Also, the degree to which the left atrial pressure rises on exercise will depend critically on the left atrial function. An enlarged left atrium is associated with adverse outcome (66;72) and with worse left ventricular diastolic dysfunction (67). However, there is little information on left atrial function in HFNEF. In other conditions such as HFREF, cardiomyopathy, coronary artery disease and normal ageing in which systolic function and early diastolic filling are impaired, left atrial function contributes significantly to stroke volume (137-139).

Hypertension is one of the commonest aetiology of HFNEF and therefore asymptomatic, but treated, hypertensive subjects make an appropriate control population and provide a better understanding of the pathophysiology of symptoms in HFNEF patients compared to hypertension alone.

This study was to test the hypothesis that patients with HFNEF have reduced left atrial functional reserve on exercise, in addition to the combined systolic and diastolic impairments found in Chapter 5. Left atrial function both at rest and on exercise was studied in a group of asymptomatic hypertensive subjects, in addition to patients with HFNEF and healthy controls.

6.3 METHODS

Left ventricular and left atrial functions were assessed non-invasively at rest and on sub-maximal exercise in the three groups of subjects. Patients with clinical diagnosis of HFNEF, asymptomatic hypertensive subjects and healthy controls were recruited as outlined in Chapter 4. All subjects underwent pulmonary function test and cardiopulmonary exercise test to determine their peak oxygen consumption and to rule out pulmonary causes of their breathlessness prior to the rest and exercise echocardiography studies.

All study subjects underwent cardiopulmonary exercise testing achieving a RER >1, and full echocardiography at rest and on semi-recumbent exercise on a tilting bicycle ergometer as described in Chapter 4.

Two-dimensional echocardiography, tissue Doppler and speckle tracking imaging and analyses were performed as described in Chapter 4.

Left atrial function was assessed by using the left atrial functional reserve index, which was calculated as: $\Delta Am \times [1-(1/Am_{rest})]$ equivalent to the method applied in the study by Ha et al. (125).

6.4 STATISTICS

Statistical analyses were performed as described in Chapter 4.

One way analysis of variance (ANOVA) was used for normally distributed data to compare all three groups of study subjects, followed by Tukey post hoc analysis to determine significant pairwise differences. Interclass comparisons of the changes of parameters from rest to exercise were made using a general linear model for repeated measurements at two levels. Non-normally distributed data was analysed using the Mann-Whitney U Test.

Pearson's correlation coefficient was used to examine associations between variables. Linear regressions were performed using peak VO_2 and E/e' as dependent variables against Am on exercise.

In addition, receiver operator curves were plotted to examine the ability of Am at rest and on exercise to differentiate HFNEF patients and healthy controls.

Inter-observer and intra-observer agreements were performed as described in section 4.6, similar to those applied in Chapter 5.

6.5 RESULTS

A total of 148 subjects were recruited in this study (90 symptomatic patients and 58 asymptomatic subjects). Forty patients were excluded (7 had evidence of respiratory restriction, 5 had atrial fibrillation, 1 had significant coronary artery disease, 1 had normal peak oxygen consumption on cardiopulmonary exercise testing, 2 failed to increase their heart rate on exercise, 24 did not have adequate exercise images for analysis either due to fusion of E and A or poorly defined Am on exercise). Thirteen asymptomatic subjects were excluded (one was tachycardic at rest due to anxiety, 12 did not have adequate exercise images for analysis). The remaining 50 symptomatic patients fulfilled the recent American Society of Echocardiography recommendations for diastolic dysfunction (38 grade I diastolic dysfunction and 12 grade II diastolic dysfunction) (32) and were classified as HFNEF patients. The remaining 45 asymptomatic subjects were further divided into asymptomatic hypertensive subjects (n=15) and healthy controls (n=30). The mean age of all study subjects was comparable between the three groups (Table 6.1). HFNEF patients were all symptomatic and were classified according to New York Heart Association classification class II and III, and had a significantly higher BMI compared to hypertensive subjects and controls. The peak VO_2 and the achieved percentage of predicted oxygen consumption were significantly lower in HFNEF patients but were comparable between hypertensive patients and healthy controls. The past medical history and drug history of all subjects are summarised in Table 6.1. All HFNEF patients had a history of hypertension and the duration of diagnosis of hypertension is significantly longer than that of the hypertensive subjects.

Table 6.1 Clinical characteristics – left atrial study

	HFNEF patients	Hypertensive subjects	Controls	p-value
Number of subjects	50	15	30	
Age (years)	72±8	70±7	71±6	0.541 *
Gender	35♀ / 15♂	9♀ / 6♂	22♀ / 8♂	0.655 †
BMI (kg/m^2)	31±5 ¶ #	25±4	24±4	<0.001 *
NYHA	class II =37 class III=13	n/a	n/a	
Peak VO_2 (ml/min/kg) (percent of predicted)	18.2±4.4 ¶ # (83±17%)	28.4±9.4 (118±28%)	29.6±.5.0 (128±21 %)	<0.001 * <0.001 *
Submaximal work load (watts)	27±8	32±12	31±10	0.197 *
Years of hypertension	8.7±6.9 ¶ #	3.7±2.4	0	<0.001 ‡
Diabetes mellitus	15 (30%)	0 (0%)	0 (0%)	0.014 §
Coronary artery disease	9 (18%)	0 (0%)	0 (0%)	0.103 §
ACE-Inhibitor	18 (36%)	4 (27%)	0 (0%)	0.757 §
AR1-Blocker	14 (28%)	0 (0%)	0 (0%)	0.028 §
β-Blocker	19 (38%)	4 (27%)	0 (0%)	0.544 §
Ca-Channel-Blocker	17 (34%)	2 (13%)	0 (0%)	0.196 §
Diuretic	26 (52%)	6 (40%)	0 (0%)	0.558 §
α-Blocker	15 (30%)	0 (0%)	0 (0%)	0.014 §
Statin	22 (44%)	5 (33%)	0 (0%)	0.558 §

Data is presented as number (and %) or mean ± standard deviation.

* One Way Anova for normally distributed data.
Tukey post hoc analysis: # $p < 0.05$ compared to hypertensive group
¶ $p < 0.05$ compared to healthy controls
† Fisher's exact test for nominal data comparing all three groups.
§ Fisher's exact test for nominal data comparing patients to hypertensive group
‡ Mann-Whitney U Test comparing patients to hypertensive group.

Annotations as per Table 5.1.

6.5.1 2D ECHOCARDIOGRAPHY

The left ventricular ejection fraction, fractional shortening, end-systolic and end-diastolic dimensions, and the left ventricular end-systolic and end-diastolic volume indexes were all comparable between the three groups (Table 6.2). The left ventricular mass index (LVMI) was not significantly different between all three groups. The diastolic interventricular septum of HFNEF patients was significantly thicker than healthy controls whereas the posterior wall was significantly thicker than both hypertensive subjects and healthy controls (Table 6.2). These findings are consistent with the longer duration of hypertension in HFNEF patients. The heart rate and blood pressure at rest and on exercise were comparable between all three groups (Table 6.3).

Table 6.2 Standard echocardiographic parameters – left atrial study

	HFNEF patients	Hypertensive subjects	Controls	p-value
IVSd (mm)	10.9±3.1 ¶	9.7±2.3	9.3±1.7	0.040 *
PWd (mm)	10.9±2.4 ¶ #	8.6±1.2	9.2±1.4	<0.001 *
LVEDD (mm)	46.1±5.6	47.7±3.9	45.3±5.1	0.392 *
LVESD (mm)	28.3±5.2	30.0±4.0	28.7±4.5	0.463 *
FS (%)	39±7	38±6	37±7	0.505 *
LVMI (g/m^2)	93.1±36.3	82.9±22.1	76.0±18.3	0.100 *
LVEDVI (ml/m^2)	40.4±9.4	41.4±9.4	39.1±9.2	0.108 *
LVESVI (ml/m^2)	15.5±4.8	15.7±5.2	15.3±5.4	0.784 *
LVEF (Simpson) (%)	62±6	62±9	62±7	0.989 *
LA (cm)	3.8±0.6 ¶	3.5±0.5	3.2±0.5	<0.001 *
LAVI (ml/m^2)	30.4±9.2 ¶	27.9±6.3	23.2±7.1	0.002 *

Data is presented as mean ± standard deviation.

* One Way Anova for normally distributed data.

Tukey post hoc analysis: # $p < 0.05$ compared to hypertensive group

¶ $p < 0.05$ compared to healthy controls

IVSd, diastolic interventricular septal thickness; PWd, diastolic posterior wall thickness; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; FS, fractional shortening; LVMI, left ventricular mass index; LVEDVI, left ventricular end-diastolic volume index; LVESVI, left ventricular end-systolic volume index, LVEF, left ventricular ejection fraction; LA, left atrial; LAVI, left atrial volume index.

Table 6.3 Haemodynamic and Doppler parameters – left atrial study

	HFNEF patients	Hypertensive subjects	Controls	p-value one-way Anova
HR rest (bpm)	72±13	65±8	70±9	0.384
HR ex (bpm)	91±11	90±11	93±5	0.117
Δ HR (bpm)	21±7	24±7	23±8	0.138
BP Rest (mmHg)	142±16/ 77±11	141±20 / 77±7	137±15 / 79±8	0.466 0.526
BP Ex (mmHg)	167±19 / 87±12	165±20 / 89±8	160±12 / 85±8	0.181 0.556
E Rest (m/s)	0.69±0.17 *	0.64±0.13	0.58±0.11	0.006
E ex (m/s)	0.95±0.17	1.05±0.16	0.94±0.12	0.101
E/A rest	0.83±0.21	0.94±0.33	0.85±0.18	0.286
E/A ex	0.96±0.21 #	1.15±0.29	1.08±0.26	0.020
DT (ms)	241±53 #	268±56 *	252±45	0.184
IVRT (ms)	97±23	97±24	103±19	0.449
Sm rest (cm/s)	5.3±1.2	5.8±1.8	5.8±1.2	0.244
Sm ex (cm/s)	6.3±1.6 *	7.4±1.8	7.7±1.5	<0.001
Δ Sm (cm/s)	1.0±1.2 *	1.8±1.4	2.0±1.3	0.003
Em rest (cm/s)	4.3±1.3 # *	6.0±1.9	5.4±1.1	<0.001
Em ex(cm/s)	6.6±1.5 # *	7.9±1.4 *	8.6±1.5	<0.001
Δ Em (cm/s)	2.2±1.3 *	1.5±2.3 *	3.3±1.6	0.003

Data is presented as mean ± standard deviation.

Tukey post hoc analysis: * p<0.05 compared to healthy controls
# p<0.05 compared to hypertensive group

ex, exercise; HR, heart rate; BP, blood pressure; E, early diastolic mitral inflow velocity; A, late diastolic mitral inflow velocity; E/A, ratio of E to A; DT, deceleration time; IVRT, isovolumic relaxation time; Sm, peak systolic myocardial mitral annular velocity; Em, peak early diastolic myocardial mitral annular velocity; Δ, (delta) change in.

6.5.2 LEFT VENTRICULAR SYSTOLIC AND DIASTOLIC FUNCTIONS

Peak E at rest was significantly higher in HFNEF patients but became comparable between all three groups on exercise. There was no significant difference in the isovolumic relaxation time (IVRT) between the three groups. The deceleration time (DT) was significantly longer in the hypertensive group compared to healthy controls (Table 6.3). Sm at rest was comparable between all subjects but was significantly lower in HFNEF patients compared to healthy controls on exercise similar to the finding in Chapter 5, but not significantly lower compared to the hypertensive group. However, Em at rest and on exercise was significantly lower in HFNEF patients compared to both hypertensive subjects and healthy controls. While there was no significant difference in Sm on exercise between hypertensive subjects and healthy controls, Em on exercise was significantly lower in hypertensive subjects compared to healthy controls (Table 6.3).

E/e' of HFNEF patients at rest was significantly higher than that of hypertensive subjects and healthy controls. Despite an increase in E/e' on exercise in hypertensive subjects approximating the same level of increase in E/e' in HFNEF patients on exercise, they remained asymptomatic at the time of exercise, indicating that hypertensive subjects had an increase in left atrial pressure on exercise to a similar level of HFNEF patients but remained asymptomatic (Table 6.4).

Table 6.4 Results of left atrial function and pressure

	HFNEF patients	Hypertensive subjects	Controls	p-value one-way Anova
A rest (m/s)	0.86±0.18 # *	0.73±0.17	0.69±0.12	<0.001
A ex (m/s)	1.01±0.18 *	0.95±0.22	0.91±0.17	0.049
Δ A (m/s)	0.16±0.13	0.22±0.16	0.22±0.13	0.132
E/e' rest	11.9±4.5 # *	8.1±1.5	8.4±1.8	<0.001
E/e' ex	10.9±3.3 *	10.1±2.6	8.3±1.6	0.035
Am rest (cm/s)	7.2±1.5	6.7±2.3	7.9±1.6	0.057
Am ex (cm/s)	8.2±1.7 # *	9.6±2.6	10.0±2.2	0.001
Δ Am (cm/s)	1.0±1.6 # *	2.9±1.5	2.1±1.6	<0.001
LAFRI	0.84±1.34 # *	2.39±1.27	1.81±1.39	<0.001

Data is presented as mean ± standard deviation.

Tukey post hoc analysis: * p<0.05 compared to healthy controls;

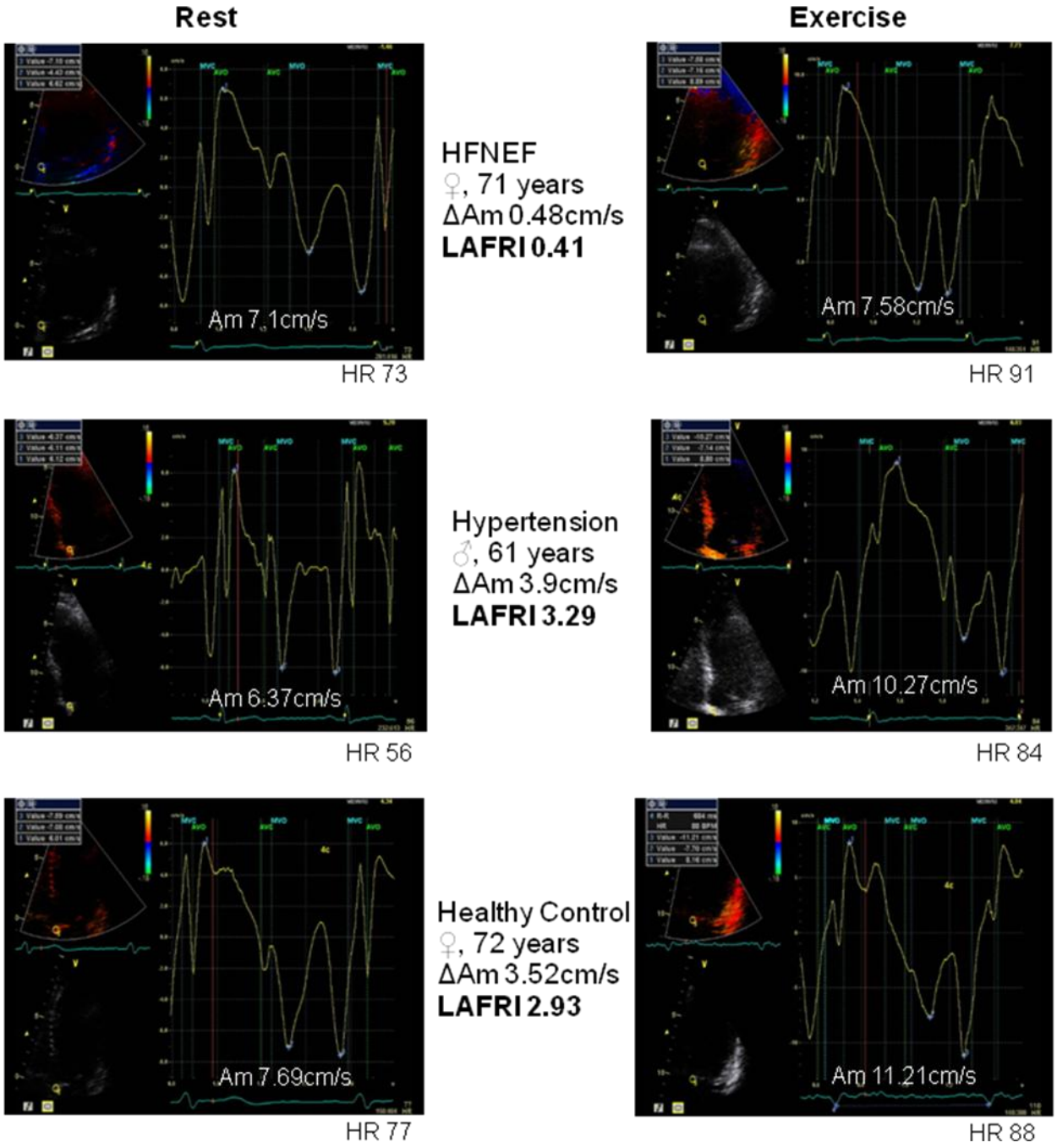
# p<0.05 compared to hypertensive group

ex, exercise; A, late diastolic mitral inflow velocity; E, early diastolic mitral inflow velocity; e', peak early diastolic myocardial mitral annular velocity; E/e', ratio of E to e'; Am, atrial systolic myocardial velocity; LAFRI, left atrial functional reserve index; Δ, (delta) change in.

6.5.3 LEFT ATRIAL FUNCTION

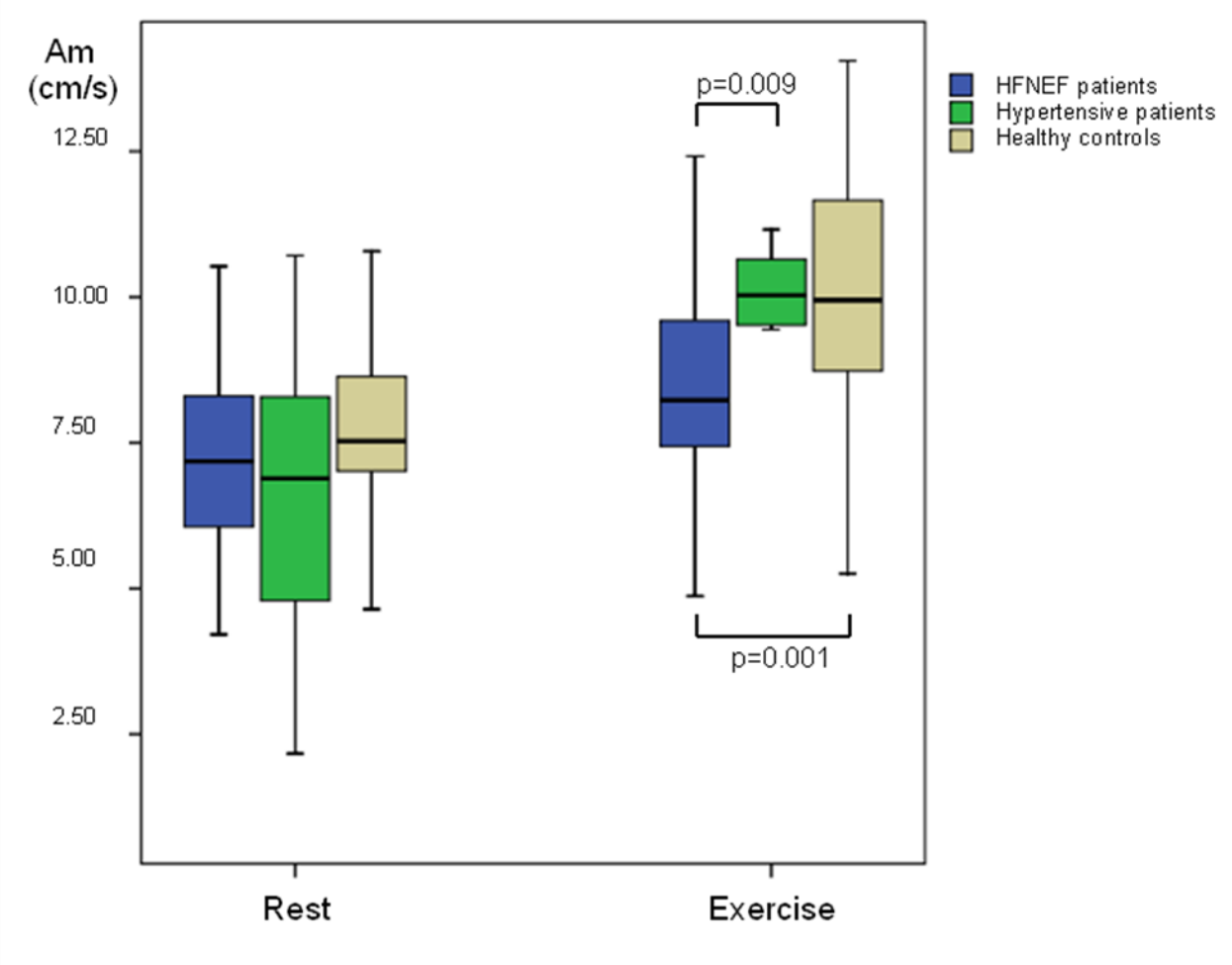
HFNEF patients had significantly larger left atrial dimensions than healthy controls but not significantly different compared to hypertensive subjects (Table 6.2). Left atrial volume index was also comparable between HFNEF patients and hypertensive subjects, but was significantly higher than healthy controls. Peak A at rest was significantly higher in HFNEF patients compared to both hypertensive subjects and healthy controls, but was only significantly higher compared to healthy controls on exercise as the peak A of hypertensive subjects approximated to that of HFNEF patients on exercise (Table 6.4). Colour tissue Doppler imaging was used to measure the late diastolic mitral annular velocity, Am, which is also equivalent to the atrial systolic myocardial velocity. There was no significant difference in Am at rest between the three groups. However, Am on exercise was lowest in HFNEF patients and was significantly lower compared to the other two groups. HFNEF patients failed to increase Am on exercise and as a result they had the lowest left atrial functional reserve index compared to all other subjects. Am at rest was lowest in hypertensive subjects, although not statistically significant, but the increase in Am on exercise was greatest in this group of subjects resulting in a similar magnitude of increase seen in the healthy controls. Hence, the hypertensive subjects had the highest left atrial functional reserve index indicating a more efficient atrial compensatory mechanism on exercise in this group of subjects (Table 6.4, Figures 6.1 and 6.2). Overall, this result suggests that the hypertensive subjects were able to compensate for their reduced Em (early diastolic function) and an increased in E/e' on exercise by increasing their Am which was not achieved by HFNEF patients.

Figure 6.1 Left atrial function by colour tissue Doppler imaging at rest and on exercise



Am, atrial systolic myocardial velocity ; LAFRI, left atrial functional reserve index; HR, heart rate; Δ, (delta) change in.

Figure 6.2 Boxplot illustrating atrial systolic myocardial velocity at rest and on exercise

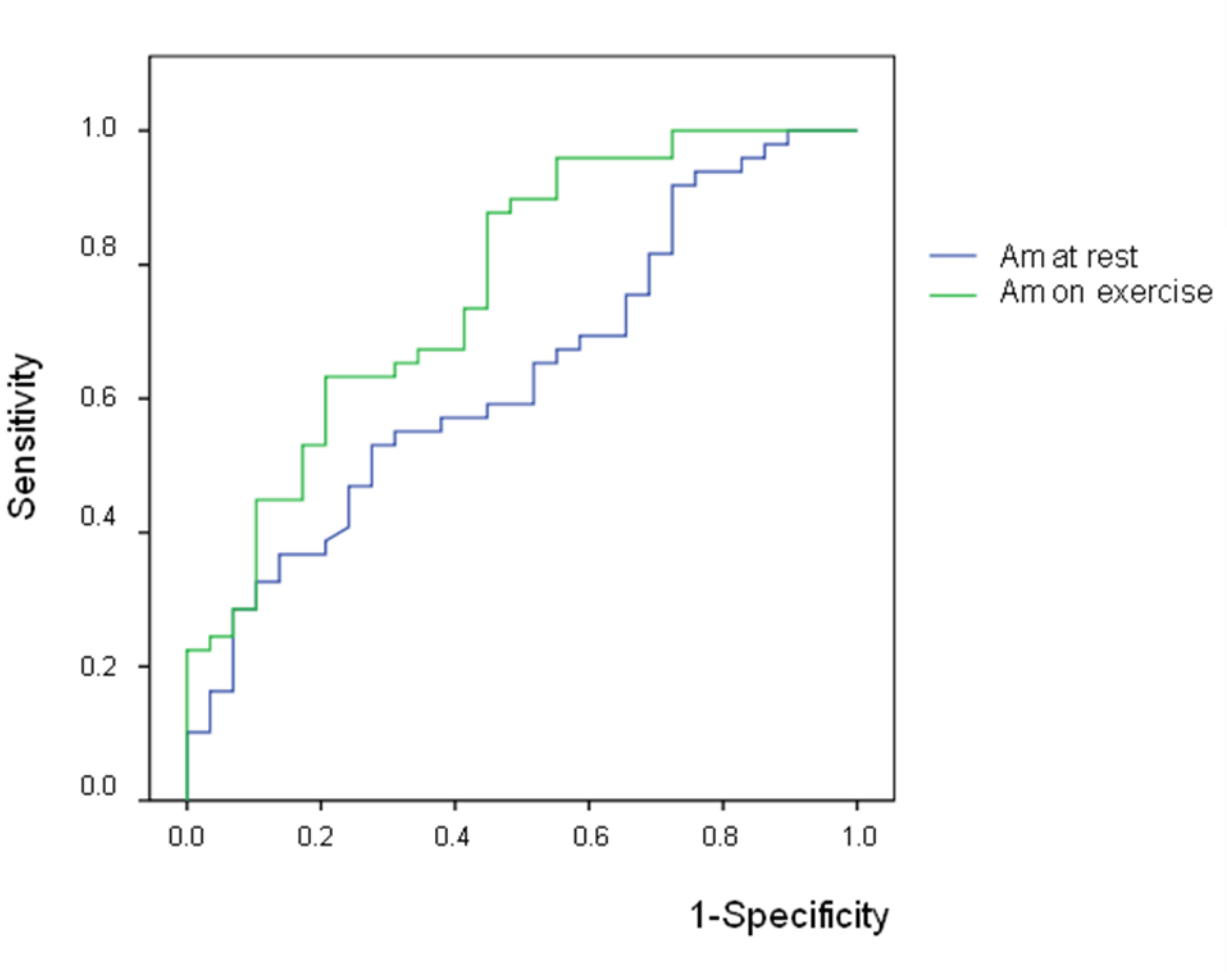


Boxplot shows minimum, first quartile, median, third quartile and maximum.

Am, atrial systolic myocardial velocity; p, probability.

The receiver operator curve (ROC) showed that Am on exercise was better at differentiating patients from controls (area under ROC 0.77, 95% CI = 0.66-0.88). The area under the ROC for Am at rest was 0.64 (95% CI = 0.51-0.76) (Figure 6.3).

Figure 6.3 Receiver operator curve of atrial systolic myocardial velocity at rest and on exercise

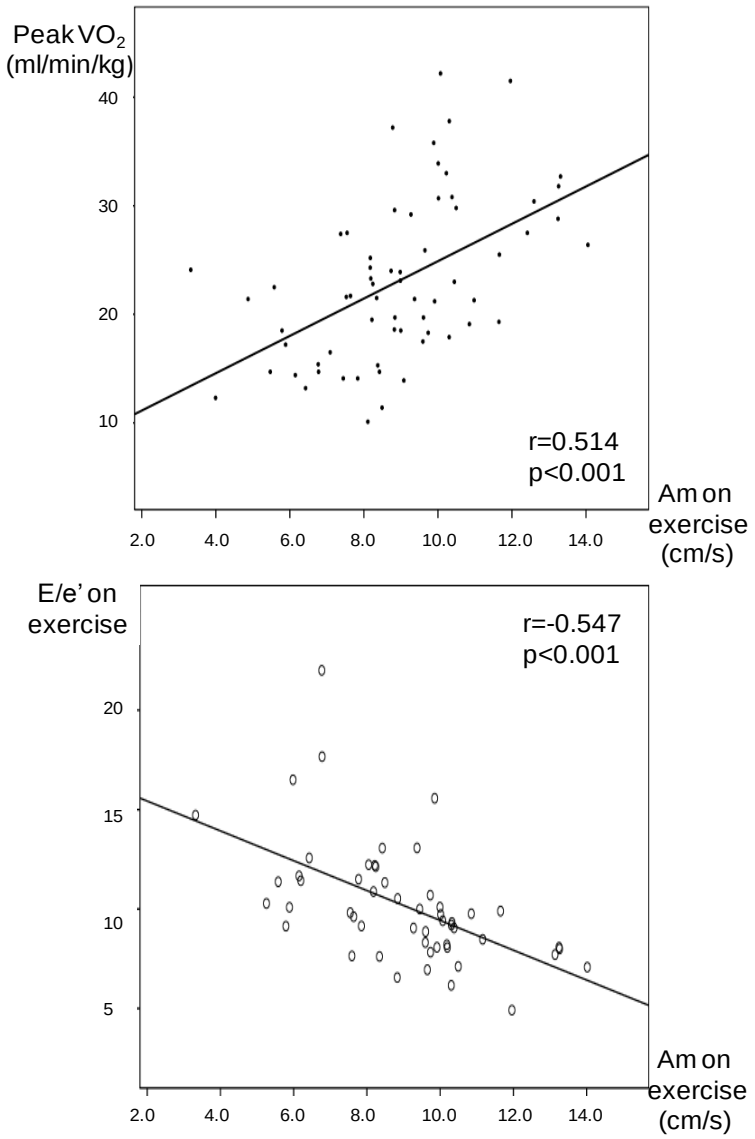


Am, atrial systolic myocardial velocity.

6.5.4 CORRELATIONS

Although Am at rest has a significant correlation with peak VO_2, ($r=0.425$, $p<0.01$) and E/e' ($r= -0.315$, $p<0.01$), Am on exercise had a stronger correlation with both peak VO_2 ($r=0.514$, $p<0.001$) and E/e' ($r= -0.547$, $p<0.001$) (Figure 6.4). There was only a weak correlation between left atrial functional reserve index and peak VO_2 ($r=0.257$, $p=0.039$). This indicates that a significantly reduced left atrial functional reserve is not the predominant cause of patients' limited exercise capacity, but it is the ultimate magnitude of Am achieved on exercise which is more important.

Figure 6.4 Correlations of peak oxygen consumption and E/e' with atrial systolic myocardial velocity on exercise



Am, atrial systolic myocardial velocity; E, early diastolic mitral inflow velocity; e', early diastolic myocardial mitral annular velocity; E/e', ratio of E to e'; VO_2, oxygen consumption; r, correlation; p, probability.

6.5.5 INTER-OBSERVER AND INTRA-OBSERVER VARIABILITY

The inter-observer variability of tissue Doppler imaging parameters used for the assessment of systolic, early and late diastolic myocardial velocities at rest by interclass correlation coefficient (ICC) was between 0.91 and 0.96. On exercise the ICC was between 0.85 and 0.94. The intra-observer variability at rest varied from 0.91 and 0.98 and on exercise between 0.87 and 0.98. The breakdown of variability of individual parameters was reported in section 5.5.9.

6.6 DISCUSSION

This study demonstrated that left atrial function is impaired on exercise in patients with HFNEF and may therefore contribute to the genesis of the symptom of dyspnoea in this condition. In addition, the major difference between HFNEF patients and asymptomatic hypertensive patients was left atrial functional reserve on exercise. Since hypertension is a common precursor of HFNEF, one of the factors that may account for the development of symptoms is progressive left atrial failure. This study, therefore, suggests that impaired left atrial function may be another factor that leads to shortness of breath in addition to the abnormalities of left ventricular function demonstrated in Chapter 5 (136). These results support the findings of Melenovsky et al. who found evidence of reduced left atrial functional reserve on handgrip exercise in HFNEF patients in comparison to both hypertensive controls and normal subjects of a comparable age (71). An inability to increase atrial systolic function on exercise may have a significant negative impact on effective and rapid diastolic filling especially during the very short time available in diastole with higher heart rates on exercise.

The atrial systolic myocardial velocity at rest is also a significant predictor of cardiovascular risk. Wang et al. demonstrated that when the Am was >4 but <7 cm/s, the hazard ratio of cardiac death was increased compared with an Am >7 cm/s, and when the Am was <4 cm/s the hazard ratio was significantly increased compared with an Am >7 cm/s (47). The predictive power of Am alone was greater than the ratio of E/e' which has been claimed to be an index of left ventricular end-

diastolic pressure (47;50). Am has also been found to be predictive of exercise capacity in chronic heart failure in several previous studies (47;69;70).

In this study, the magnitude of Am achieved on exercise correlated better with exercise capacity as measured by peak VO_2, suggesting again that peak atrial performance on exercise is the more critical and relevant measurement. The initial rise in left atrial contribution to left ventricular filling in mild left ventricular dysfunction probably represents a compensatory response to the reduction of early left ventricular filling. As the left ventricular function worsens, the work load of the left atrium increases further , consequently causing left atrial morphological changes and remodelling, which leads to a subsequent impairment of left atrial function. This has been shown in an early study in dogs (140).

Left atrial volume index (LAVI) is used as one of the diagnostic parameters for diagnosing HFNEF. It is not surprising that LAVI was increased in the HFNEF patients. The hypertensive subjects in this study had a LAVI in between HFNEF patients and controls, similar to the results reported by Wakatsuki et al. (141). Left atrial volumes are viewed increasingly as a marker of chronic elevation of left atrial pressure and hence indirectly used as a marker of diastolic dysfunction. The fact that LAVI was higher in the HFNEF patients suggests that over time, left atrial pressure was higher than in the hypertensive subjects leading to more atrial remodelling as discussed in section 1.4.3. This would lead to reduced contractile function which would also be affected directly by the high incidence of co-morbidities

in HFNEF, such as diabetes (present in about 30%), sub-clinical coronary artery disease (approximately 40-50%), obesity (prevalence of body mass index >30 kg/m^2 approximately 40%) and renal failure (23).

Atrial fibrillation (AF) is common in HFNEF and the prevalence ranges from 20 to 40% in both epidemiological studies and randomised controlled clinical trials (23). Fung et al. reported that HFNEF patients with AF had a poorer quality of life, lower exercise capacity and, as expected, larger left atrial dimensions (65). In addition, patients with HFNEF and AF had more severe diastolic dysfunction when compared to those in sinus rhythm. It is likely that left atrial remodelling combined with progressive left atrial failure will lead to the onset of AF. Hypertension itself is also associated with a higher prevalence of AF and structural changes of the extracellular matrix, perhaps related to activation of the renal-angiotensin-aldosterone system (142).

6.7 LIMITATIONS

The number of asymptomatic hypertensive subjects was smaller than the other two groups but the exercise data illustrated a significant difference despite the similarity of the echocardiographic findings at rest.

The late diastolic myocardial velocity was used as an index of left atrial systolic function. The limitation of this measurement is that it only reflects left atrial mechanical function in the long axis. Newer techniques measuring strain by tissue Doppler imaging or speckle tracking may provide a better measurement of global left atrial function (143;144). However, it is technically challenging to obtain sufficiently good images of the left atrium, particularly on exercise for meaningful speckle tracking analysis. As mentioned in section 5.7, exercise was submaximal to maintain a maximum heart rate of 100 beats per minute to avoid fusion of E and A waves and to allow image acquisition while patients are breathless.

As similarly mentioned in section 5.7, all HFNEF patients and hypertensive subjects with regular prescriptions were studied on medications. The proportion of HFNEF patients and hypertensive subjects who were on angiotensin converting enzyme inhibitors, beta-blockers, calcium channel blockers and diuretics were comparable, although 28% of HFNEF patients were on angiotensin-1 receptor blocker compared to none of the hypertensive subjects, but this is unlikely to have affected the results as there is no evidence that angiotensin-1 receptor blocker therapy impairs left atrial function, in fact the contrary (135).

6.8 CONCLUSION

In summary, this study demonstrated that left atrial function is impaired on exercise with an impaired left atrial reserve in patients with HFNEF. Combined with the findings in Chapter 5 demonstrating reduced early diastolic filling, suction and delayed untwisting (136), these observations add further to the understanding of left ventricular and left atrial function at rest and on exercise in a typical cohort of HFNEF patients, illustrating the wider spectrum of abnormalities in this condition.

CHAPTER 7:

TORSIONAL DYSSYNCHRONY

ON EXERCISE

Contributory publication:

Tan YT, Wenzelburger F, Sanderson JE, Leyva F. Exercise-induced torsional dyssynchrony relates to impaired functional capacity in patients with heart failure and normal ejection fraction. Heart 2013;99(4):259-66

7. TORSIONAL DYSSYNCHRONY ON EXERCISE

7.1 SUMMARY

Left ventricular systole and diastole are intimately dependent on myocardial torsion, which involves coupling between myocardial rotation (twisting in systole and untwisting in diastole) and longitudinal motion. This study tested the hypothesis that HFNEF involves torsional dyssynchrony and that these disturbances are exaggerated by exercise.

Seventy two patients with HFNEF and 38 healthy controls underwent echocardiography study at rest and on supine exercise. Analysis of three plane motion was performed using a combination of speckle tracking and tissue Doppler imaging. Torsional dyssynchrony was quantified as the standard deviation of the time to peak systolic motions (SDSM) (basal and apical rotation, longitudinal and radial displacement); the time difference between peak twist and peak longitudinal displacement (twist-longitudinal motion delay, TLMD) and the ratio of untwist to longitudinal extension (UT:LE).

At rest, SDSM, TLMD and UT:LE were not significantly different between patients with HFNEF and controls. However, exercise was associated with significant systolic and diastolic dyssynchrony in the HFNEF patients. The SDSM correlated with left ventricular wall thickness ($r= 0.45$, $p<0.001$), peak VO_2 ($r=-0.27$, $p=0.030$) and changes in stroke volume on exercise ($r=-0.38$, $p=0.003$).

This study concluded that HFNEF involves exercise induced torsional dyssynchrony in systole and diastole, which relates to left ventricular hypertrophy as well as exercise capacity.

7.2 INTRODUCTION

In this chapter, the role of left ventricular dyssynchrony in HFNEF was studied at rest and on exercise. Left ventricular dyssynchrony is another factor that could impact upon left ventricular function and could contribute to the haemodynamic disturbances observed in HFNEF. Previously, studies have shown a high prevalence of dyssynchrony in HFNEF (78;79). As discussed in section 1.4.4, these studies assessed dyssynchrony in single myocardial planes, assessing time delays between different left ventricular segments using tissue Doppler imaging. Importantly however, myocardial motion occurs in various directions, namely longitudinal, radial, circumferential and oblique directions, reflecting the orientations of myocardial fibres throughout the left ventricular wall (80). The combined effect of such motion is torsion, or wringing and unwringing of the left ventricle in systole and diastole respectively.

The notion of torsional synchrony arises from the recognition that cardiac motion occurs in three dimensions involving the cohesive movement of all the myocardial fibres, particularly the longitudinal and the oblique fibers, to enable synchronous and energy-efficient left ventricular mechanics throughout the cardiac cycle especially during exercise when the duration of diastole shortens significantly with increase in heart rate. In addition, changes in left ventricular wall properties such as left ventricular hypertrophy and fibrosis may lead to temporal dispersion of wall motion contributing to torsional dyssynchrony which could affect both systole (left ventricular

ejection) and diastole (relaxation and suction). Thus, torsional dyssynchrony could account for the impairment of functional capacity observed in patients with HFNEF.

As an extension to the findings of exercise induced left ventricular and left atrial dysfunction in patients with HFNEF reported in Chapters 5 and 6 (136;145), this study explores whether torsional dyssynchrony in systole and / or diastole, at rest or during exercise, relates to cardiac output and functional capacity in patients with HFNEF. In addition, the effects of exercise on torsional dyssynchrony and relevant aetiological factors were also explored.

7.3 METHODS

The left ventricular systolic and diastolic function was assessed non-invasively at rest and on exercise in patients with the clinical diagnosis of HFNEF and in healthy controls. Patients and age-matched healthy controls were recruited as described in Chapter 4.

All study subjects underwent cardiopulmonary exercise testing and full echocardiography at rest and on semi-recumbent exercise on a tilting bicycle ergometer as described in Chapter 4.

Two-dimensional echocardiography, tissue Doppler and speckle tracking imaging and analyses were undertaken as described in Chapter 4.

In addition, the raw data from speckle tracking of apical and basal rotation and rotation rate, radial displacement and displacement velocity from the short axis mid ventricular level, and the longitudinal displacement and displacement rate derived from colour tissue Doppler of the septal and lateral mitral annulus, was transferred to a custom written Microsoft Excel algorithm for further analysis. All co-ordinates were interpolated and all time intervals were normalised to enable comparison of events of different durations within the cardiac cycle. The raw data was used to plot and construct the twist-displacement loops to illustrate the coordination of these two motions at rest and on exercise. This algorithm was applied from methods used by Borg et al. (146), and they provided the algorithm software.

7.3.1 TORSIONAL DYSSYNCHRONY IN SYSTOLE

Dyssynchrony in three planes namely longitudinal, radial and rotation, was calculated using the interpolated timing information. The standard deviation of the time to peak systolic motions (SDSM), timed from R-wave to the peak of the individual motions (basal rotation, apical rotation, longitudinal displacement and radial displacement), was taken as a measure of systolic torsional dyssynchrony. The maximum time difference between the duration to reach peak twist and peak longitudinal displacement was calculated and expressed as twist-longitudinal motion delay (TLMD). All measurements were undertaken at rest and on exercise.

7.3.2 TORSIONAL DYSSYNCHRONY IN DIASTOLE

In diastole, there is no obvious peak motion due to the split in an early (E) and a late (A) component of the motion. Therefore, the ratio of the percentage change in untwist to longitudinal extension (UT:LE) over a set time duration (isovolumic relaxation time, IVRT) was taken as a measure of torsional dyssynchrony in diastole. Accordingly, UT:LE was calculated as follows:

$$\frac{\Delta \text{ Untwist } \%}{\Delta \text{ Longitudinal extension } \%}$$

This ratio is consistent with the early slope of the diastolic limb (red arrow) of the twist-displacement loops in Figures 7.4 and 7.5 illustrated in the results section later in this chapter.

7.4 STATISTICS

Statistical analyses were performed as described in Chapter 4.

Comparisons between HFNEF patients and controls were performed using unpaired t-test for normally distributed data and the Mann-Whitney U-test for non-normally distributed data. Comparisons within HFNEF patients and controls were performed using paired t-test for normally distributed data and the Wilcoxon test was used for non-normally distributed data. Logarithmic transformation was used when variables were not normally distributed. Linear regression was performed to test correlations.

Inter-observer and intra-observer agreements for measurements that were applied for torsional dyssynchrony (rotational by speckle tracking, radial strain by speckle tracking, longitudinal displacement by colour TDI) were performed as described in section 4.5.

7.5 RESULTS

A total of 148 subjects were recruited in this study (90 patients and 58 asymptomatic healthy subjects). Eighteen patients were excluded (seven had evidence of respiratory restriction, one had significant coronary artery disease, two were unable to exercise, one had normal peak VO_2, two failed to increase their heart rate on exercise and five did not have adequate images for analysis). Twenty asymptomatic subjects were excluded (16 had elevated blood pressure not previously diagnosed), one was tachycardic at rest due to anxiety, three did not have adequate images for analysis). The remaining 72 symptomatic patients fulfilled the criteria of Vasan and Levy for probable diastolic heart failure (33). Thirty eight remaining asymptomatic subjects had no past medical history and were not on any medications.

The mean age of the patients was 73 ± 7 years and 67% were female. Control subjects were of comparable age (71 ± 7 years) and 76% were female. The past medical history and drug history of patients are summarised in Table 7.1. All patients had symptoms of heart failure with New York Heart Association (NYHA) class II or III despite being on medications. Patients had a significantly higher BMI compared to controls but the peak VO_2 which was indexed to BMI was significantly lower in patients compared to controls (Table 7.1).

Table 7.1 Clinical characteristics – dyssynchrony study

	HFNEF patients	Controls	p-value
Number of subjects	72	38	
Age (years)	73±7	71±7	0.219
Gender	48♀ / 24♂	29♀ / 9♂	0.383 *
BMI (kg/m^2)	30±5	24±4	<0.001
NYHA	class II =51 class III=21	n/a	
Peak VO_2 (ml/min/kg) (percent of predicted)	18.4±4.9 (80±17%)	28.6±5.1 (123±21%)	<0.001
Years of hypertension	8.2±9.9	0	<0.001 ‡
Atrial fibrillation	5 (7%)	0	
Diabetes mellitus	17 (24%)	0	
ACE-Inhibitor	25 (35%)	0	
AR1-Blocker	21 (29%)	0	
β-Blocker	11 (15%)	0	
Calcium Channel-Blocker	19 (26%)	0	
Diuretic	36 (50%)	0	
α-Blocker	15 (21%)	0	
Statin	33 (46%)	0	

Data is presented as number (and %) or mean ± standard deviation.

p-value: unpaired t-test between patients and controls except * Fisher exact test between patients and controls and ‡ Mann-Whitney U test between patients and controls.

Annotations as per Table 5.1.

7.5.1 2D ECHOCARDIOGRAPHY

The left ventricular ejection fraction, fractional shortening, end-systolic and end-diastolic dimensions, E/A ratio, deceleration time (DT) and isovolumic relaxation time (IVRT) were all comparable between the two groups (Table 7.2). Patients had a significantly increased left ventricular wall thickness (posterior and interventricular septal walls), left ventricular mass index, left atrial volume index, mitral inflow E and A waves and E/e'.

Table 7.2 Standard echocardiographic parameters – dyssynchrony study

	Patients	Controls	p-value
IVSd(mm)	11.1±3.0	9.4±1.9	0.004
PWd (mm)	11.0±2.4	9.1±1.4	<0.001
LVEDD(mm)	46.7±6.9	45.7±4.9	0.459
LVEDDI (mm/m^2)	25.2±3.8	27.4±2.7	0.007
LVESD(mm)	33.1±3.7	28.7±4.2	0.497
FS (%)	39.7±9.2	36.8±7.4	0.118
LVMI (g/m^2)	94.2±32.4	78.9±21.4	0.022
LVEF (%)	60.4±6.6	62.6±6.9	0.132
LAVI (ml/m^2)	32.6±10.9	23.9±8.6	<0.001
E (m/s)	0.70±0.17	0.59±0.10	0.001
A (m/s)	0.84±0.19	0.71±0.14	<0.001
E/A	0.83±0.22	0.88±0.22	0.374
DT (ms)	239.1±55.4	242.3±43.4	0.758
IVRT (ms)	99.5±24.4	96.9±18.3	0.568
E/e’	11.5±4.4	8.1±1.2	<0.001

Data is presented as mean ± standard deviation.

p-value: unpaired t-test between patients and controls.

IVSd, diastolic interventricular septal thickness; PWd, posterior wall thickness; LVEDD, left ventricular end-diastolic diameter; LVEDDI, left ventricular end-diastolic diameter index; LVESD, left ventricular end-systolic diameter; FS, fractional shortening; LVMI, left ventricular mass index; LVEF, left ventricular ejection fraction; LAVI, left atrial volume index; E, early mitral diastolic inflow velocity; A, late mitral diastolic inflow velocity; E/A, ratio of early to late mitral inflow velocities; DT, deceleration time of peak early Doppler mitral filling velocity; IVRT, isovolumic relaxation time; E/e’, ratio of early mitral diastolic inflow velocity to early diastolic mitral annular velocity.

7.5.2 HAEMODYNAMIC CHANGES

Heart rate and blood pressure were comparable between the two groups at rest and were maintained at comparable levels on exercise (Table 7.3). Cardiac output was not significantly different at rest. Despite a significant increase in cardiac output on exercise in both groups, the cardiac output of patients was lower than controls on exercise. While there was increase in stroke volume index in the control group, there was no significant increase in HFNEF patients on exercise. There were no significant changes in left ventricular volumes in both groups.

Table 7.3 Haemodynamic measurements at rest and on exercise – dyssynchrony study

	Patients rest	Patients exercise	Patients p-value (paired t-test)	Controls rest	Controls exercise	Controls p-value (paired t-test)	Patients / controls p-value (unpaired t-test)
HR (bpm)	69±11	91±10	<0.001	69±10	93±8	<0.001	0.842 * 0.138 #
BP (mmHg)	145±16 / 77±11	167±17 / 87±12	<0.001 <0.001	136±15 / 78±7	162±15 / 86±8	<0.001 <0.001	0.008 * 0.139 # 0.362 * 0.717 #
LVEDVI (ml/m^2)	40.3±10.5	38.7±8.1	0.192	38.1±8.4	40.1±7.1	0.475	0.414 * 0.190 #
LVESVI (ml/m^2)	15.6±5.0	14.7±3.5	0.368	14.4±5.0	13.7±2.8	0.491	0.289 * 0.040 #
SV (ml)	72.9±23.0	76.7±24.2	0.216	63.5±14.6	82.5±23.9	0.001	0.033 * 0.314 #
ΔSV (ml)		4.4±24.0			18.8±25.7		0.019
SVI (ml/m^2)	39.1±9.9	43.8±13.8	0.101	37.2±8.4	48.8±13.0	0.001	0.361 * 0.045 #
ΔSVI (ml/m^2)		3.9±12.8			11.2±14.8		0.038
CO (l/min)	5.1±2.0	6.6±2.3	<0.001	4.4±1.2	7.8±2.5	<0.001	0.079 * 0.034 #

Data is presented as mean ± standard deviation.

p-value (paired t-test): paired t-test of patients (or controls) at rest and on exercise.

p-value (unpaired t-test): * unpaired t-test between patients and controls at rest

unpaired t-test between patients and controls on exercise.

HR, heart rate; BP, blood pressure; LVEDVI, left ventricular end-diastolic volume index; LVESVI, left ventricular end-systolic volume index; SV, stroke volume; SVI, stroke volume index; CO, cardiac output; Δ, (delta) change.

7.5.3 TISSUE DOPPLER IMAGING AND SPECKLE TRACKING

In HFNEF patients, left ventricular twist and torsion were significantly lower at rest compared to the controls, but this difference became even more significant on exercise. In fact, the magnitude of these measurements on exercise in patients remained lower than the resting results of control subjects (Table 7.4). These results are consistent with the findings of the stand alone apical rotation in Chapter 5. Longitudinal and radial displacement were comparable at rest, but became significantly different on exercise (Table 7.4).

Table 7.4 Tissue Doppler and speckle tracking results – dyssynchrony study

	Patients rest	Patients exercise	Patients p-value (paired t-test)	Controls rest	Controls exercise	Controls p-value (paired t-test)	Patients / controls p-value (unpaired t-test)
Twist (°)	18.0±5.7	19.5±5.9	0.066	21.0±4.9	25.9±6.0	<0.001	0.010 * <0.001 #
LV length (mm)	70.8±6.9	69.3±7.9	0.184	70.4±6.0	69.9±6.1	0.653	0.750 * 0.728 #
Torsion (º/cm)	2.6±0.8	2.9±0.9	0.035	3.0±0.7	3.7±1.0	<0.001	0.009 * <0.001 #
Long. disp. (mm)	-9.5±2.6	-11.0±2.7	0.001	-10.4±2.4	-12.7±3.1	0.001	0.073 * 0.011 #
Radial disp. (mm)	-6.9±1.5	-6.9±1.6	0.524	-6.7±0.8	-7.7±1.4	0.001	0.427 * 0.039 #

Data is presented as mean ± standard deviation.

p-value (paired t-test): paired t-test of patients (or controls) at rest and on exercise.

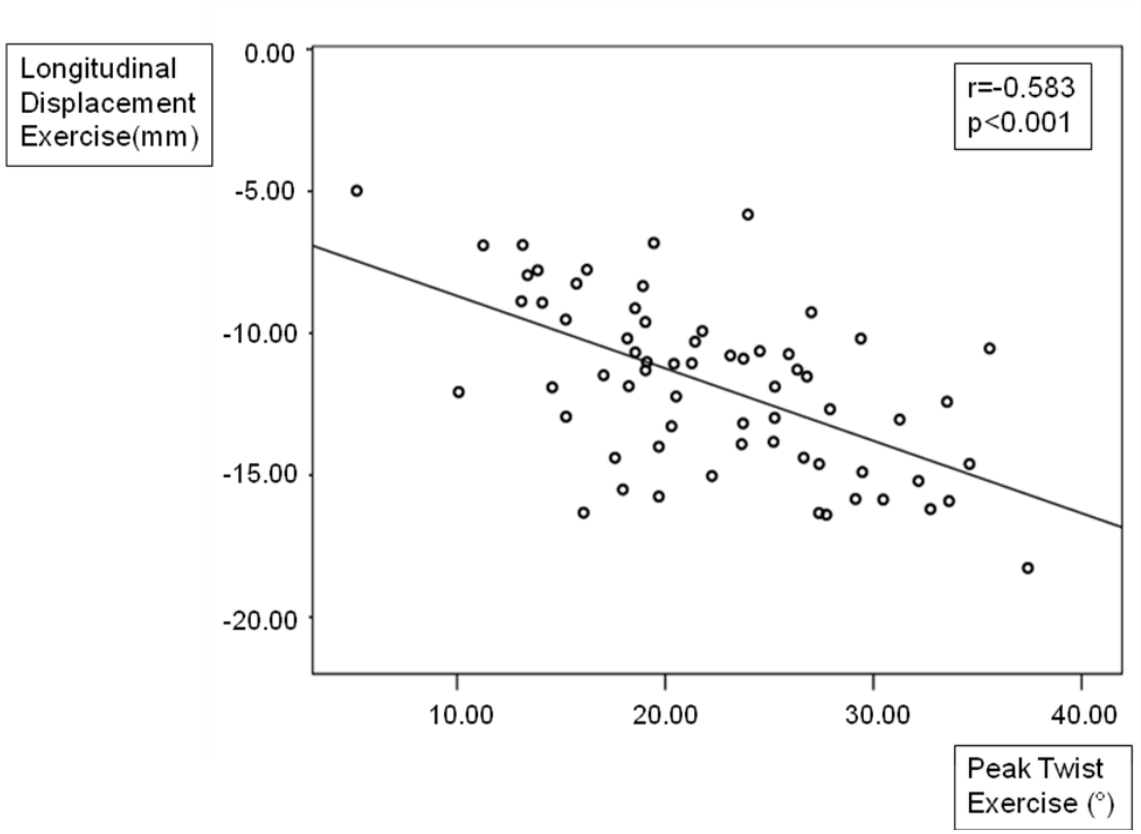
p-value (unpaired t-test): * unpaired t-test between patients and controls at rest

unpaired t-test between patients and controls on exercise.

LV, left ventricular; Long., longitudinal; disp., displacement.

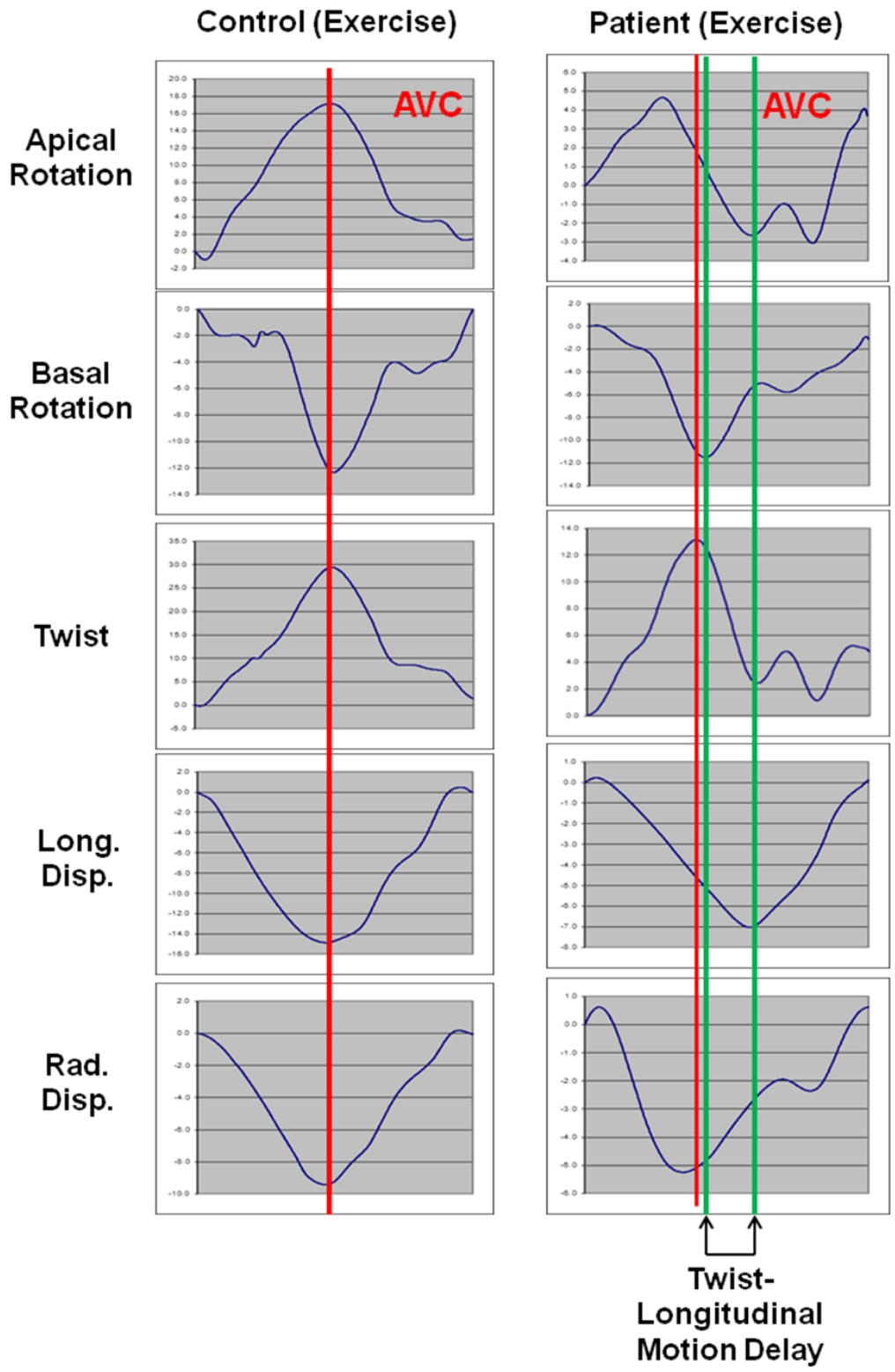
There was a good correlation between the magnitude of left ventricular twist and longitudinal displacement on exercise ($r=-0.583$, $p<0.001$) (Figure 7.1), confirming the important mechanical link between these two motions which contribute to the overall mitral annular motion. Any time delay between these two motions would contribute to the uncoupling of left ventricular mechanics. The overall mitral annular motion is dependent on the coherent motion of the longitudinal fibres and the oblique fibres, resulting in the coordinated longitudinal displacement and twist in systole, both reaching peak at about the same time. Due to their strong mechanical association, any disco-ordination between these two motions is expected to affect left ventricular systolic function particularly on exercise (Figure 7.2).

Figure 7.1 Correlation between longitudinal displacement and twist on exercise



r, correlation; p, probability.

Figure 7.2 Twist-longitudinal motion delay in HFNEF



AVC, aortic valve closure.

7.5.4 SYSTOLIC TORSIONAL DYSSYNCHRONY

At rest, the time to reach peak systolic motion (peak longitudinal displacement, radial displacement, basal and apical rotation), expressed as the standard deviation of systolic motion (SDSM), was comparable between HFNEF patients and controls (48.6 ± 32.9 ms versus 43.1 ± 25.3 ms, p=0.63). On exercise, controls were able to reduce SDSM significantly (p=0.002) whereas patients failed to show a significant decrease (p=0.505) (Table 7.5). The SDSM correlated inversely with peak oxygen consumption (r= -0.27, p=0.03) as well as with the increase in stroke volume on exercise (r=-0.38, p=0.003) (Figure 7.3). Importantly, the lower SDSM in control subjects on exercise was mainly due to a reduction in the time delay between twist and longitudinal contraction (twist-longitudinal motion delay, TLMD) (25.5 ± 54.3 ms at rest and 2.9 ± 31.2 ms on exercise in controls, p=0.025) as illustrated in Figure 7.2. However, this did not occur to the same extent in HFNEF patients (51.4 ± 68.0 ms at rest and 26.1±48.6 ms on exercise, p=0.229) (Table 7.5) (Figure 7.2). In addition, SDSM on exercise correlated strongly with interventricular septal wall thickness (IVSd) (r=0.36, p=0.005) and left ventricular posterior wall (PW) thickness (r=0.45, p<0.001).

In view of the inclusion of patients with atrial fibrillation as part of the ESC recommendation for diagnosing HFNEF (31), this study included five HFNEF patients with atrial fibrillation. Some might argue that the electrical and mechanical activations in patients with atrial fibrillation are different from those in sinus rhythm, despite comparable cycle length and heart rate. It is possible that these differences

could amplify dyssynchrony when the heart rate is increased on exercise. Sub-analysis performed excluding patients with atrial fibrillation did not change the outcome of the study but strengthened the statistical data (Table 7.5).

Table 7.5 Torsional dyssynchrony measurements at rest and on exercise

	Patients rest	Patients exercise	Patients p-value †	Controls rest	Controls exercise	Controls p-value†	Patients / controls p-value
SDSM (ms)	48.6±32.9	40.1±27.2	0.505	43.1±25.3	25.9±15.5	0.002	0.630 ‡ 0.025 §
TLMD (ms)	51.4±68.0	26.1±48.6	0.229	25.5±54.3	2.9±31.2	0.025	0.127 ‡ 0.016 §
UT:LE	25.3±51.4	9.6±14.7	0.135	7.1±10.7	3.3±3.8	0.095	0.279 ‡ 0.011 §
UT:LE (log)	1.77±1.63	1.54±1.13	0.506**	1.29±1.18	0.67±1.3	0.042**	0.152 * 0.006 #
SDSM nonAF (ms)	47.7±32.5	38.8±27.6	0.655	43.1±25.3	25.9±15.5	0.002	0.469 ‡ 0.022 §
TLMD nonAF (ms)	56.1±67.0	28.4±46.2	0.205	25.5±54.3	2.9±31.2	0.025	0.033 ‡ 0.005 §
UT:LE nonAF	23.1±54.9	10.4±15.3	0.055	7.1±10.7	3.3±3.8	0.095	0.064 ‡ 0.022 §

Data is mean ± standard deviation.

† Wilcoxon test of patients (or controls) at rest and on exercise.

‡ Mann-Whitney U test between patients and controls at rest.

§ Mann-Whitney U test between patients and controls on exercise.

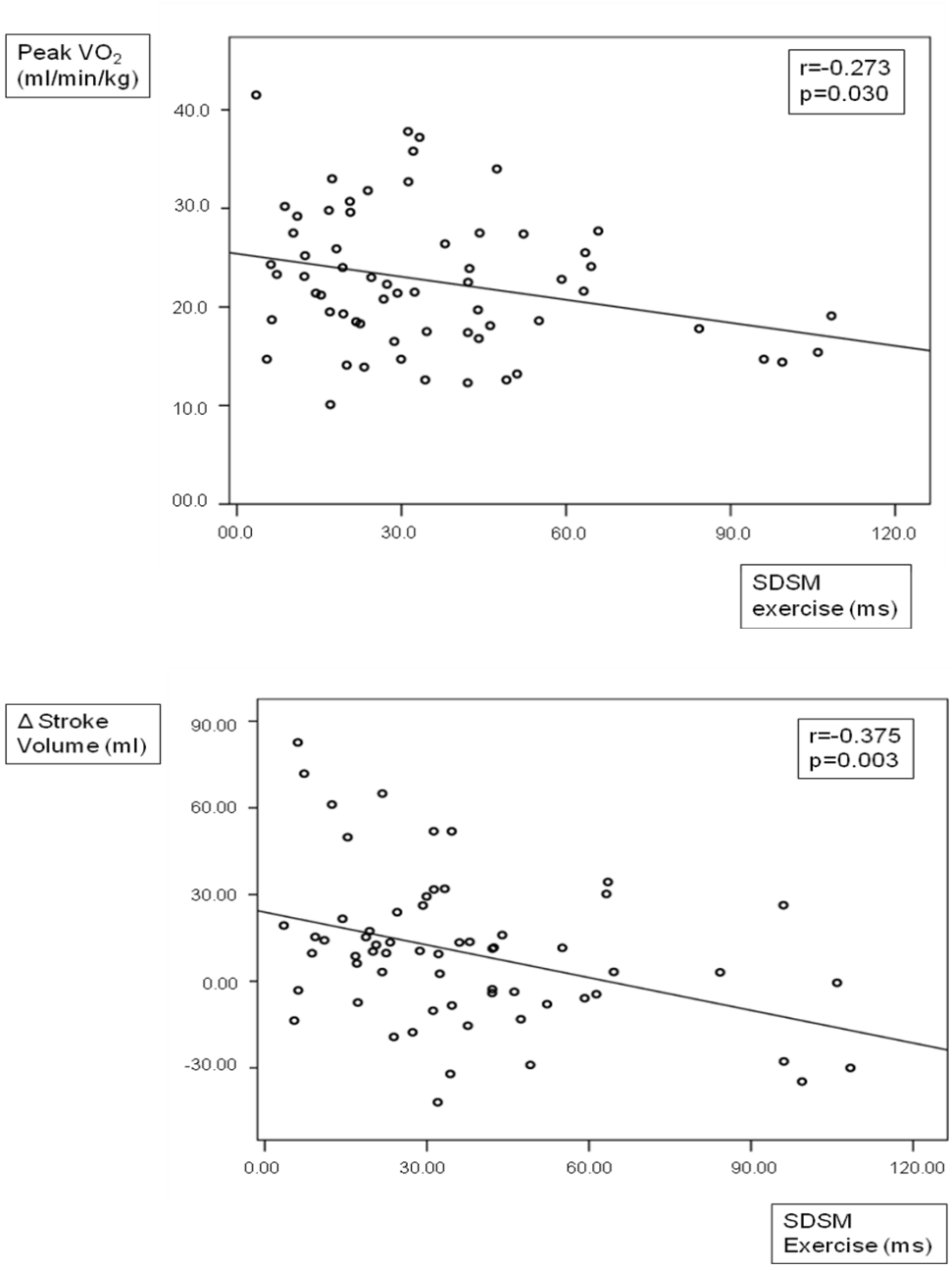
* unpaired t-test between patients and controls at rest.

unpaired t-test between patients and controls on exercise.

** paired t-test of patients (or controls) at rest and on exercise.

SDSM, standard deviation systolic motion; TLMD, twist-longitudinal motion delay; UT:LE, ratio of untwist to longitudinal extension; log; logarithm; nonAF, data excluding patients with atrial fibrillation.

Figure 7.3 Correlations between systolic torsional dyssynchrony and peak oxygen consumption and change in stroke volume



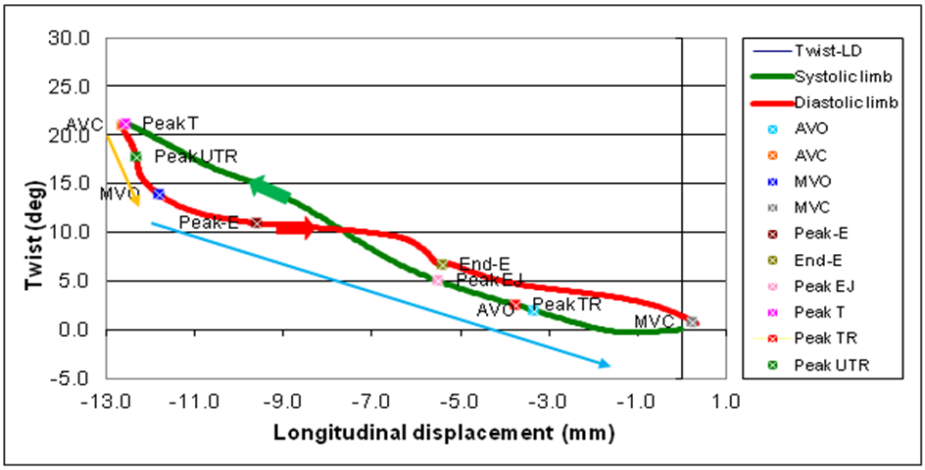
VO_2, oxygen consumption; SDSM, standard deviation systolic motion; r, correlation; p, probability; Δ, (delta) change in.

7.5.5 DIASTOLIC TORSIONAL DYSSYNCHRONY

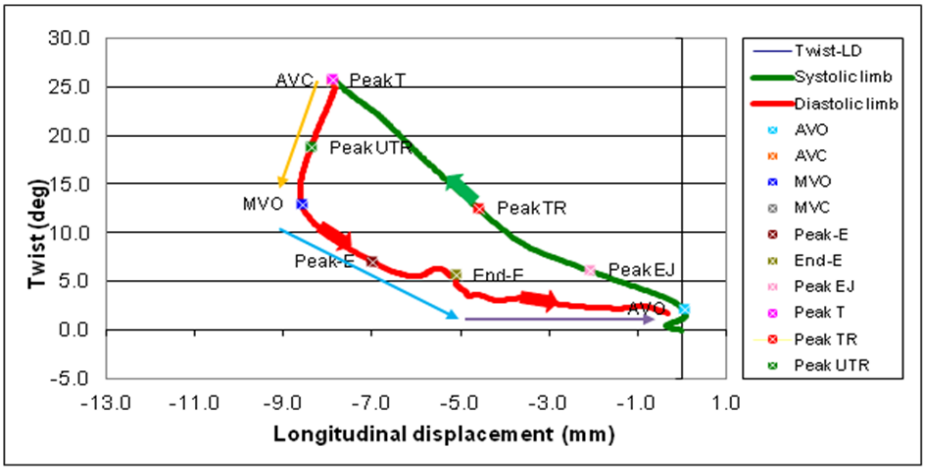
The ratio of untwist to longitudinal extension (UT:LE) which was not significantly different between HFNEF patients and control subjects at rest, became significantly different on exercise (Table 7.5). The logarithmic transformation of UT:LE ($UT:LE_{(log)}$) was calculated in view of non-normally distributed UT:LE data. This did not change the finding that diastolic dyssynchrony was present on exercise but not at rest (Table 7.5). Excluding the patients with atrial fibrillation did not change the message of this study (Table 7.5).

As shown in Figures 7.4 and 7.5, the relationship between twist and longitudinal displacement was very different in HFNEF patients, with a steeper slope in HFNEF patients during diastole, indicating that more untwist occurring before a given longitudinal displacement is achieved.

Figure 7.4 Twist-longitudinal displacement loops at rest



Twist-longitudinal displacement loop of healthy control at rest.

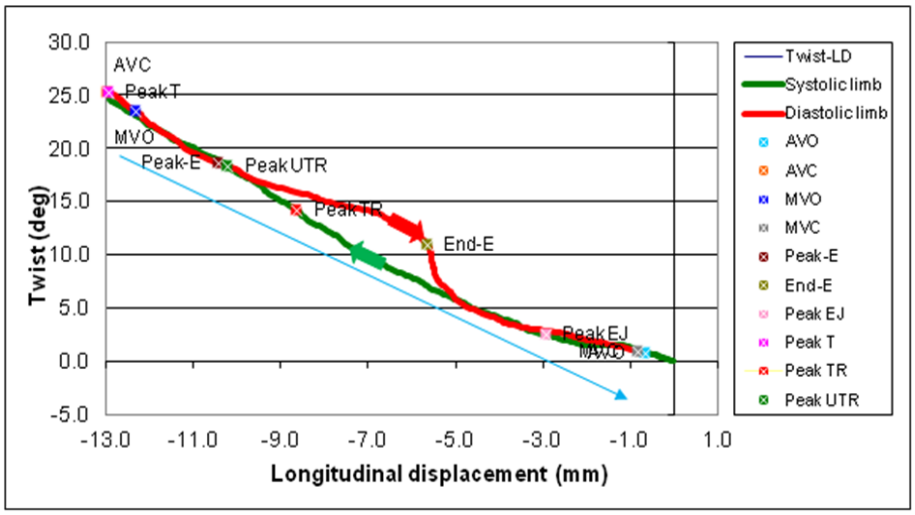


Twist-longitudinal displacement loop of HFNEF patient at rest.

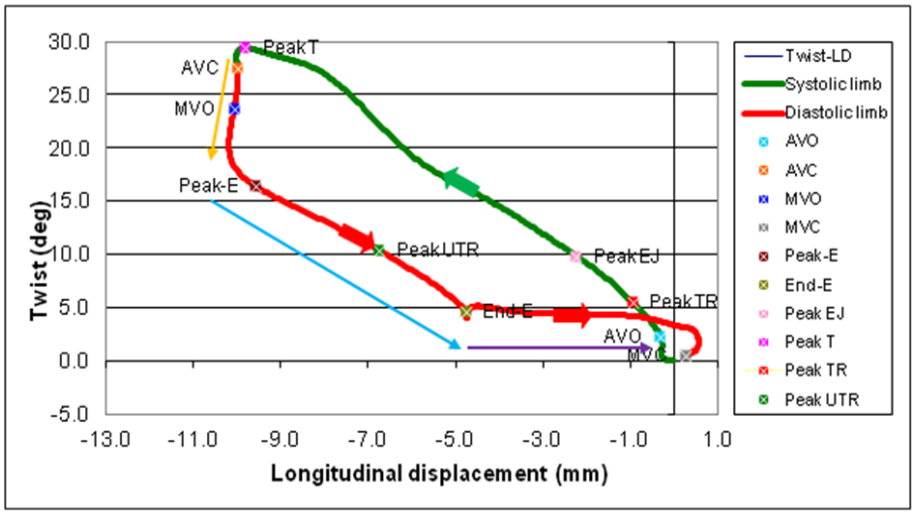
This figure illustrates the twist and longitudinal displacement (LD) relationship during systole and diastole in a healthy control and a HFNEF patient at rest. Green curve, systolic motion; red curve, diastolic motion; orange arrow, untwist without longitudinal extension in diastole; blue arrow, untwist and longitudinal extension in diastole; purple arrow, longitudinal extension without untwist in diastole.

AVO, aortic valve opening; AVC, aortic valve closure; MVO, mitral valve opening; MVC, mitral valve closure; Peak-E, peak mitral inflow E wave; End-E, end of mitral inflow E wave; Peak EJ, peak ejection; Peak T, peak twist; Peak TR, peak twist rate; Peak UTR, peak untwist rate.

Figure 7.5 Twist-longitudinal displacement loops on exercise



Twist-longitudinal displacement loop of healthy control on exercise.



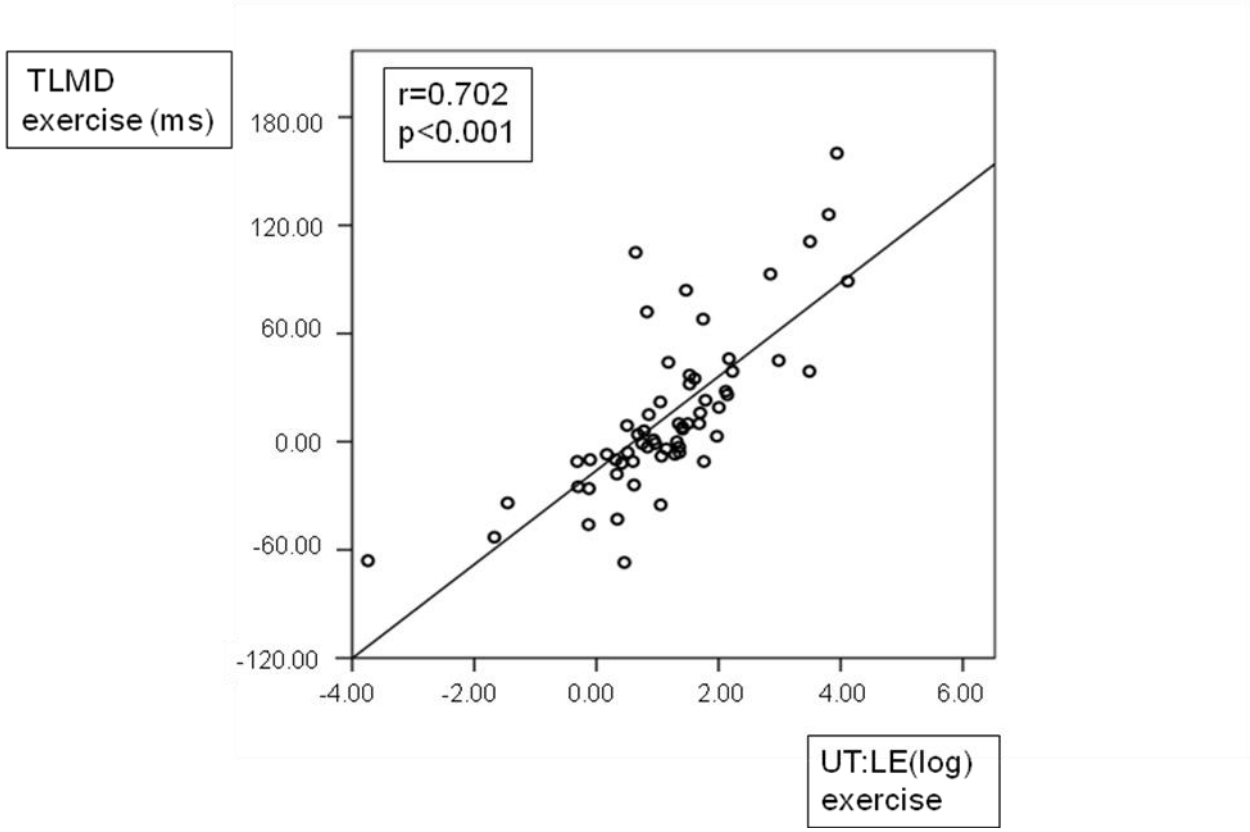
Twist-longitudinal displacement loop of HFNEF patient on exercise.

Descriptions are as per Figure 7.4. In addition to the synchronous untwist and longitudinal motion in diastole (blue arrow) seen in control subject, there are two distinct separation of motions (orange and purple arrows) in patient.

Annotations as per Figure 7.4.

In addition, HFNEF involved a delay in both untwisting and longitudinal displacement, particularly on exercise. In contrast, diastolic untwisting and longitudinal extension appeared to occur simultaneously in healthy controls. This uncoupling of diastolic left ventricular motion correlated with interventricular septal wall thickness, IVSd ($r=0.364$, $p=0.004$) and posterior wall thickness ($r=0.340$, $p=0.007$). There is a significant correlation between TLMD and $UT:LE_{(log)}$ at rest ($r=0.265$, $p=0.014$) which became stronger on exercise ($r=0.702$, $p<0.001$), indicating the close relationship between systole and diastole particularly during exercise (Figure 7.6).

Figure 7.6 Correlation between systolic and diastolic dyssynchrony



TLMD, twist-longitudinal motion delay; UT:LE(log), log of ratio of untwist to longitudinal extension; r, correlation; p, probability.

7.5.6 INTER-OBSERVER AND INTRA-OBSERVER VARIABILITY

The inter-observer variability at rest assessed by interclass correlation coefficient (ICC) was between 0.90 and 0.95. On exercise, the ICC varied from 0.70 to 0.98. The intra-observer variability ICC at rest varied from 0.86 to 0.98 and on exercise from 0.88 to 0.98. These were similar to the results reported in Chapter 5.

7.6 DISCUSSION

In addition to the widespread left ventricular and left atrial dysfunction shown in Chapters 5 and 6, this chapter demonstrated that left ventricular dyssynchrony is present in patients with HFNEF especially on exercise, by employing novel measures of torsional dyssynchrony, which were derived from left ventricular myocardial rotation, radial and longitudinal displacement as well as the coupling between twist and longitudinal displacement. The temporal dispersion of these parameters, quantified in terms of standard deviation, was used as a measure of torsional dyssynchrony. This study showed that in healthy controls, exercise leads to marked reductions in the SDSM and the TLMD, reflecting a reduction in the temporal dispersion of motion in the three planes as well as the coupling of left ventricular twist with longitudinal motion. In contrast, HFNEF was associated with lesser reductions in the SDSM and the TLMD, reflecting a proportionally greater temporal dispersion and uncoupling of left ventricular twist and longitudinal motion on exercise, when patients became breathless. In addition, HFNEF was also associated with uncoupling of untwist and longitudinal motion (extension) in diastole, measured using the ratio UT:LE. These observations indicate that HFNEF involves exercise induced torsional dyssynchrony, in both systole and diastole.

The coupling between rotational and longitudinal wall motion is crucial for left ventricular ejection and suction. As discussed in Chapters 2 and 5, during systole, contraction of the longitudinal fibres pulls the mitral annulus towards the apex at the same time as the oblique fibres contract resulting in the wringing motion to further

bring the mitral annulus towards the apex to maximise left ventricular ejection. During diastole, the release of potential energy enables the oblique fibres to spring back and hence untwisting the left ventricle, creating an apex-base pressure gradient to enhance diastolic filling while the simultaneous longitudinal fibres relax to facilitate mitral annulus movement towards the base . The efficiency and coupling of these motions are crucial to maintain left ventricular systolic and diastolic function, and particularly on exercise as illustrated in the strong correlation between TLMD and UT:LE.

This study showed no significant difference in torsional dyssynchrony between HFNEF patients and age-matched controls at rest. On exercise however, dyssynchrony was observed in patients with HFNEF, evidenced by a relatively higher SDSM compared with control subjects. Importantly, this measure of systolic torsional dyssynchrony correlated negatively with changes in stroke volume and with peak oxygen consumption on cardiopulmonary exercise testing. This suggests that in HFNEF, torsional dyssynchrony contributes to the inability to increase stroke volume and that this is related to dyspnoea and reduced exercise tolerance. Accordingly, a mechanical effect may ensue even in the absence of changes in traditional echocardiographic parameters, such as left ventricular volumes.

This study also showed that in HFNEF, untwisting occurs before longitudinal extension, unlike the coupled and nearly simultaneous longitudinal and untwisting motion observed in control subjects. This temporal dispersion, or uncoupling, of

diastolic motions amounts to diastolic torsional dyssynchrony. Speculatively, early diastolic torsional dyssynchrony could lead to reduced suction and therefore, an increase in the left ventricular end-diastolic and left atrial pressure, hence the symptom of breathlessness, the hallmark of HFNEF. Correction of systolic torsional dyssynchrony could, in theory, lead to correction of early diastolic torsional dyssynchrony simply by correcting dyssynchrony before it continues into the diastolic phase, therefore, it is possible that cardiac resynchronisation therapy (CRT) might correct exercise induced torsional dyssynchrony by the same mechanism that it corrects dyssynchrony in HFREF.

The primary abnormality most probably resides in the extracellular matrix and the nature of the collagen related to left ventricular hypertrophy, and this may be a promising therapeutic target (147). It is well established that most of the known conditions associated with HFNEF such as diabetes, hypertension, ischaemia and ageing all affect the extracellular matrix (148). In addition, the subendocardially situated fibres that sustain the long axis movement by the nature of their position are more prone to injury (22;149). Left ventricular hypertrophy itself is known to be associated with abnormal coronary flow reserve that may result in subendocardial ischaemia particularly on exercise (150). But it is unlikely there is one pathophysiology mechanism common to all HFNEF subjects and a variety of abnormalities of the left ventricular mechanics will be present depending on the exact underlying pathology.

In contrast to previous studies of dyssynchrony in HFNEF (78;79), this study found a close relationship between the degree of systolic and diastolic dyssynchrony. This makes more sense as physiologically, systole and diastole are closely intertwined. For example, there is a close relationship between the mitral annular systolic and diastolic velocities across a wide range of left ventricular ejection fractions (57). In addition, left ventricular wall thickness was found to correlate with the degree of dyssynchrony suggesting that there is a conduction delay particularly between the longitudinal fibres found mainly in the subendocardium and the oblique fibres located mainly in the subepicardium.

7.7 LIMITATIONS

As discussed in previous chapters, one limitation of speckle tracking is a lower frame rate so possibly peak velocities could be missed. However, the exercise during echocardiography was deliberately sub-maximal, enough to induce symptoms of breathlessness in patients while keeping the heart rate less than 100bpm. This may reflect the limitation of speckle tracking itself. Plane motion measurements and timings were not taken from the same frame but these were all corrected to cycle length and interpolated. Given that this is the first study to demonstrate dyssynchrony in different planes, there was no standard value of plane motion dyssynchrony to compare.

7.8 CONCLUSION

Using novel measures of left ventricular dyssynchrony, this study demonstrated that in HFNEF, exercise leads to systolic and diastolic torsional dyssynchrony. This amounts to an increase in the temporal dispersion of motion in three planes as well as an uncoupling of the left ventricular twist and longitudinal motions.

CHAPTER 8:

LEFT VENTRICULAR DYSFUNCTION IN CONTROLLED HYPERTENSIVE SUBJECTS

Contributory publication:

Tan YT, Wenzelburger F, Lee E, Heatlie G, Frenneaux M, Sanderson JE. Abnormal left ventricular function occurs on exercise in well-treated hypertensive subjects with normal resting echocardiography. Heart 2010;96(12):948-55.

8. LEFT VENTRICULAR DYSFUNCTION IN CONTROLLED HYPERTENSIVE SUBJECTS

8.1 SUMMARY

This study tested the hypothesis that hypertensive patients with exertional dyspnoea despite well-controlled blood pressure, normal resting echocardiographic findings and absence of left ventricular hypertrophy, may have abnormalities of left ventricular function which only occur on exercise and contribute to their symptoms.

Symptomatic hypertensive patients with well-controlled blood pressure on medications and normal baseline echocardiography underwent cardiopulmonary exercise testing to determine their peak oxygen consumption, followed by rest and submaximal supine exercise echocardiography.

Thirty treated hypertensive patients with exertional dyspnoea and 22 age-matched healthy controls had rest and exercise images of sufficient quality for analysis. Both groups had comparable standard echocardiographic findings at rest. On exercise, patients had reduced overall left ventricular long axis function and ventricular rotation in systole, delayed untwist and reduced suction in diastole in addition to significantly lower overall left ventricular longitudinal functional reserve which correlated with significantly reduced peak VO_2.

This study concluded that treated hypertensive patients with exercise limitation can have widespread systolic and diastolic left ventricular dysfunction on exercise despite normal resting echocardiography. Normal resting echocardiography does not preclude the presence of significant functional abnormalities on exercise that can contribute to symptoms. This group of patients might progress to develop HFNEF with time.

8.2 INTRODUCTION

There is a high prevalence of hypertension amongst patients diagnosed with HFNEF (3). Melenovsky et al. found many shared clinical features between patients with HFNEF and asymptomatic hypertensive patients with left ventricular hypertrophy which are significantly different from healthy subjects (71). This is one of the very few exercise studies which compared these two groups of subjects. They found many left ventricular systolic, diastolic and arterial abnormalities which were thought to contribute to the pathophysiology of HFNEF in patients with hypertension and left ventricular hypertrophy without symptoms of heart failure. However, many patients with treated hypertension have exercise-induced dyspnoea despite normal standard echocardiography (no evidence of left ventricular hypertrophy) and frequently it is concluded that the breathlessness is therefore not cardiac.

In view of the previous findings in HFNEF patients shown in Chapters 5 to 7, this study aimed to establish if patients with hypertension alone and without left ventricular hypertrophy who complained of breathlessness, would have similar abnormalities of the left ventricular and left atrial function on exercise, particularly those involving longitudinal ventricular function and twist mechanics. This study involved a group of treated hypertensive subjects without left ventricular hypertrophy or chamber dilatation and apparently normal systolic function on resting echocardiography.

8.3 METHODS

Left ventricular systolic and diastolic functions were assessed non-invasively at rest and on sub-maximal exercise in patients with an established diagnosis of hypertension and healthy controls. All subjects underwent pulmonary function test and cardiopulmonary exercise test, rest and exercise echocardiography studies as described in Chapter 4.

8.3.1 STUDY SUBJECTS

Patients with well controlled blood pressure on medication and complaining of exertional dyspnoea without an alternative explanation for their symptoms and with normal echocardiographic findings during their initial assessment were studied. Data of the same cohort of healthy controls recruited for studies in Chapters 5 to 7 was used as comparison.

Well controlled blood pressure was defined as systolic blood pressure of ≤ 140 mmHg and / or diastolic blood pressure of ≤ 90 mmHg while on medication. Exclusion criteria applied in this study included uncontrolled blood pressure on medications and the presence of left ventricular hypertrophy on echocardiography, in addition to the exclusion criteria outlined in section 4.1.

8.3.2 CARDIOPULMONARY EXERCISE TESTING

All subjects underwent full pulmonary function assessment with standard spirometry (forced expiratory volume in one second and forced vital capacity) followed by cardiopulmonary exercise testing as described in Chapter 4.

8.3.3 TWO-DIMENSIONAL AND TISSUE DOPPLER ECHOCARDIOGRAPHY

All subjects underwent full echocardiography examination at rest and on exercise using a semi-recumbent and tilting bicycle ergometer as described in Chapter 4.

Two-dimensional (2D) images and colour-coded tissue Doppler images (TDI) from the parasternal (long axis and short axis at basal, mid ventricular and apical levels) and apex (two, three and four chamber views) were obtained and stored digitally and analysed as described in Chapter 4.

Left ventricular dimensions, wall thickness, volume and ejection fraction were measured as previously described in Chapter 4. Left ventricular mass was calculated according to Devereux formula (110). Left ventricular mass index (LVMI) of > 115 g/m^2 (male) and > 95 g/m^2 (female) were defined as left ventricular hypertrophy. Left atrial volume and left atrial volume index were measured and calculated as described in Chapter 4. Systolic and diastolic longitudinal function reserve indexes were calculated by: ΔSm (or Em) x [1-(1/Sm (or Em)$_{rest}$)] (125).

8.3.4 SPECKLE TRACKING ECHOCARDIOGRAPHY

Left ventricular longitudinal strain, radial strain and rotation were assessed using the speckle tracking method and offline analysis was performed as described in Chapter 4. The average longitudinal strain of all four walls (12 segments) was taken as the global longitudinal strain as reported in Chapter 5. Radial strain was taken as the average of six segments of the mid ventricular short axis plane. The percentage untwist was assessed by marking the averaged rotation curve at 25% time increment points from peak rotation (0%) to peak untwist (100%) as illustrated in Chapter 4 (Figure 4.8).

8.4 STATISTICS

Statistical analyses were performed as described in Chapter 4.

Comparisons between patients and controls were performed using an unpaired t-test for normally distributed data and the Mann-Whitney U-test for non-normally distributed data. Comparisons within patients and controls were performed using a paired t-test only as all data was normally distributed. Linear regression was performed to test correlations.

Inter-observer and intra-observer agreements were performed to test the variability of tissue Doppler analysis, speckle tracking analysis and mitral flow propagation velocity.

8.5 RESULTS

A total 70 subjects were recruited in this study (48 patients and 22 controls). Eighteen patients were excluded: three had evidence of left ventricular hypertrophy on repeat echocardiography, one had evidence of ischaemia on exercise, six had poor picture quality not suitable for analysis, two were unable to exercise and six had left atrial enlargement on subsequent analysis of left atrial volume. The remaining 30 symptomatic hypertensive patients and 22 healthy controls had adequate images at rest and on exercise for analysis.

The mean age of patients was 71 ± 8 years and 60% were female. Control subjects were of comparable age (70 ± 6 years) and 72% were female. The past medical history and drug history of patients are summarised in Table 8.1. Patients had a significantly higher BMI compared to controls. The peak VO_2 and the achieved percentage of predicted oxygen consumption were significantly lower in patients than controls.

Table 8.1 Clinical characteristics – hypertension study

	Hypertensive patients	Controls	p-value
Number of subjects	30	22	
Age	71±8	70±6	0.524
Gender	18♀/ 12♂	16♀/6♂	0.390 *
BMI (kg/m^2)	30±5	25±4	<0.001
NYHA	class II =19 class III =11	n/a	
Peak VO_2 (ml/min/kg) (percent of predicted)	18.0±4.0 (77±18%)	29.0±.5.6 (133±22%)	<0.001
Years of hypertension	6.6±5.2	0	<0.001 ‡
Diabetes mellitus	6 (20%)	0 (0%)	
Coronary artery disease	6 (20%)	0 (0%)	
ACE-Inhibitor	10 (33%)	0 (0%)	
AR1-Blocker	7 (23%)	0 (0%)	
β-Blocker	11(37%)	0 (0%)	
Calcium channel blocker	9 (30%)	0 (0%)	
Diuretic	15 (50%)	0 (0%)	
α-Blocker	4 (13%)	0 (0%)	
Statin	11 (37%)	0 (0%)	

Data is presented as number (and %) or mean ± standard deviation.

p-value: unpaired t-test between patients and controls except * Fisher exact test between patients and controls and ‡ Mann-Whitney U test between patients and controls.

Annotations as per Table 5.1..

8.5.1 2D ECHOCARDIOGRAPHY

The left ventricular ejection fraction, dimensions, wall thickness, left ventricular mass index (LVMI) and left atrial volume index (LAVI) were all comparable between patients and controls, and all parameters were within normal limits (Table 8.2). Diastolic parameters were also comparable between the two groups except the early (E) and the late (A) mitral inflow velocity, which were statistically significantly higher in patients but still within normal limits (Table 8.3). Heart rate and blood pressure were comparable between the two groups both at rest and on exercise (Table 8.3).

Table 8.2 Standard echocardiographic parameters – hypertension study

	Hypertensive patients	Controls	p-value
IVSd (mm)	9.7±2.4	9.8±2.0	0.841
PW thickness (mm)	9.6±1.7	9.0±1.1	0.158
LVEDD (mm)	46.7±5.7	46.1±5.8	0.682
LVESD (mm)	29.0±4.6	28.7±4.6	0.793
FS (%)	38±7	38±7	0.859
LVMI (g/m^2)	78.6±22.4	81.0±18.8	0.693
LVEDVI (ml)	42.7±12.2	40.9±9.6	0.614
LVESVI (ml)	16.4±6.5	15.8±5.8	0.775
LVEF (%)	62±6	62±8	0.944
LAVI (ml/m^2)	26.9±6.0	25.4±8.4	0.457

Data is presented as mean ± standard deviation.

p-value: unpaired t-test between patients and controls.

IVSd, interventricular septal wall thickness; PW, posterior wall; LVEDD, left ventricular end-diastolic diameter ; LVESD, left ventricular end-systolic diameter; FS, fractional shortening; LVMI, left ventricular mass index; LVEDVI, left ventricular end-diastolic volume index; LVESVI, left ventricular end-systolic volume index; LVEF, left ventricular ejection fraction; LAVI, left atrial volume index.

Table 8.3 Haemodynamic and Doppler data – hypertension study

	Patients rest	Patients exercise	Patients p-value (paired t-test)	Controls rest	Controls exercise	Controls p-value (paired t-test)	Patients / controls p-value (unpaired t-test)
HR (bpm)	69±12	89±9	<0.001	70±10	91±5	<0.001	0.877 * 0.271 #
BP (mmHg)	141±18 / 74±11	163±19 / 85±14	<0.001 <0.001	139±14 / 79±9	163±12 / 87±9	<0.001 <0.001	0.617 * 0.934 # 0.081 * 0.564 #
E (m/s)	0.68±0.16	0.93±0.15	<0.001	0.56±0.12	0.96±0.11	<0.001	0.006 * 0.420 #
Δ E (m/s)		0.26±0.15			0.40±0.12		0.001
A (m/s)	0.84±0.20	1.00±0.19	<0.001	0.68±0.15	0.90±0.18	<0.001	0.003 * 0.070 #
E/A	0.83±0.20	0.96±0.23	<0.001	0.86±0.27	1.10±0.24	<0.001	0.569 * 0.039 #
DT (ms)	250±48	180±39	<0.001	257±47	166±45	<0.001	0.599 * 0.234 #
IVRT (ms)	93±19	61±13	<0.001	100±24	67±11	<0.001	0.293 * 0.155 #
E/e’	9.4±2.6	10.1±2.1	0.178	8.4±2.1	9.3±2.2	0.367	0.141 * 0.171 #

Data is presented as mean ± standard deviation.

p-value (paired t-test): paired t-test for patients (or controls) at rest and on exercise.

p-value (unpaired t-test): * unpaired t-test between patients and controls at rest and

unpaired t-test between patients and controls on exercise.

HR, heart rate; BP, blood pressure; E, early diastolic mitral inflow velocity; A, late diastolic mitral inflow velocity; E/A, ratio of E to A; DT, deceleration time; IVRT, isovolumic relaxation time; e’, peak early diastolic myocardial mitral annular velocity; E/e’ ratio of E to e’; Δ, (delta) change in.

8.5.2 LONGITUDINAL FUNCTION

Sm and Em at rest were comparable between patients and controls but became significantly different on exercise (Table 8.4). Exercise tissue Doppler imaging data of 83% of patients and 91% of controls were acceptable for analysis. An example of a recording is given in Figure 8.1. Patients failed to increase Sm and Em to the same extent as controls on exercise (Figure 8.2a). As a result, the systolic and diastolic longitudinal function reserve indexes were significantly lower in patients (Table 8.4). These results were very similar to those reported in Chapter 5 comparing HFNEF patients and healthy controls. In addition, Am was significantly higher in controls at rest and on exercise, similar to the results in Chapter 6 comparing Am between HFNEF patients and healthy controls.

Table 8.4 Tissue Doppler data – hypertension study

	Patients rest	Patients exercise	Patients p-value (paired t-test)	Controls rest	Controls exercise	Controls p-value (paired t-test)	Patients / controls p-value (unpaired t-test)
Sm (cm/s)	5.41±1.23	6.12±1.07	<0.001	5.75±0.91	7.77±0.95	<0.001	0.336 * <0.001 #
Δ Sm (cm/s)		0.82±0.59			1.85±0.95		0.003
SLFRI		0.97±1.34			2.32±1.24		0.001
Em (cm/s)	4.82±1.02	6.74±1.34	<0.001	5.39±1.14	8.48±1.19	<0.001	0.103 * 0.001 #
Δ Em (cm/s)		1.92±1.19			3.05±1.63		0.042
DLFRI		1.83±1.65			3.40±3.02		0.020
Am (cm/s)	7.12±1.23	8.37±1.20	0.008	8.12±1.24	9.79±1.79	0.002	0.016 * 0.022 #
ΔAm (cm/s)		1.33±1.50			1.54±1.45		0.721

Data is presented as mean ± standard deviation.

p-value (paired t-test): paired t-test for patients (or controls) at rest and on exercise.

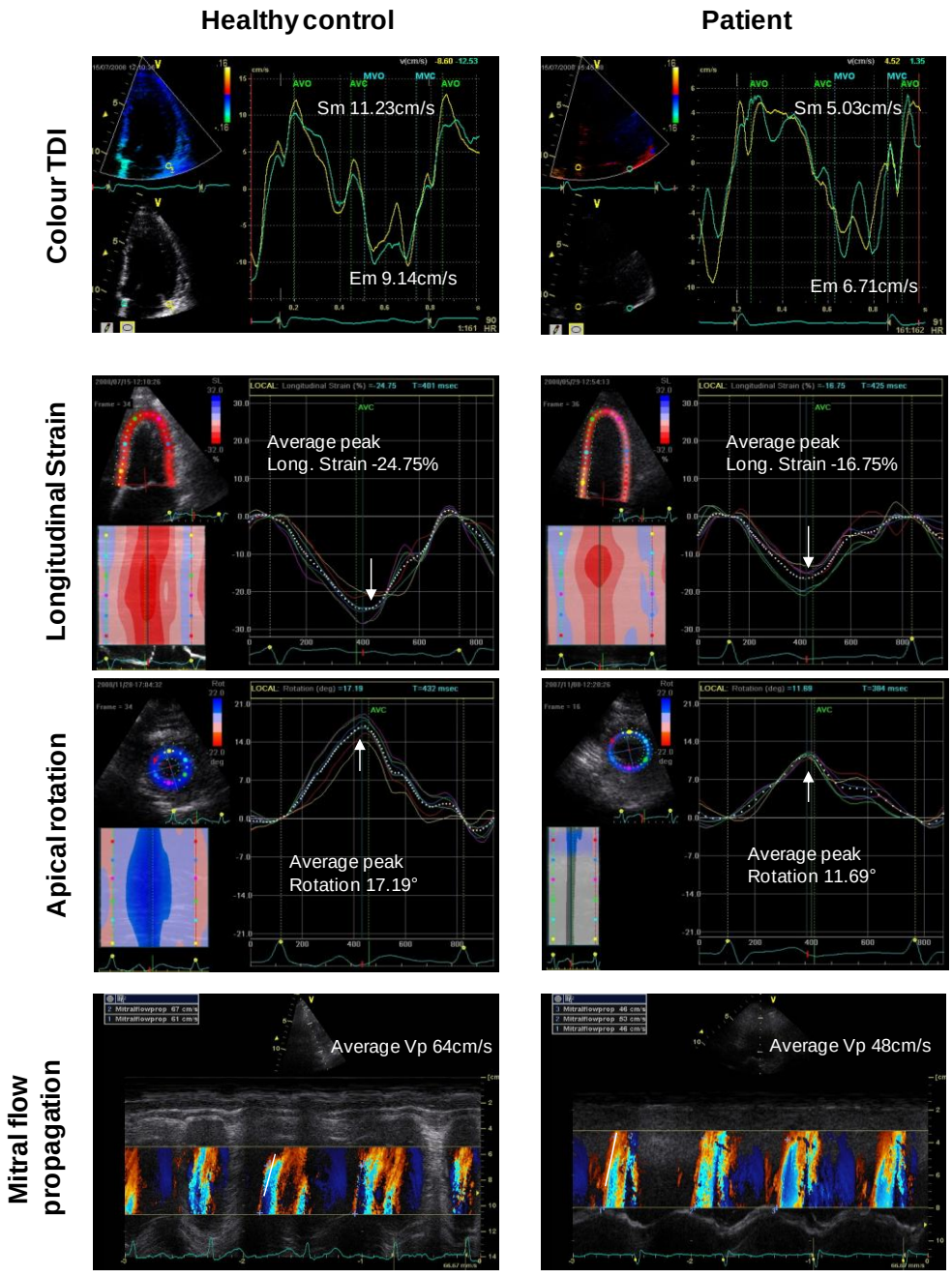
p-value (unpaired t-test): * unpaired t-test between patients and controls at rest and

unpaired t-test between patients and controls on exercise.

Sm, peak systolic myocardial mitral annular velocity; SLFRI, systolic longitudinal function reserve index; Em, peak early diastolic myocardial mitral annular velocity; DLFRI, diastolic longitudinal function reserve index; Am, peak late diastolic myocardial mitral annular velocity; Δ, (delta) change in.

When longitudinal function was assessed using speckle tracking, the global longitudinal strain was found to be significantly lower in patients not only on exercise but also at rest (Table 8.5). The global longitudinal strain result was based on the 63% of patients and 82% of controls who had exercise images of sufficient quality for speckle tracking. Even though patients had a significant increase in longitudinal strain on exercise, the magnitude of longitudinal strain on exercise was only comparable to the magnitude of longitudinal strain in controls at rest. An example of longitudinal strain recording is given in Figure 8.1. Only Am and global longitudinal strain were found to be significantly lower in patients compared to controls at rest, while other parameters were comparable at rest and only became abnormal on exercise. These results are in contrast with the results of patients with HFNEF reported in Chapter 5 which showed that measures of longitudinal function, radial function, apical rotation and untwist were all significantly lower than controls at rest.

Figure 8.1 Example of exercise parameters of hypertensive patient and control



TDI, tissue Doppler imaging; Sm, peak systolic myocardial mitral annular velocity; Em, peak early diastolic myocardial mitral annular velocity; MVC, mitral valve closure; AVO, aortic valve opening; AVC, aortic valve closure; MVO, mitral valve opening; Vp, mitral flow propagation velocity.

Table 8.5 Speckle tracking and mitral flow propagation velocity data – hypertension study

	Patients rest	Patients exercise	Patients p-value (paired t-test)	Controls rest	Controls exercise	Controls p-value (paired t-test)	Patients / controls p-value (unpaired t-test)
GlobLong Strain (%)	-19.0±2.4	-21.2±3.8	0.007	-20.9±3.1	-23.8±2.6	0.001	0.031 * 0.020 #
Rad Strain (%)	41.6±9.9	53.3±14.4	0.014	45.3±8.5	59.6±14.5	<0.001	0.204 * 0.185 #
Apical Rot (º)	10.9±4.3	13.1±4.6	0.056	12.8±2.7	17.0±3.4	<0.001	0.106 * 0.013 #
Early UT (%)	27.6±10.5	20.4±7.6	0.056	29.9±9.5	30.6±7.8	0.907	0.518 * 0.001 #
Mid UT (%)	55.0±13.3	51.9±14.1	0.829	57.4±8.3	63.3±7.5	0.040	0.533 * 0.012 #
Late UT (%)	77.2±4.5	78.7±12.4	0.986	81.3±7.9	84.7±5.0	0.111	0.090 * 0.105 #
Vp (m/s)	37.3±7.6	47.2±9.7	0.001	38.4±7.3	63.3±12.3	<0.001	0.615 * <0.001 #
Δ Vp (m/s)		10.6±10.9			24.5±12.2		<0.001

Data is presented as mean ± standard deviation.

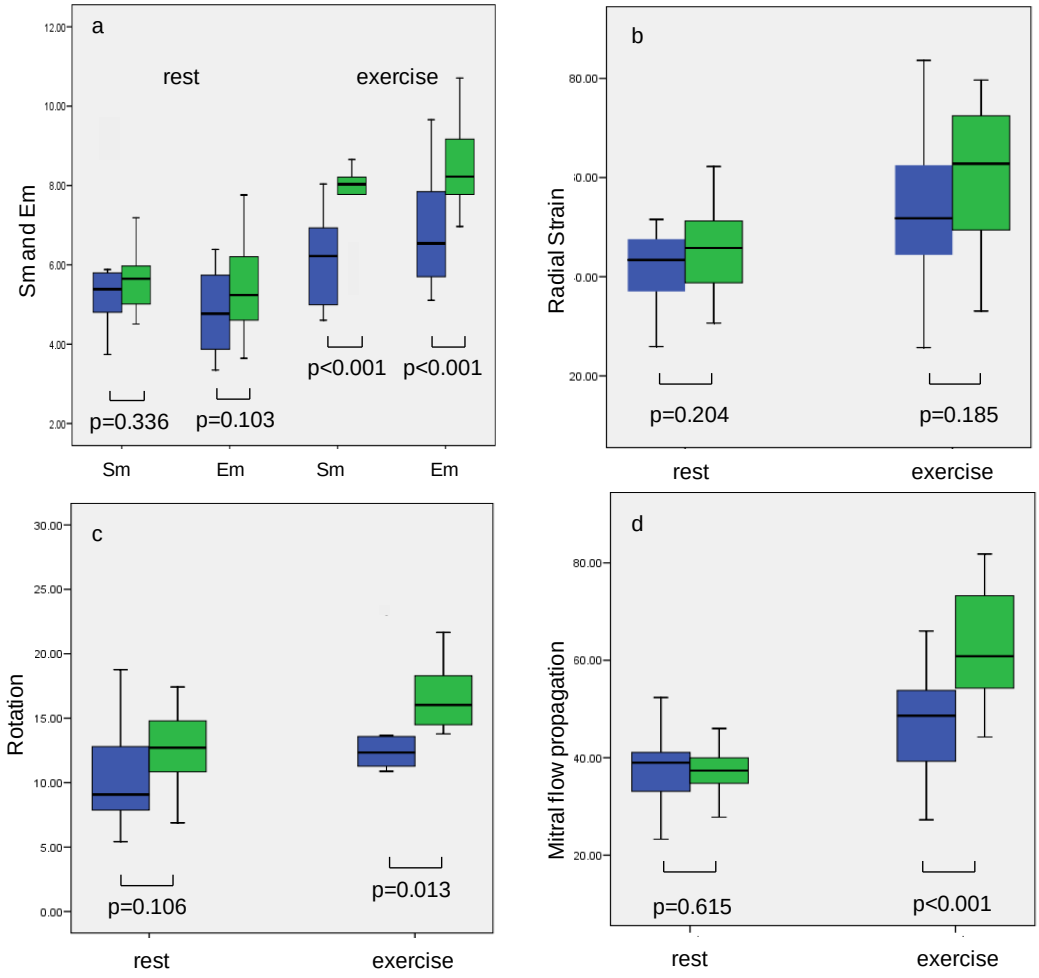
p-value (paired t-test): paired t-test for patients (or control) at rest and on exercise.

p-value (unpaired t-test): * unpaired t-test between patients and controls at rest and

unpaired t-test between patients and controls on exercise.

GlobLong, global longitudinal; Rad, radial; Rot, rotation; UT, untwist; Vp, mitral flow propagation velocity; Δ, (delta) change in.

Figure 8.2 Boxplots of long axis function, radial function, apical rotation and mitral flow propagation velocity at rest and on exercise



Boxplot shows minimum, first quartile, median, third quartile and maximum.

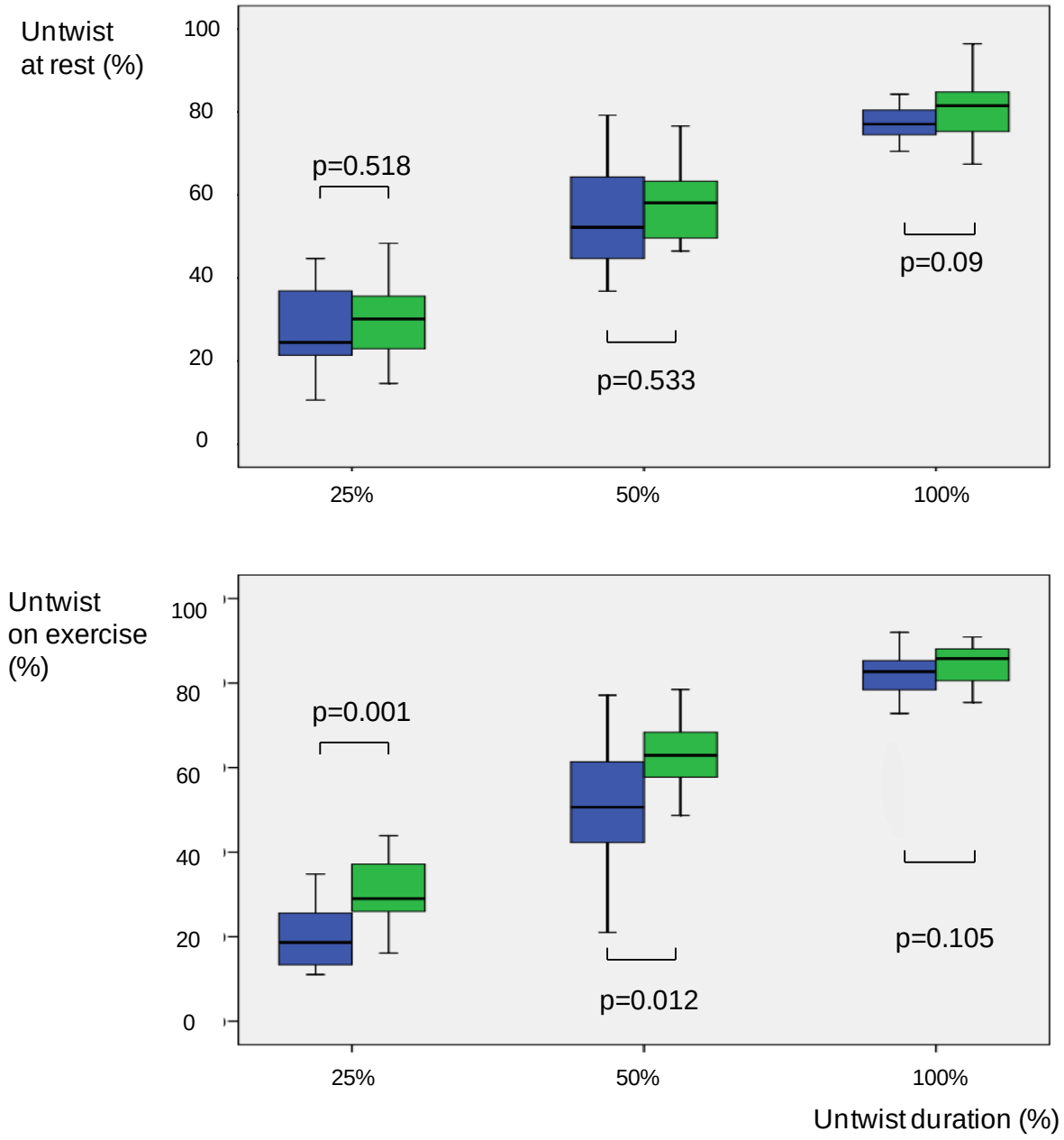
Sm, peak systolic myocardial mitral annular velocity; Em, peak early diastolic myocardial mitral annular velocity; p, probability.

8.5.3 RADIAL FUNCTION, ROTATION AND UNTWIST

Only 63% of patients and 82% of controls had mid left ventricular short axis images of adequate quality on exercise for analysis. There were no significant differences in radial strain at rest and on exercise between patients and controls (Table 8.5, Figure 8.2b). This was reflected in the comparable ejection fraction and fractional shortening between the two groups of subjects at rest indicating that radial function is largely preserved. However, ventricular rotation in systole which was comparable at rest in both groups, was found to be significantly reduced in patients on exercise (Table 8.5, Figure 8.2c). An example of left ventricular rotation analysis is given in Figure 8.1.

Five patients were found to have increased peak apical rotation at rest (> 15˚). Patients who had higher peak rotation at rest failed to increase left ventricular rotation on exercise. Similar to the findings for longitudinal strain, the magnitude of apical rotation on exercise in patients increased only to a level comparable to controls at rest, which is very similar to the findings in HFNEF patients as reported in previous chapters. In diastole, the percentage left ventricular untwist in early diastole and mid-diastole were comparable at rest but became significantly different on exercise, indicating delayed untwisting in early diastole on exercise (Table 8.5, Figure 8.3).

Figure 8.3 Percentage untwist at rest and on exercise between hypertensive patients and controls



Boxplot shows minimum, first quartile, median, third quartile and maximum.

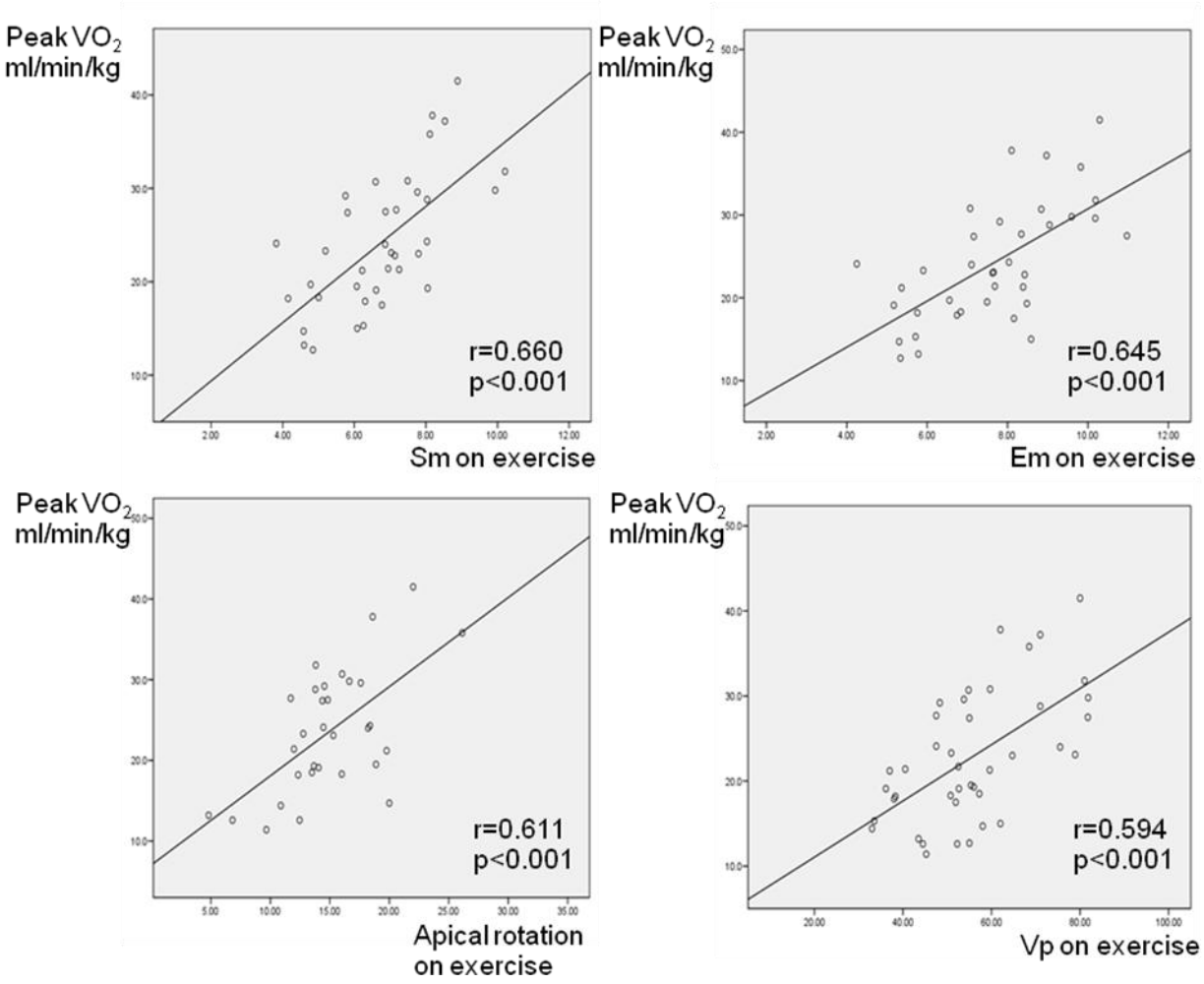
p, probability.

8.5.4 LEFT VENTRICULAR SUCTION

Ninety seven percent of patients and 100% of controls had good quality colour M-mode profile on exercise for analysis. Mitral flow propagation velocity (Vp) was found to be comparable between patients and controls at rest but became significantly different only on exercise due to a significant increase in Vp on exercise in control subjects (Table 8.5, Figure 8.2d).

Peak VO_2 correlated with the following echocardiographic parameters on exercise (Figure 8.4): Sm ($r=0.66$, $p<0.001$), Em ($r=0.645$, $p<0.001$), apical rotation ($r=0.611$, $p<0.001$), Vp ($r=0.594$, $p<0.001$) and early untwist ($r=0.523$, $p=0.007$).

Figure 8.4 Correlation between parameters on exercise and peak VO_2



VO_2, oxygen consumption; Sm, peak systolic myocardial mitral annular velocity; Em, peak early diastolic myocardial mitral annular velocity; Vp, mitral flow propagation velocity; r, correlation; p, probability.

8.5.5 INTER-OBSERVER AND INTRA-OBSERVER VARIABILITY

Similar to Chapter 5, the interclass correlation coefficient (ICC) for inter-observer variability at rest was between 0.88 and 0.95. On exercise the ICC varied from 0.70 to 0.98 and Vp had the highest inter-observer variability. The intra-observer variability ICC at rest varied from 0.88 to 0.98 and on exercise from 0.69 to 0.98 and Vp had the highest variability.

8.6 DISCUSSION

This study showed that in patients with well-treated hypertension, there were surprisingly significant abnormalities of ventricular function affecting longitudinal function, rotation, untwisting rates and left ventricular suction on exercise despite a normal standard echocardiography examination at rest and in the absence of left ventricular hypertrophy. These abnormalities, which are only apparent on exercise, correlate significantly with peak oxygen consumption and probably account for the symptom of breathlessness on exertion.

The results of this study have significant implication for the treatment of hypertension and emphasise the importance of using agents that may prevent or reverse these early significant abnormalities of ventricular architecture and function.

These results are especially relevant to the clinical problem of deciding whether the symptom of breathlessness is cardiac in origin or not. Often in practice a normal echocardiogram is used to exclude a cardiac cause and the breathlessness is then considered to be respiratory or due to obesity. Previous studies have questioned the true incidence of HFNEF because of normal echocardiography and other presumed aetiologies such as obesity or lung disease (151). Patients in this study had higher BMIs but this study confirmed that despite normal standard echocardiography these patients have major abnormalities of the left ventricular function which become apparent only on exercise and are only detected with more sophisticated measurements and analysis. Left ventricular function is clearly not normal despite a

normal left ventricular ejection fraction at rest. More importantly, the trend of the abnormalities found in this group of patients was very similar to those found in patients with HFNEF.

Previous studies have shown reduced long axis function or mitral annular motion associated with left ventricular hypertrophy and hypertrophic cardiomyopathy (152;153). However, this study demonstrated the presence of a reduced long axis function at rest in hypertensive patients without left ventricular hypertrophy. There was also markedly reduced longitudinal functional reserve on exercise in this group of patients. Borges et al. also found reduced mitral annular systolic and diastolic velocities in hypertensive subjects with or without left ventricular hypertrophy compared to normotensive controls (154). In their study mitral annular velocities correlated with left ventricular mass index (LVMI) and hypertensive subjects with clinically defined 'normal' LVMI had higher LVMI than normotensive subjects, implying that even sub-clinical levels of left ventricular mass increase are associated with impaired long axis function. They also found a significant correlation between the systolic and diastolic velocities similar to another study (57), illustrating the important link between systolic and early diastolic filling. As discussed in previous chapters, longitudinal shortening is mainly dependent on the subendocardial fibres (155) and these may be affected first by the effects of fibrosis and reduced subendocardial flow reserve (156).

There have been a few studies on the effects on anti-hypertensive therapies on longitudinal ventricular function. Borges et al. found that acute treatment with Captopril had no significant effect on either Sm or Em in hypertensive subjects with or without left ventricular hypertrophy (154). In heart failure subjects, Andersson et al. found that treatment with Metoprolol CR/XL led to an increase in atrioventricular plane displacement (or long axis longitudinal function) after six weeks (157). In patients with HFNEF, diuretics combined with Irbesartan or Ramipril led to a small but significant improvement in longitudinal myocardial velocities (135). It is unlikely therefore that the depression in longitudinal velocities seen in this study is due to the drug therapies per se. There does not appear to be any significant previous work on the effect of anti-hypertensive drug therapy on ventricular twist mechanics.

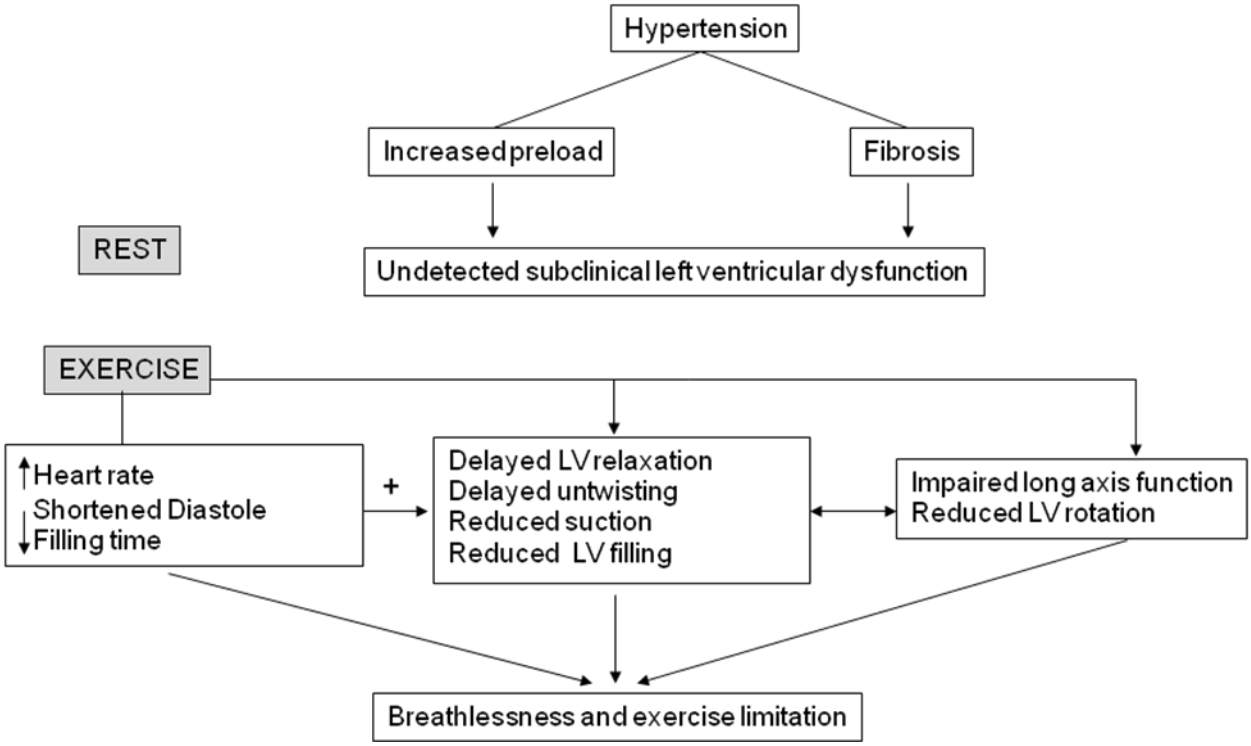
8.7 LIMITATIONS

Similar to the limitations in previous chapters, exercise was submaximal but this was dictated by the frame-rate limitations of speckle tracking. However, this level of exercise is more appropriate for this age group and probably reflects more realistically the level of daily activities. Also, speckle tracking imaging on exercise is technically demanding and this study only reported apical rotation given that the left ventricular apex is relatively fixed in position and allows very reliable speckle tracking analysis even on exercise. In addition, apical rotation has been shown to represent the dominant component of the overall left ventricular torsion as discussed in previous chapters.

8.8 CONCLUSION

In conclusion, this study showed that treated hypertensive subjects, without evidence of left ventricular hypertrophy and normal standard echocardiography, have abnormalities of the longitudinal function, twist, strain and ventricular suction which worsen on exercise. It is likely that these abnormalities are relevant to the symptom of breathlessness that they experienced despite optimal blood pressure control. It remains unknown if this group of patients would progress to develop HFNEF. Figure 8.5 provides an illustrated synopsis of the probable pathophysiology.

Figure 8.5 Schema illustrating the pathophysiology of breathlessness in hypertensive patients without left ventricular hypertrophy



LV, left ventricular.

CHAPTER 9:

MITRAL ANNULAR PEAK SYSTOLIC EXCURSION ON EXERCISE – A SIMPLE TEST FOR THE DIAGNOSIS OF HFNEF?

Contributory publication:

Wenzelburger FW, Tan YT, Choudhary FJ, Lee ES, Leyva F, Sanderson JE. Mitral annular plane systolic excursion on exercise: a simple diagnostic tool for heart failure with preserved ejection fraction. Eur J Heart Fail 2011;13(9):953-60.

9. MITRAL ANNULAR PEAK SYSTOLIC EXCURSION ON EXERCISE - A SIMPLE TEST FOR THE DIAGNOSIS OF HFNEF?

9.1 SUMMARY

Patients with HFNEF mainly present with exertional symptoms. It is not surprising that left ventricular dysfunction is more apparent on exercise and often undetected at rest. Current guidelines for the diagnosis of HFNEF are predominantly based on measurements at rest. Imaging and analysis performed on exercise is challenging and is not readily available. A simple and reliable test which can be performed on exercise would be a useful diagnostic tool. This study tests the hypothesis that mitral annular plane systolic excursion (MAPSE) which is easy to acquire and measure on exercise could be used to detect occult left ventricular impairment and to distinguish patients with HFNEF.

Sixty two patients with HFNEF and 36 control subjects were studied. MAPSE at rest which was significantly lower in patients became even more pronounced on exercise. At rest MAPSE correlated with longitudinal strain ($r= 0.432$, $p=0.001$), peak systolic myocardial velocity ($r= 0.545$, $p<0.001$), and early diastolic myocardial velocity ($r=0.322$, $p=0.02$). On exercise, MAPSE correlated with left ventricular apical rotation ($r=0.582$, $p<0.001$), longitudinal strain ($r=0.589$, $p<0.001$) and myocardial tissue velocities ($r=0.730$, $p<0.001$). The area under the ROC curve for MAPSE was 0.66

(confidence interval 0.54-0.77) at rest and 0.90 (confidence interval 0.84-0.97) on exercise to differentiate between patients and controls.

MAPSE at rest and on exercise correlated well with more sophisticated measurements of left ventricular function in HFNEF patients. It is easy to acquire and measure, particularly on exercise, therefore it is a potentially useful test for diagnosing HFNEF.

9.2 INTRODUCTION

As discussed in Chapter 1, the diagnosis of HFNEF is challenging and not straightforward. The European Society of Cardiology (ESC) and the American Society of Echocardiography (ASE) published guidelines and recommendations with comprehensive and complex echocardiographic parameters to assess the left ventricular function, particularly diastolic dysfunction, to diagnose patients with HFNEF (31;32). However, some of the suggested parameters might be technically challenging to measure particularly in obese patients such as Ard-Ad (difference between duration of reversed pulmonary vein atrial systolic flow (Ard) and duration of late diastole mitral inflow (Ad)). Some of the parameters such as LAVI or LVMI are indexed to body surface area which might not be measured in routine clinical practice, even though increasingly applied in clinical settings. Sophisticated echocardiographic techniques and subsequent analyses, such as colour tissue Doppler imaging or speckle tracking imaging, applied and reported in Chapters 5 to 8, are time consuming and not applicable for routine clinical practice. More importantly, left ventricular dysfunction not seen at rest is more apparent on exercise which is when patients are most symptomatic (136). Consequently, problems with accurate diagnosis make assessment of prognosis difficult (158).

Therefore, a simple measurement to diagnose left ventricular impairment at rest and on exercise may be useful to address the issues above. In Chapter 5, speckle tracking (strain) and colour TDI (Sm, Em) assessments have shown that systolic and diastolic longitudinal functions are significantly impaired in HFNEF patients at rest

and on exercise (136). Mitral annular peak systolic excursion (MAPSE) is an easy way to assess longitudinal function and had been shown to be a sensitive marker of left ventricular impairment in many different cardiac conditions (159-161).

This study tests the hypothesis that MAPSE correlates with more complex echocardiographic parameters and can be used as a simple and reliable tool to detect left ventricular impairment at rest , particularly on exercise, and could differentiate between HFNEF patients and healthy controls.

9.3 METHODS

Patients and healthy controls with a comparable mean age were recruited as outlined in Chapter 4. Patients were categorised according to the criteria outlined in the European Society of Cardiology 2007 guidelines (31). Those who fulfilled all the criteria were labelled as HFNEF and those who did not were labelled as non-HFNEF. All subjects underwent cardiopulmonary exercise testing as described in Chapter 4.

9.3.1 TWO-DIMENSIONAL AND TISSUE DOPPLER ECHOCARDIOGRAPHY

Rest and exercise echocardiography was performed as outlined in Chapter 4. Blood pressure was measured at rest and on peak exercise. Image acquisitions and analyses including those of colour tissue Doppler imaging and speckle tracking imaging were performed as described in Chapter 4.

Mitral annular peak systolic excursion (MAPSE) was measured by using the apical four chamber view focused on the left ventricle. An M-Mode vector was placed through the mitral annulus close to the septal and the lateral wall, respectively. The vector was adjusted to be as parallel to the walls as possible, optimised by using anatomical M-Mode where necessary. MAPSE was measured in millimetres as previously described (159-161). Values of both septal and lateral walls were averaged.

9.4 STATISTICS

Statistical analyses were performed as described in Chapter 4.

Comparisons between patients and controls were performed using an unpaired t-test for normally distributed data and the Mann-Whitney U-test for non-normally distributed data. Comparisons between HFNEF patients, non-HFNEF patients and controls were performed using ANOVA with Tukey post-hoc analysis. A paired t-test was used to compare resting and exercise data within the patients and the controls.

Receiver operator curves (ROC) were plotted to examine the ability of MAPSE to differentiate patients and healthy controls, at rest and on exercise, and also to differentiate between patients fulfilling the HFNEF criteria outlined by the European Society of Cardiology and healthy controls at rest and on exercise. Pearson's correlation coefficient was used to examine associations between variables.

Inter-observer and intra-observer agreements were performed using readings of 20 randomly selected subjects and reported as interclass correlation coefficient (ICC) with 95% confidence interval.

9.5 RESULTS

A total of 149 subjects (92 patients and 57 controls) were recruited into this study. Thirty patients were excluded due to reasons outlined in Chapters 5-7. In summary, seven had respiratory limitation on cardiopulmonary exercise testing, three had no increase in heart rate on exercise, one was found to have evidence of ischaemia on cardiopulmonary exercise testing, one had normal peak VO_2 on exercise, one had completely normal echocardiogram, and 17 were unable to exercise or had poor picture quality for analysis. Data of 36 healthy controls recruited as outlined in Chapter 4 was used for comparison. Demographic data of patients and healthy controls is presented in Table 9.1.

Table 9.1 Clinical characteristics – mitral annular peak systolic excursion study

	Patients	Controls	p-value
Number	62	36	
Age	71±8	70±7	0.599
Gender	41♀ / 21♂	29♀ / 7 ♂	0.166 *
BMI (kg/m^2)	30.5±4.8	24.4±3.4	<0.001
NYHA	class II=44 class III=18	n/a	
Peak VO_2 (ml/min/kg) (percent of predicted)	18.6±5.2 (77±18%)	29.4±4.8 (133±22%)	<0.001
Years of hypertension	9.0±9.6	0	<0.001 ‡
NT-proBNP (pg/ml)	138.2±147.2	54.3±24.8	0.012
Diabetes mellitus	16 (26%)	0 (0%)	
Atrial fibrillation	5 (8%)	0 (0%)	
ACE-inhibitor	19 (31%)	0 (0%)	
AR1-blocker	20 (32%)	0 (0%)	
Beta-blocker	22 (35%)	0 (0%)	
Ca-channel blocker	15 (24%)	0 (0%)	
Diuretic	31 (50%)	0 (0%)	
Alpha-blocker	11 (18%)	0 (0%)	
Statin	19 (31%)	0 (0%)	

Data is presented as number (and %) or mean ± standard deviation.

p-value: unpaired t-test between patients and controls except * Fisher exact test between patients and controls and ‡ Mann-Whitney U test between patients and controls.

Annotations as per Table 5.1

The left ventricular ejection fraction and left ventricular dimensions were comparable between patients and controls. Left ventricular mass index, left atrial volume index (LAVI), mitral inflow E and A waves, and E/e' were all significantly higher in patients (Table 9.2). Twenty three (23/62) patients were found to fulfil the HFNEF criteria outlined by the European Society of Cardiology (Figure 9.1).

Table 9.2 Standard echocardiographic parameters – mitral annular peak systolic excursion study

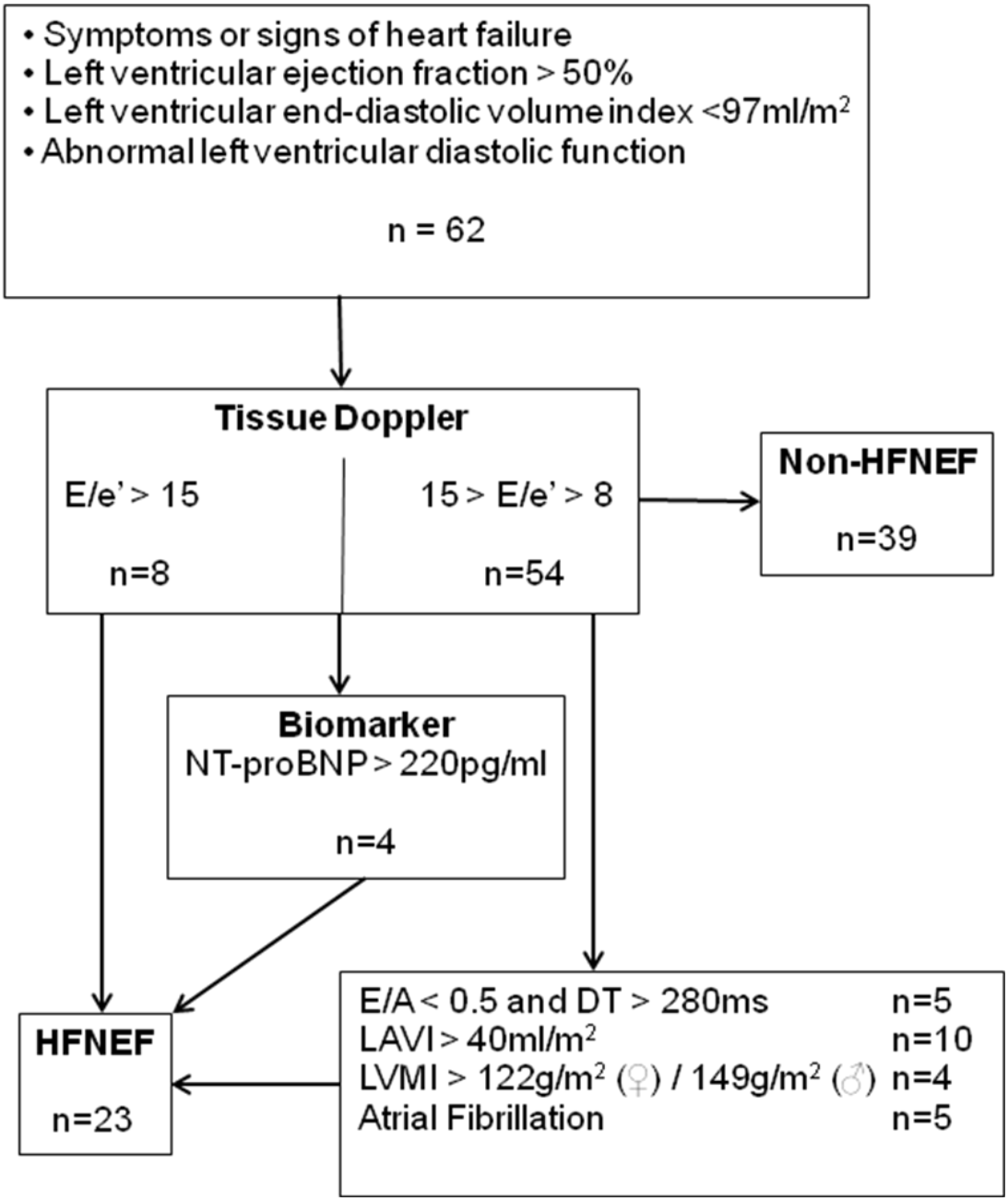
	Patients	Controls	p-value
LVEF (Simpson) (%)	60±7	62±7	0.187
IVSd (mm)	11.3±3.2	9.4±1.8	0.004
PW thickness (mm)	11.0±2.5	9.2±1.5	0.001
LVEDD (mm)	46.6±6.4	45.6±5.1	0.440
LVESD (mm)	28.8±5.5	28.5±4.2	0.747
FS (%)	38.4±7.7	37.6±6.9	0.618
LVMI (g/m^2)	94.7±33.2	76.5±19.2	0.010
LVEDVI (ml)	40.0±9.3	38.9±8.9	0.441
LVESVI (ml)	16.3±4.8	14.9±5.1	0.265
LAVI (ml/m^2)	31.7±10.8	22.9±7.7	<0.001
A (m/s)	0.86±0.20	0.72±0.16	0.001
E (m/s)	0.70±0.17	0.60±0.11	0.001
E/A	0.82±0.20	0.86±0.23	0.403
DT (ms)	239±57	250±49	0.319
IVRT (ms)	99±25	97±20	0.723
E/e’	11.3±4.2	8.2±1.9	<0.001

Data is presented as mean ± standard deviation.

p-value: unpaired t-test between patients and controls.

LVEF, left ventricular ejection fraction; IVSd, interventricular septal wall thickness; PW, posterior wall; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end systolic diameter; FS, fractional shortening; LVMI, left ventricular mass index; LVEDVI, left ventricular end-diastolic volume index; LVESVI, left ventricular end-systolic volume index; LAVI, left atrial volume index; A, late diastolic mitral inflow velocity; E, early diastolic mitral inflow velocity; E/A, ratio of E to A; DT, deceleration time; IVRT, isovolumic relaxation time; e’, peak early diastolic myocardial mitral annular velocity; E/e’, ratio of E to e’.

Figure 9.1 Patients fulfilling ESC HFNEF criteria



ESC, European Society of Cardiology; HFNEF, heart failure with a normal ejection fraction; n, number; E, early diastolic mitral inflow velocity; A, late diastolic mitral inflow velocity, E/A, ratio of E to A; DT, deceleration time; LAVI, left atrial volume index; LVMI, left ventricular mass index; e', peak early diastolic myocardial mitral annular velocity; E/e', ratio of E to e'; NT-proBNP, N-terminal pro B-type natriuretic peptide.

9.5.1 HAEMODYNAMIC CHANGES

The resting and exercise heart rates were comparable between both groups. Patients had a slightly increased systolic blood pressure at rest compared to healthy controls. On exercise, systolic and diastolic blood pressures were comparable between the groups. Patients had a higher stroke volume at rest but they were unable to increase their stroke volume on exercise as much as healthy controls (Table 9.3).

Table 9.3 Haemodynamic data – mitral annular peak systolic excursion study

	Patients rest	Patients exercise	Patients p-value (paired t-test)	Controls rest	Controls exercise	Controls p-value (paired t-test)	Patients / controls p-value (unpaired t-test)
HR (bpm)	69±12	91±10	<0.001	69±11	93±9	<0.001	0.985 * 0.368 #
BP (mmHg)	146±14 / 79±11	167±16 88±11	<0.001 <0.001	138±12 / 79±8	162±14 / 86±8	<0.001 <0.001	0.045 * 0.133 # 0.905 * 0.044 #
SV (ml/min)	73±25	76±24	0.375	65±15	80±24	0.006	0.070 * 0.514 #
CO (l/min)	5.3±2.2	6.7±2.2	<0.001	4.5±1.2	7.5±2.6	<0.001	0.056 * 0.150 #

Data is presented as mean ± standard deviation.

p-value (paired t-test): paired t-test for patients (or controls) at rest and on exercise.

p-value (unpaired t-test): * unpaired t-test between patients and controls at rest and

unpaired t-test between patients and controls on exercise.

HR, heart rate; BP, blood pressure; SV, stroke volume; CO, cardiac output.

9.5.2 LONGITUDINAL FUNCTION AND MITRAL FLOW PROPAGATION VELOCITY

Similar to the results in Chapter 5, the mitral annular velocities in systole and early diastole (Sm and Em), longitudinal strain, radial strain and apical rotation at rest were significantly lower in patients compared to controls and these differences were more pronounced on exercise. Mitral flow propagation velocity (Vp) was comparable between patients and controls at rest, but became significantly different on exercise as previously described in Chapter 5 (136) (Table 9.4).

Table 9.4 Doppler and speckle tracking data – mitral annular peak systolic excursion study

	Patients rest	Patients exercise	Patients p-value (paired t-test)	Controls rest	Controls exercise	Controls p-value (paired t-test)	Patients / controls p-value (unpaired t-test)
Sm (cm/s)	5.0±0.9	6.0±1.2	<0.001	5.9±1.4	7.7±1.4	<0.001	0.001 * <0.001 #
Em (cm/s)	4.6±1.6	6.5±1.8	<0.001	5.6±1.3	8.3±1.8	<0.001	0.003 * <0.001 #
GlobLong Strain (%)	-18.3±3.3	-19.9±4.0	<0.001	-21.1±3.0	-23.9±2.5	<0.001	0.002 * <0.001 #
Rad strain (%)	41.8±14.5	48.9±16.0	0.039	49.2±13.6	58.9±13.1	0.002	0.046 * 0.021 #
Apical Rot (º)	10.9±4.3	13.6±4.6	0.001	13.0±3.1	18.0±3.8	<0.001	0.030 * <0.001 #
Vp (m/s)	39.7±8.5	52.8±13.0	<0.001	39.8±7.9	67.0±17.9	<0.001	0.990 * <0.001 #

Data is presented as mean ± standard deviation.

p-value (paired t-test): paired t-test for patients (or controls) at rest and on exercise.

p-value (unpaired t-test): * unpaired t-test between patients and controls at rest and

unpaired t-test between patients and controls on exercise.

Sm, peak systolic myocardial mitral annular velocity; Em peak early diastolic myocardial mitral annular velocity; GlobLong, global longitudinal; Rad, radial; Rot, rotation; Vp, mitral flow propagation velocity; Δ, (delta) change in.

9.5.3 MITRAL ANNULAR PEAK SYSTOLIC EXCURSION (MAPSE)

In patients, MAPSE was significantly reduced at rest and even more so on exercise (Table 9.5, Figure 9.2). Patients had a smaller increase in MAPSE compared to controls (Δ MAPSE 1.2 ± 1.2 mm versus 4.0 ± 2.4 mm, p<0.001).

HFNEF patients had a comparable MAPSE at rest compared to non-HFNEF patients (10.6 ± 2.6 mm versus 11.0 ± 1.7 mm, p=0.737). On exercise there was only a slight but not significant difference in MAPSE between the two patient groups (11.2 ± 1.8 mm versus 12.4 ± 2.3mm, p=0.147). ANOVA analysis for all three groups (HFNEF patients, non-HFNEF patients and healthy controls) showed a significant difference in MAPSE at rest (p=0.023) and on exercise (p<0.001).

Table 9.5 Mitral annular peak systolic excursion

	Patients rest	Patients exercise	Patients p-value (paired t-test)	Controls rest	Controls exercise	Controls p-value (paired t-test)	Patients / controls p-value (unpaired t-test)
MAPSE (mm)	10.9±2.1	12.0±2.2	<0.001	12.1±2.2	16.2±2.7	<0.001	0.008 * <0.001 #
Δ MAPSE (mm)		1.2±1.2			4.0±2.4		<0.001

Data is presented as mean ± standard deviation.

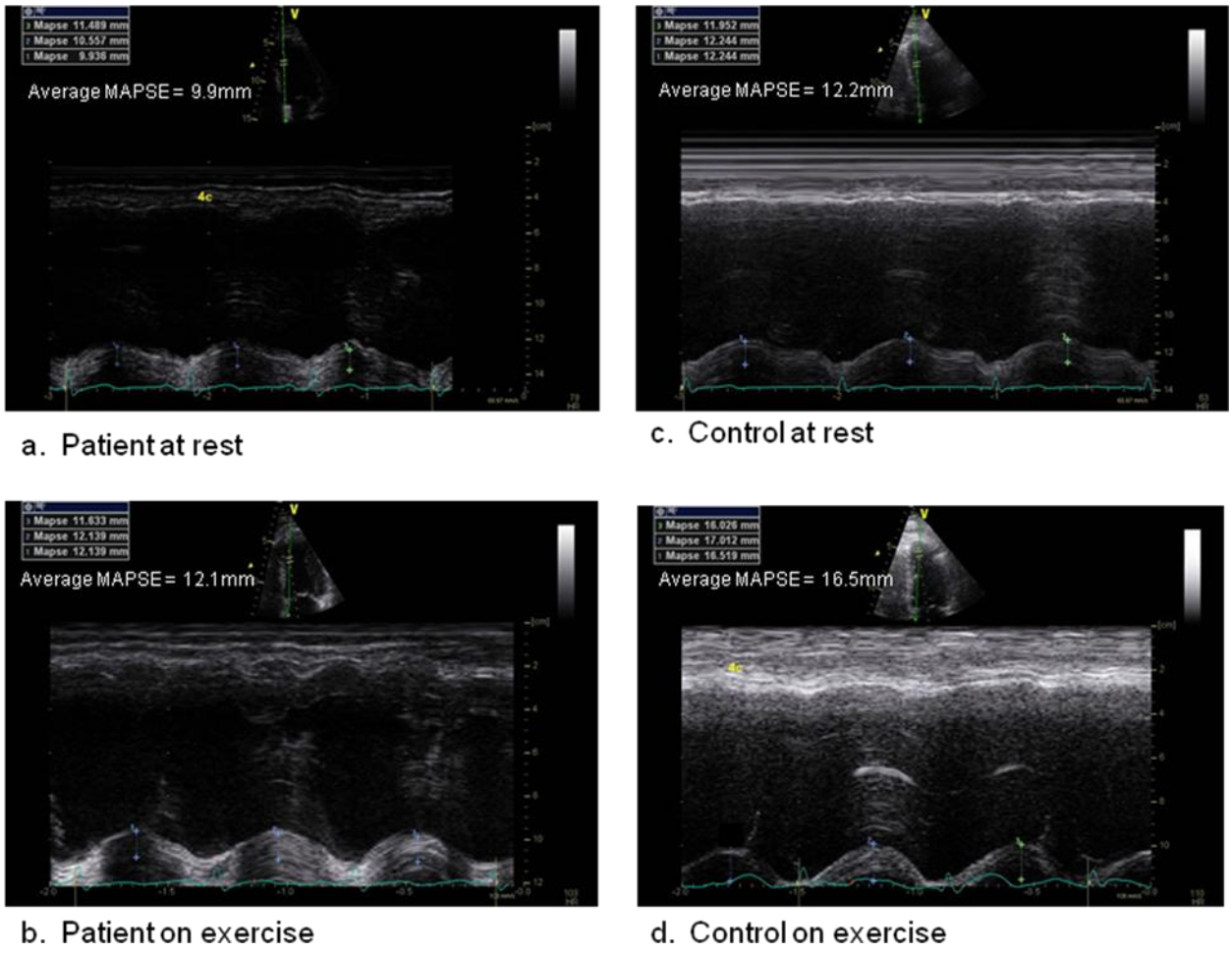
p-value (paired t-test): paired t-test for patients (or controls) at rest and on exercise.

p-value (unpaired t-test): * unpaired t-test between patients and controls at rest and

unpaired t-test between patients and controls on exercise.

MAPSE, mitral annular peak systolic excursion; Δ, (delta) change in.

Figure 9.2 Examples of mitral annular peak systolic excursion at rest and on exercise for HFNEF patient and control



HFNEF, heart failure with a normal ejection fraction; MAPSE, mitral annular peak systolic excursion.

Correlations and receiver operator curves (ROC)

MAPSE at rest correlated well with many echocardiographic parameters which were reduced in HFNEF patients as shown in Chapter 5. It correlated with measurements used for the diagnosis of HFNEF as suggested by the European Society of Cardiology guidelines, such as the left atrial volume index (LAVI) and E/e'. More importantly, these parameters correlated even more significantly with MAPSE on exercise. In addition, peak VO_2 also correlated with MAPSE on exercise (Table 9.6).

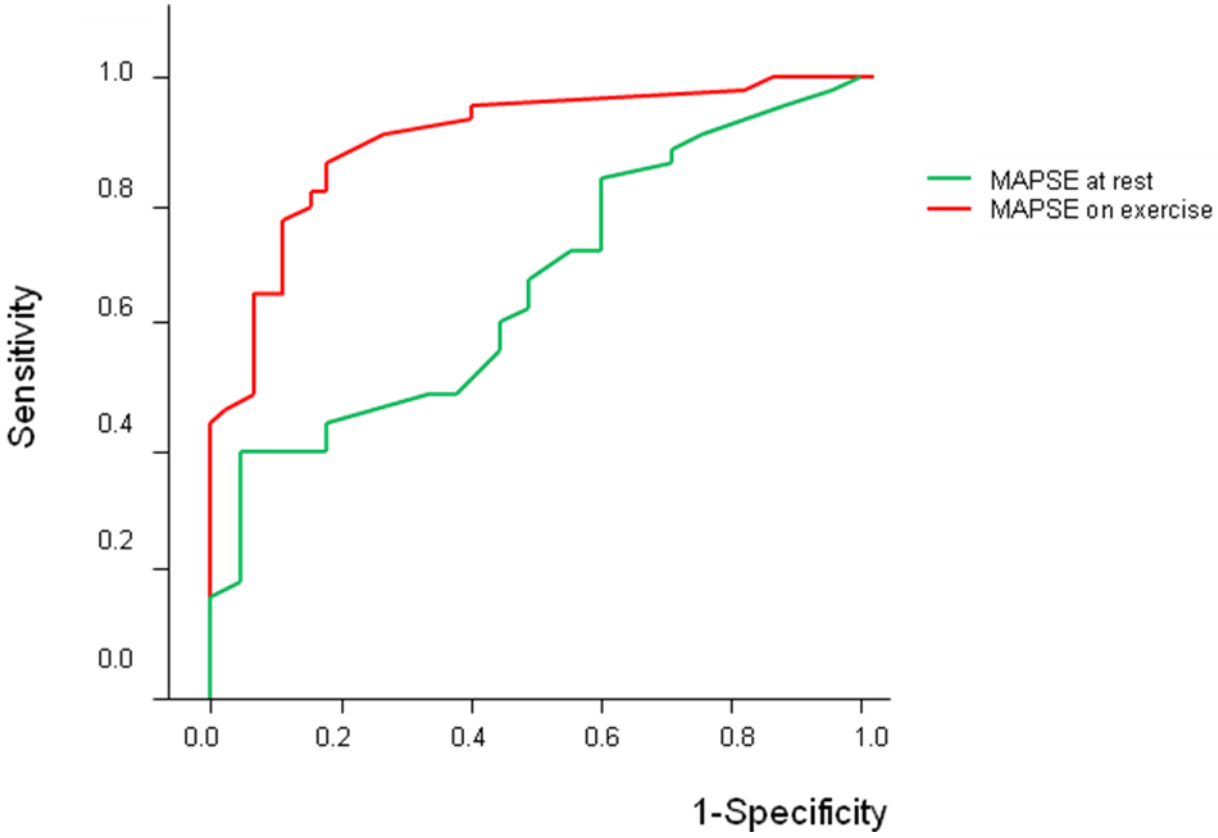
Table 9.6 Correlations with mitral annular peak systolic excursion at rest and on exercise

	MAPSE at Rest		MAPSE on Exercise	
	Pearson correlation	Significance (p-value)	Pearson correlation	Significance (p-value)
LVMI	0.176	0.128	0.204	0.086
LAVI	0.220	0.038	0.279	0.009
CO	0.156	0.148	0.303	0.011
Sm	0.545	<0.001	0.730	<0.001
Em	0.322	0.002	0.357	0.001
E/e’	0.331	0.001	0.359	0.001
Longitudinal strain	0.432	0.001	0.589	<0.001
Radial strain	0.196	0.133	0.338	0.017
Apical rotation	0.283	0.019	0.582	<0.001
Vp	0.105	0.319	0.519	<0.001
Peak VO_2	0.197	0.097	0.512	<0.001
LVEF	0.282	0.014	0.326	0.013

MAPSE, mitral annular peak systolic excursion; LVMI, left ventricular mass index; LAVI, left atrial volume index; CO, cardiac output; Sm, peak systolic myocardial mitral annular velocity; Em, peak early diastolic myocardial mitral annular velocity; E, early diastolic mitral inflow velocity; e’, peak early diastolic myocardial mitral annular velocity; E/e’, ratio of E to e’; Vp,mitral flow propagation velocity; VO_2, oxygen consumption; LVEF, left ventricular ejection fraction.

The receiver operator curve for MAPSE at rest showed an area under the curve (AUC) of 0.665 (CI = 0.540-0.770) and for MAPSE on exercise it showed an area under the curve of 0.901 (CI = 0.835-0.967) (Figure 9.3) to differentiate between patients and controls. Using MAPSE on exercise of < 14.5 mm as a cut off to identify patients, the sensitivity was 91% and the specificity 76%. The receiver operator curves to differentiate between patients fulfilling the European Society of Cardiology criteria for HFNEF and controls showed an AUC of 0.707 (CI = 0.539-0.875) for MAPSE at rest and an AUC of 0.964 (CI = 0.914-1.014) for MAPSE on exercise (Figure 9.4). Using MAPSE on exercise < 13.5mm as a cut off to identify patients fulfilling the European Society of Cardiology criteria for HFNEF, sensitivity was 95% and specificity was 85%.

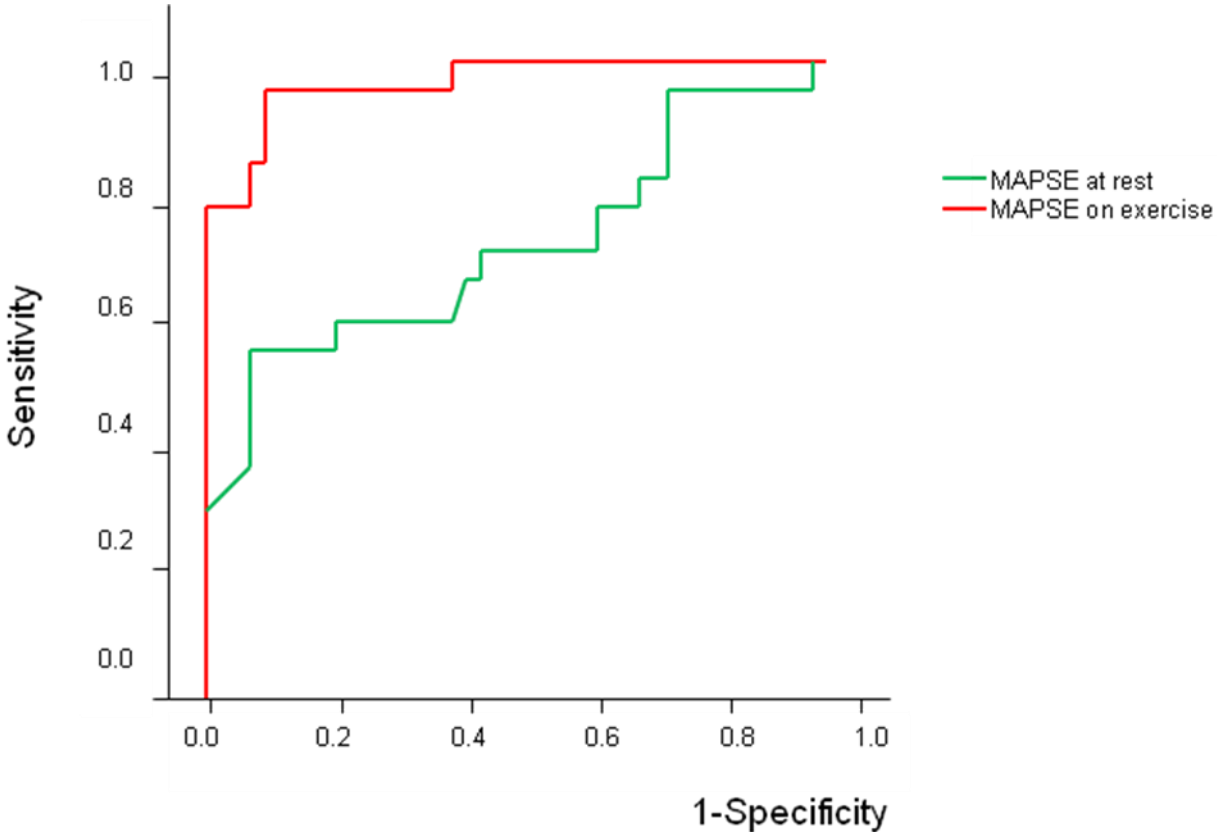
Figure 9.3 Receiver operator curve of mitral annular peak systolic excursion at rest and on exercise to differentiate patients from healthy controls



MAPSE, mitral annular peak systolic excursion.

Area under the curve of 0.665 (confidence interval = 0.540-0.770) for MAPSE at rest and area under the curve of 0.901 (confidence interval = 0.835-0.967) for MAPSE on exercise to differentiate all patients (HFNEF and non-HFNEF) from controls.

Figure 9.4 Receiver operator curve of mitral annular peak systolic excursion at rest and on exercise to differentiate patients with HFNEF from healthy controls



MAPSE, mitral annular peak systolic excursion.

Area under the curve of 0.707 (confidence interval = 0.539-0.875) for MAPSE at rest and area under the curve of 0.964 (confidence interval = 0.914-1.014) for MAPSE on exercise to differentiate patients fulfilling the European Society of Cardiology criteria for HFNEF from controls.

9.5.4 INTER-OBSEVER AND INTRA-OBSERVER VARIABILITY

The interclass correlation coefficient (ICC) for inter-observer variability at rest was between 0.82 and 0.96 and on exercise, the ICC varied from 0.67 to 0.99 as reported in Chapter 5 (for tissue Doppler, speckle tracking and colour M-mode Doppler measurements). In addition, the ICC for MAPSE at rest was 0.82, 95% confidence interval (CI =0.52-0.92)and on exercise it was 0.83, 95% confidence interval (CI =0.40-0.91).

The interclass correlation coefficient (ICC) for intra-observer variability at rest varied from 0.88 to 0.98 and on exercise from 0.66 to 0.98 as reported in Chapter 5 (for tissue Doppler, speckle tracking and colour M-mode Doppler measurements). The ICC for MAPSE at rest was 0.83, 95% confidence interval (CI =0.60-0.92) and on exercise it was 0.88, 95% confidence interval (CI =0.70-0.95).

9.6 DISCUSSION

This study demonstrated that MAPSE measured at rest and on exercise is a potentially useful measurement to identify patients with HFNEF. It is a simple way to assess left ventricular function, particularly the long axis function, and it is reduced even when the left ventricular ejection fraction is still normal. It correlates with parameters such as E/e' and left atrial volume index which are considered markers of diastolic dysfunction essential in the diagnosis of HFNEF as outlined by recent guidelines (31;32). More importantly, MAPSE correlates with more sophisticated and time consuming measurements of systolic left ventricular function (longitudinal strain, apical rotation and Sm) as well as diastolic parameters (Em and mitral flow propagation velocity). Furthermore, MAPSE on exercise correlates with exercise capacity as measured by peak VO_2.

MAPSE is potentially a very useful tool for the diagnosis of HFNEF in view of its ease to obtain and measure during exercise, even in obese patients which constitute 50% of the patient group in this study. Many patients with significant exercise intolerance may have normal physical examination, echocardiography and haemodynamics at rest. Borlaug et al. showed that many of these patients had elevated left ventricular filling pressures on exercise (162). Based on the findings reported in Chapters 5 to 8, left ventricular assessments performed on exercise give a more complete evaluation and are key to evaluate patients with exertional symptoms such as those with HFNEF.

MAPSE was used in early studies as a marker of left ventricular function but was shortly replaced by more advanced imaging modalities such as tissue Doppler imaging and speckle tracking imaging. Willenheimer et al. showed that MAPSE, as a measure of long axis function or atrioventricular displacement, was strongly related to one year mortality in heart failure patients. They showed a 36% one year mortality in those with MAPSE of < 6.4 mm and no deaths in those with MAPSE > 10 mm (163). More recently, a 10-year follow-up study found that MAPSE was a strong independent risk predictor of long-term survival after adjusting for age, gender, heart rate, systolic blood pressure and short axis fractional shortening (164).

These results emphasise the importance of left ventricular longitudinal function and the contribution of the mitral annulus or atrioventricular displacement in the overall function and mechanics of the left ventricle. As discussed in earlier chapters, the movement of the mitral annulus away from the base during systole is also a reflection of left ventricular twist or torsion, which helps to pull the annulus towards the apex. Interestingly, this study also found a good correlation between MAPSE and apical rotation in addition to measurements of longitudinal function such as Sm and longitudinal strain. Carlsson et al. estimated that left ventricular longitudinal shortening contributed 60% of normal stroke volume (165). Furthermore, the recoil of the atrioventricular plane in diastole is very important to aid early left ventricular filling. Hence, the loss of longitudinal or atrioventricular plane motion will have a significant impact on the overall left ventricular function, and may explain why

longitudinal function is one of the earliest markers of overall left ventricular mechanical dysfunction.

E/e' is an indirect marker of left ventricular end-diastolic pressure and its measurement at rest is an essential non-invasive marker for diastolic dysfunction used in the European Society of Cardiology guidelines for the diagnosis of HFNEF (31). Burgess et al. found that E/e' > 13 on exercise could accurately identify a raised left ventricular end-diastolic pressure of > 15 mmHg (166). However, E/e' did not rise consistently in patients with HFNEF on exercise in the results reported in this thesis. Recently, doubts have been raised about the validity of E/e' as a non-invasive measurement of left ventricular end diastolic pressure in conditions such as decompensated heart failure (167). In addition, fusion of the mitral inflow E and A waves seen in higher heart rates makes precise measurement of E/e' difficult. In contrast, MAPSE which is relatively easy and quick to obtain, particularly on exercise, appears to be a robust measurement which also correlates with E/e'.

9.7 LIMITATIONS

Sm and Em may be after-load dependent (168), and this is likely to apply in the measurement of MAPSE. The arterial blood pressure was similar in patients and controls both at rest and on exercise to minimise the effects of after-load difference. Yip et al. showed that diuretics reduce symptoms of breathlessness in patients with HFNEF and there has been suggestion that angiotensin converting enzyme inhibitors or receptor antagonists may improve longitudinal function (135). It is probable that the effect of treatment would be to improve longitudinal function and therefore reduce the differences in MAPSE seen between patients and controls. In addition, it would have been difficult to account for a resulting increase in arterial blood pressure on exercise if treatment was stopped in these patients.

9.8 CONCLUSION

MAPSE is a simple and technically easy measurement to obtain at rest and on exercise and it reflects more sophisticated indices of left ventricular function. Left ventricular atrioventricular motion is a fundamental property of the left ventricular function and a simple M-mode measurement such as MAPSE appears to be a robust and good discriminator especially when applied on exercise.

CHAPTER 10:

CONCLUSION AND DISCUSSION

10. CONCLUSION AND DISCUSSION

10.1 DISCUSSION

It remains unclear whether HFNEF and HFREF are part of a spectrum of heart failure or whether they are distinct diagnosis. The unimodal distribution of left ventricular ejection fraction in large studies suggests a single syndrome with increasing degrees of left ventricular remodelling. However, the different structural and biomolecular aspects which might be associated with neutral outcomes in drug trials with angiotensin converting enzyme inhibitor (169), angiotensin receptor blocker (170) and beta blocker (171) compared to HFREF might support that clinical heart failure presents and evolves not as a single, but as two syndromes each with specific mechanisms responsible for left ventricular diastolic dysfunction seen in heart failure, regardless of whether the left ventricular ejection fraction is reduced or preserved. The exact progression of HFNEF is not clear. Long term follow up study would be the only way to demonstrate if patients evolve from HFNEF to HFREF, and understand the natural progression of the condition.

The diagnosis of HFNEF remains challenging and not at all straightforward given that the symptom of exercise intolerance or dyspnoea are both non-specific, difficult to quantify, and are common presentations in many other medical conditions. In addition, many patients with such symptoms have multiple comorbidities. HFNEF constitutes 50% of the heart failure population and its rising prevalence threatens to make it the most common form of heart failure in the near future. It is unclear if the

increasing prevalence of HFNEF is a reflection of the increase in obesity and metabolic syndrome, both of which are commonly seen in patient with HFNEF, or over-diagnosis because of inexact diagnostic criteria and difficulties in precisely assessing diastolic dysfunction which is not exclusive to the pathophysiology of HFNEF.

The body mass index (BMI) of HFNEF patients in many studies is more then 25 and commonly more than 30. In this project, 73% of HFNEF patients had a BMI > 25kg/m^2, and 53% had a BMI > 30kg/m^2. This could be due to a regional difference in population, but the mean BMI was not dissimilar to many other HFNEF studies (23). It is difficult to determine the effects of increase loading due to obesity alone on the overall cardiovascular function given that, diabetes and hypertension are commonly found in obesity. Diastolic dysfunction is found to be associated with obesity (172) and could precede systolic dysfunction. Even though many parameters used to study the pathophysiology of HFNEF are corrected to either body mass index or body surface area, the true impact of body weight on cardiac function remains unknown. Therefore, a future study to compare the pathophysiology between obese HFNEF patients and non-obese HFNEF patients might shed some light. Metabolic syndrome is very common in developing countries. The question is whether HFNEF is a diagnosis of metabolic syndrome in older people.

The main aim to study the pathophysiological mechanism underlying HFNEF is to diagnose and treat the condition. To date, the pathophysiology of HFNEF remains

uncertain given the complexity of the condition. Patients with HFNEF are likely to display a mixture of abnormalities as shown in the extensive research over the past two decades. Fundamentally, HFNEF is a condition of cardiovascular reserve disorder encompassing systolic, diastolic, chronotropic, energetics and vascular abnormalities. The root of all these problems could be a degenerative signalling compound which is responsible in triggering a cascade of changes in the extracellular matrix or myocytes, interfering with the normal structure and function of the myocardium. The presence of conditions such as hypertension, diabetes and obesity might have accelerated or contributed towards its degeneration. Future research focus should be to identify and interfere with such myocardial signalling pathway.

In order to carry out appropriate research specific to the condition, accurate identification of patients is crucial. Therefore, improvement in the diagnosis of HFNEF using non-invasive methods is important. The current diagnosis guidelines for HFNEF are complex and not without flaws. The guidelines identify a proportion of patients with signs of congestion associated with high filling pressures at rest, detected using a selection of echocardiographic parameters. However, HFNEF patients can present at different stages of the condition. In early stages, these patients commonly have normal resting haemodynamical and echocardiographical findings and would not meet the criteria for diagnosis of HFNEF. The majority of HFNEF patients are symptomatic on exertion and therefore, it is not surprising that tests performed at rest are frequently negative. The studies in this thesis identified

complex left ventricular systolic and diastolic dysfunction which became apparent on exercise in a group of HFNEF patients, some of whom do not fulfil the criteria of the current European Society of Cardiology guidelines. Furthermore, left ventricular function abnormalities were found in a group of well controlled hypertensive patients implying that these patients could be in the early stage of HFNEF, and with time could progress to developing signs and symptoms meeting the criteria for diagnosis of HFNEF. Of note, these findings also suggest that controlling blood pressure might not entirely stop the progression of disease and that changes at the molecular level have taken place much earlier than the presentation of disease. Failing to diagnose the condition early could explain the high morbidity and mortality of the condition.

10.2 FINAL CONCLUSION

“Diastolic Heart Failure” is an obsolete term as diastolic dysfunction rarely if at all occurs in isolation. The findings of this thesis showed that patients who previously would have been labelled as diastolic heart failure have left ventricular systolic dysfunction which is not apparent at rest given that they only become symptomatic on exercise. Therefore, using exercise echocardiography, complex abnormalities of left ventricular systolic and diastolic function at rest and on exercise were found using a combination of tissue Doppler and speckle tracking imaging. The findings of this thesis confirmed that left ventricular systolic function is impaired due to longitudinal dysfunction, including reduced longitudinal strain, impaired left ventricular twist (Chapter 5) (136) and left ventricular dyssynchrony(173). These systolic abnormalities affect left ventricular diastolic function and delay left ventricular relaxation which lead to reduced and delayed untwisting (136).

The release of potential energy stored in systole for left ventricular recoil during untwisting in diastole generates sufficient intraventricular pressure gradient to create a suction effect for rapid filling of the left ventricle, particularly during exercise when diastolic filling time is shortened as heart rate increases. In HFNEF, left ventricular untwisting is impaired, leading to reduced left ventricular suction and hence early left ventricular filling which is not compensated by late diastolic filling during atrial contraction, secondary to diminished left atrial functional reserve (Chapter 6) (145).

Furthermore, this project confirmed that exercise induces torsional dyssynchrony due to the uncoupling of left ventricular longitudinal and twist mechanics, which are the two main components responsible for the overall atrioventricular plane motion. The disco-ordination of these two motions contributes to the reduction of exercise capacity (Chapter 7)(173).

In addition, there is a significantly reduced systolic and diastolic functional reserve, as seen in patients with HFNEF, in a group of treated hypertensive patients with normal resting echocardiography examination (Chapter 8) (174). This showed that normal resting echocardiography does not preclude the presence of significant functional abnormalities on exercise that contribute to symptoms, and suggests that subclinical level of left ventricular mass increase might be associated with impaired left ventricular function which could represent the early stage of HFNEF.

Left ventricular systolic and diastolic dysfunction can be detected using echocardiography at rest. But, more importantly these abnormalities become more apparent on exercise which is when the patients are symptomatic. The additional information from exercise studies could identify HFNEF patients at an early stage when they do not meet the current criteria of diagnosis and hence exercise parameters should be included as part of the HFNEF diagnostic pathway.

Current guidelines for diagnosing HFNEF involve multiple echocardiographical and invasive haemodynamic measurements (31) which might not be applicable in daily

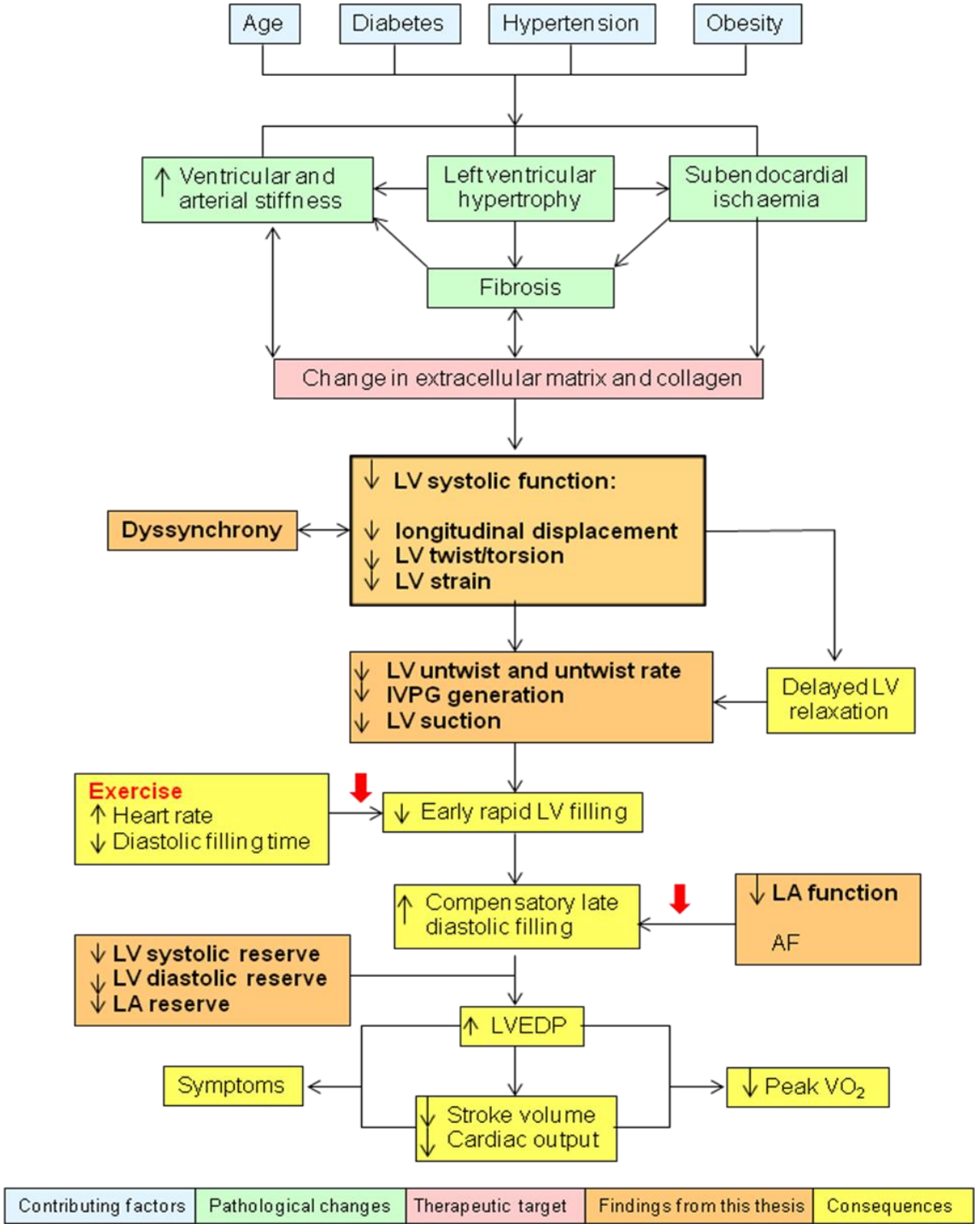
clinical settings. The current guidelines do not include any exercise assessments. Admittedly, multiple echocardiographical measurements during exercise is time consuming, requires certain expertise and accurate data analyses require training and experience. A simple and technically easy measurement at rest and on exercise which reflects more complicated left ventricular function indices might ease the diagnosis of HFNEF.

The measurement of MAPSE is easily obtainable on exercise even in technically challenging imaging subjects. Furthermore, MAPSE was shown to reflect more sophisticated indices of left ventricular function, particularly indices which relate to diastolic dysfunction and appears to be a robust and good discriminator for HFNEF, making it a potential diagnostic measurement (Chapter 9) (175).

The pathophysiology of HFNEF is unlikely to be explained by a single causal mechanism. Research has provided, and continues to provide, crucial information about the molecular, structural and physiological mechanisms involved in HFNEF but no novel target for precise therapy has been found yet. Nevertheless, the understanding of the pathophysiology of HFNEF would aid the establishment of an accurate investigation pathway which could increase diagnostic yield in this group of patients. This would enable more accurate recruitment of HFNEF patients in medical trials in search for treatment for this condition.

To date, the management of HFNEF involves risk modification by treating contributory conditions such as hypertension, diabetes and obesity, and preventing subendocardial ischaemia, development of left ventricular hypertrophy and myocardial fibrosis, in the hope that these patients who are at risk do not progress to develop HFNEF. In those presenting with symptoms of heart failure, the search for therapeutic targets which improve morbidity and mortality continues. The findings in this thesis are suggestive that the primary abnormality more likely resides in the extracellular matrix, a common pathway involved in all the comorbidities of HFNEF, and this may be a potential therapeutic target (Figure 10.1).

Figure 10.1 Flow chart illustrating unifying hypothesis



LV, left ventricular; IVPG, intraventricular pressure gradient; LA, left atrial; AF, atrial fibrillation; LVEDP, left ventricular end diastolic pressure; VO_2,oxygen consumption.

APPENDICES

APPENDIX 1 LIST OF ABBREVIATIONS

2D	two-dimensional
A	late diastolic mitral inflow velocity
A'	peak late diastolic myocardial mitral annular velocity by pulse wave Doppler imaging
ACE	angiotensin converting enzyme
Ad	duration of late diastole mitral inflow
AF	atrial fibrillation
AFRI	atrial functional reserve index
Am	peak late diastolic myocardial mitral annular velocity by colour tissue Doppler imaging
ANOVA / Anova	analysis of variance analysis
ARB	angiotensin receptor blocker
Ard - Ad	difference between duration of reversed pulmonary vein atrial systolic flow (Ard) and duration of late diastole mitral inflow (Ad)
ARP	abnormal relaxation pattern
AVC	aortic valve closure
BMI	body mass index
BNP	B-type natriuretic peptide
BP	blood pressure
bpm	beats per minute

BSA	body surface area
CO	cardiac output
CPET	cardiopulmonary exercise testing
DHF	diastolic heart failure
DLFRI	diastolic longitudinal function reserve index
dP/dt	left ventricular pressure change
DT	deceleration time of early mitral inflow velocity
E	early diastolic mitral inflow velocity
E’ or e'	early diastolic myocardial mitral annular velocity by pulse wave Doppler imaging
E/A	ratio of early to late diastolic mitral inflow velocity
E/e'	ratio of early mitral diastolic inflow velocity to early diastolic mitral annular velocity
Ea	arterial elastance
ECG	electrocardiogram
EDP	end diastolic pressure
EDPVR	end diastolic pressure-volume relationship
EDV	end diastolic volume
Ees	end systolic elastance
EF	ejection fraction
Em	peak early diastolic myocardial mitral annular velocity by colour tissue Doppler imaging
ESC	European Society of Cardiology

ESPVR	end systolic pressure-volume relationship
FS	fractional shortening
HFNEF	heart failure with a normal ejection fraction
HFPEF	heart failure with a preserved ejection fraction (same as HFNEF)
HFREF	heart failure with a reduced ejection fraction
ICC	interclass correlation coefficient
IVPG	intraventricular pressure gradient
IVRT	isovolumic relaxation time
IVSd	interventricular septal thickness in diastole
K	chamber stiffness
LA	left atrium / left atrial
LAFRI	left atrial functional reserve index
LAVI	left atrial volume index
LE	longitudinal extension
LV	left ventricle / left ventricular
LVEDD	left ventricular end diastolic dimension
LVEDP	left ventricular end diastolic pressure
LVEDVI	left ventricular end diastolic volume index
LVEDSI	left ventricular end systolic volume index
LVEF	left ventricular ejection fraction
LVH	left ventricular hypertrophy
LVMI	left ventricular mass index

LVOT	left ventricular outflow tract
LVPVR	left ventricular pressure-volume relationship
MAPSE	mitral annular peak systolic excursion
MRI	magnetic resonance imaging
NT-proBNP	N-terminal pro B-type natriuretic peptide
NYHA	New York Heart Association
p	probability
PCWP	pulmonary capillary wedge pressure
Peak VO_2	peak oxygen consumption
PPI	peak power index
PW	posterior wall
PWD	pulse wave Doppler
r	correlation
RER	respiratory exchange ratio
RFP	restrictive filling pattern
ROC	receiver operator curve
ROI	region of interest
S'	peak systolic myocardial mitral annular velocity by pulse wave Doppler imaging
SD	standard deviation
SDSM	standard deviation systolic motion
SHF	systolic heart failure
SLFRI	systolic longitudinal function reserve index

Sm	peak systolic myocardial mitral annular velocity by colour tissue Doppler
STI	speckle tracking imaging
SV	stroke volume
SWI	stroke work index
TDI	tissue Doppler imaging
TLMD	twist-longitudinal motion delay
UT	untwist
UT:LE	ratio of untwist to longitudinal extension
UTR	untwisting rate
VO_2	oxygen consumption
Vp	mitral flow propagation velocity
VTI	velocity time integral

REFERENCE LIST

(1) Chen CH, Nakayama M, Nevo E, Fetics BJ, Maughan WL, Kass DA. Coupled systolic-ventricular and vascular stiffening with age: implications for pressure regulation and cardiac reserve in the elderly. J Am Coll Cardiol 1998 Nov;32(5):1221-7.

(2) Kawaguchi M, Hay I, Fetics B, Kass DA. Combined ventricular systolic and arterial stiffening in patients with heart failure and preserved ejection fraction: implications for systolic and diastolic reserve limitations. Circulation 2003 Feb 11;107(5):714-20.

(3) Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Trends in prevalence and outcome of heart failure with preserved ejection fraction. N Engl J Med 2006 Jul 20;355(3):251-9.

(4) Westermann D, Kasner M, Steendijk P, Spillmann F, Riad A, Weitmann K, et al. Role of left ventricular stiffness in heart failure with normal ejection fraction. Circulation 2008 Apr 22;117(16):2051-60.

(5) Zile MR, Baicu CF, Gaasch WH. Diastolic heart failure--abnormalities in active relaxation and passive stiffness of the left ventricle. N Engl J Med 2004 May 6;350(19):1953-9.

(6) De Keulenaer GW, Brutsaert DL. Diastolic heart failure: a separate disease or selection bias? Prog Cardiovasc Dis 2007 Jan;49(4):275-83.

(7) Solomon SD, Anavekar N, Skali H, McMurray JJ, Swedberg K, Yusuf S, et al. Influence of ejection fraction on cardiovascular outcomes in a broad spectrum of heart failure patients. Circulation 2005 Dec 13;112(24):3738-44.

(8) Cleland JG, Swedberg K, Follath F, Komajda M, Cohen-Solal A, Aguilar JC, et al. The EuroHeart Failure survey programme-- a survey on the quality of care among patients with heart failure in Europe. Part 1: patient characteristics and diagnosis. Eur Heart J 2003 Mar;24(5):442-63.

(9) Flather MD, Shibata MC, Coats AJ, Van Veldhuisen DJ, Parkhomenko A, Borbola J, et al. Randomized trial to determine the effect of nebivolol on mortality and cardiovascular hospital admission in elderly patients with heart failure (SENIORS). Eur Heart J 2005 Feb;26(3):215-25.

(10) Brutsaert DL. Diastolic heart failure: perception of the syndrome and scope of the problem. Prog Cardiovasc Dis 2006 Nov;49(3):153-6.

(11) Yu CM, Lin H, Yang H, Kong SL, Zhang Q, Lee SW. Progression of systolic abnormalities in patients with "isolated" diastolic heart failure and diastolic dysfunction. Circulation 2002 Mar 12;105(10):1195-201.

(12) Yip G, Wang M, Zhang Y, Fung JW, Ho PY, Sanderson JE. Left ventricular long axis function in diastolic heart failure is reduced in both diastole and systole: time for a redefinition? Heart 2002 Feb;87(2):121-5.

(13) Nikitin NP, Witte KK, Clark AL, Cleland JG. Color tissue Doppler-derived long-axis left ventricular function in heart failure with preserved global systolic function. Am J Cardiol 2002 Nov 15;90(10):1174-7.

(14) Petrie MC, Caruana L, Berry C, McMurray JJ. "Diastolic heart failure" or heart failure caused by subtle left ventricular systolic dysfunction? Heart 2002 Jan;87(1):29-31.

(15) Bruch C, Gradaus R, Gunia S, Breithardt G, Wichter T. Doppler tissue analysis of mitral annular velocities: evidence for systolic abnormalities in patients with diastolic heart failure. J Am Soc Echocardiogr 2003 Oct;16(10):1031-6.

(16) Vinereanu D, Nicolaides E, Tweddel AC, Fraser AG. "Pure" diastolic dysfunction is associated with long-axis systolic dysfunction. Implications for the diagnosis and classification of heart failure. Eur J Heart Fail 2005 Aug;7(5):820-8.

(17) Richartz BM, Werner GS, Ferrari M, Figulla HR. Comparison of left ventricular systolic and diastolic function in patients with idiopathic dilated cardiomyopathy and mild heart failure versus those with severe heart failure. Am J Cardiol 2002 Aug 15;90(4):390-4.

(18) van Heerebeek L, Borbely A, Niessen HW, Bronzwaer JG, van d, V, Stienen GJ, et al. Myocardial structure and function differ in systolic and diastolic heart failure. Circulation 2006 Apr 25;113(16):1966-73.

(19) Yip GW, Fung JW, Tan YT, Sanderson JE. Hypertension and heart failure: a dysfunction of systole, diastole or both? J Hum Hypertens 2009 May;23(5):295-306.

(20) Skaluba SJ, Litwin SE. Mechanisms of exercise intolerance: insights from tissue Doppler imaging. Circulation 2004 Mar 2;109(8):972-7.

(21) Sanderson JE. Heart failure with a normal ejection fraction. Heart 2007 Feb;93(2):155-8.

(22) Yip GW, Frenneaux M, Sanderson JE. Heart failure with a normal ejection fraction: new developments. Heart 2009 Oct;95(19):1549-52.

(23) Maeder MT, Kaye DM. Heart failure with normal left ventricular ejection fraction. J Am Coll Cardiol 2009 Mar 17;53(11):905-18.

(24) Borlaug BA, Melenovsky V, Russell SD, Kessler K, Pacak K, Becker LC, et al. Impaired chronotropic and vasodilator reserves limit exercise capacity in patients with heart failure and a preserved ejection fraction. Circulation 2006 Nov 14;114(20):2138-47.

(25) Bhatia RS, Tu JV, Lee DS, Austin PC, Fang J, Haouzi A, et al. Outcome of heart failure with preserved ejection fraction in a population-based study. N Engl J Med 2006 Jul 20;355(3):260-9.

(26) Tribouilloy C, Rusinaru D, Mahjoub H, Souliere V, Levy F, Peltier M, et al. Prognosis of heart failure with preserved ejection fraction: a 5 year prospective population-based study. Eur Heart J 2008 Feb;29(3):339-47.

(27) Abhayaratna WP, Marwick TH, Smith WT, Becker NG. Characteristics of left ventricular diastolic dysfunction in the community: an echocardiographic survey. Heart 2006 Sep;92(9):1259-64.

(28) Henein M, Lindqvist P, Francis D, Morner S, Waldenstrom A, Kazzam E. Tissue Doppler analysis of age-dependency in diastolic ventricular behaviour and filling: a cross-sectional study of healthy hearts (the Umea General Population Heart Study). Eur Heart J 2002 Jan;23(2):162-71.

(29) Wong CY, O'Moore-Sullivan T, Leano R, Byrne N, Beller E, Marwick TH. Alterations of left ventricular myocardial characteristics associated with obesity. Circulation 2004 Nov 9;110(19):3081-7.

(30) Ingle L, Cleland JG, Clark AL. Perception of symptoms is out of proportion to cardiac pathology in patients with "diastolic heart failure". Heart 2008 Jun;94(6):748-53.

(31) Paulus WJ, Tschope C, Sanderson JE, Rusconi C, Flachskampf FA, Rademakers FE, et al. How to diagnose diastolic heart failure: a consensus statement on the diagnosis of heart failure with normal left ventricular ejection fraction by the Heart Failure and Echocardiography Associations of the European Society of Cardiology. Eur Heart J 2007 Oct;28(20):2539-50.

(32) Nagueh SF, Appleton CP, Gillebert TC, Marino PN, Oh JK, Smiseth OA, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. J Am Soc Echocardiogr 2009 Feb;22(2):107-33.

(33) Vasan RS, Levy D. Defining diastolic heart failure: a call for standardized diagnostic criteria. Circulation 2000 May 2;101(17):2118-21.

(34) Yturralde RF, Gaasch WH. Diagnostic criteria for diastolic heart failure. Prog Cardiovasc Dis 2005 Mar;47(5):314-9.

(35) Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr 2005 Dec;18(12):1440-63.

(36) Mahler F, Ross J, Jr., O'Rourke RA, Covell JW. Effects of changes in preload, afterload and inotropic state on ejection and isovolumic phase measures of contractility in the conscious dog. Am J Cardiol 1975 May;35(5):626-34.

(37) Maciver DH, Townsend M. A novel mechanism of heart failure with normal ejection fraction. Heart 2008 Apr;94(4):446-9.

(38) Maurer MS, Kronzon I, Burkhoff D. Ventricular pump function in heart failure with normal ejection fraction: insights from pressure-volume measurements. Prog Cardiovasc Dis 2006 Nov;49(3):182-95.

(39) Aurigemma GP, Gaasch WH. Clinical practice. Diastolic heart failure. N Engl J Med 2004 Sep 9;351(11):1097-105.

(40) Gibson DG, Francis DP. Clinical assessment of left ventricular diastolic function. Heart 2003 Feb;89(2):231-8.

(41) De Boeck BW, Cramer MJ, Oh JK, van der Aa RP, Jaarsma W. Spectral pulsed tissue Doppler imaging in diastole: a tool to increase our insight in and assessment of diastolic relaxation of the left ventricle. Am Heart J 2003 Sep;146(3):411-9.

(42) Mottram PM, Marwick TH. Assessment of diastolic function: what the general cardiologist needs to know. Heart 2005 May;91(5):681-95.

(43) Rushmer RF, Crystal DK, Wagner C. The functional anatomy of ventricular contraction. Circ Res 1953 Mar;1(2):162-70.

(44) Henein MY, Gibson DG. Normal long axis function. Heart 1999 Feb;81(2):111-3.

(45) Ommen SR, Nishimura RA, Appleton CP, Miller FA, Oh JK, Redfield MM, et al. Clinical utility of Doppler echocardiography and tissue Doppler imaging in the estimation of left ventricular filling pressures: A comparative simultaneous Doppler-catheterization study. Circulation 2000 Oct 10;102(15):1788-94.

(46) Hasegawa H, Little WC, Ohno M, Brucks S, Morimoto A, Cheng HJ, et al. Diastolic mitral annular velocity during the development of heart failure. J Am Coll Cardiol 2003 May 7;41(9):1590-7.

(47) Wang M, Yip GW, Wang AY, Zhang Y, Ho PY, Tse MK, et al. Peak early diastolic mitral annulus velocity by tissue Doppler imaging adds independent and incremental prognostic value. J Am Coll Cardiol 2003 Mar 5;41(5):820-6.

(48) Wang M, Yip G, Yu CM, Zhang Q, Zhang Y, Tse D, et al. Independent and incremental prognostic value of early mitral annulus velocity in patients with impaired left ventricular systolic function. J Am Coll Cardiol 2005 Jan 18;45(2):272-7.

(49) Wang M, Yip GW, Wang AY, Zhang Y, Ho PY, Tse MK, et al. Tissue Doppler imaging provides incremental prognostic value in patients with systemic hypertension and left ventricular hypertrophy. J Hypertens 2005 Jan;23(1):183-91.

(50) Nagueh SF, Middleton KJ, Kopelen HA, Zoghbi WA, Quinones MA. Doppler tissue imaging: a noninvasive technique for evaluation of left ventricular relaxation and estimation of filling pressures. J Am Coll Cardiol 1997 Nov 15;30(6):1527-33.

(51) Pritchett AM, Jacobsen SJ, Mahoney DW, Rodeheffer RJ, Bailey KR, Redfield MM. Left atrial volume as an index of left atrial size: a population-based study. J Am Coll Cardiol 2003 Mar 19;41(6):1036-43.

(52) Lim TK, Ashrafian H, Dwivedi G, Collinson PO, Senior R. Increased left atrial volume index is an independent predictor of raised serum natriuretic peptide in patients with suspected heart failure but normal left ventricular ejection fraction: Implication for diagnosis of diastolic heart failure. Eur J Heart Fail 2006 Jan;8(1):38-45.

(53) Emery WT, Jadavji I, Choy JB, Lawrance RA. Investigating the European Society of Cardiology Diastology Guidelines in a practical scenario. Eur J Echocardiogr 2008 Sep;9(5):685-91.

(54) Maurer MS, King DL, El-Khoury RL, Packer M, Burkhoff D. Left heart failure with a normal ejection fraction: identification of different pathophysiologic mechanisms. J Card Fail 2005 Apr;11(3):177-87.

(55) Garcia EH, Perna ER, Farias EF, Obregon RO, Macin SM, Parras JI, et al. Reduced systolic performance by tissue Doppler in patients with preserved and abnormal ejection fraction: new insights in chronic heart failure. Int J Cardiol 2006 Apr 4;108(2):181-8.

(56) Shan K, Bick RJ, Poindexter BJ, Shimoni S, Letsou GV, Reardon MJ, et al. Relation of tissue Doppler derived myocardial velocities to myocardial structure and beta-adrenergic receptor density in humans. J Am Coll Cardiol 2000 Sep;36(3):891-6.

(57) Yip GW, Zhang Y, Tan PY, Wang M, Ho PY, Brodin LA, et al. Left ventricular long-axis changes in early diastole and systole: impact of systolic function on diastole. Clin Sci (Lond) 2002 May;102(5):515-22.

(58) Steine K, Stugaard M, Smiseth OA. Mechanisms of retarded apical filling in acute ischemic left ventricular failure. Circulation 1999 Apr 20;99(15):2048-54.

(59) Gibson DG, Prewitt TA, Brown DJ. Analysis of left ventricular wall movement during isovolumic relaxation and its relation to coronary artery disease. Br Heart J 1976 Oct;38(10):1010-9.

(60) Ashikaga H, Criscione JC, Omens JH, Covell JW, Ingels NB, Jr. Transmural left ventricular mechanics underlying torsional recoil during relaxation. Am J Physiol Heart Circ Physiol 2004 Feb;286(2):H640-H647.

(61) Zile MR, Gaasch WH, Carroll JD, Feldman MD, Aurigemma GP, Schaer GL, et al. Heart failure with a normal ejection fraction: is measurement of diastolic function necessary to make the diagnosis of diastolic heart failure? Circulation 2001 Aug 14;104(7):779-82.

(62) Borlaug BA, Kass DA. Mechanisms of diastolic dysfunction in heart failure. Trends Cardiovasc Med 2006 Nov;16(8):273-9.

(63) Stefanadis C, Dernellis J, Toutouzas P. A clinical appraisal of left atrial function. Eur Heart J 2001 Jan;22(1):22-36.

(64) Matsuda Y, Toma Y, Ogawa H, Matsuzaki M, Katayama K, Fujii T, et al. Importance of left atrial function in patients with myocardial infarction. Circulation 1983 Mar;67(3):566-71.

(65) Fung JW, Sanderson JE, Yip GW, Zhang Q, Yu CM. Impact of atrial fibrillation in heart failure with normal ejection fraction: a clinical and echocardiographic study. J Card Fail 2007 Oct;13(8):649-55.

(66) Abhayaratna WP, Seward JB, Appleton CP, Douglas PS, Oh JK, Tajik AJ, et al. Left atrial size: physiologic determinants and clinical applications. J Am Coll Cardiol 2006 Jun 20;47(12):2357-63.

(67) Tsang TS, Barnes ME, Gersh BJ, Bailey KR, Seward JB. Left atrial volume as a morphophysiologic expression of left ventricular diastolic dysfunction and relation to cardiovascular risk burden. Am J Cardiol 2002 Dec 15;90(12):1284-9.

(68) Leung DY, Boyd A, Ng AA, Chi C, Thomas L. Echocardiographic evaluation of left atrial size and function: current understanding, pathophysiologic correlates, and prognostic implications. Am Heart J 2008 Dec;156(6):1056-64.

(69) Donal E, Raud-Raynier P, de PC, Gervais R, Rosier A, Roulaud M, et al. Resting echocardiographic assessments of left atrial function and filling pressure interest in the understanding of exercise capacity in patients with chronic congestive heart failure. J Am Soc Echocardiogr 2008 Jun;21(6):703-10.

(70) Terzi S, Dayi SU, Akbulut T, Sayar N, Bilsel T, Tangurek B, et al. Value of left atrial function in predicting exercise capacity in heart failure with moderate to severe left ventricular systolic dysfunction. Int Heart J 2005 Jan;46(1):123-31.

(71) Melenovsky V, Borlaug BA, Rosen B, Hay I, Ferruci L, Morell CH, et al. Cardiovascular features of heart failure with preserved ejection fraction versus nonfailing hypertensive left ventricular hypertrophy in the urban Baltimore community: the role of atrial remodeling/dysfunction. J Am Coll Cardiol 2007 Jan 16;49(2):198-207.

(72) Rossi A, Cicoira M, Bonapace S, Golia G, Zanolla L, Franceschini L, et al. Left atrial volume provides independent and incremental information compared with exercise tolerance parameters in patients with heart failure and left ventricular systolic dysfunction. Heart 2007 Nov;93(11):1420-5.

(73) Kurt M, Wang J, Torre-Amione G, Nagueh SF. Left atrial function in diastolic heart failure. Circ Cardiovasc Imaging 2009 Jan;2(1):10-5.

(74) Gibson DG, Sanderson JE, Traill TA, Brown DJ, Goodwin JF. Regional left ventricular wall movement in hypertrophic cardiomyopathy. Br Heart J 1978 Dec;40(12):1327-33.

(75) Henein MY, Gibson DG. Suppression of left ventricular early diastolic filling by long axis asynchrony. Br Heart J 1995 Feb;73(2):151-7.

(76) Yu CM, Chau E, Sanderson JE, Fan K, Tang MO, Fung WH, et al. Tissue Doppler echocardiographic evidence of reverse remodeling and improved synchronicity by simultaneously delaying regional contraction after biventricular pacing therapy in heart failure. Circulation 2002 Jan 29;105(4):438-45.

(77) Yu CM, Lin H, Zhang Q, Sanderson JE. High prevalence of left ventricular systolic and diastolic asynchrony in patients with congestive heart failure and normal QRS duration. Heart 2003 Jan;89(1):54-60.

(78) Wang J, Kurrelmeyer KM, Torre-Amione G, Nagueh SF. Systolic and diastolic dyssynchrony in patients with diastolic heart failure and the effect of medical therapy. J Am Coll Cardiol 2007 Jan 2;49(1):88-96.

(79) Yu CM, Zhang Q, Yip GW, Lee PW, Kum LC, Lam YY, et al. Diastolic and systolic asynchrony in patients with diastolic heart failure: a common but ignored condition. J Am Coll Cardiol 2007 Jan 2;49(1):97-105.

(80) Streeter DD, Jr., Spotnitz HM, Patel DP, Ross J, Jr., Sonnenblick EH. Fiber orientation in the canine left ventricle during diastole and systole. Circ Res 1969 Mar;24(3):339-47.

(81) Lunkenheimer PP, Redmann K, Kling N, Jiang X, Rothaus K, Cryer CW, et al. Three-dimensional architecture of the left ventricular myocardium. Anat Rec A Discov Mol Cell Evol Biol 2006 Jun;288(6):565-78.

(82) Torrent-Guasp F, Kocica MJ, Corno AF, Komeda M, Carreras-Costa F, Flotats A, et al. Towards new understanding of the heart structure and function. Eur J Cardiothorac Surg 2005 Feb;27(2):191-201.

(83) Buckberg GD, Castella M, Gharib M, Saleh S. Active myocyte shortening during the 'isovolumetric relaxation' phase of diastole is responsible for ventricular suction; 'systolic ventricular filling'. Eur J Cardiothorac Surg 2006 Apr;29 Suppl 1:S98-106.

(84) Greenbaum RA, Ho SY, Gibson DG, Becker AE, Anderson RH. Left ventricular fibre architecture in man. Br Heart J 1981 Mar;45(3):248-63.

(85) Sengupta PP, Krishnamoorthy VK, Korinek J, Narula J, Vannan MA, Lester SJ, et al. Left ventricular form and function revisited: applied translational science to cardiovascular ultrasound imaging. J Am Soc Echocardiogr 2007 May;20(5):539-51.

(86) Torrent-Guasp F, Ballester M, Buckberg GD, Carreras F, Flotats A, Carrio I, et al. Spatial orientation of the ventricular muscle band: physiologic contribution and surgical implications. J Thorac Cardiovasc Surg 2001 Aug;122(2):389-92.

(87) Sengupta PP, Khandheria BK, Korinek J, Wang J, Belohlavek M. Biphasic tissue Doppler waveforms during isovolumic phases are associated with asynchronous deformation of subendocardial and subepicardial layers. J Appl Physiol 2005 Sep;99(3):1104-11.

(88) Rademakers FE, Rogers WJ, Guier WH, Hutchins GM, Siu CO, Weisfeldt ML, et al. Relation of regional cross-fiber shortening to wall thickening in the intact heart. Three-dimensional strain analysis by NMR tagging. Circulation 1994 Mar;89(3):1174-82.

(89) Bogaert J, Rademakers FE. Regional nonuniformity of normal adult human left ventricle. Am J Physiol Heart Circ Physiol 2001 Feb;280(2):H610-H620.

(90) Nikolic SD, Yellin EL, Dahm M, Pajaro O, Frater RW. Relationship between diastolic shape (eccentricity) and passive elastic properties in canine left ventricle. Am J Physiol 1990 Aug;259(2 Pt 2):H457-H463.

(91) Nikolic SD, Feneley MP, Pajaro OE, Rankin JS, Yellin EL. Origin of regional pressure gradients in the left ventricle during early diastole. Am J Physiol 1995 Feb;268(2 Pt 2):H550-H557.

(92) Nikolic S, Yellin EL, Tamura K, Vetter H, Tamura T, Meisner JS, et al. Passive properties of canine left ventricle: diastolic stiffness and restoring forces. Circ Res 1988 Jun;62(6):1210-22.

(93) Sengupta PP, Khandheria BK, Korinek J, Wang J, Jahangir A, Seward JB, et al. Apex-to-base dispersion in regional timing of left ventricular shortening and lengthening. J Am Coll Cardiol 2006 Jan 3;47(1):163-72.

(94) Beyar R, Yin FC, Hausknecht M, Weisfeldt ML, Kass DA. Dependence of left ventricular twist-radial shortening relations on cardiac cycle phase. Am J Physiol 1989 Oct;257(4 Pt 2):H1119-H1126.

(95) Rademakers FE, Buchalter MB, Rogers WJ, Zerhouni EA, Weisfeldt ML, Weiss JL, et al. Dissociation between left ventricular untwisting and filling. Accentuation by catecholamines. Circulation 1992 Apr;85(4):1572-81.

(96) Notomi Y, Popovic ZB, Yamada H, Wallick DW, Martin MG, Oryszak SJ, et al. Ventricular untwisting: a temporal link between left ventricular relaxation and suction. Am J Physiol Heart Circ Physiol 2008 Jan;294(1):H505-H513.

(97) Notomi Y, Martin-Miklovic MG, Oryszak SJ, Shiota T, Deserranno D, Popovic ZB, et al. Enhanced ventricular untwisting during exercise: a mechanistic manifestation of elastic recoil described by Doppler tissue imaging. Circulation 2006 May 30;113(21):2524-33.

(98) Ingels NB, Jr., Daughters GT, Stinson EB, Alderman EL. Measurement of midwall myocardial dynamics in intact man by radiography of surgically implanted markers. Circulation 1975 Nov;52(5):859-67.

(99) Mirro MJ, Rogers EW, Weyman AE, Feigenbaum H. Angular displacement of the papillary muscles during the cardiac cycle. Circulation 1979 Aug;60(2):327-33.

(100) Buchalter MB, Weiss JL, Rogers WJ, Zerhouni EA, Weisfeldt ML, Beyar R, et al. Noninvasive quantification of left ventricular rotational deformation in normal humans using magnetic resonance imaging myocardial tagging. Circulation 1990 Apr;81(4):1236-44.

(101) Garot J, Pascal O, Diebold B, Derumeaux G, Gerber BL, Dubois-Rande JL, et al. Alterations of systolic left ventricular twist after acute myocardial infarction. Am J Physiol Heart Circ Physiol 2002 Jan;282(1):H357-H362.

(102) Urheim S, Edvardsen T, Torp H, Angelsen B, Smiseth OA. Myocardial strain by Doppler echocardiography. Validation of a new method to quantify regional myocardial function. Circulation 2000 Sep 5;102(10):1158-64.

(103) Helle-Valle T, Crosby J, Edvardsen T, Lyseggen E, Amundsen BH, Smith HJ, et al. New noninvasive method for assessment of left ventricular rotation: speckle tracking echocardiography. Circulation 2005 Nov 15;112(20):3149-56.

(104) Notomi Y, Lysyansky P, Setser RM, Shiota T, Popovic ZB, Martin-Miklovic MG, et al. Measurement of ventricular torsion by two-dimensional ultrasound speckle tracking imaging. J Am Coll Cardiol 2005 Jun 21;45(12):2034-41.

(105) van Dalen BM, Soliman OI, Vletter WB, ten Cate FJ, Geleijnse ML. Age-related changes in the biomechanics of left ventricular twist measured by speckle tracking echocardiography. Am J Physiol Heart Circ Physiol 2008 Oct;295(4):H1705-H1711.

(106) Albouaini K, Egred M, Alahmar A, Wright DJ. Cardiopulmonary exercise testing and its application. Heart 2007 Oct;93(10):1285-92.

(107) Arruda AL, Pellikka PA, Olson TP, Johnson BD. Exercise capacity, breathing pattern, and gas exchange during exercise for patients with isolated diastolic dysfunction. J Am Soc Echocardiogr 2007 Jul;20(7):838-46.

(108) Witte KK, Nikitin NP, Cleland JG, Clark AL. Excessive breathlessness in patients with diastolic heart failure. Heart 2006 Oct;92(10):1425-9.

(109) Schiller NB, Shah PM, Crawford M, DeMaria A, Devereux R, Feigenbaum H, et al. Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. American Society of Echocardiography Committee on Standards, Subcommittee on Quantitation of Two-Dimensional Echocardiograms. J Am Soc Echocardiogr 1989 Sep;2(5):358-67.

(110) Devereux RB, Alonso DR, Lutas EM, Gottlieb GJ, Campo E, Sachs I, et al. Echocardiographic assessment of left ventricular hypertrophy: comparison to necropsy findings. Am J Cardiol 1986 Feb 15;57(6):450-8.

(111) Courtois M, Kovacs SJ, Jr., Ludbrook PA. Transmitral pressure-flow velocity relation. Importance of regional pressure gradients in the left ventricle during diastole. Circulation 1988 Sep;78(3):661-71.

(112) Garcia MJ, Palac RT, Malenka DJ, Terrell P, Plehn JF. Color M-mode Doppler flow propagation velocity is a relatively preload-independent index of left ventricular filling. J Am Soc Echocardiogr 1999 Feb;12(2):129-37.

(113) Moller JE, Sondergaard E, Seward JB, Appleton CP, Egstrup K. Ratio of left ventricular peak E-wave velocity to flow propagation velocity assessed by color M-mode Doppler echocardiography in first myocardial infarction: prognostic and clinical implications. J Am Coll Cardiol 2000 Feb;35(2):363-70.

(114) Stugaard M, Risoe C, Ihlen H, Smiseth OA. Intracavitary filling pattern in the failing left ventricle assessed by color M-mode Doppler echocardiography. J Am Coll Cardiol 1994 Sep;24(3):663-70.

(115) Sessoms MW, Lisauskas J, Kovacs SJ. The left ventricular color M-mode Doppler flow propagation velocity V(p): in vivo comparison of alternative methods including physiologic implications. J Am Soc Echocardiogr 2002 Apr;15(4):339-48.

(116) Oki T, Tabata T, Yamada H, Wakatsuki T, Shinohara H, Nishikado A, et al. Clinical application of pulsed Doppler tissue imaging for assessing abnormal left ventricular relaxation. Am J Cardiol 1997 Apr 1;79(7):921-8.

(117) Langeland S, D'hooge J, Wouters PF, Leather HA, Claus P, Bijnens B, et al. Experimental validation of a new ultrasound method for the simultaneous assessment of radial and longitudinal myocardial deformation independent of insonation angle. Circulation 2005 Oct 4;112(14):2157-62.

(118) Becker M, Bilke E, Kuhl H, Katoh M, Kramann R, Franke A, et al. Analysis of myocardial deformation based on pixel tracking in two dimensional echocardiographic images enables quantitative assessment of regional left ventricular function. Heart 2006 Aug;92(8):1102-8.

(119) Takeuchi M, Borden WB, Nakai H, Nishikage T, Kokumai M, Nagakura T, et al. Reduced and delayed untwisting of the left ventricle in patients with hypertension and left ventricular hypertrophy: a study using two-dimensional speckle tracking imaging. Eur Heart J 2007 Nov;28(22):2756-62.

(120) Sun JP, Pu M, Fouad FM, Christian R, Stewart WJ, Thomas JD. Automated cardiac output measurement by spatiotemporal integration of color Doppler data. In vitro and clinical validation. Circulation 1997 Feb 18;95(4):932-9.

(121) Baicu CF, Zile MR, Aurigemma GP, Gaasch WH. Left ventricular systolic performance, function, and contractility in patients with diastolic heart failure. Circulation 2005 May 10;111(18):2306-12.

(122) Borlaug BA, Melenovsky V, Redfield MM, Kessler K, Chang HJ, Abraham TP, et al. Impact of arterial load and loading sequence on left ventricular tissue velocities in humans. J Am Coll Cardiol 2007 Oct 16;50(16):1570-7.

(123) Marino P, Little WC, Rossi A, Barbieri E, Anselmi M, Destro G, et al. Can left ventricular diastolic stiffness be measured noninvasively? J Am Soc Echocardiogr 2002 Sep;15(9):935-43.

(124) King GJ, Murphy RT, Almuntaser I, Bennett K, Ho E, Brown AS. Alterations in myocardial stiffness in elite athletes assessed by a new Doppler index. Heart 2008 Oct;94(10):1323-5.

(125) Ha JW, Lee HC, Kang ES, Ahn CM, Kim JM, Ahn JA, et al. Abnormal left ventricular longitudinal functional reserve in patients with diabetes mellitus: implication for detecting subclinical myocardial dysfunction using exercise tissue Doppler echocardiography. Heart 2007 Dec;93(12):1571-6.

(126) Kim HK, Sohn DW, Lee SE, Choi SY, Park JS, Kim YJ, et al. Assessment of left ventricular rotation and torsion with two-dimensional speckle tracking echocardiography. J Am Soc Echocardiogr 2007 Jan;20(1):45-53.

(127) Opdahl A, Helle-Valle T, Remme EW, Vartdal T, Pettersen E, Lunde K, et al. Apical rotation by speckle tracking echocardiography: a simplified bedside index of left ventricular twist. J Am Soc Echocardiogr 2008 Oct;21(10):1121-8.

(128) Ingels NB, Jr., Hansen DE, Daughters GT, Stinson EB, Alderman EL, Miller DC. Relation between longitudinal, circumferential, and oblique shortening and torsional deformation in the left ventricle of the transplanted human heart. Circ Res 1989 May;64(5):915-27.

(129) Wang J, Khoury DS, Yue Y, Torre-Amione G, Nagueh SF. Left ventricular untwisting rate by speckle tracking echocardiography. Circulation 2007 Nov 27;116(22):2580-6.

(130) Park SJ, Miyazaki C, Bruce CJ, Ommen S, Miller FA, Oh JK. Left ventricular torsion by two-dimensional speckle tracking echocardiography in patients with diastolic dysfunction and normal ejection fraction. J Am Soc Echocardiogr 2008 Oct;21(10):1129-37.

(131) Sanderson JE, Wang M, Yu CM. Tissue Doppler imaging for predicting outcome in patients with cardiovascular disease. Curr Opin Cardiol 2004 Sep;19(5):458-63.

(132) Nakai H, Takeuchi M, Nishikage T, Kokumai M, Otani S, Lang RM. Effect of aging on twist-displacement loop by 2-dimensional speckle tracking imaging. J Am Soc Echocardiogr 2006 Jul;19(7):880-5.

(133) Shmuylovich L, Kovacs SJ. E-wave deceleration time may not provide an accurate determination of LV chamber stiffness if LV relaxation/viscoelasticity is unknown. Am J Physiol Heart Circ Physiol 2007 Jun;292(6):H2712-H2720.

(134) Brubaker PH, Joo KC, Stewart KP, Fray B, Moore B, Kitzman DW. Chronotropic incompetence and its contribution to exercise intolerance in older heart failure patients. J Cardiopulm Rehabil 2006 Mar;26(2):86-9.

(135) Yip GW, Wang M, Wang T, Chan S, Fung JW, Yeung L, et al. The Hong Kong diastolic heart failure study: a randomised controlled trial of diuretics, irbesartan and ramipril on quality of life, exercise capacity, left ventricular global and regional function in heart failure with a normal ejection fraction. Heart 2008 May;94(5):573-80.

(136) Tan YT, Wenzelburger F, Lee E, Heatlie G, Leyva F, Patel K, et al. The pathophysiology of heart failure with normal ejection fraction: exercise echocardiography reveals complex abnormalities of both systolic and diastolic ventricular function involving torsion, untwist, and longitudinal motion. J Am Coll Cardiol 2009 Jun 30;54(1):36-46.

(137) Barbier P, Solomon SB, Schiller NB, Glantz SA. Left atrial relaxation and left ventricular systolic function determine left atrial reservoir function. Circulation 1999 Jul 27;100(4):427-36.

(138) Thomas L, Levett K, Boyd A, Leung DY, Schiller NB, Ross DL. Changes in regional left atrial function with aging: evaluation by Doppler tissue imaging. Eur J Echocardiogr 2003 Jun;4(2):92-100.

(139) Yu CM, Fung JW, Zhang Q, Kum LC, Lin H, Yip GW, et al. Tissue Doppler echocardiographic evidence of atrial mechanical dysfunction in coronary artery disease. Int J Cardiol 2005 Nov 2;105(2):178-85.

(140) Kono T, Sabbah HN, Rosman H, Alam M, Stein PD, Goldstein S. Left atrial contribution to ventricular filling during the course of evolving heart failure. Circulation 1992 Oct;86(4):1317-22.

(141) Wakatsuki Y, Funabashi N, Mikami Y, Shiina Y, Kawakubo M, Takahashi M, et al. Left atrial compensatory function in subjects with early stage primary hypertension assessed by using left atrial volumetric emptying fraction acquired by transthoracic echocardiography. Int J Cardiol 2009 Aug 21;136(3):363-7.

(142) Wachtell K, Hornestam B, Lehto M, Slotwiner DJ, Gerdts E, Olsen MH, et al. Cardiovascular morbidity and mortality in hypertensive patients with a history of atrial fibrillation: The Losartan Intervention For End Point Reduction in Hypertension (LIFE) study. J Am Coll Cardiol 2005 Mar 1;45(5):705-11.

(143) Vianna-Pinton R, Moreno CA, Baxter CM, Lee KS, Tsang TS, Appleton CP. Two-dimensional speckle-tracking echocardiography of the left atrium: feasibility and regional contraction and relaxation differences in normal subjects. J Am Soc Echocardiogr 2009 Mar;22(3):299-305.

(144) Wang T, Wang M, Fung JW, Yip GW, Zhang Y, Ho PP, et al. Atrial strain rate echocardiography can predict success or failure of cardioversion for atrial fibrillation: a combined transthoracic tissue Doppler and transoesophageal imaging study. Int J Cardiol 2007 Jan 8;114(2):202-9.

(145) Tan YT, Wenzelburger F, Lee E, Nightingale P, Heatlie G, Leyva F, et al. Reduced left atrial function on exercise in patients with heart failure and normal ejection fraction. Heart 2010 Jul;96(13):1017-23.

(146) Borg AN, Harrison JL, Argyle RA, Ray SG. Left ventricular torsion in primary chronic mitral regurgitation. Heart 2008 May;94(5):597-603.

(147) Shirwany A, Weber KT. Extracellular matrix remodeling in hypertensive heart disease. J Am Coll Cardiol 2006 Jul 4;48(1):97-8.

(148) Spinale FG. Myocardial matrix remodeling and the matrix metalloproteinases: influence on cardiac form and function. Physiol Rev 2007 Oct;87(4):1285-342.

(149) Henein MY, Priestley K, Davarashvili T, Buller N, Gibson DG. Early changes in left ventricular subendocardial function after successful coronary angioplasty. Br Heart J 1993 Jun;69(6):501-6.

(150) Vatner SF, Hittinger L. Myocardial perfusion dependent and independent mechanisms of regional myocardial dysfunction in hypertrophy. Basic Res Cardiol 1993;88 Suppl 1:81-95.

(151) Caruana L, Petrie MC, Davie AP, McMurray JJ. Do patients with suspected heart failure and preserved left ventricular systolic function suffer from "diastolic heart failure" or from misdiagnosis? A prospective descriptive study. BMJ 2000 Jul 22;321(7255):215-8.

(152) Serri K, Reant P, Lafitte M, Berhouet M, Le B, V, Roudaut R, et al. Global and regional myocardial function quantification by two-dimensional strain: application in hypertrophic cardiomyopathy. J Am Coll Cardiol 2006 Mar 21;47(6):1175-81.

(153) Vinereanu D, Florescu N, Sculthorpe N, Tweddel AC, Stephens MR, Fraser AG. Differentiation between pathologic and physiologic left ventricular hypertrophy by tissue Doppler assessment of long-axis function in patients with hypertrophic cardiomyopathy or systemic hypertension and in athletes. Am J Cardiol 2001 Jul 1;88(1):53-8.

(154) Borges MC, Colombo RC, Goncalves JG, Ferreira JO, Franchini KG. Longitudinal mitral annulus velocities are reduced in hypertensive subjects with or without left ventricle hypertrophy. Hypertension 2006 May;47(5):854-60.

(155) Jones CJ, Raposo L, Gibson DG. Functional importance of the long axis dynamics of the human left ventricle. Br Heart J 1990 Apr;63(4):215-20.

(156) Henein MY, Gibson DG. Long axis function in disease. Heart 1999 Mar;81(3):229-31.

(157) Andersson B, Svealv BG, Tang MS, Mobini R. Longitudinal myocardial contraction improves early during titration with metoprolol CR/XL in patients with heart failure. Heart 2002 Jan;87(1):23-8.

(158) Somaratne JB, Berry C, McMurray JJ, Poppe KK, Doughty RN, Whalley GA. The prognostic significance of heart failure with preserved left ventricular ejection fraction: a literature-based meta-analysis. Eur J Heart Fail 2009 Sep;11(9):855-62.

(159) Hoglund C, Alam M, Thorstrand C. Effects of acute myocardial infarction on the displacement of the atrioventricular plane: an echocardiographic study. J Intern Med 1989 Oct;226(4):251-6.

(160) Pai RG, Bodenheimer MM, Pai SM, Koss JH, Adamick RD. Usefulness of systolic excursion of the mitral anulus as an index of left ventricular systolic function. Am J Cardiol 1991 Jan 15;67(2):222-4.

(161) Simonson JS, Schiller NB. Descent of the base of the left ventricle: an echocardiographic index of left ventricular function. J Am Soc Echocardiogr 1989 Jan;2(1):25-35.

(162) Borlaug BA, Nishimura RA, Sorajja P, Lam CS, Redfield MM. Exercise hemodynamics enhance diagnosis of early heart failure with preserved ejection fraction. Circ Heart Fail 2010 Sep;3(5):588-95.

(163) Willenheimer R, Cline C, Erhardt L, Israelsson B. Left ventricular atrioventricular plane displacement: an echocardiographic technique for rapid assessment of prognosis in heart failure. Heart 1997 Sep;78(3):230-6.

(164) Svealv BG, Olofsson EL, Andersson B. Ventricular long-axis function is of major importance for long-term survival in patients with heart failure. Heart 2008 Mar;94(3):284-9.

(165) Carlsson M, Ugander M, Heiberg E, Arheden H. The quantitative relationship between longitudinal and radial function in left, right, and total heart pumping in humans. Am J Physiol Heart Circ Physiol 2007 Jul;293(1):H636-H644.

(166) Burgess MI, Jenkins C, Sharman JE, Marwick TH. Diastolic stress echocardiography: hemodynamic validation and clinical significance of estimation of ventricular filling pressure with exercise. J Am Coll Cardiol 2006 May 2;47(9):1891-900.

(167) Mullens W, Borowski AG, Curtin RJ, Thomas JD, Tang WH. Tissue Doppler imaging in the estimation of intracardiac filling pressure in decompensated patients with advanced systolic heart failure. Circulation 2009 Jan 6;119(1):62-70.

(168) Oki T, Fukuda K, Tabata T, Mishiro Y, Yamada H, Abe M, et al. Effect of an acute increase in afterload on left ventricular regional wall motion velocity in healthy subjects. J Am Soc Echocardiogr 1999 Jun;12(6):476-83.

(169) Cleland JG, Tendera M, Adamus J, Freemantle N, Polonski L, Taylor J. The perindopril in elderly people with chronic heart failure (PEP-CHF) study. Eur Heart J 2006 Oct;27(19):2338-45.

(170) Massie BM, Carson PE, McMurray JJ, Komajda M, McKelvie R, Zile MR, et al. Irbesartan in patients with heart failure and preserved ejection fraction. N Engl J Med 2008 Dec 4;359(23):2456-67.

(171) Hernandez AF, Hammill BG, O'Connor CM, Schulman KA, Curtis LH, Fonarow GC. Clinical effectiveness of beta-blockers in heart failure: findings from the OPTIMIZE-HF (Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure) Registry. J Am Coll Cardiol 2009 Jan 13;53(2):184-92.

(172) Peterson LR, Waggoner AD, Schechtman KB, Meyer T, Gropler RJ, Barzilai B, et al. Alterations in left ventricular structure and function in young healthy obese women: assessment by echocardiography and tissue Doppler imaging. J Am Coll Cardiol 2004 Apr 21;43(8):1399-404.

(173) Tan YT, Wenzelburger FW, Sanderson JE, Leyva F. Exercise-induced torsional dyssynchrony relates to impaired functional capacity in patients with heart failure and normal ejection fraction. Heart 2013 Feb;99(4):259-66.

(174) Tan YT, Wenzelburger F, Lee E, Heatlie G, Frenneaux M, Sanderson JE. Abnormal left ventricular function occurs on exercise in well-treated hypertensive subjects with normal resting echocardiography. Heart 2010 Jun;96(12):948-55.

(175) Wenzelburger FW, Tan YT, Choudhary FJ, Lee ES, Leyva F, Sanderson JE. Mitral annular plane systolic excursion on exercise: a simple diagnostic tool for heart failure with preserved ejection fraction. Eur J Heart Fail 2011 Sep;13(9):953-60.