Mechanisms of dyspnoea and poor exercise tolerance in a representative cohort of elderly patients with a relatively normal ejection fraction on echocardiography

Thesis submitted by
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Table of Contents

List of tables vii
List of figures viii
Publications and Presentations ix
Declaration x
Acknowledgements xi
Abstract xii

chapter 1
Introduction 1
  1.1 Context of the study 1
  1.2 Statement of the research problem 1
  1.3 The objectives of the studies described in this thesis 3
    1.3.1 Study aims
    1.3.2 Summary of activity to address the aims
  1.4 Methods 4
    1.4.1 Conceptual framework of the study
    1.4.2 Method
    1.4.3 Analysis of the data
  1.5 The significance of the described studies 6
  1.6 Definitions of the key terms 7
  1.7 Organization of the thesis 8

chapter 2
Literature review 11
  2.1 Heart failure 11
    2.1.1 Heart failure with reduced ejection fraction (HFrEF)
    2.1.2 Heart failure with preserved ejection fraction (HFpEF)
  2.2 Epidemiology 13
    2.2.1 Epidemiology of HFpEF
    2.2.2 Studies investigating Stage A of the disease
    2.2.3 Studies investigating Stage B of the disease
    2.2.4 Studies investigating Stage C of the disease
  2.3 Pathophysiology and etiology 19
    2.3.1 Potential mechanisms of HFpEF/diastolic dysfunction
    2.3.2 Hypertension and HFpEF
    2.3.3 Reversible ischemia/previous infarcts
    2.3.4 Ageing and hypothyroidism
    2.3.5 Diabetes mellitus
    2.3.6 Acute pulmonary oedema and HFpEF
  2.4 Diagnostic criteria for HFpEF 29
2.5 Assessment of HFpEF
2.5.1 Cardiac catheterization
2.5.2 Echocardiography
2.5.3 Cardiopulmonary exercise testing (CPEX)
2.5.4 Neurohormonal levels

2.6 Prognosis of HFpEF

2.7 Management of HFpEF
2.7.1 Randomized controlled trials
2.7.2 Observational and retrospective trials
2.7.3 Future therapies

2.8 Scope of currently described studies

chapter 3

Methods, subject selection and subject characteristics
3.1 Introduction
3.1.1 Sample selection
3.1.2 Sample size considerations
3.2 Baseline characteristics and questionnaire for symptom status and quality of life
3.2.1 Baseline characteristics
3.2.2 Health questionnaire
3.3 Echocardiography
3.4 Cardiopulmonary exercise testing (CPEX)
3.5 Subject characteristics
3.5.2 Dyspnœic subjects’ characteristics
3.5. Subject characteristics based on CPEX performance
3.6 Baseline echo characteristics
3.7 Statistical analysis

chapter 4

Clinical, echocardiographic and exercise predictors of dyspnoea
in the community
4.1 Introduction
4.1.1 Evaluating abnormalities in exercise physiology
4.1.2 Correlation of abnormal exercise physiology with diastolic parameters
4.2 Methods
4.2.1 Study population
4.2.2 Statistical analysis
4.3 Results
4.3.1 Subject demographics
4.3.2 Implications of diastolic dysfunction: Correlation with presence of symptoms
4.3.3 Correlation between abnormal exercise physiology and resting diastolic abnormalities: Does VO2 max reflect diastolic function?
4.3.4 Beyond a single VO2 max cut off: Does stratification of VO2 max according to age and gender norms improve the correlation with resting diastolic abnormalities?

4.4 Discussion 81

Chapter 5

Is the ejection fraction in HFpEF ‘truly’ preserved? Defining the contribution of subtle systolic dysfunction to the pathophysiology of HFpEF 85

5.1 Introduction 85
5.2 Method 87
  5.2.2 Statistical analysis
5.3 Results 88
  5.3.1 Establishing the presence of systolic abnormalities and correlations with diastolic abnormalities in a dyspnoic cohort with preserved ejection fraction on echocardiography
  5.3.2 Correlating abnormal exercise physiology, subtle left ventricular systolic abnormalities and diastolic abnormalities
5.4 Discussion 95

Chapter 6

Conclusions and future directions 99

6.1 Review of the research 99
6.2 Future directions 102

References 104

Addenda & corrigenda
Table 3.1  Baseline subject characteristics of the entire subject cohort
Table 3.2  Comparison: subjects with and without dyspnoea. Comparisons were performed utilizing Chi-squared tests for proportions and non-paired t-test for age
Table 3.3  Does VO2 max <25 mls/kg/min imply different demographics?
Table 3.4  Demographics according to age and gender matched VO2 max
Table 3.5  Baseline echo characteristics: Entire group (n=1744)
Table 4.1  Echo characteristics
Table 4.2(a)  Chi squared analysis for the presence of an E/E' >11 in patients with and without dyspnoea
Table 4.2(b)  Chi squared analysis of the presence of atrial fibrillation: Comparisons between dyspnoeic and non dyspnoeic patients
Table 4.2(c)  Chi squared analysis for the presence of LA dilatation: comparisons between dyspnoeic and non dyspnoeic individuals
Table 4.3  Multivariate predictor of dyspnoea
Table 4.4  VO2 max < 25mls/kg/min* ESC criteria cross tabulation
Table 4.5  Comparisons of E/E'(L) between groups
Table 4.9  Presence of ESC criteria in the different groups
Table 5.1  Comparisons of parameters of systolic function between dyspnoeic and asymptomatic individuals
Table 5.2  Comparisons of S'm(cm/sec) between groups
Table 5.3  Comparisons of S'(l)(cm/sec) between groups
Table 5.4  Comparisons of E/E'(S)/S'm between groups
List of figures

Figure 3.1  Flow chart of recruitment process 50
Figure 3.2  General health questionnaire 52
Figure 3.3a  VO2 data accepted as ‘peak’ if corresponding peak RER> 1.0 59
Figure 3.3b  Diagnostic algorithm: Interpretation of VO2 max data 60
Figure 3.5a  Causes of dyspnoea in a community population over the age of 60 62
Figure 3.5b  Objective cardiac limitation based on age and gender matched VO2 max : subject stratification 63
Figure 4.1a  Area under the curve of 0.59 P<0.0001 E/E' (s)>9 predicts dyspnoea with sensitivity of 60% specificity of 55% 70
Figure 4.1b  Are under the curve of 0.57 P=0.0002 E/E' (L)>8 predicts dyspnoea with a sensitivity of 60% and specificity of 54% 70
Figure 4.2a  Correlation of E/E'(L) and (S) in the asymptomatic population Slope =0.77 R^2=0.51 P<0.0001 71
Figure 4.2b  Correlation between E'(L) and E'(S) in the dyspnoeic population Slope=0.81 +/- 0.05 R^2=0.51 P<0.0001 71
Figure 4.3  Result of the analysis of the frequency distribution of E/E' values between the dyspnoeic and asymptomatic groups 74
Figure 4.4  the percentage of the asymptomatic and dyspnoiec population with a combination of diastolic abnormalities 75
Figure 4.5  Correlation of E/E'(L) and V02 max 77
Figure 4.6  Abnormal V02 (>25mls/kg/min) to predict an abnormal E/E' (L) 78
Figure 4.7  ROC analysis: E/E'(L) to predict cardiac limitation on CPEX 80
Figure 5.1a  Correlation of E/E' (cm/s) and S'(L)(cm/s) R = -0.7, p<0.01 89
Figure 5.1b  Correlation between E/E'(S)(cm/sec )and S'm(cm/sec) R value of -0.65, p<0.001 89
Figure 5.2  ROC analysis: S’m to predict cardiac limitation on CPEX 91
Figure 5.3  Comparison of frequency of distribution of diastolic and systolic abnormalities among three groups A=cardiac limitation by CPEX (n=28) B=VO2<25mls/kg/min but not cardiac limited (n=30) C=healthy controls( n=34) 92
Figure 5.4  Correlation between E/E'(S) – S’m and age/gender adjusted predicted VO2 max R value − 0.21 with a p value of 0.061 93
Figure 5.5  Correlation between E/E'(S)/S’m and age/and gender adjusted predicted VO2 max R value - 0.2 and p value of 0.02 94
Figure 5.6  ROC analysis: E/E'(S)/S’m to predict cardiac limitation on CPEX 95
Publications and Presentations

Publications and presentations related to the thesis

**Mahadevan G**, Davis RC, Frenneaux MP, Hobbs FDR, Lip GYH, Sanderson JE, Davies MK

T T Phan, K Abozguia, G Nallur Shivu, **Mahadavan G**, I Ahmed, L Williams, M Frenneaux. Left ventricular torsion and strain patterns in heart failure with normal ejection fraction are similar to age-related changes. *European Journal of Echo Advance Access*.


**Invited speaker**

Asia Pacific Doppler Echocardiography Congress 2009. Presentation *When is fibrosis important?* Diastology Symposium 3D workshop.

**Oral presentation of abstract**


**Accepted abstracts**


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Signed ..............................
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I would like to dedicate my thesis to my beautiful children, Sharanya and Sarvin, who patiently let Daddy work on his thesis, when he should have been playing with them.
**Abstract**

Heart failure and preserved ejection fraction (HFpEF) is a syndrome that has experienced increasing interest over the last two decades, as there have been significant limitations in defining, diagnosing and treating the condition, as opposed to the great strides made in treating heart failure and reduced ejection fraction (HFrEF).

The limitations are related to the incomplete characterization of the affected individuals in epidemiological studies due to the lack of robust definitions for the syndrome, as well as the lack of easy to use and widely available investigational tools.

Most of the investigational tools measure resting cardiac physiological abnormalities, but the predominant symptom of HFpEF is exertional breathlessness, and therefore a robust investigational tool should be able to measure abnormal exercise physiology.

The contribution of subtle systolic impairment, despite a preserved overall ejection fraction to the pathophysiology of HFpEF, has not been fully established, which adds to the overall difficulties in diagnosis and establishing therapeutics.

The aims of this thesis were therefore to:

- establish the community prevalence and population characteristics of HFpEF
- determine the extent of correlation between the presence of abnormal exercise physiology of presumptive cardiac cause and that of impaired left ventricular relaxation/filling at rest
- determine whether minor impairment of left ventricular systolic function may represent a substantial contributor to the development of dyspnoea.

The studies from this doctoral thesis have established that not all patients with dyspnoea and a preserved ejection fraction are cardiac limited and dyspnoic patients in a community setting are a heterogeneous group. The true prevalence of HFpEF in a community setting was established, albeit underestimated for reasons that are outlined in the thesis. The dyspnoic group also have significantly more resting diastolic abnormalities than asymptomatic individuals, but the degree of difference was not strongly associated with symptomatic status.

Combining diastolic abnormalities had an incremental impact in predicting dyspnoea, but a significant number of dyspnoeic patients did not have more than one diastolic abnormality.

The significant but weak correlation between abnormal exercise physiology and that of impaired left ventricular relaxation/filling at rest was established. The correlation improved when abnormal exercise physiology was fully characterized with cardio-pulmonary exercise testing.

Finally, the presence of subtle systolic impairment in patients who were dyspnoeic with cardiac limitation was established. Combining resting systolic and diastolic abnormalities improved the correlation with abnormal exercise physiology.

Research from this doctoral thesis has contributed to the epidemiology, diagnostic algorithms and pathophysiology of HFpEF. Clinically this will help define the syndrome and aid in finding suitable therapeutics for the syndrome.
Mechanisms of dyspnoea and poor exercise tolerance in a representative cohort of elderly patients with a relatively normal ejection fraction on echocardiography
Introduction

1.1 Context of the study

Heart failure constitutes a major clinical problem. Despite being an ancient diagnosis, it remains a diagnostic and therapeutic conundrum reflecting varying pathophysiological process that alter the physiological and anatomical properties of the heart. Attention has focused mainly on those patients with left ventricular systolic dysfunction, as evidenced by a markedly impaired left ventricular ejection fraction (LVEF) on echocardiography. There is a strong evidence base for effective therapies in such patients. However, a substantial proportion of patients (around 40 to 50%) with clinical features of chronic heart failure have a preserved left ventricular ejection fraction (HFpEF syndrome) (Kitzman et al. 2001; Senni et al. 1998; Vasan et al. 1999). Given increasing evidence that such patients differ markedly from those with systolic dysfunction, there has been recent interest in the diagnosis and pathophysiology of this HFpEF syndrome (Kitzman et al. 2001).

1.2 Statement of the research problem

Despite major advances in our understanding of ‘systolic’ heart failure, at present the epidemiology, pathophysiology and therapy of HFpEF are poorly understood, in large part because of the lack of robust and widely accepted diagnostic criteria. The available (very imperfect) epidemiological data suggest that these patients are more commonly elderly, female, obese, and/or hypertensive than patients with a reduced LVEF (Thomas et al. 2002; Klapholz et al. 2004), and are less likely to have recognized coronary artery disease.

The prognosis for patients with HFpEF is significantly worse than that for age-matched controls (Brogan et al. 1992; Setaro et al. 1992). Indeed, in one study, patients > 70 years of age with HFpEF had a mortality rate similar to that of systolic heart failure (Philbin and Rocco 1997; O'Connor et al. 2000). The syndrome of HFpEF is an important economic burden on the health service. Approximately 40-50% of all patients hospitalized with a clinical diagnosis of heart failure have a ‘normal’ LVEF, and their length of hospital stay is similar to that of patients with systolic dysfunction (Malki et al. 2002; Ahmed et al. 2002). The current lack of standardized,
reliable and easily applicable diagnostic criteria is a key factor in limiting the accurate assessment of the true prevalence of the syndrome of HFpEF.

Various criteria have been used to establish the diagnosis of HFpEF. Some studies have employed the combination of clinical features of heart failure in the presence of a preserved left ventricular ejection fraction, in a sense making HFpEF a diagnosis of exclusion. However, whilst some clinical features are quite robust (e.g. elevated jugular venous pressure), others are much less specific (e.g. pulmonary crackles). Since many of these patients have coexisting lung disease and/or obesity, the clinical diagnosis of heart failure in such patients may be erroneous. Furthermore, the distinction between HFpEF and systolic heart failure is somewhat vague and arbitrary. There is no consistency in the arbitrary cut-off point for normality in these studies, and systolic dysfunction may be under-reported. In some patients with preserved left ventricular ejection fraction, there may be marked impairment of long axis systolic function (Nikitin et al. 2002; Yip et al. 2002); and if echocardiographic windows are suboptimal, significant regional wall motion abnormalities may be missed. Finally, symptoms of heart failure occur predominantly with exertion, while assessment of cardiac function by echocardiography is usually performed at rest, exercise induced left ventricular systolic dysfunction and/or diastolic dysfunction may not be adequately characterized.

In an attempt to overcome some of these problems, the European Society of Cardiology have established criteria which stipulate the demonstration of abnormal left ventricular relaxation, filling, diastolic distensibility, or stiffness based on the presumption that ‘diastolic dysfunction’ is the underlying pathophysiological mechanism for the syndrome (European Study Group,1998). However, as will be discussed later, resting measurements of diastolic function appear to be rather insensitive and non specific for the identification of heart failure, and it has been argued that these well -intentioned criteria may have added more confusion than clarity to the situation (Banerjee et al. 2004; Redfield 2004). Clearly, before the pathophysiology, epidemiology and treatment of the syndrome can be investigated, there need to be robust, generally accepted criteria for its diagnosis.
1.3 The objectives of the studies described in this thesis

1.3.1 Study aims

In addressing the objectives, the research incorporated two major components, which investigated the epidemiology and correlates of HFpEF in the community and subsequently sought to refine the current diagnostic criteria. The study explored the underlying pathophysiology in terms of an associated systolic component to HFpEF, this defining what constitutes the term ‘preserved’ in heart failure preserved ejection fraction. The specific aims of the research therefore were:

AIM 1: to establish the community prevalence, and population characteristics of HFpEF (Chapter 3)

AIM 2: to assess the diagnostic accuracy of echocardiographic parameters for the identification of HFpEF patients in the sample population (Chapter 4)

AIM 3: to explore the added benefits of exercise modalities of investigating HFpEF using CPEX, compared to resting echocardiographic measures, given that symptoms of HFpEF are predominantly exertional (Chapter 4)

AIM 4: to establish suitable cut offs for the utilization of CPEX in diagnosing HFpEF (Chapter 4)

AIM 5: to investigate the contribution of subtle systolic dysfunction in the pathophysiology of HFpEF according to current definitions (Chapter 5).

1.3.2 Summary of activity to address the aims

The aims were established and worked through systematically, as indicated by the following summary of research activity, which is explained in detail in various chapters, as indicated above:

1 The univariate and multivariate clinical correlates of dyspnoea were identified. given that dyspnoea is the predominant symptom of HFpEF. The variables used were a combination of clinical risk factors for HFpEF, as well as the echocardiographic measures of diastolic dysfunction.

2 Based on the findings of the research, the relevant echocardiographic cut-offs for the main diastolic variables in predicting dyspnoea in this data set were established.

3 As the symptoms of HFpEF occur predominantly on exertion, it was important to establish the utility of investigational tools with an exercise component. CPEX was the investigational modality used in the study. All patients undergoing CPEX studies would be classified as
having HFpEF, on the basis of the criteria set out by the European society of Echocardiography. Subsequently, they were re-evaluated using additional criteria based on available literature related to CPEX testing.

4 Based on the patient classifications, we:

- established the relationship of an abnormal VO2 max by CPEX testing to resting echocardiographic measures of an elevated wedge pressure (E/E’)
- defined the clinical utility of an abnormal VO2 max to predict abnormal diastology on echocardiography
- identified the best method for classifying an abnormal VO2 max by its correlation with resting diastolic echocardiographic abnormalities.

5 Next, the role of subtle systolic dysfunction in the pathophysiology of HFpEF was assessed. This was done by measuring long axis ventricular function (S’m and l) by the tissue Doppler imaging (TDI) method and analysing:

- its correlation with symptoms and an abnormal VO2 max as well as other resting diastolic variables (E/E’).
- its ability to predict the degree of dyspnoea.

1.4 Methods

1.4.1 Conceptual framework of the study

The studies were designed to elucidate further the epidemiology and prevalence of HFpEF, evaluate current diagnostic criteria, as well as evaluate alternative methods of diagnosis and subsequently explore the actual concept of a preserved ejection in the establishment of heart failure symptoms. This would include an assessment of the potential role of subtle systolic impairment as part of the pathophysiology of HFpEF, and establishing the cut-off for what constitutes a ‘preserved’ ejection fraction.

During the first part of the research, establishing the community prevalence and associated population characteristics of HFpEF in subjects aged 60 years and older, and examining the utility of non-invasive resting techniques for identifying these patients were the focus. The overall goal of the research was to establish the prevalence of HFpEF and whether it can be identified non-invasively.
During the second part of the research, the actual concept of a ‘preserved’ ejection fraction was delved into more closely, and current definitions examined to determine whether they required refinement to make them more meaningful in everyday clinical use, as well as define robust measurements of systolic function for future clinical trials.

1.4.2 Method

Just under 2000 subjects aged ≥ 60 were randomly selected from the community to undergo screening. Primary care practices from the 500 Midlands Research Practices Network (MidRec) were stratified into quartiles of the Townsend socioeconomic deprivation score (Townsend 1988) for the populations they serve, and the ethnicity selected to represent this age group in the United Kingdom as a whole. Four practices were then selected for investigation from each quartile, and systematic random sampling of men and women aged over 60 years was then undertaken. The following investigations were performed to establish an initial screening base in the registered practice.

- A questionnaire based on the Framingham Criteria (McKee et al. 1971) was administered in order to assess symptoms and quality of life.
- Baseline blood tests (full blood count, urea and electrolytes, random glucose, lipids, thyroid function tests, resting plasma NT-pro BNP) were administered.
- Echocardiography was conducted with assessment of LVEF (Biplane Simpson’s), left atrial area/volumes, LV wall thickness. Resting diastolic parameters (E/A ratio, deceleration time, mitral inflow propagation velocity pulmonary vein flow A duration/velocity, long axis tissue Doppler velocities) and valvular function E/E’ ratio were calculated.
- All subjects who were breathless (New York Heart Association class II-III) and had a LVEF > 50% underwent the following:
  - clinical examination and/or lung function tests (including spirometry and diffusion factor)
  - subgroup underwent cardio-pulmonary exercise testing (CPEX) with oximetry to assess peak VO2 and to define whether exercise is limited by cardiac or non-cardiac factors
  - Plasma BNP response to exercise (samples taken at rest, at peak exercise, and 20 minutes post-exercise).
1.4.3 Analysis of the data

SPSS (version 21.0, SPSS Inc. Chicago, Illinois) was used for statistical analyses. Continuous variables are expressed as median with interquartile range. All tests of proportion utilized Chi-squared comparisons. Two-sample comparisons were performed using an unpaired t test for normally distributed variables. The Pearson coefficients for linear and Spearman coefficients for nonlinear correlations were used. Regression analyzes and curve fitting were performed to determine exact relations. A value of p < 0.05 was considered to be statistically significant in all analyses. Receiver operator characteristics (ROC) curves were constructed to assess the diagnostic accuracy of and ‘optimal cut off values’ for all variables outlined above to determine clinical significance.

1.5 The significance of the described studies

The goal of this study was to define the true prevalence and determinants of the syndrome of HFpEF and evaluate current diagnostic criteria and redefine the criteria if necessary. The contribution of systolic abnormalities was established and the actual concept of a ‘preserved’ ejection fraction was also explored, central to the diagnosis of HFpEF. This would help to define a target population for future therapeutic interventions.

In part one, the goal was to establish the community prevalence and population characteristics of HFpEF in subjects aged 60 years and older and examine the utility of non-invasive resting techniques for identifying these patients. In part two, the goal was to define accurately ‘preserved’ ejection fraction and evaluate a consecutive series of patients presenting with HFpEF for subclinical evidence of LV systolic dysfunction, as well as to investigate whether current definitions of HFpEF are valid or require further refinement in everyday clinical use. Robust measurements of systolic function were defined for future clinical trials.

In summary, the research described in this thesis was aimed at elucidating the epidemiology, evaluating current diagnostic criteria and exploring the contribution of systolic abnormalities in the pathophysiology of HFpEF.
### 1.6 Definitions of the key terms

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>ACC/AHA</td>
<td>American College of Cardiology/American Heart Association</td>
</tr>
<tr>
<td>ADP</td>
<td>adenosine diphosphate</td>
</tr>
<tr>
<td>ATP</td>
<td>adenosine triphosphate</td>
</tr>
<tr>
<td>A</td>
<td>pulmonary vein a wave duration</td>
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<tr>
<td>Ar</td>
<td>mitral wave a velocity duration</td>
</tr>
<tr>
<td>Ar</td>
<td>A: mitral wave a velocity duration pulmonary vein a wave duration</td>
</tr>
<tr>
<td>BNP</td>
<td>brain natriuretic peptide</td>
</tr>
<tr>
<td>CPEX</td>
<td>cardiopulmonary exercise testing</td>
</tr>
<tr>
<td>CHF</td>
<td>congestive heart failure</td>
</tr>
<tr>
<td>CO2</td>
<td>carbon dioxide</td>
</tr>
<tr>
<td>DLco</td>
<td>transfer factor</td>
</tr>
<tr>
<td>dp/dt(max)</td>
<td>left ventricle (LV) pressure rise in early systole measuring LV global contractility.</td>
</tr>
<tr>
<td>E/A</td>
<td>mitral E velocity(LV filling) as measured by echo Doppler method/mitral A velocity (atrial contraction) as measured by echo Doppler method</td>
</tr>
<tr>
<td>E/Vp</td>
<td>mitral E velocity/mitral valve propagation velocity as measured by colour M mode.</td>
</tr>
<tr>
<td>E'</td>
<td>annular velocity at either the septal or lateral wall of the left ventricle as measured by tissue Doppler velocity.</td>
</tr>
<tr>
<td>E/E’</td>
<td>estimation of left ventricular filling as measured during echocardiography.</td>
</tr>
<tr>
<td>ECM</td>
<td>extracellular matrix</td>
</tr>
<tr>
<td>Ees</td>
<td>end systolic elastance</td>
</tr>
<tr>
<td>HFrEF</td>
<td>heart failure with reduced ejection fraction</td>
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<tr>
<td>HFpEF</td>
<td>heart failure with preserved ejection fraction</td>
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<tr>
<td>HFnEF</td>
<td>heart failure with normal ejection fraction</td>
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<tr>
<td>HR</td>
<td>heart rate</td>
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<tr>
<td>LV</td>
<td>left ventricle</td>
</tr>
<tr>
<td>LVEF</td>
<td>left ventricular ejection fraction</td>
</tr>
<tr>
<td>LVEDVI</td>
<td>left ventricular end diastolic volume index</td>
</tr>
<tr>
<td>LVEDP</td>
<td>left ventricular end diastolic pressure</td>
</tr>
<tr>
<td>LVH</td>
<td>left ventricular hypertrophy</td>
</tr>
<tr>
<td>MVV</td>
<td>maximum voluntary ventilation</td>
</tr>
<tr>
<td>N2B</td>
<td>short titin isoform</td>
</tr>
<tr>
<td>N2BA</td>
<td>long titin isoform</td>
</tr>
<tr>
<td>NYHA</td>
<td>New York Heart Association</td>
</tr>
<tr>
<td>O2</td>
<td>oxygen</td>
</tr>
<tr>
<td>PCWP</td>
<td>pulmonary capillary wedge pressures</td>
</tr>
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</table>
1.7 Organization of the thesis

The thesis is divided into six chapters.

**Chapter 1** introduces the goals of the research and explains the methodology and the methods that established the framework for the research, as well as the organization of the thesis.

**Chapter 2** is a review of the literature relating to various aspects of the syndrome of HFpEF, concentrating on definitions, epidemiology, pathophysiology, diagnostic algorithms and investigative tools as well as current therapeutics. The limitations and controversies in the current literature are highlighted.

**Chapter 3** includes the overall objective of the study and the inherent difficulties that were anticipated. The criteria for the syndrome under investigation are explained, including the exclusion criteria. In addition, the nature and clinical data associated with members of the study group are described, along with details of all protocols used with the investigative modalities, including transthoracic echocardiography and cardiopulmonary exercise testing.

Tables and discussion are provided about the entire 1833 subjects and the following subsets:

- Those with dyspnoea and preserved ejection fraction (n=222)
- Those without dyspnoea (n=1518)
Those excluded from CPEX for various reasons are noted, including individuals with:

- presumptive lung disease
- presumptive severe HFpEF and inability to exercise
- those undergoing CPEX who had the following performance characteristics:
  - VO2 max<25
  - VO2max >age-adjusted norm
  - VO2max 70-85% of age-adjusted norm
  - VO2 max <70% of age-adjusted norm
  - non-dyspnoeic CPEX controls
  - extensive tabular/figure/statistical comparison of subgroups

The objectives of subsequent analyses and the power of study implications are considered.

**Chapter 4** describes the analysis of the data, examining the strength of the association between dyspnoea and abnormal LV diastolic function on echocardiography:

- implications of dyspnoea per se (ie, n=222)
- implications of dyspnoea with VO2max<25mls/kg/min
- Implications of dyspnoea: data stratified according to VO2 max as classified as percentage predicted against an age and gender matched nomogram.

The severity of CPEX impairment correlated to that of LV diastolic impairment is explained in this chapter, along with the observed correlations between dyspnoea and abnormal exercise physiology and abnormal LV diastolic function are discussed.

The limitations of the study are also considered.

**Chapter 5** describes our observations regarding LV systolic dysfunction and how it contributes to the severity of symptoms in patients with HFpEF. The research findings are discussed in light of three main questions:

- Did LVEF vary within subgroups and if so, how?
- Did subtle systolic measurements vary within subgroups, and is this correlated with extent of symptoms and also with extent of impairment of VO2max?
Is it possible that a combined estimate of LV systolic and diastolic dysfunction might correlate more closely with impairment or non-impairment of VO2max (age and gender adjusted) using additive and subsequently multiplicative models.

Chapter 6 concludes the thesis and suggests future directions for work in this area of investigation.
chapter 2

Literature review

The studies described in this thesis address primarily some aspects of the epidemiology, diagnostic criteria and diagnostic tools, as well as the pathophysiology of the clinical syndrome termed *heart failure and preserved ejection fraction* (HFpEF).

Therefore, this chapter initially explores the definition of this clinical syndrome and how it differs from other forms of heart failure. Introducing the epidemiological/pathophysiological studies undertaken, a review of this area with regards to HFpEF is undertaken. An in depth analysis of the different types of epidemiologic studies published to date, their limitations and residual questions are highlighted in the epidemiology section.

In terms of pathophysiology, both evidence and recent postulates are summarized, and the major gaps in knowledge and uncertainties of this syndrome are described. Next, current established diagnostic criteria and available diagnostic tools are reviewed. This is an area on which the studies reported in this thesis focussed.

Finally, this literature review explores current (limited) management options and how the application of our findings may help re-evaluate existing options or discover newer options.

2.1 Heart failure

Heart failure is a pathophysiological state in which an impairment of cardiac function is responsible for an inability of the heart to pump blood at a rate commensurate to meet the metabolic requirements of the body, and/or only being able to do so at elevated filling pressures. Patients who meet these criteria are a heterogeneous group and have very diverse reasons for their presentations with elevated left ventricular filling pressures and/or low cardiac output states (Braunwald 1992).

2.1.1 Heart failure with reduced ejection fraction (HFrEF)

Heart failure with reduced ejection fraction (HFrEF) is a clinical syndrome where heart failure is accompanied by signs of pulmonary and peripheral congestion and exhibits abnormal systolic properties of the left ventricle in terms of performance, function and contractility (Braunwald 1992).
2.1.2 Heart failure with preserved ejection fraction (HFpEF)

When heart failure is accompanied by a predominant or isolated abnormality in diastolic function and concentric ventricular remodelling, this clinical syndrome is called heart failure with preserved ejection fraction (HFpEF), according to current European Society guidelines (Paulus et al. 2007). From a conceptual perspective, HFpEF occurs when the heart is unable to accept an adequate volume of blood during diastole at normal diastolic pressures and at volumes sufficient to maintain an adequate stroke volume. These abnormalities are caused by a decrease in ventricular relaxation and/or an increase in ventricular stiffness. Inherent in this definition is the idea that the consequences of ‘cardiac insufficiency’ will be expressed symptomatically.

Although the natural history of heart failure may be punctuated by episodes of acute decompensation with overt systemic volume overload and pulmonary oedema, the primary chronic symptoms are reduced exercise intolerance and dyspnoea. The symptomology of HFpEF mimics that of HFrEF with symptoms that can occur at rest (New York Heart Association (NYHA) class IV), with less than ordinary physical activity (NYHA class III), or with ordinary physical activity (NYHA class II) (Zile and Brutsaert 2002a).

As mentioned above, HFpEF can also present acutely with pulmonary oedema that occurs very rapidly and ‘flash pulmonary oedema’. Recent studies have shown that up to 30-40% of patients arriving in hospital emergency department with clear-cut pulmonary oedema have normal ejection fractions measured within two hours of arrival and no difference in ejection fraction before and after stabilization (Gandhi et al. 2001).

Differentiating diastolic dysfunction from HFpEF. Diastole encompasses the time period during which the myocardium loses its ability to generate force and shorten, and returns to an unstressed length and force. By extension, diastolic dysfunction occurs when these processes are prolonged, slowed or incomplete.

Therefore, the term diastolic dysfunction is used to describe the condition when abnormalities in mechanical function occur during diastole. These abnormalities can occur in the presence or absence of a clinical syndrome of heart failure and with normal or abnormal systolic function (Gaasch and Zile 2004).
Differentiating diastolic heart failure from HFpEF. The term diastolic heart failure presumes we understand the mechanisms leading to this disorder and can therefore justify the substitution of a mechanistic term for a descriptive phrase. A less presumptuous approach is to refer to these patients as having HFpEF, a descriptive term that makes no assumptions about our knowledge of the pathophysiology of this disorder. This term also implies that systolic function is preserved since that is part of the definition of diastolic heart failure (Burkhoff, Maurer and Packer 2003).

Heart failure with normal ejection fraction (HFnEF) is also a term commonly used in the literature. Preserved function would appear to be a more apt term since all the term suggests is that the ejection fraction is in the accepted normal range, although the heart may well be subclinically impaired and the ejection fraction not completely normal.

2.2 Epidemiology

2.2.1 Epidemiology of HFpEF

Heart failure is a highly prevalent disorder, the incidence and prevalence of which increases dramatically with age. As the segment of the population aged 65 and over is expanding rapidly, the number of people with heart failure is likely to continue to increase (Owan and Redfield 2005).

The epidemiology of HFpEF, as opposed to HFrEF, is poorly defined in the literature, in large part due to lack of robust definitions of this syndrome. In order to have an informed consideration of the epidemiology of HFpEF as it stands currently, it must include the entire spectrum of HFpEF.

Recognition of the progressive nature of heart failure has resulted in the current American College of Cardiology/American Heart Association (ACC/AHA) staging system for heart failure. In this system persons with cardiovascular disease are often considered to be at risk for future heart failure and are classified as having stage A heart failure. Cardiovascular disease is recognized as leading to ventricular remodelling and dysfunction that can occur without the clinical syndrome of heart failure. Preclinical ventricular remodelling and dysfunction are recognized to be associated with future heart failure, and their presence is referred to as stage B heart failure. Once clinical
signs and symptoms of heart failure are present, the patient is considered to have overt or stage C heart failure.

2.2.2 Studies investigating Stage A of the disease

Risk factors. Five studies have attempted to differentiate risk factors associated with HFrEF (Stage A of disease) from HFrEF (Senni et al. 1998; Vasan et al. 1999; Gottdiener et al. 2002; Yip et al. 1999; Devereux et al. 2000). These are, however, not longitudinal studies, such as the Framingham Heart study, which identified both traditional and emerging risk factors for heart failure without differentiating HFpEF from HFrEF.

In general, the five studies which are cited in this thesis confirm the findings of previous clinical studies that suggest that patients with HFpEF are older and more likely to be female than patients with HFrEF (Kupari et al. 1997). Studies vary regarding the relative prevalence of hypertension, but most suggest a somewhat higher prevalence of antecedent hypertension in patients with HFpEF as compared with those with HFrEF (Levy et al. 1996). The other two risk factors that are associated with HFpEF are diabetes and obesity (Arnett et al. 2002, Mokdad et al. 2000). Whereas the prevalence of hypertension and coronary artery disease have declined over the years, the prevalence of diabetes and obesity have increased dramatically (Mokdad et al. 2000).

2.2.3 Studies investigating Stage B of the disease

Prevalence of asymptomatic diastolic dysfunction. There have been three studies which have evaluated the prevalence of asymptomatic diastolic dysfunction in the community (Stage B heart failure). The first study by Fischer et al. (2003) used basic Doppler echocardiography and no advanced modalities such as tissue Doppler imaging to assess diastolic dysfunction. 1274 randomly sampled subjects aged 25 years or older (mean age [SD] age, 51 [14 years]) were enrolled in this study. The prevalence of diastolic abnormalities (E/A ratio) in the setting of preserved ejection fraction (EF>0.45) was 11.1%.

The second study by Abhayaratne et al. (2006) included a cross-sectional survey of 1275 randomly selected residents of Canberra (participation rate 75%), aged 60 to 86 years (mean age 69.4; 50% men), and assessed the prevalence rates of LV diastolic dysfunction as characterized using comprehensive Doppler echocardiography, including mitral valve propagation velocity and tissue Doppler imaging. The prevalence of any criteria of diastolic dysfunction was 34.7% (95%
confidence interval [CI] 32.1%-37.4%) and that of moderate-severe diastolic dysfunction was 7.3% (95%CI 5.9%-8.9%). Of those with moderate-severe diastolic dysfunction, 77.4% had a LV ejection fraction (EF) ≥50% and 76.3% were asymptomatic.

The final study by Redfield et al. (2003) in Olmstead County in 2003 assessed 2042 randomly sampled subjects aged 45 years and older (mean [SD] age 63[11] years) using comprehensive tissue Doppler imaging. 6.8% of participants exhibited ‘significant’ diastolic dysfunction (more than just impaired relaxation) despite having no symptoms of heart failure and EF>50%.

Furthermore, the cohort from the initial Olmstead County study was subsequently followed up over a period of four years and had a repeat echocardiogram and subsequently followed up for a period of six more years to assess new onset heart failure.

The prevalence of diastolic dysfunction increased over the period of four years from 23.8% (95% CI 21.2–26.4) to 39.2% (95% CI 36.3–42.2) (P <0.001), while that of moderate-severe diastolic dysfunction increased from 6.4% (95% CI 4.9–7.9) to 16.0% (95% CI 13.7–18.2) (P <0.001).

During 6.3 ± 2.3 years of subsequent follow up, 81 participants developed symptomatic heart failure.

Persistent or worsening diastolic dysfunction was associated with heart failure. Participants whose diastolic function remained normal or normalized between subsequent echocardiograms had a 2.6% (95% CI 1.4–3.8) cumulative heart failure incidence. Participants with persistent, or new onset, mild diastolic dysfunction had a 7.8% (95% CI 5.8–13.0) cumulative heart failure incidence. Participants with, moderate-severe diastolic dysfunction experienced a cumulative heart failure incidence of 12.2% (95% CI 8.5–18.4) (P<0.001).

In the second Strong Heart study (the follow up of a population cohort survey of cardiac risk factors and prevalent and incident cardiac disease in middle aged and elderly adults), mitral E/A>1.5 at baseline echocardiography was associated with a two-fold increase in all-cause and a three-fold increase in cardiac mortality independent of covariates, such as age, diabetes, sex, hypertension and ischemic heart disease). Mitral E/A<0.6 was also associated with a two-fold increase in all-cause mortality, but not independent of covariates (Bella et al. 2002). However, to put Stage B diastolic dysfunction in context, it should be noted that only about one in four persons
with moderate-severe diastolic dysfunction at the second follow-up developed incident heart failure during long-term follow-up.

This suggests that superimposed clinical events, such as the onset of diabetes, worsening hypertension and ischemia may play an important role in the transition from asymptomatic diastolic dysfunction to overt heart failure with preserved ejection fraction. Nevertheless, diastolic dysfunction was associated with incident heart failure after adjustment for age, hypertension, diabetes, and coronary disease.

2.2.4 Studies investigating Stage C of the disease

Incident studies. A number of studies have reviewed patients with Stage C heart failure. Two incident studies differentiated between individuals with preserved and reduced systolic function, the Olmstead County study and the Bromley CHF study. Both showed a much smaller percentage of patients with HFpEF (Senni et al. 1998; Cowie et al. 2002). In more detail, the Olmstead County study identified 216 patients who presented during the 1991 calendar year with new CHF. Of these, 137 (63%) had recent echocardiographic assessment of left ventricular ejection fraction (LVEF), with 54 (39%) showing preserved ejection fraction (EF>50%) and no valve disease.

The patients with HFpEF were more likely female, older and diagnosed as an outpatient (Senni et al. 1998). In the Bromley CHF study, local primary care physicians were asked to refer all new patients to a special clinic and all local patients admitted to hospital with CHF were identified. Of the 332 new cases of CHF identified between February 1996 and April 1997, 310 (93%) had an echocardiogram. A qualitative assessment LVEF was undertaken and 16% had preserved systolic function. 68% had mild to moderate systolic dysfunction and 16% had severe systolic dysfunction. The three groups were not compared (Cowie et al. 2002). The discrepancies between the two studies can be explained at least in part by the higher frequency of acute myocardial infarctions in the Bromley group, the different methods of left ventricular assessment and the increased number of patients with echocardiograms in the Bromley group (Hogg, Swedberg and McMurray 2004).

Cross sectional population studies. There have been eleven cross sectional population studies addressing the prevalence of HFpEF (Cortina et al. 2001; Nielsen et al. 2001; Mosterd et al. 1999; Hedberg et al. 2001; Morgan et al. 1999; Kupari et al. 1997; Ceia et al. 2002; Kitzman et al. 2001;
Redfield et al. 2003; Devereux et al. 2000). The number of individuals screened and their age varied widely among the investigations. The means of identification of congestive heart failure varied from clinical opinion to the use of a questionnaire (e.g. Framingham score). The methods used to define preserved systolic function varied from qualitative assessment of left ventricular ejection fraction (LVEF) to quantitative measurements of LVEF, fractional shortening (FS) or a wall motion score. The threshold used to differentiate reduced from preserved ejection fraction also resulted in vastly differing reported prevalences of HFpEF.

There is no simple binary division between reduced and preserved systolic function. Instead, there is a border zone or gray area that results in uncertainty and differing opinions amongst investigators as to what is preserved and what is mildly reduced systolic function.

In a comprehensive review of the population studies of HFpEF (Owan and Redfield 2005), the following points are summarized:

- The 11 population studies basically fall into two study designs. In the first type of study design (comprising two of the 11 studies), all patients with prevalent heart failure from a defined population over a specified period of time were studied prospectively or retrospectively, and the relative frequency of preserved versus reduced ejection fraction was defined. In this type of study, the base population is not rigorously enumerated and the true population prevalence of heart failure and of HFpEF may not be accurately determined.

- In the second type of study (comprising the remainder of the studies) a large cross sectional population of a segment of the population (usually a specific age range) underwent assessment of the past and current presence of symptomatic HF and also echocardiography. In this type of study, both the prevalence of HFpEF amongst patients with heart failure and the population prevalence of HFpEF can be estimated. However, with the latter type of study, a change in ejection fraction between the time of heart failure onset and the time of study cannot be excluded. Thus, this type of study defines the fraction of the heart failure population that have HFpEF at variable times since the onset of heart failure.

Based on these studies, the prevalence of HFpEF within the population varies from 1.14% to 5.5%, depending on the age of the population. The prevalence of HFpEF among patients with clinically overt HF ranged from 41% to 70% (mean 56%).

**Cross sectional studies of hospitalized patients.** There have been 12 cross sectional studies of hospitalized patients with heart failure (Stage C-D heart failure) since the year 2000 (Redfield et
al. 2003). These studies were heterogeneous, ranging from small single-centre studies with a majority of African American patients, through to a large sample of Medicare beneficiaries in the United States, to a countrywide epidemiological survey from France. Most have incomplete information on the assessment of LV function. The proportion of patients with HFrEF was less than in the population studies, ranging from 24% to 55% (mean 41%). Patients with HFrEF were less likely to have had a prior history of, or hospitalization for, heart failure. As in the population studies, there was a clear preponderance of females, which on multivariate analysis, showed female gender as an independent predictor of HFrEF in patients with heart failure (Rumsfeld et al. 2013).

Landmark studies. Additionally, there have been two landmark studies regarding hospitalized patients with heart failure and preserved ejection fractions. Bhatia et al. (2006) studied 2082 patients who had been admitted with a discharge diagnosis of heart failure and whose ejection fraction had been assessed from the year 1999 till 2001 at hospitals in London, Ontario. The patients were divided into two groups, those with an ejection fraction less than 40% and those with an ejection fraction of more than 50%. About a third of patients (31%) had a preserved ejection fraction. The unadjusted mortality rates for patients with an ejection fraction of more than 50% were not significantly different from those for patients with an ejection fraction of less than 40% at 30 days (5% vs. 7%, P=0.08) and at one-year (22% vs. 26%, P=0.07); the adjusted one-year mortality rates were also not significantly different in the two groups (hazard ratio, 1.13; 95% confidence interval, 0.94 to 1.36; P=0.18). The rates of readmission for heart failure and of in-hospital complications did not differ between the two groups.

In the second study, Owan et al. (2006) studied consecutive patients hospitalized with decompensated heart failure at Mayo Clinic Hospitals in Olmsted County, Minnesota, from 1987 through 2001. The patients were classified as having either preserved or reduced ejection fraction. A total of 6076 patients with heart failure were discharged over the 15-year period; data on ejection fraction were available for 4596 of these patients (76%). Of these, 53% had a reduced ejection fraction and 47% had a preserved ejection fraction. The proportion of patients with the diagnosis of heart failure with preserved ejection fraction increased over time. The prevalence
rates of hypertension, atrial fibrillation, and diabetes among patients with heart failure increased significantly over time. Survival was slightly better among patients with preserved ejection fraction (adjusted hazard ratio for death, 0.96; P=0.01). Survival improved over time for those with reduced ejection fraction but not for those with preserved ejection fraction.

In summary, epidemiological studies have established that a substantial number of patients with congestive heart failure have a preserved ejection fraction, that is, HFP EF. However, the actual prevalence varies among studies due to the different definitions, methodology and thresholds used to define preserved ejection fractions in the various studies. This syndrome predominantly afflicts older hypertensive individuals. The prevalence of HFP EF is increasing, paralleling the demographic shift in the population towards older ages. Although HFP EF was previously thought to have a more favourable course than heart failure with reduced ejection fraction (HFrEF), recent studies have shown that the mortality rate, hospital re-admission rate and the economic cost of HFP EF rival those of HFrEF.

The morbidity and mortality of patients with HFrEF have gradually improved over the past two decades, reflecting the impact of several evidence-based interventions that have been incorporated into the care of patients with chronic HFrEF. In contrast, the prognosis of patients with HFP EF has remained unchanged over the same time period, reflecting both the dearth of therapeutic interventions that have been evaluated in HFP EF, and the failure of these therapies to show any benefit on survival in patients with this syndrome. Thus, there is an urgent need to develop novel and efficacious strategies for the treatment of HFP EF, particularly ones that specifically target the pathophysiologic mechanisms that underlie HFP EF, which will be discussed in the following subsection.

2.3 Pathophysiology and etiology

2.3.1 Potential mechanisms of HFP EF/diastolic dysfunction

Conceptually, the mechanisms that can contribute to the abnormalities in diastolic function that lead to the development of diastolic heart failure can be divided into factors that are intrinsic to the myocardium itself (myocardial) and extrinsic to the myocardium (extramyocardial). This was extensively reviewed by Zile and Brutsaert (2002b) and the following points were summarized:
- **Myocardial factors.** Myocardial factors can be divided into structures and processes within the cardiac muscle cell (cardiomyocyte), and within the extracellular matrix (ECM) that surround the cardiac muscle cell, and that activate the autocrine and paracrine production of neurohormones. Each of these mechanisms is active in the major pathological processes that cause HFpEF, such as ischemia, pressure overloaded hypertrophy from hypertension, as well as restrictive, infiltrative and hypertrophic cardiomyopathies.

- **Intrinsic factors: Cardiomyocyte.** One of the changes in the cardiomyocyte responsible for diastolic dysfunction involves calcium homeostasis. Intracellular calcium is a critically important determinant of normal myocardial contraction and relaxation. Increased cytosolic diastolic calcium concentration, a slow decline in calcium concentration in diastole and prolongation in calcium transients, plays a role in active relaxation and passive stiffness of the myocardium (Zile and Brutsaert 2002b). Calcium homeostasis is affected by a decrease in the levels or activity of the sarcoplasmic reticulum calcium ATPase pump (SERCA, which can slow the removal of calcium from the cytosol (Angeja and Grossman 2003). Increased levels and activity of phospholamban, the naturally occurring SERCA -inhibiting protein, can also delay relaxation. Finally, defects in the sarcolemmal channels responsible for short and long term extrusion of calcium from the cytosol, such as the sodium calcium exchanger and the calcium pump, can also contribute to delayed relaxation (Zile and Brutsaert 2002b).

- **Myofilament contractile protein.** The myofilament contractile protein in the cardiomyocyte consists of the thick filament myosin and thin filament actin proteins. Bound to actin are a complex of regulatory proteins that include tropomyosin and troponin (Tn) T, C and I. ATP hydrolysis plays an important role in the detachment of myosin from actin, as well as calcium detachment from troponin and calcium sequestration in the sarcoplasmic reticulum. Modification of any of these steps, as well as the ATPase that catalyzes them can alter diastolic function. Thus, relaxation is an energy consuming process (Tian et al. 1997; Spindler et al. 1998; Ingwall and Kelly 1998).

The energetic factors required to maintain normal diastolic function include the requirements to maintain low concentrations of ADP and inorganic phosphates, the end product of ATP hydrolysis. Energy is also required to maintain the appropriate ratio of ADP to ATP. A decrease in phosphocreatine may limit ability to recycle ADP to ATP (Zile and Brutsaert 2002b).

A reduced cardiac energy reserve in HFpEF patients has been demonstrated by the use of magnetic resonance spectroscopy, which may explain the underlying marked dynamic slowing of
active LV relaxation and vasculoventricular coupling (VVC) in these same groups of patients (Phan et al. 2009a).

**Titin.** The changes in the cytoskeletal proteins of the cardiomyocyte may also alter diastolic function. Titin is a giant molecule, which spans the entire half-sarcomere from the M-line to the Z-line. It is responsible for passive and restoring forces within the myofilament during sarcomere elongation and compression respectively (Helmes et al. 2003). Titin appears to be the major determinant of passive force development at shorter slack lengths. Titin also acts as a ‘spring’ during shortening below slack length, generating a restoring force which opposes further shortening (Granzier and Labeit 2002).

The protein is expressed in two major isoforms via differential splicing. This results in two isoform transcripts – N2BA (long isoform) and N2B (short isoform) – which may coexist within the same sarcomere. The expression ratio of these isoforms demonstrates interspecies variation, as well as variable expression in different locations within the heart (Cazorla et al. 2000). Changes in isoform expression have been demonstrated in certain pathological states. A recent study showed that in patients with dilated cardiomyopathy there was a shift towards increased expression of the longer N2BA isoform, which correlated with both lower left ventricular stiffness and an improvement in diastolic function (Nagueh et al. 2004). However, at the end stage of dilated cardiomyopathy there is a shift to the N2B isoform which increases passive stiffness, in keeping with the restrictive filling pattern seen in these patients.

In the canine rapid pacing heart failure model, a change in isoform expression towards the shorter N2B isoform has been reported, which may account in part for the higher passive ventricular stiffness which develops in this model (Wu et al. 2002). Spontaneously hypertensive rats were shown to have a higher N2B/N2BA expression ratio than the normotensive WKY rat, potentially explaining the higher passive ventricular stiffness of the former (Warren et al. 2003). Cardiac myocytes that express predominantly N2BA have a longer extensible region and are predicted to develop less force than those that express predominantly N2B. Passive stiffness of cardiac myocytes is much higher in N2B-expressing myocytes than in N2BA myocytes, thus a change in titin isoform expression may (together with increased collagen content) contribute to the increase in passive left ventricular diastolic and systolic stiffness in patients with HFpEF.
Role of titin function in LV relaxation. In a recent review by Paulus and Tschope (Paulus and Tschope 2012), the high nitrosative/oxidative stress state in HFpEF myocardium as visualized by both nitrotyrosine and dihydroethidium (DHE) stainings was highlighted. The review suggests that low nitric oxide (NO) bioavailability in HFpEF myocardium is due to the diversion of NO to peroxynitrate by superoxide anion. In cardiomyocytes adjacent to the dysfunctional endothelium, low NO bioavailability and high peroxynitrite level predispose to reduced cGMP production by soluble guanylate cyclase (sGC).

Both low cGMP content and low protein kinase G activity were recently demonstrated in myocardial homogenates of HFpEF patients. Activation of protein kinase A or protein kinase G makes titin more compliant, in contrast to protein kinase C, which makes it less compliant. Recent work has demonstrated that single cardiomyocytes isolated from the LV myocardium of HFpEF patients characteristically have a high resting tension. This high resting tension was attributed to hypophosphorylation of the N2B segment of titin because of low PKG activity and was corrected by in-vitro administration of PKG (van Heerebeek et al. 2012).

Extrinsic factors: Extracellular matrix (ECM). The myocardial ECM is composed of three important constituents: (1) fibrillar protein, such as collagen type I, collagen III and elastin, (2) proteoglycans and (3) basement membrane proteins, such as collagen type IV, laminin and fibronectin. Fibrillar collagen is thought to be the most important component within the ECM that contributes to the development of diastolic heart failure (Borg and Caulfield 1981; Weber 1989; Weber and Brilla 1991; Weber, Sun and Guarda 1994; Covell 1990).

There is evidence that disease processes that alter diastolic function also alter ECM fibrillar collagen, particularly in terms of its amount geometry and distribution, degree of cross-linking and ratio of collagen type I versus collagen type III. There is also evidence that treatment of these disorders is associated with normalization of fibrillar collagen. The role of other fibrillar proteins, proteoglycans and basement membrane proteins remain largely unexplored (Brilla 2000; Villari et al. 1993; Villari et al. 1995; Weber et al. 1990; Kato et al. 1995; Jalil et al. 1989).

Cardiovascular structure and function in HFpEF. HFpEF is typically associated with significant remodeling that affects the left ventricle and left atrium, reflecting the change in the
cardiomyoctes and extracellular matrix as described above. The structural remodeling that occurs in HFpEF differs dramatically from that in systolic heart failure (Quinones et al. 2006).

*Left ventricular chamber remodeling.* Patients with HFpEF generally exhibit a concentric pattern of hypertrophy that is characterized by a normal or near-normal end diastolic volume, increased wall thickness, and an increased ratio of mass to volume with an increased ratio of wall thickness to chamber radius. By contrast, patients with HFrEF exhibit a pattern of eccentric remodeling with an increase in end diastolic volume (which is usually progressive over time), an increase in LV mass, but little increase in wall thickness, and a substantial decrease in the ratios of mass to volume and thickness to radius (Aurigemma, Zile and Gaasch 2006, Baicu et al. 2005).

*Left atrial chamber remodeling.* The principal role of the left atrium is to modulate left ventricular filling and cardiovascular performance through the interplay of the atrial reservoir, conduit and booster pump functions. Enlargement of the left atrium suggests the presence of elevated filling pressures and diastolic dysfunction, that is, altered reservoir and conduit function (Mitchell, Gupta and Payne 1965). Although left ventricular adaptation to chronic hemodynamic loading has been extensively studied, the mechanisms by which the left atrium compensates for sustained increase in pressure and volume are less well understood, but recent work has suggested patients with HFpEF have increased atrial contribution to LV filling as a compensatory response to impaired early LV filling during cycle exercise (Phan et al. 2009b).

*Left ventricular diastolic function in HFpEF.* Abnormal diastolic function is a universal finding in HFpEF and represents the major pathophysiologic basis for the development of the associated symptoms of HFpEF (Kitzman et al. 2002). The major abnormalities that occur during the development of HFpEF include:

- slowed, delayed and incomplete myocardial relaxation
- impaired rate and extent of left ventricular filling
- shift of filling from early to late diastole
- decreased early diastolic suction/recoil
- augmented left atrial pressure during the early filling
- altered passive elastic properties of the ventricle.
These abnormalities increase passive stiffness and decrease diastolic distensibility (Zile, Baicu and Gaasch 2004; Brucks et al. 2005). They may not be obvious at rest but become more pronounced with exercise, as there is an inability to utilize the Frank-Starling mechanism due to the underlying abnormalities (Kitzman et al. 1991). The redistribution of left ventricular filling from early to late diastole means that patients with HFpEF will not tolerate tachycardic states, such as atrial fibrillation or those driven by anemia or thyrotoxicosis (Phan et al. 2009b).

In patients with HFpEF, short-term treatment with ivabradine (reduces heart rate by acting on the I\textsubscript{f} ion current, highly expressed in the sino-atrial node) increases exercise capacity, with a contribution from improved left ventricular filling pressure response to exercise as reflected by the ratio of peak early diastolic mitral flow velocity to peak early diastolic mitral annular velocity.

In a placebo-controlled study conducted by Kosmala et al. in 2012, a group of patients treated with ivabradine for seven weeks demonstrated significant improvement between baseline and follow-up exercise capacity (4.2 ± 1.8 METs vs. 5.7 ± 1.9 METs, p = 0.001) and peak oxygen uptake (14.0 ± 6.1 ml/min/kg vs. 17.0 ± 3.3 ml/min/kg, p = 0.001), with a simultaneous reduction in exercise-induced increase in the ratio of peak early diastolic mitral flow velocity to peak early diastolic mitral annular velocity (3.1 ± 2.7 vs. 1.3 ± 2.0, p = 0.004).

Paradoxically, chronotropic incompetence is similarly not tolerated by patients with HFpEF as an ability to physiologically increase heart rate is required to overcome the abnormalities described previously (Phan et al. 2009b).

**Left ventricular systolic function in HFpEF.** Although ejection fraction is normal in patients with HFpEF, the debate about the contribution of abnormalities in left ventricular systolic properties to its pathophysiology has remained an area of active investigation. Studies have shown that global systolic properties, such as left ventricular performance measured as stroke work, left ventricular function measured as ejection fraction and preloaded recruitable stroke work, and left ventricular contractility measured as peak (+) dp/dt, end systolic elastance (Ees), and the endocardial stress-shortening relationship are comparable to age matched controls (Aurigemma et al. 2006). However, regional measures of systole, such as long axis function and regional strain may be abnormal in some patients with HFpEF, although they have not as yet been causally linked to the pathophysiology or development of HFpEF (Yip et al. 2002; Nikitin et al. 2002).
**Left atrial function in HFpEF.** Knowledge of atrial function lags considerably behind that related to the left ventricle. However, there has been resurgence in interest regarding the atrial contribution to cardiovascular performance. This is due to the recognition of the important role of atrial function as an important and critical determinant of left ventricular filling. In animal models of left ventricular diastolic dysfunction, both atrial end systolic elastance and atrial work remain normal despite abnormalities of load dependent indices, such as ejection fraction and systolic ejection rate. LA stiffness and reservoir volumes remain abnormal. The relevance of these findings in the pathophysiology and clinical presentation of HFpEF is yet to be established (Nattel et al. 2005).

Additionally, diastolic and systolic dysfunction of the LV may co-exist, for example in HFrEF. This is not discussed in this document, given the focus on HFpEF.

**2.3.2 Hypertension and HFpEF**

Exclusive of valvular, genetic and infiltrative causes, most cases of left ventricular hypertrophy are attributable at least in part to systemic hypertension. Systolic hypertension is predominantly due to increased large artery stiffness and results in increased left ventricular pulsatile afterload (impedance), often eventually inducing development of left ventricular hypertrophy (LVH). Pathological LVH secondary to hypertension has been shown to result in decreased SERCA and increased phospholamban, leading to impaired relaxation (Angeja and Grossman 2003). Apart from causing LVH, increased large artery stiffness and increased Ees associated with hypertension are postulated to cause exercise-induced diastolic heart failure.

A study showed that in older patients with ‘diastolic heart failure’, impaired exercise tolerance correlated with aortic stiffness, which was significantly increased versus age-matched controls (Hundley et al. 2001). Another study showed that in such patients, Verapamil increased exercise capacity in association with reduced resting pulse wave velocity and carotid pressure augmentation, implying improved large artery distensibility (Chen et al. 1999).

In an invasive hemodynamic study conducted by Kawaguchi et al. (2003), a small group of patients with HFpEF were compared with healthy age and gender-matched controls. Left ventricular pressure-volume loops were constructed before and during acute balloon occlusion of the inferior vena cava to cause reductions in preload. Ees, a measure of end-systolic left
ventricular stiffness ($\Delta P/\Delta V$), was then calculated by measuring the slope of this pressure/volume relation. Arterial elastance was calculated as the ratio of systolic pressure/stroke volume, and is a measure of impedance (being influenced by static and pulsatile afterload and by heart rate). In HFpEF patients, both of these relationships were considerably steeper than in controls. That is, for a given increase in systolic volume these patients demonstrated much larger increases in left ventricular end-systolic pressure (Kawaguchi et al. 2003).

Active cardiac relaxation is slowed by acute increases in left ventricular afterload, and consistent with this, handgrip exercise increased tau (an invasive measurement of active relaxation) in patients with HFpEF (from resting values which were near normal), while reducing tau in healthy controls. This slowing of active relaxation resulted in an exercise-related impairment of left ventricular filling in these patients, causing an upward displacement of the left ventricular end-diastolic pressure-volume relation. Thus, although passive chamber stiffness and tau were normal in some patients at rest, both became markedly abnormal during handgrip exercise, a finding consistent with that of our previous non-invasive study. This small study provides a potentially attractive link between increased large artery stiffness and exercise-induced diastolic dysfunction (Lele et al. 1996).

Protein kinase G functioning as a brake on myocardial hypertrophy has been observed in a wide variety of experimental and clinical settings. Previously discussed was the effect of low NO biovalialbility in HFpEF myocardium resulting in low cyclic GMP and protein kinase G levels. In cardiomyocytes cultured from neonatal rat hearts, NO or a cGMP analogue has been shown to attenuate the norepinephrine-induced hypertrophic response (Calderone et al. 1998). A number of other prohypertensive factors may contribute to the development of HFpEF. The upregulation of endothelin-1 has been demonstrated in hypertrophied left ventricles that transition to progressive LV diastolic dysfunction (Iwanaga et al. 1998).

The potential link between large artery stiffness and increased left ventricular end systolic elastance could be explained by the fact a shift to expression of the shorter N2B titin isoform in response to increased arterial stiffness would increase ‘contractility’ to compensate for increased aortic impedance at the price of increased LV systolic stiffness. This situation would lead in turn to dynamic impairment of LV active relaxation during acute increases in blood volume and/or exercise.
2.3.3 Reversible ischemia/previous infarcts
The ability of SERCA to remove calcium from the sarcoplasmic reticulum in diastole is energy-dependent; it is not surprising that ischemia leads to impaired relaxation and diastolic dysfunction. Normally the rate of left ventricular relaxation increases markedly during exercise via sympathetically mediated activation of SERCA, and via PKA-mediated phosphorylation of troponin I (Aroesty et al. 1985). Consequently, even at the high heart rates associated with maximal exercise, the rate of relaxation should not limit LV filling in health. Myocardial ischaemia and/or increased afterload might therefore prevent the normal increase in the rate of relaxation during exercise, limiting LV filling. Passive stiffness is also increased in patients with focal scars and aneurysms from previous myocardial infarcts, resulting in diastolic dysfunction (Angeja and Grossman 2003).

2.3.4 Ageing and hypothyroidism
The process of ageing results in decreased levels of SERCA, as well as increased passive stiffness due to diffuse fibrosis. Pathological studies have shown an increase in serum markers of collagen turnover. Procollagen type I C terminal propeptide is released during the synthesis of collagen type 1, and serum concentrations seem to be increased in cardiac fibrosis (Cain et al. 1998). Hypothyroidism decreases SERCA and increases phospholamban resulting in impaired relaxation. The opposite effect occurs with hyperthyroidism to increase relaxation (Angeja and Grossman 2003).

2.3.5 Diabetes mellitus
The Framingham Heart study was the first to demonstrate an increased risk of heart failure in patients with diabetes. The development of diabetic cardiomyopathy is probably multifactorial with putative mechanisms, including metabolic disturbances, myocardial fibrosis, small vessel disease, autonomic dysfunction and insulin resistance. Left ventricular diastolic dysfunction may be the first stage of a diabetic cardiomyopathy. Poirier et al. (2003) reported that patients with well-controlled diabetes and without overt coronary artery disease, hypertension or heart failure had lower exercise performance on maximal treadmill testing than age-matched controls.

The exercise limitation correlated with the severity of diastolic dysfunction as assessed by Doppler echocardiography. The Olmstead County observational study (Owan et al. 2006) found
that even mild impairment in diastolic function is associated with an eight-fold increase in all cause mortality compared with normal diastolic function. And 50% of diabetic individuals had echocardiographic evidence of diastolic dysfunction compared with 27% of non-diabetics.

The abnormal myocardial metabolism in diabetes leads to an accumulation of toxic molecules (e.g., free radicals), which in turn results in alterations in function of regulatory and contractile proteins and decreased calcium sensitivity (Malhotra and Sanghi 1997).

The metabolic abnormalities are in turn related to a significantly lower ratio of myocardial phosphocreatine to ATP in diabetic patients compared to controls (Diamant et al. 2003). The metabolic abnormalities are also associated with myocardial structural changes including myocardial fibrosis and myocyte hypertrophy. This is attributed to the increased production of transforming growth factor beta that results in promotion of angiotensin II activity with an increase in myocardial collagen content (Taegtmeyer, McNulty and Young 2002).

As diabetes progresses, accumulation of collagen may become obvious and play a major role in the development of diastolic dysfunction.

2.3.6 Acute pulmonary ooedema and HFP EF

Patients with HFP EF often have markedly labile symptoms, and can present not only with chronic symptoms of breathlessness and/or fatigue, but also in pulmonary oedema, which may occur with very rapid onset (‘flash’ pulmonary oedema). The exact cause is often unclear, and it is not known what proportion of these episodes are precipitated by an acute worsening of systolic function, or to dynamic mitral regurgitation (Stone et al. 1991; Bogaty, Mure and Dumesnil 2002).

Recent studies have shown that up to 30-40% of patients presenting to hospital emergency departments with clear-cut acute pulmonary oedema have normal LVEF measured within two hours of arrival, and (Gandhi et al. 2001) reported no significant difference between LVEF measured before and after stabilization. This does not entirely exclude the possibility of transient systolic dysfunction that had fully recovered by the time of initial echocardiography. Some episodes of ‘flash’ pulmonary oedema in patients with HFP EF may be precipitated by acute myocardial ischemia by one of three mechanisms: (a) transient systolic dysfunction, (b) ischemia-
mediated diastolic dysfunction or (c) ischemia-mediated mitral regurgitation. Other precipitating factors may include arrhythmias (especially paroxysmal atrial fibrillation), bilateral renal artery stenosis (Brammah et al. 2003) and phaeochromocytomas. However, many cases remain unexplained.

Patients presenting with flash pulmonary oedema usually also have very high blood pressures at presentation. LV end-systolic elastance is usually increased in these patients, and a small change in blood volume results in large changes in the left ventricular end systolic pressures and subsequent afterload (reflected in the high blood pressures). This results in slowing of the LV active relaxation with the concomitant energetic impairment (Kawaguchi et al. 2003; Phan et al. 2009a).

**Dynamic mitral regurgitation as a cause of HFpEF.** Dynamic mitral regurgitation due to ischemia and/or tethering is common in patients with heart failure who have left ventricular systolic dysfunction. This transient change in regurgitant volume is sufficient to increase pulmonary vascular pressure and to precipitate acute dyspnoea. In a recent study exercise echocardiography was performed on patients with systolic dysfunction who had presented a few days earlier in acute pulmonary oedema. A large exercise-induced increase in mitral regurgitation and pulmonary arterial pressure was observed, suggesting that dynamic mitral regurgitation was an important mechanism in these patients (Pierard and Lancellotti 2004). Unrecognized dynamic mitral regurgitation may potentially be a contributor to both the chronic syndrome of HFpEF and to the pathogenesis of acute pulmonary oedema in patients with a normal ejection fraction. Exercise echocardiography provides a better appreciation of the dynamic characteristics of mitral regurgitation, and may provide a useful marker to identify those patients in whom dynamic mitral regurgitation may explain symptoms in patients presenting with HFpEF.

Note that, although diastolic dysfunction or diastolic heart failure secondary to the infiltrative cardiomyophies, pericardial disease and valvular pathology are beyond the scope of this review, they should be considered in the differential diagnosis of HFpEF.

### 2.4 Diagnostic criteria for HFpEF

A number of different criteria in the literature are used to define diastolic heart failure. The most widely used diagnostic criteria for heart failure with preserved ejection fraction (HFpEF) are those
proposed by the Heart Failure and Echocardiography Association of the European Society of Cardiology, which were released in 2007 (Paulus et al. 2007). The diagnosis of HFpEF requires the following conditions to be satisfied:

- signs or symptoms of heart failure
- normal or mildly abnormal systolic left ventricular function
- evidence of diastolic left ventricular dysfunction.

Normal or mildly abnormal systolic left ventricular function implies both an LVEF ≥50% and a left ventricular end-diastolic volume index (LVEDVI) ≤97 mL/m².

Diagnostic evidence of diastolic left ventricular dysfunction can be obtained invasively (left ventricular end-diastolic pressure >16 mmHg or mean pulmonary capillary wedge pressure >12 mmHg) or non-invasively by tissue Doppler (TD) (E/E’ of >15). If TD yields an E/E’ ratio suggestive but not diagnostic of diastolic left ventricular dysfunction (15 <E/E’< 8), additional non-invasive investigations are required for diagnostic evidence of diastolic left ventricular dysfunction. These can consist of blood flow Doppler of mitral valve or pulmonary veins, echocardiographic measures of left ventricular mass index or left atrial volume index, electrocardiographic evidence of atrial fibrillation, or plasma levels of natriuretic peptides.

If plasma levels of natriuretic peptides are elevated, diagnostic evidence of diastolic left ventricular dysfunction also requires additional non-invasive investigations such as TD, blood flow Doppler of the mitral valve or pulmonary veins, echo measures of the left ventricular mass index or left atrial volume index, or electrocardiographic evidence of atrial fibrillation. A similar strategy with focus on a high negative predictive value of successive investigations is proposed for the exclusion of HFpEF in patients with breathlessness and no signs of congestion.

In summary, all published criteria for HFpEF require definite and reliable evidence of heart failure at the bedside. In addition to clinical evidence of a congestive state emphasized in the Framingham (McKee et al. 1971) and Boston criteria (Carlson et al. 1985) for CHF, the diagnosis should be supported by laboratory evidence of pulmonary oedema on chest x-ray or elevated plasma BNP. The Boston and Framingham criteria are based largely on the presence of a congestive state. In the absence of overt congestion, cardiopulmonary exercise testing can be used to confirm the diagnosis of cardiac dyspnoea (and exclude physical deconditioning and
respiratory factors as a cause of dyspnoea and fatigue). Thus the first requirement for the diagnosis of diastolic heart failure is the definitive clinical evidence of heart failure (Yturralde and Gaasch 2005). A second requirement is the presence of a normal or near normal LVEF (which does not necessarily equate to normal myocardial contractility). The left ventricular chamber or size is normal or small, but modest left ventricular enlargement does not preclude the diagnosis of diastolic heart failure.

The most available and reasonably accurate method to assess LVEF would be echocardiography. It can also provide information about systolic and diastolic function, ventricular geometry and wall thickness, regional wall motion, valve structure, pericardial disease, left atrial size and information about the right heart and pulmonary artery pressure (Yturralde and Gaasch 2005).

There is no definite consensus on the lower limit of LVEF that should be used as a component of the diagnostic criteria of HFpEF. An EF of > 45% has been used in the European criteria for HFpEF (1998), but values of between 40% and 50% do not represent significant depression of systolic function. The lower limit of a normal ejection fraction is 50%, where two thirds of the end diastolic volume are ejected. Until there are further data, a value of 50% should be considered the lower limit of a normal ejection fraction.

There is also a lack of agreement as to the exact limits of ventricular volume or chamber size. Most criteria require normal or near normal volumes as defined by standard echocardiographic guidelines, whilst others do not use volume as a criteria for diagnosis.

Importantly, the measurement of ventricular function and size need to be contemporary with the assessment of heart failure. The Vasan and Levy criteria are more precise in suggesting a cut of 72 hours after initial presentation (Vasan and Levy 2000).

The final criteria are the confirmatory evidence of HFpEF, which would include one or more of the following: (i) evidence of left ventricular hypertrophy, (ii) left atrial enlargement (in the absence of AF); and/or (iii) the echocardiographic or cardiac catheterization evidence of diastolic dysfunction. It remains controversial as to whether it is necessary to evaluate diastolic function with cardiac catheterization or Doppler echocardiography in the presence of left ventricular hypertrophy and LV remodeling, and in the absence of this evidence, of left atrial enlargement.
The main argument for not performing an echocardiogram is that many of the indices of diastolic dysfunction are load-dependent and there are difficulties associated with their interpretation (Zile et al. 2001). Cardiac catheterization, on the other hand, is an invasive procedure with inherent risks. Nevertheless, it has been shown that in patients with diastolic heart failure, the presence of hypertrophic remodeling is always associated with abnormal hemodynamic indices of diastolic function (Yturralde and Gaasch 2005). When there is uncertainty as to the clinical diagnosis, echocardiography and cardiac catheterization can certainly provide additional, although not confirmatory, evidence of HFpEF, as will be discussed in the following section.

2.5 Assessment of HFpEF

Assessment of HFpEF includes a history, physical examination and investigations to first confirm the presence of HFpEF based on the previously described diagnostic criteria and subsequently to elucidate a possible mechanism or etiology for it. However, since not all cardiac disease affects relaxation and stiffness to the same degree, a wide range of clinical findings and diagnostic findings are seen from one patient to another. Ideally, one would like to have an accurate and widely available technique to measure myocardial relaxation and chamber stiffness. To date, however, all available methods have limitations (Quinones 2005).

2.5.1 Cardiac catheterization

This is a clinically invasive method. Although considered by many experts to be the ‘gold standard’, the measurements are clinically difficult to obtain and require the use of expensive catheters. Due to their limited use, there are no large-scale clinical studies defining the normal range over a wide spread of ages or different disease states. Thus, cardiac catheterization is reserved for research investigations and has limited clinical use. Furthermore, it is difficult, if not impossible, to perform invasive evaluation at the time of clinical presentation.

To date, the most accurate clinical assessment of relaxation is obtained by recording left ventricular pressures with catheter tip high fidelity micromanometers and measuring any of the following parameters: peak (-) dp/dt, the time constant of relaxation (Tau), and the lowest early diastolic pressure (Udelson et al. 1990; Weiss, Frederiksen and Weisfeldt 1976). Chamber stiffness is defined by the diastolic left ventricular pressure-volume relationship curves that are quite cumbersome to derive.
A consequence of increased chamber stiffness is an elevation of diastolic left ventricular pressures, intracardiac pressures, such as left ventricular end diastolic pressure (LVEDP) and mean pulmonary capillary wedge pressures (PCWP), which are easily measured as surrogates for chamber stiffness. PCWP is clinically more important, as it is the pressure that finally leads to dyspnoea and pulmonary oedema (Rahimtoola et al. 1972). However, these elevated pressures alone do not provide much insight into the mechanism responsible for diastolic dysfunction, as they are also determined by central blood volume.

2.5.2 Echocardiography

Echocardiography plays a pivotal role in assessment of HFpEF. Assessment of left ventricular size and function, left atrial size and concentric left ventricular hypertrophy are all reasonably and reproducibly measured on two-dimensional echocardiography (Lang et al. 2005). There is however no consensus on the evaluation of diastolic dysfunction on echocardiography. The European working group on HFpEF has provided criteria which relate to abnormal relaxation, abnormal left ventricular filling or reduced left ventricular diastolic distensibility based on transmitral and pulmonary vein Doppler data, as described previously in the section on diagnostic criteria (Paulus et al. 2007).

The American Society of Echocardiography (ASE) has also released a consensus statement on how to diagnose HFpEF using similar parameters, and the minor differences between the two groups will be highlighted at the end of this section (Nagueh et al. 2009). The evaluation of diastolic function should be based on a comprehensive echocardiographic study integrating all available two dimensional and Doppler data. (Mottram and Marwick 2005). These echocardiographic parameters have therefore been explored individually in more detail.

The most important function of an echocardiographic study is to evaluate the systolic function of the heart to ensure that it is ‘preserved’ to satisfy the first requirement of the HFpEF syndrome. The current guidelines use ejection fraction as a surrogate for systolic function, hence the syndrome being named HFpEF. There are two main problems with the use of the ejection fraction. Firstly, establishing cut- off values for preserved versus reduced ejection fraction is difficult and somewhat arbitrary. This is addressed in a viewpoint paper published by our group and the subject of Chapter 6 in this thesis (Mahadevan et al. 2008). The second problem of using
an ejection fraction to represent systolic function is that it is a load dependent measurement and may not truly represent cardiac contractility and subclinical left ventricular function. This issue and possible alternative methods for assessing systolic function are addressed in Chapter 5.

Apart from the ejection fraction, the other two-dimensional parameter that is essential for the diagnosis of HFpEF is the left atrial size. As the left atrium is connected to the left ventricle, enlargement of the left atrial size suggests the presence of elevated filling and diastolic dysfunction, whether due to left ventricular diastolic dysfunction and/or to mitral valve disease. The left atrial size is usually measured at end systole, when it is most dilated. Both the left atrial area and volume are measured and have been shown to correlate with the severity and duration of diastolic dysfunction, which may reflect the cumulative effect of elevated filling pressures over time and are less susceptible to loading conditions than the Doppler parameters.

Initial investigations used left atrial diameter as an index of size, and Vaziri et al. (1995) showed a correlation between systolic pressure and increased LA diameter in the Framingham study. Recent studies however have demonstrated that LA volume indexed to body surface area, correcting for body size, may be a more suitable marker of diastolic dysfunction. Pritchett et al. (Pritchett et al. 2003) demonstrated the high sensitivity and specificity of LA volume index for detection of severe diastolic dysfunction, but not mild-moderate diastolic dysfunction.

For these reasons, the present consensus document (Paulus 2007), considers a left atrial volume index 40 mL/m² to provide sufficient evidence of diastolic left ventricular dysfunction when the E/E’ ratio (discussed below) is non-conclusive (i.e. 15 >E/E’> 8) or when plasma levels of natriuretic peptides are elevated. Similarly, a left atrial volume index less than 29mL/m² is proposed as a prerequisite to exclude HFNEF (left atrial volume index values of 29 and 40 mL/m² correspond, respectively, to the lower cut-off values of mildly abnormal and severely abnormal left atrial size in the recent recommendations for cardiac chamber quantification of the American Society of Echocardiography and the European Association of Echocardiography (Lang et al. 2005).

The problem with the guidelines remains that LA size and volume are a function of chronic reflection of LA pressure. These parameters are unable to reflect patients with a normal resting left ventricular end diastolic pressure, where the diastolic abnormalities are present only on exercise.
The next two-dimensional parameter required for assessment of diastolic dysfunction and HFpEF is left ventricular hypertrophy or mass. Although diastolic dysfunction is not uncommon in patients with normal wall thickness, left ventricular hypertrophy is among the important reasons for it. In patients with diastolic heart failure, concentric hypertrophy (increased mass and relative wall thickness), or remodelling (normal mass but increased relative wall thickness), can be observed. Left ventricular mass may be best, although laboriously, measured using 3-dimensional echocardiography. Nevertheless, it is possible to measure it in most patients using 2D echocardiography, although certain assumptions have to be made.

The essential approach to the diagnosis of diastolic dysfunction relates to Doppler parameters. The most commonly used Doppler parameter is transmitral flow and velocities from the apical window using pulse-wave Doppler analysis. It is easy to use and generally obtainable in 95% of subjects. A ‘delayed relaxation’ pattern (reversal of the E/A ratio) is often referred to as indicating ‘diastolic dysfunction’; however, this pattern is common in asymptomatic elderly populations (Sim et al. 2004; Mandinov et al. 2000).

When left ventricular end-diastolic pressure rises, a ‘pseudo normal’ or ‘restrictive’ pattern may supervene. Indeed, the presence of a ‘delayed relaxation’ pattern at rest appears not to identify elderly subjects with ‘diastolic heart failure’, but rather is associated with a significantly greater exercise capacity than the presence of a ‘normal’ filling pattern (Peterson et al. 2003). In the Strong Heart Study of elderly subjects, the presence of a ‘normal’ E/A profile was associated with an increased risk of developing heart failure and of subsequent mortality compared with the ‘delayed relaxation’ profile, possibly because some patients with a ‘normal’ profile actually had a ‘pseudo normal’ pattern (Aurigemma et al. 2001). Other Doppler measures include the deceleration time of the E wave, which is characteristically prolonged in patients with impaired relaxation, and IVRT (isovolaemic relaxation time), which tends to parallel deceleration time.

The Doppler parameter assessed during the current research was the pulmonary vein flow, which helps to differentiate between normal and ‘pseudo normal’ patterns. Pulmonary vein flow requires establishing the difference between the duration of the mitral wave a velocity (Ar) and the duration of the pulmonary vein a velocity (A). It is obtained from the apical images using pulse wave Doppler analysis and reflects the filling dynamics of the left atrium.
With experience, high quality recordings of the pulmonary vein flow can be obtained in 85-90% of subjects. There are limitations to its use in a number of conditions. Sinus tachycardia and first-degree atrioventricular block often result in the start of atrial contraction occurring before diastolic mitral and pulmonary venous flow velocity has declined to the zero baseline. This increases the width of the mitral A-wave velocity and decreases that of the reversal in the pulmonary vein, making the Ar-A relationship difficult to interpret during the assessment of increases in left ventricular A-wave pressure.

With atrial fibrillation, the loss of atrial contraction and relaxation reduces pulmonary venous systolic flow regardless of filling pressures. With a first-degree atrioventricular block of 300 ms, flow into the left atrium with its relaxation (S1) cannot be separated from later systolic flow (S2), or can even occur in diastole. Most importantly, however, is the fact that with normal EF and diastolic dysfunction, the transmitral pulmonary vein flow are insensitive and will require the use of newer techniques, such as propogation velocity by colour m-mode (Vp) and mitral annular tissue velocity (E’), which are less influenced by preload (Mottram and Marwick 2005).

Mitral annular propagation velocity by colour M-mode, as the name suggests, combines colour Doppler and M-mode to assess left ventricular filling pressures. However, caution should be exercised when using the E/Vp ratio for the prediction of left ventricular filling pressures in patients with normal EF. In particular, patients with normal left ventricular volumes and EF but abnormal filling pressures can have a misleadingly normal Vp. In addition, there are reports showing a positive influence of preload on Vp in patients with normal EF, as well as those with depressed EFs.

Due to the limitations mentioned for all of the above Doppler parameters, tissue Doppler imaging has become essential in the diagnosis of diastolic dysfunction and HFpEF. Pulse wave spectral Doppler is used to measure mitral annular velocities, which are related to left ventricular contraction and relaxation. In interpreting LV filling pressures, Doppler imaging has its greatest use in distinguishing normal and pseudonormal filling, used in conjunction with other 2D and Doppler parameters discussed above. There are limitations with this modality that are both technical and clinical. For technical limitations, proper attention to the location of the sample size, as well as gain, filter, and minimal angulation with annular motion, is essential for reliable velocity measurements. With experience, these observations are highly reproducible with low variability.
There are a number of clinical settings in which annular velocity measurements and the E/E’ ratio should not be used. In normal subjects, E’ velocity is positively related to preload, and therefore the E/E’ ratio may not provide a reliable estimate of filling pressures. These individuals can be recognized by history, normal cardiac structure and function, and the earlier (or simultaneous) onset of annular E’ in comparison with mitral E velocity. Additionally, E’ velocity is usually reduced in patients with significant annular calcification, surgical rings, mitral stenosis, and prosthetic mitral valves (Mottram and Marwick 2005). There is also only a modest correlation of E/E’ with invasively measured filling pressures in patients with hypertrophic cardiomyopathy (Geske et al. 2007).

Both tissue Doppler and second-generation modalities such as speckle tracking, which is independent of Doppler incident angle, have enabled measurements of myocardial deformation parameters such as strain and strain rate. The techniques have shown promise in recently published studies of being superior to the measurement of tissue velocities in detecting relaxation abnormalities. Similarly, other new developments allow the assessment of clockwise and counter clockwise rotation of the base and apex of the heart (also referred to as torsion) (Opdahl et al. 2012). Quantification of this motion may provide a more global assessment of contraction and relaxation. Whilst these modalities show promise, they are not used in mainstream clinical practice to diagnose diastolic dysfunction.

Importantly, diastole is highly dynamic and load-dependent. Therefore, standard resting measures may provide little information about diastolic function during exercise. Consequently, even sophisticated resting measures of diastolic function as outlined above may not accurately identify patients with HFpEF.

2.5.3 Cardiopulmonary exercise testing (CPEX)

Given that resting measures of diastolic dysfunction may be flawed, how then can we identify those patients with clinical features of heart failure who have a primarily cardiac cause for their symptoms? The greatest weakness in conventional diagnostic criteria for heart failure is that absolutely all the objective evidence collected (by examination or by imaging) is at rest, despite this being a disease exacerbated by exercise. As argued by Coats, CPEX is the nearest one can achieve to a ‘gold’ standard for evaluating the mechanism of exercise limitation in patients.
with breathlessness on exertion, especially in patients in whom cardiac and respiratory disease co-exist (Francis, Davies and Coats 2001). Compared with normal subjects, those with pulmonary, cardiovascular or metabolic diseases have a reduced tolerance to exercise and show clear abnormalities in their physiologic adaptation to exercise in terms of the principal exercise variables (e.g. ventilation and heart rate) (Ferrazza et al. 2009).

During the test, patients are subjected to symptom-limited incremental exercise, breath-by-breath monitoring of cardiopulmonary variables [e.g. pulmonary O2 uptake (VO2), pulmonary CO2 output (VCO2), minute ventilation (VE), heart rate (HR)], assessment of perceptual responses (e.g. dyspnoea, leg discomfort) and measurements such as exercise-related arterial oxygen desaturation, dynamic hyperinflation and limb-muscle strength. Peak VO2, an indicator of oxygen uptake, is a particularly reproducible variable in exercise physiology. Secondly, peak VO2 predicts mortality in heart failure better than any resting measurement.

These observations are recognised in guidelines for the management of severe heart failure: a peak VO2 below 14 ml/kg/min implies a prognosis poor enough to be considered for cardiac transplantation (Mancini et al. 1991). Clinically most interesting is the identification of a peak VO2 below 14 ml/kg/min as the cause of impaired exercise capacity specifically, whether it limits aerobic response to exercise (characteristic of heart failure) or leads to failure to utilise aerobic capacity fully (indicating that cardiac output is not the rate limiting step). These distinctions are made from the temporal course of metabolism during exercise and measurement of the respiratory exchange ratio of VCO2 to VO2.

The third useful piece of information that the clinician can obtain is the behaviour of oxygen saturation on exercise. CHF on its own does not cause desaturation during exercise. In one series of 37 patients with CHF, the only three patients showing desaturation on exercise were found to have alternative diagnoses: patent foramen ovale with right to left shunt during exercise, pulmonary embolic disease, and clinically unsuspected obstructive airways disease (Lavie, Milani and Mehra 2004).

Fourth, the ventilatory response to exercise (slope of the ratio of expired ventilation to VCO2) can be measured. This is abnormally augmented in most patients with CHF, closely related to
symptoms of breathlessness, and carries additional prognostic significance that has recently been suggested to be even more powerful than that of peak VO2.

A respiratory exchange ratio (RER) of <1.1 (particularly 1.0) in the absence of other metabolic abnormalities suggests poor effort, or anxiety, and may be considered non-diagnostic. Alongside these data, all the information obtained from a conventional exercise test is also available, including exercise induced arrhythmias, ST segment changes, and chronotropic incompetence. These abnormalities may merit specific treatment.

Patients also undergo full resting assessment of respiratory function, including measurement of MVV (maximum voluntary ventilation) and transfer factor (DLCO – a measure of lung diffusion). Breath by breath assessment of gas exchange and finger oximetry is performed at rest and during incremental exercise, with an optimal duration of 8-10 minutes. The criteria used to distinguish the mechanism of exercise limitation are summarized here:

**Circulatory cause for dyspnoea**

1. Subjects must attain a peak or maximal effort; this has been achieved when the respiratory exchange ratio (RER – measured as VCO2/VO2) is greater than 1.0.

2. If a peak effort is made the subject must demonstrate significant limitation, defined as a VO2 peak < 70% of age and gender-predicted.

3. The patient must not be limited by lung function, defined by a maximal ventilation (VE) <70% of maximum voluntary ventilation (MVV).

4. The patient must not be limited gas diffusion, defined as an arterial oxygen saturation at peak exercise >90% (i.e. they do not desaturate on exercise).

5. That patient should show an abnormal ventilation in response to an increase in carbon dioxide; defined as a VE/VCO2 slope in >34. VE/VCO2 is inversely related to cardiac output and a steep slope indicates a low cardiac output.

6. VO2 at anaerobic threshold should be <40% of age and gender predicted peak VO2.
**Non-circulatory cause for dyspnoea**

If a subject fails to meet any one of the previous five criteria it is not possible to confirm that they are limited by cardiac function. Unfortunately, particularly in the elderly, locomotor problems or lack of volition may limit the ability to perform an adequate exercise test. Using an incremental ramp protocol, however, it was found during the current study that approximately 75% of elderly patients presenting with symptoms of heart failure were able to undertake a metabolic exercise test to a level sufficient to generate diagnostic data (Kitzman 2005).

In a comparative study by Kitzman et al. (Kitzman et al. 2002), maximal exercise testing with expired gas was performed in a total of 119 older subjects divided into three groups: heart failure with severe left ventricular systolic dysfunction (mean EF 30%), isolated diastolic heart failure (EF >50% and no significant coronary, valvular, pericardial or pulmonary disease and anemia), and age matched controls.

Compared to normal controls, peak VO2 was severely reduced in the patients with diastolic heart failure and to a similar degree to those with systolic heart failure. In addition, ventilatory anaerobic thresholds were similarly reduced in HFpEF patients and those with systolic heart failure, and this was accompanied by a reduced health related quality of life (Kitzman et al. 2002).

**By utilizing metabolic exercise testing it is possible to confirm whether or not patients thought clinically to have HFpEF truly have a cardiac cause for their limited exercise capacity.**

However, in contrast to normal subjects, in whom physiologic limitation to oxygen transport may be evident, patients are often symptom limited, and may stop exercise before reaching physiologic limits of metabolic or gas transport capacity. The presence of deconditioning in many patients and normal humans has increased awareness of the role of peripheral limitation (skeletal muscle dysfunction) in exercise performance, and the importance of considering deconditioning, as well as marked obesity, as a contributing factor in their symptoms and exercise limitation.

The selection of normal reference values for use in the evaluation of CPEX testing results is critical to any interpretative scheme. Normal reference values provide the comparative basis for answering important questions concerning the normalcy of exercise responses in patients,
significantly impacting the clinical decision-making process. Standardization of normal reference values processes and practices for CPEX is necessary to facilitate accurate interpretation and optimize clinical value. When selecting reference values from the literature, a number of factors should be considered, including the following: the study sample size and randomization, quality assurance and CPEX protocols, data validation, and statistical interpretation of the data set. In the end, each clinical exercise laboratory must select an appropriate set of reference values that best reflects the characteristics of their population tested, and the equipment and methodology utilized (2003).

From the analysis of currently available sets of reference values, it can be concluded that none of these studies fulfil the requirements for ‘optimal’ reference values noted previously. Among the most commonly used sets of reference values, there are significant differences in the population characteristics, sample size, equipment, methodology, and measurements reported. The reference values given by Jones and co-workers (Jones, Summers and Killian 1989) and by Hansen and co-workers (Hansen, Sue and Wasserman 1984) are most widely used. This data however mainly represents middle aged people (many smokers and hypertensives), with results extrapolated to the elderly.

Jones and co-workers (Jones et al. 1989), as well as Blackie and co-workers (Blackie et al. 1989), studied an older population to correct for the skewness of the predicted values for this group. However, only work rate (WR), VO2, and VE were reported, with much discussion concerning the reliability of the data from the turbine equipment used in the studies. Age and gender matched reference values with nomograms for predicting a peak VO2 max using treadmill and cycle metabolic exercise testing have been published (Schneider 2013). This issue will be addressed in more detail in Chapter 6.

2.5.4 Neurohormonal levels

Plasma BNP and N-Terminal BNP have been shown to correlate closely with left ventricular end-diastolic pressure, and are consistently elevated at rest in patients with LV systolic dysfunction (McDonagh et al. 1998). Whilst resting plasma BNP is frequently also elevated in patients with HFpEF, although with different cut-offs, this is less consistent, and generally offers little additive value, than the standard echo criteria in diagnosing HFpEF. Work by (Jorge et al. 2013; Anjan et
al. 2012), for example, found normal BNP levels were present in 29% of symptomatic outpatients with HFpEF who had elevated pulmonary capillary wedge pressures. And, although BNP is useful as a prognostic marker in HFpEF, a normal BNP does not exclude the outpatient diagnosis of HFpEF. In the studies, subjects with normal BNP were younger, were more often women, had higher rates of obesity and higher body mass index, and less commonly had chronic kidney disease and atrial fibrillation.

Whether this is because LVEDP is less consistently raised at rest in such patients or whether it is because many patients labeled as having HFpEF do not in fact have heart failure, as discussed above, is uncertain. Whilst resting plasma BNP is frequently also elevated in patients with HFpEF, this is less consistent, and generally less marked. Whether this is because LVEDP is less consistently raised at rest in such patients or whether it is because many patients labeled as having HFpEF do not in fact have heart failure, as discussed above, is uncertain (Hogg and McMurray 2005).

Dahlstrom et al. (2004) have shown that asymptomatic patients with only mild abnormalities of relaxation (reversal of the E/A ratio) have relatively normal concentrations of natriuretic peptides, whereas patients with a ‘pseudo normal’ or restrictive transmitral filling pattern show more consistent elevations in BNP at rest (Dahlstrom et al. 2004). In healthy subjects, plasma BNP rises very little with exercise, but in patients with systolic heart failure, the rise is marked. BNP is also known to rise markedly during episodes of cardiac ischemia (Hogg and McMurray 2005).

Plasma BNP has also been shown to be an important prognostic marker in patients with HFpEF in terms of predicting mortality (Yan et al. 2013). There have not, however, been studies assessing the utility of plasma BNP during exercise for diagnosing patients with HFpEF. The acute rise in BNP may enhance the diagnostic utility of plasma BNP in diagnosing HFpEF at the early stages prior to hospitalization, as well as improving its prognostic capabilities.

Van Veldhuisen et al. (2013) determined that the BNP levels for patients with HFpEF were lower for patients with reduced ejection fractions, but for a given BNP level the risk of hospitalization and all cause mortality was similar in both groups. BNP also appeared to be a better predictor of outcome than the left ventricular ejection fraction. In a post hoc analysis of the I-Preserve trial, there was evidence that treatment with Irberstan prior to BNP elevation above the median levels
established for the entire cohort, produced a beneficial effect on the primary outcome (HR, 0.74; 95% CI, 0.60 to 90; P = 0.003), all-cause mortality (HR, 0.75; 95% CI, 0.56 to 0.99; P = 0.046), and HF composite outcome (HR, 0.57; 95% CI, 0.41 to 0.80; P = 0.001) (Anand et al. 2011).

BNP may also play a role in the pathophysiology and therapeutics of HFpEF. This has been the basis for a phase two study to try to increase the level of BNP with neprilysin inhibition in patients with HFpEF. The results of the study showed significant reductions in left atrial volumes at 36 weeks and a reduction in NT-pro BNP which is biologically inert and not a substrate for this enzyme (Solomon et al. 2012).

2.6 Prognosis of HFpEF

It is well known that the morbidity associated with HFpEF is generally quite high. The one-year hospital readmission rate can approach 50% in some series. Patients with HFpEF have frequent outpatient visits. For these reasons, the expenditure associated with HFpEF rivals that of systolic heart failure (Franklin and Aurigemma 2005). As described previously, the two studies by Bhatia and Owan published in the NEJM did not show a significant mortality difference between patients with preserved and reduced systolic function. The slightly better survival rates in the HFpEF group in the Owen study was offset by the improved survival over time of those with reduced systolic function (Bhatia et al. 2006; Owan et al. 2006).

Two of the population-based prevalence studies reported prognosis. In the Helsinki Ageing Study, four-year mortality in individuals free of CHF was 30%. Of those with CHF, the mortality was 43% amongst those with preserved ejection fraction and 54% for those with reduced systolic function (Kupari et al. 1997). In the Cardiovascular Health Study (CHS), the 6.4 year mortality rate in subjects without CHF was 16% compared to 45 % for those with CHF. The mortality rates in HFpEF patients were 87 deaths per 1000 patient years, as compared with 25 deaths for those without CHF (Gottdiener et al. 2002).

Classifying the modes of death in population studies is frequently unreliable, but using data from the registry office, the follow-up Echocardiographic Heart of England Screening Study (ECHOES) reported a significantly lower proportion of cardiovascular deaths in patients with HFpEF than patients with HFrEF (45% vs 74%). Death from ‘definite’ HF was also significantly lower in patients with HFpEF compared to those with HFrEF (17.2% vs 38.5%) (Hobbs et al.
2007). These data suggest that the mode of death in patients with HFpEF may differ significantly from patients with HFrEF.

Finally, in a review of modes of death in published studies of HFpEF patients, there were fewer deaths from heart failure in HFpEF patients than among HFrEF patients (Lim, Beadle and Frenneaux 2009).

2.7 Management of HFpEF
There is little objective data to guide the therapy of patients with HFpEF. This relative paucity of objective information is reflected in the American College of Cardiology and the European Society of Cardiology guidelines for the treatment of HFpEF, or diastolic heart failure, as it is referred to in the guidelines (Hunt 2005). To paraphrase the recommendations of these guidelines, the goal of therapy for diastolic heart failure is to:

- control symptoms by reducing ventricular filling pressures without reducing cardiac output,
- control symptoms using diuretics and nitrates
- control arterial hypertension
- calcium channel blockers, beta blockers, angiotensin-converting enzyme inhibitor and angiotensin II receptor blockers may be of benefit beyond the treatment of systemic hypertension
- consider other possible but unproven therapeutic strategies, including myocardial revascularization, avoiding tachycardia and restoring sinus rhythm (Little and Brucks 2005).

As the pathophysiology of this condition is complex and yet to be fully elucidated, it is not unexpected that the treatment is still ambiguous.

2.7.1 Randomized controlled trials
Despite growing awareness of the burden of HFpEF, there have been few controlled clinical studies of drug therapies for patients with diastolic heart failure. These have been small and generally lacked clinical endpoint outcomes.

The main randomized controlled trial in patients with predominantly diastolic heart failure has been the CHARM preserved study (Yusuf et al. 2003). Patients, who were randomized to receive an angiotensin receptor antagonist, candersartan, had a strong trend toward less rehospitalisation than those who received a placebo. There was no difference in overall mortality. It is also important to note that patients in this study were enrolled with ejection fractions greater than 40%.
There were fewer men in the study, and the mean age was less than usually seen in patients with HFpEF in the community (Yusuf et al. 2003).

The use of perindopril in Elderly People with Chronic Heart Failure (PEP-CHF) study was published in 2006 (Cleland et al. 2006). The study did not show a mortality benefit with perindopril, although there was a significant reduction in heart failure related hospitalizations at one year. The Irbersatan in Heart Failure with Preserved EF (I-Preserve study) was a large randomized placebo-controlled trial of over 4000 patients with a follow up period of five years. There was surprisingly no difference in the primary end-points of death with cardiovascular hospitalization or the secondary end-points, which included quality of life scores and changes in BNP. The patients in this study experienced substantial mortality and cardiovascular morbidity with a five-year cumulative incidence close to 40% in both groups. However, the rate of heart failure related mortality was only about 23% of all mortality, reinforcing the observation that the mode of death in HFpEF may vary significantly from HFrEF (Massie et al. 2008).

The Seniors Trial randomized 2128 elderly patients with heart failure to nebivolol versus placebo. 35% of the patients in this study had an EF above 35%. The primary outcome of all cause mortality or cardiovascular hospitalization was 31.1% of those receiving nebivolol versus 35.3% receiving a placebo. Subgroup analyses were performed in patients less than and greater than 35%. The hazard ratios for the primary outcome were 0.87 and 0.82 respectively, indicating no significant difference between the two groups (Flather et al. 2005).

There has been interest in an endothelin receptor antagonist despite unsuccessful attempts use them in cases of systolic heart failure. Sitaxsentan sodium, a potent antagonist of the endothelin receptor (isoform endothelin receptor A), is currently being evaluated in a phase II multicentre trial.

There have been three trials of note in the last two years with predominantly negative results. The first trial involved a phosphodiesterase -5 inhibitor, sildanefil (Relax trial) (Redfield et al. 2013), a multicenter, double-blind, placebo-controlled, parallel-group, randomized clinical trial of 216 stable outpatients with HF, ejection fraction >50%, elevated N-terminal brain-type natriuretic peptide or elevated invasively measured filling pressures, and reduced exercise capacity. Despite a well-selected group of patients with significant symptoms and a practical, well selected primary
end point of a peak VO2 max after 24 weeks of therapy, there was no treatment benefit in terms of an improvement in VO2 max.

There were two other trials involving the aldosterone receptor antagonist, spironolactone, ALDO-DHF (Edelmann et al. 2012) and the TOPCAT study (Pitt et al. 2014). ALDO DHF was a small 422 patient randomized controlled trial, with a primary end-point of a change in VO2 max and a change in echocardiographic parameters, namely E/E’. The outcomes were disappointing, with no change in VO2 max and the six minute walk test with treatment, although there was a small, statistically significant improvement in E/E’. The change was probably of minimal clinical relevance despite the statistics, as the difference in E/E’ was 13.6 (13.0-14.2) to 12.1 (11.6-12.6) P < 0.001.

The TOPCAT study was a large randomized controlled trial of 3445 patients who were treated with spironolactone with a mean follow up of 3.3 years. The primary outcome was a composite of death from cardiovascular causes, aborted cardiac arrest, or hospitalization for the management of heart failure. Of the components of the primary outcome, only hospitalization for heart failure had a significantly lower incidence in the spironolactone group than in the placebo group (206 patients [12.0%] vs. 245 patients [14.2%]; hazard ratio, 0.83; 95% CI, 0.69 to 0.99, P=0.04). Neither total deaths nor hospitalizations for any reason were significantly reduced by spironolactone.

The importance of patient selection was never more evident than in these studies, however, where patients selected by elevated BNP levels showed an improvement in the primary outcomes, but not patients selected on the basis of previous hospitalization for heart failure. The lack of mortality benefit across the board in all these trials begs the obvious question: wrong patients or wrong paradigm in terms of targeted pathophysiology?

2.7.2 Observational and retrospective trials

A retrospective analysis by Little’s group (Little 2005) evaluated 137 patients with HFpEF and a propensity analysis confirmed that statin therapy was associated with improved survival. No follow up randomised trial has been published to date confirming this finding.

Several observational studies with ACE inhibitors (Aronow and Kronzon 1993) and angiotensin II blockers (Cohn and Tognoni 2001) have demonstrated improved survival and shorter length of stay during index hospitalization, but these have not been reproduced in the large randomized trials involving these agents as described above.
2.7.3 **Future therapies**

There has been interest in a number of novel methods to treat HFpEF, including restoring calcium homeostasis, metabolic modulation and targeting extracellular collagen, crosslinks and matrix deposition. Although there has been some early promise, results have not translated to a significant clinical impact in the management of HFpEF.

### 2.8 Scope of currently described studies

The team of which I was a member during my PhD candidacy conducted a large epidemiological prevalence study of diastolic heart failure in the community. This study, as opposed to previous epidemiological studies, aimed at establishing that patients identified as being breathless were actually limited due to their cardiac status. Data were collected using metabolic exercise testing, as well as full lung function testing.

This chapter explored the various definitions of HFpEF in the literature and the differing modes of investigations used to establish this diagnosis and subsequently reviewed the literature in terms of the reported prevalence in the community based on the various definitions reported in the literature. The etiology of the syndrome was also reviewed and the current knowledge about the pathophysiology and modes of assessing for the syndrome, using either invasive or non-invasive methods. The range of current diagnostic criteria for this syndrome was summarized. Finally the prognosis and management of this syndrome was described. The current limitations in the literature are highlighted, with particular reference to the areas that are examined in this thesis.
Methods, subject selection and subject characteristics

3.1 Introduction

The methodology described in this chapter was common to all the research studies described in Chapters 4 and 5. The sample population and investigations included here were common to all studies with their use adjusted according to the theme of the research. That is, from the initial sample population, research participants were subselected and investigations conducted according to the goals of the specific research program.

The overall objectives of the studies outlined in this thesis were to:

- clarify the association between dyspnoea and abnormal LV diastolic function on echocardiography in patients with a preserved ejection fraction, and determine the extent of correlation between the presence of abnormal exercise physiology of presumptive cardiac cause and that of impaired left ventricular relaxation/filling at rest
  Dyspnoea was classified both subjectively and objectively, based on cardiopulmonary exercise testing (CPEX). The definition of dyspnoea due to cardiac limitation at CPEX was derived from an age and gender-matched nomogram, as well as the current European Society Guidelines as outlined by the Working Group of the European Society of Echocardiography (Paulus 2007).

- use tissue Doppler velocity on echocardiography to analyse the contribution of subtle LV systolic dysfunction to the severity of symptoms in patients with a preserved ejection fraction, and determine whether minor impairment of left ventricular systolic function may represent a substantial contributor to the development of dyspnoea.

3.1.1 Sample selection

The population selected for the study consisted of patients aged 60 years and more randomly selected from the community. This age group was chosen as exertional dyspnoea is a common complaint in this population (Redfield, JAMA, 2003) and the common precursors for HFrEF, such as hypertension, diabetes, obesity and ischemic heart disease, are also relatively prevalent in this age group.

A consecutive series of 1833 subjects aged ≥ 60 was randomly selected from the community to undergo screening. Recruitment was as inclusive as possible, and the only significant exclusion
criteria were terminal illness or an inability to attend the registered practice for the initial screening during which:

- A questionnaire based on the Framingham Criteria (McKee et al. 1971) was administered in order to assess symptoms and quality of life.
- Baseline blood tests (full blood count, urea and electrolytes, random glucose, lipids, thyroid function tests, resting plasma NT-pro BNP were taken.
- Echocardiography with assessment of LVEF (Biplane Simpson’s rule), left atrial area/volumes, LV wall thickness. resting diastolic parameters (e.g., E/A ratio, deceleration time, mitral inflow propagation velocity pulmonary vein flow A duration/velocity, long axis tissue Doppler velocities, calculation of E/E’ ratio), and valvular function

Subjects experiencing breathlessness (New York Heart Association class II-III) and a LVEF > 50% underwent the following:

- clinical examination
- lung function tests (including spirometry and diffusion factor)
- CPEX testing with oximetry as described earlier to assess peak VO2 and to define whether exercise was limited by cardiac or non-cardiac factors.
- With the following exceptions:
  - Subjects who had previous lung function test demonstrating clinically restrictive or obstructive disease did not undergo repeated lung function test or CPEX.
  - Subjects with severe physical exercise limitations, whether due to dyspnoea and/or to non cardiac disease states, were exempted form CPEX.

### 3.1.2 Sample size considerations

Extrapolating the data from the ECHOES study [Davies M, Lancet 2001] by screening 2000 subjects over the age of 60, it was anticipated that 700 individuals with NYHA Class II to III symptoms and normal/near normal LVEF would be located. It was assumed that approximately one quarter of the patients would be truly limited by cardiac factors. Therefore, if 2000 participants were screened, and CPEX testing was carried out on all those with NYHA Class II to III symptoms, it was expected that 150-200 individuals with HFpEF would be identified.

Experience indicated that satisfactory exercise testing would be possible in 75% of the sample, with approximately 100-120 patients satisfying the metabolic exercise criteria for heart failure.
The number of dyspnoic individuals identified, however, was far fewer than anticipated. Therefore the number of individuals with symptomatic cardiac limitation on metabolic exercise testing and a preserved ejection fraction on echocardiography was relatively small, as will be discussed in the following chapters.

Among asymptomatic individuals, 60 with no cardiovascular risk factors were invited to perform CPEX in order to validate (and utilize) normal values for the population. 34 consented to perform CPEX. A flowchart of the recruitment process has been provided in Figure 3.1.

Figure 3.1  Flow chart of recruitment process
3.2 Baseline characteristics and questionnaire for symptom status and quality of life

3.2.1 Baseline characteristics

The following baseline characteristics were reviewed and recorded where appropriate for the individual’s screened weight, height, medications, relevant risk factors, including hypertension, diabetes mellitus, obesity, heart failure, a history of myocardial infarction or ischemic heart disease, atrial fibrillation and smoking history.

- past medical history, especially a history of airways disease, occupational lung disease or asthma
- relevant available investigations, including pulmonary function tests, full blood count for anaemia and thyroid function tests
- medical records, to detect any presumptive heart failure/pulmonary oedema admission to hospital in the past

Subsequently, a questionnaire was administered to assess patients’ symptomatic status (Figure 3.2). Based on the results of this questionnaire, a NYHA class was assigned to each participant.

3.2.2 Health questionnaire

The answers to the questionnaire were assessed individually by two independent investigators and a consensus was required that the dyspnoea experienced during the activities of daily living limited those activities significantly.

A scoring system was used to help quantify the level of dyspnoea. The answers to the 11 components to question 3 on the questionnaire was graded as follows:

- never was given a score of 1
- sometimes given a score of 2
- always was given a score of 3
**General Health Questionnaire**

1. In general would you say your health is:

   - [ ] Excellent
   - [ ] Very good
   - [ ] Good
   - [ ] Fair
   - [ ] Poor

2. Compared to one year ago, how would you rate your health in general now?

   - [ ] Much better than a year ago
   - [ ] Somewhat better than a year ago
   - [ ] About the same as a year ago
   - [ ] Somewhat worse than a year ago
   - [ ] Much worse than a year ago

3. The following are activities you might do during a typical day. Do you get short of breath doing these activities? If so, how often?

<table>
<thead>
<tr>
<th>Activity</th>
<th>Everyday</th>
<th>Sometimes</th>
<th>Never</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) Bathing or dressing yourself</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>b) Bending, kneeling or stooping</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>c) Lifting or carrying groceries</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>d) Walking from room to room</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>e) Doing housework</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>f) Climbing one flight of stairs</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>g) Climbing several flights of stairs</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>h) Walking one hundred yards</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>i) Walking a quarter of a mile</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>j) Walking more than a mile</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>k) Difficulty sleeping due to shortness of breath</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
</tbody>
</table>

4. Do you ever experience any of the following symptoms? If so, how often?

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Everyday</th>
<th>Sometimes</th>
<th>Never</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) Chest pain or tightness when walking</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>b) Chest pain at rest</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>c) Dizziness</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>d) Faints or blackouts</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>e) Sensation of irregular heartbeats</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
</tbody>
</table>

---

**Figure 3.2** General health questionnaire
A score of < or equal to 13 was classified as NYHA class I – no limitation to activities of daily living

A score of between 14-16 was classified as NYHA class IIa – minor limitations to activities of daily living but not affecting quality of life

A score of 16-22 was classified as NYHA IIB – moderate limitations to activities of daily living affecting quality of life

A score of 22-33-NYHA class III – severe limitations on activities of daily significantly limiting quality of life

NYHA class IV – dyspnoea at rest.

Subjects were classed IIB dyspnoea or worse were then classified as symptomatic.

3.3 Echocardiography

An echocardiographic study was performed with a GE Vivid I portable machine by an experienced sonographer. The studies were performed according to the following protocol:

Community echo protocol

General instructions for all echo data acquisition

1 Optimize ECG signal (consistent signal with high amplitude R wave) ensuring that lead II is used throughout the entire study period. Ensure that the onset of the QRS complex is clearly identifiable. Images not accompanied by good quality ECG complexes were not analyzable and could not be used in this study. This was especially important for spectral Doppler and tissue Doppler images.

2 Harmonic imaging is the default for all data acquisition. The goal is for optimal endocardial definition. Non harmonic imaging should be considered when the presence of cardiac amyloid is suspected.

3 The greatest limitation of a sequential 2D echo is the use of a different imaging window/angle from the baseline study. Therefore, before a follow-up study, pull up the baseline study on a workstation, if at all possible have this image close to the monitor so you can mimic the baseline as closely as possible. Even a printout of the screen is better than nothing (or your memory) as a frame of reference.

4 Minimize extrinsic motion, especially during tissue Doppler acquisitions. Recordings should be made in end-tidal expiration where possible but avoid inspiratory breath-holds.
5 Record three cardiac cycles of the 2D, color-flow Doppler and color tissue Doppler images. Record at least five cardiac cycles for all PW/CW Doppler measurements (preferably 10 if the patient is in AF). Record generously so that if premature ventricular beats, premature atrial beats per minute are present the analyses can still be completed.

6 Use M-mode and Doppler sweep speed of 50 mm/sec

7 For color tissue Doppler recordings drop depth so that the mitral annulus is just included at the bottom of the screen and reduce sector width to a minimum that includes all of the LV myocardium.

8 On Doppler recordings, valve transients must be clear (so that AV and MV opening and closure can be timed precisely), optimize the wall filter (not too much) and adjust the gain (use minimal gain) to provide thin spectral envelopes. Beware the dual focus on GE machines for TDI images (it drops the color Doppler frame-rate).

9 For 2-D imaging, beware narrowing the sector angle because this crops the LV images and gives a frame rate higher than can be managed by 2D strain (GE system). Measure and display the maximum cavity length in apical imaging planes and try to maintain the same length in all apical images to avoid fore-shortening (especially A2C). For difficult 2D images, try turning the patient more/less and end-expiratory/-inspiratory images. If you need dual focus, turn it off for color TVI.

Image acquisition

1 Parasternal long axis

- 2D of left ventricle with enough depth to see descending aorta
- 2D of left ventricle, aortic valve, mitral valve and ascending aorta
- M mode of the left ventricle /M-mode with TVI settings level to measure septal to infero-lateral wall delay.
- 2D measurements of left ventricle if indicated(unable to obtain m-mode, M-mode off axis
- M-mode of the mitral valve if indicated(mitral stenosis or HOCM)
- color Doppler of aortic and mitral valves
- PLAX PA
- color and spectral Doppler (PW of RV outflow tract and CW of pulmonary artery for peak velocity and PR end diastolic velocity).
2 Parasternal short axis
   - short-axis view at the aortic valve level and RVOT
   - color flow Doppler should be used to evaluate pulmonic, aortic and tricuspid valves
   - spectral Doppler of RVOT and pulmonic valve (PW and CW)
     (Using pulse wave Doppler pulmonary pre-ejection delay may be measured at the time of QRS onset to the start of pulmonary blood flow.)
   - left ventricle at MV level (colour and planimetry if MR/ MS study) (all images at a frame rate of between 50-70fps)
   - left ventricle at mid level
   - left ventricle at apex
   - M-mode through the LV just below the mitral valve and also M-mode with TVI settings at this level to measure septal to infero-lateral wall delay.

3 Apical four and five chamber views
   - 2D imaging of the four chambers (maximizing length of left ventricle)
   - 2D imaging of the left ventricle at a reduced depth and with two focus points for Simpson’s Biplane measurement
   - 2D imaging of LV at reduced depth and narrowed sector aiming for a frame rate of 50-70fps
   - Use a focus point at the level of the mitral valve
   - color flow Doppler of valvular inflow and regurgitation should assessed at the valves
   - mitral regurgitation quantification for functional MR- DP/DT
   - CW of MR jet
   - PW at level of annulus for regurgitation fraction calculation
   - EROA from PISA calculation on zoom
   - pulmonary vein flow for systolic flow reversal in the pulmonary veins
   - M-mode of MR jet for presence of diastolic MR
   - Doppler tissue imaging (for diastolic function) septum; lateral and RV free wall at annulus
   - 2D images of the LA on zoom at a depth of 17cm at a high frame rate 50-70fps
   - 2D images of the LA in TVI format.
Apical five chamber
- 2D imaging
- color flow Doppler of LVOT
- pulsed-wave Doppler of LVOT for calculation of stroke volume/cardiac output as well as measurement of an aortic pre-ejection time
- calculating an interventricular delay from previous pulmonary pre-ejection
- CW Doppler of aortic valve if aortic stenosis is present or suspected.

4 Apical two and three chamber views
- 2D imaging of the two chambers (maximizing length of left ventricle)
- 2D imaging of the left ventricle at a reduced depth and with two focus points for Simpson’s Biplane measurement
- 2D imaging of LV at reduced depth and narrowed sector aiming for a frame rate of 50-70fps
- focus point at the level of the mitral valve
- 2D images of the LA on zoom at a depth of 17cm at a high frame rate 50-70fps
- 2D images of the LA in TVI format.

Apical long axis view
- 2D imaging of the three chambers (maximizing length of left ventricle)
- 2D imaging of LV at reduced depth and narrowed sector aiming for a frame rate of 50-70fps (save two to three images of 3 cycles in length for speckle tracking)
- focus point at the level of the mitral valve
- color flow Doppler of LVOT
- pulsed-wave Doppler of LVOT for calculation of stroke volume/cardiac output as well as measurement of an aortic pre-ejection time
- calculate an interventricular delay from previous pulmonary pre-ejection time
- CW Doppler of aortic valve if aortic stenosis is present or suspected.

Each study was subsequently assessed by three investigators on an EchoPAC platform and the results were saved into a database and a report generated for the subjects general practitioner.

The main measurements included a LVEF (calculated via Biplane Simpson’s rule), left atrial area/volumes, LV wall thickness. Resting diastolic parameters (E/A ratio, deceleration time,
mitral inflow propagation velocity pulmonary vein flow A duration/velocity, long axis tissue Doppler velocities) and valvular function. E/E’ ratio were calculated for the septum and lateral wall.

Given the main aim of the study was to assess the contribution of subtle systolic dysfunction despite a relatively preserved ejection fraction, -Sm (septal) and Sm (lateral) were measured using tissue Doppler imaging (TDI) method to evaluate subclinical LV systolic dysfunction.

Given the age of the population evaluated, it was expected that early aortic valve disease would be present in up to 30% of cases (Ngo et al. 2011). While presence of aortic sclerosis was not an exclusion criterion, in the presence of haemodynamically significant aortic stenosis (calculated aortic valve area<1.5cm2), no further investigation was performed.

The following measurements were performed to assess the severity of aortic valve disease:

- 2-3 repeat measurements of the left ventricular outflow tract diameter
- pulse wave of the left ventricular outflow tract
- continuous wave through the aortic valve with the standard probe as well as the Pedoff probe for haemodynamically significant stenosis(V max >3m/sec).

### 3.4 Cardiopulmonary exercise testing (CPEX)

Patients who were breathless were then evaluated with pulmonary function testing if there was reason to suspect the presence of respiratory disease, both obstructive and restrictive, and a recent test was not available in their medical records. The definitions of significant obstructive airways disease were adapted from Salzman (1999). They were:

- the forced expiratory volume in 1 second to forced vital capacity ratio (FEV1/FVC) < or equal to 0.7
- increased total lung capacity.

The definition of restrictive lung disease were:

- both forced expiratory volume in one second (FEV1) and forced vital capacity (FVC) are reduced, with a greater decline in FVC, resulting in a higher than 80% FEV1/FVC ratio
- reduced total lung capacity (<80%).

All other patients proceeded directly to a CPEX study.
The general protocol and basic definitions for the study are outlined below, while the algorithm for utilizing CPEX data for detailed review on CPEX and diagnosing cardiac limitation is detailed below.

Measurements of gas exchange were performed breath by breath, with the results displayed almost simultaneously on a computer screen by rapid computer processing and by correction for the time delay from expiration to measurement. We used a combination of protocols to help the patient to achieve a respiratory exchange ratio of at least one and ensure they achieved an anaerobic threshold. The exercise protocols used were the modified Naughton-protocol. However, in the presence of mild heart failure this protocol results in a long exercise time. An exercise test duration of 10-15 minutes is generally considered optimal and therefore in some cases a modified Bruce or Bruce protocol was used in preference.(Ferraza 2009).

Repeated daily calibrations and proof of tightness of face masks with no air leaking during maximal respiration, as well as the familiarity of patients with the exercise situation, are very important aspects of CPEX testing and were adhered to with a qualified technician in charge of the testing and the exercise cart.

The parameters measured during CPEX adapted from Milani (Circ 2004), were:

- Peak oxygen uptake (PkVO2): The highest VO2 achieved during the CPEX, generally occurring at or near peak exercise. Reported as a weight-adjusted parameter in mL/kg per minute.
- Maximal oxygen uptake (VO2 max): The value achieved when VO2 remains stable despite a progressive increase in the intensity of exercise. This was synonymous with peak aerobic capacity.
- Breathing reserve (BR): The reserve capacity of the ventilatory system, calculated as 1 minus the ratio of peak exercise minute ventilation (VE) to maximal voluntary ventilation (MVV). A normal value was >30%.
- Anaerobic threshold (AT): The highest oxygen uptake attained without a sustained increase in blood lactate concentration and lactate/pyruvate ratio. Reported as a weight-adjusted parameter in mL/kg per minute.
- Respiratory exchange ratio (RER): Defined as the ratio of VCO2 to VO2.
- Oxygen saturation (SpO2): Measured by pulse oximetry.
- Ventilation/carbon dioxide production slope (\( V'\ E/V'\ CO2 \) slope):
- Continuous ECG monitoring was performed to ensure ischemia or arrhythmias were not a cause of dyspnoea. Subjects with a history of formally diagnosed angina were excluded from CPEX testing.

Subjects were stratified according to VO2 max (see Figure 3.3a&b). Data were categorized according to:
- \( \text{VO2 max} < 25\text{mls/kg/min according to current ESC guidelines (Paulus 2007)} \)
- \( \text{Extent of impairment of VO2 max relative to age and gender based normative values.} \)

Predicted values are those for corresponding age and gender (Schneider, 2013; McDonough, Kusumi and Bruce, 1970; Bruce et al. 1985).

The reasons they were stratified as such is explained in detail in the next chapter.

![Figure 3.3a VO2 data accepted as ‘peak’ if corresponding peak RER> 1.0](image-url)
3.5 Subject characteristics

1833 individuals screened – 89/1933(4.1%) had an LV ejection fraction significantly less than 50% on echocardiography and were not subsequently evaluated further. The clinical parameters related to the remaining 1744 subjects are summarized in Table 3.2, according to the presence or absence of reported dyspnoea. Table 3.1 records baseline characteristics of the whole cohort for comparison.

Table 3.1 Baseline subject characteristics of the entire subject cohort

<table>
<thead>
<tr>
<th></th>
<th>Entire cohort with a preserved ejection fraction (n=1744)</th>
</tr>
</thead>
<tbody>
<tr>
<td>age (mean +/- SD)</td>
<td>69.7 +/- 7.7</td>
</tr>
<tr>
<td>gender (female)</td>
<td>899 (51.5%)</td>
</tr>
<tr>
<td>diabetes</td>
<td>216 (12.3%)</td>
</tr>
<tr>
<td>hypertension (HT)</td>
<td>864 (49.5%)</td>
</tr>
<tr>
<td>atrial fibrillation AF)</td>
<td>80 (4.6%)</td>
</tr>
<tr>
<td>past myocardial infarction (MI)</td>
<td>102 (5.8%)</td>
</tr>
<tr>
<td>known ischemic heart disease</td>
<td>182 (10.4%)</td>
</tr>
<tr>
<td>obesity (BMI&gt;35)</td>
<td>55 (3.1%)</td>
</tr>
<tr>
<td>current smoker</td>
<td>322 (18.4%)</td>
</tr>
</tbody>
</table>
Table 3.2  Comparison: subjects with and without dyspnoea. Comparisons were performed utilizing Chi-squared tests for proportions and non-paired t-test for age

<table>
<thead>
<tr>
<th></th>
<th>Dyspnoea (n=222)</th>
<th>No dyspnoea (n=1522)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>age (mean +/- SD)</td>
<td>71.3 +/- 8.7</td>
<td>69.5 +/- 7.3</td>
<td>0.001</td>
</tr>
<tr>
<td>gender (female)</td>
<td>130 (58.6%)</td>
<td>769 (50.5%)</td>
<td>0.025</td>
</tr>
<tr>
<td>diabetes</td>
<td>43 (19.4%)</td>
<td>173 (11.4%)</td>
<td>0.001</td>
</tr>
<tr>
<td>hypertension (HT)</td>
<td>135 (60.8%)</td>
<td>729 (47.9%)</td>
<td>0.001</td>
</tr>
<tr>
<td>atrial fibrillation (AF)</td>
<td>23 (10.4%)</td>
<td>57 (3.4%)</td>
<td>0.001</td>
</tr>
<tr>
<td>past myocardial infarction (MI)</td>
<td>41 (18.5%)</td>
<td>61 (4.0%)</td>
<td>0.001</td>
</tr>
<tr>
<td>known ischemic heart disease</td>
<td>62 (27.9%)</td>
<td>120 (7.9%)</td>
<td>0.001</td>
</tr>
<tr>
<td>obesity (BMI &gt; 35)</td>
<td>40 (18%)</td>
<td>15 (0.9%)</td>
<td>0.001</td>
</tr>
<tr>
<td>current smoker</td>
<td>56 (25.2%)</td>
<td>286 (17.5%)</td>
<td>0.005</td>
</tr>
</tbody>
</table>

Of the 1744 individuals studied, there was a small majority of women, consistent with the overall population demographics for population aged approximately 70 years. About 10% of the population evaluated were over 80 years. A total of 10.4% of the cohort had known heart disease, with the majority of these having documented myocardial ischemia or infarction.

Stratification of this population according to the presence or absence of dyspnoeic individuals were slightly older, or likely to be women, with a higher prevalence of smoking and obesity. Diabetes, hypertension, previous atrial fibrillation and past myocardial infarction were all significantly more prevalent in dyspnoeic individuals.

### 3.5.2 Dyspnoeic subjects’ characteristics

222 individuals were identified as having subjectively significant dyspnoea resulting in significant limitations in the activities of daily living, based on answers to the questionnaire described earlier.

**Subclassification.** These 222 were further sub-classified based on results of clinical examination, history and in some subjects pulmonary function tests and CPEX.

- 78 patients individuals metabolic exercise testing. 58 recorded a VO2 max below 25mls/kg/min and 20 (9.4%) had a VO2 max of > 25mls/kg/min values corresponding to a normal VO2 max.
- 36 (16.9%) of the original 222 subjects were thought to have significant lung disease on the basis of previous pulmonary function testing or a substantial history of respiratory disease to explain their dyspnoea, and did not undergo metabolic exercise testing.
- It was recognised that is was possible that these subjects might also have heart disease.
- 34 (15.3%) subjects had a history of significant angina pectoris moderate/severe aortic or mitral valvular pathology to which their symptoms could be attributed and did not undergo metabolic exercise testing.
- 24 (10.8%) subjects were unable to exercise for a variety of reasons, the majority of which included physical or locomotor problems.
- 30 (13.5%) subjects were unwilling to participate or were not contactable and did not respond to an invitation to take part in further testing.
- 20 (9.4%) subjects who met the criteria for HFpEF on history, for example, admission to hospital with pulmonary oedema or severe breathless (NYHA class 3B) underwent a CPEX study.

The 58 participants with a VO2 max < 25mls/kg/min were subsequently subclassified using the age and gender matched nomogram described previously. In the event:
- 28/58 participants had a ‘true’ cardiac limitation and would be classified as HFpEF
- of the remaining 30 participants:
  - 24 were deconditioned
  - four recorded a VO2 max that was normal for their age and gender
  - two were actually lung-limited with a breathing reserve<30

The (Figure 3.5a&b) summarizes the presumptive causes of dyspnoea in these individuals with a preserved ejection fraction based on history, clinical examination, echocardiography and pulmonary function tests and CPEX.

![Figure 3.5a Causes of dyspnoea in a community population over the age of 60](image)
Therefore about 21% of the dyspnoeic subjects could be classified as having HFpEF. This would correspond to 2.5% of the entire population with a preserved ejection fraction and 2.4% of the entire cohort. However, this would represent an underestimate of the true prevalence of HFpEF, given that some individuals were unable or unwilling to undergo objective investigations into their cause of dyspnoea.

3.5. Subject characteristics based on CPEX performance

Table 3.3 Does VO2 max < 25 mls/kg/min imply different demographics?

<table>
<thead>
<tr>
<th></th>
<th>VO2 &gt; 25 mls/kg/min N=20</th>
<th>VO2 &lt; 25 mls/kg/min N=58</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>age, (mean +/-SD)</td>
<td>67 +/- 6</td>
<td>68.9 +/- 7</td>
<td>0.4</td>
</tr>
<tr>
<td>gender, F (% female)</td>
<td>8 (40%)</td>
<td>42 (72.4%)</td>
<td>0.04</td>
</tr>
<tr>
<td>MI (%)</td>
<td>1 (5%)</td>
<td>5 (8.6%)</td>
<td>0.6</td>
</tr>
<tr>
<td>IHD (%)</td>
<td>4 (20%)</td>
<td>12 (20.6%)</td>
<td>0.114</td>
</tr>
<tr>
<td>HT (%)</td>
<td>7 (35%)</td>
<td>30 (51.7%)</td>
<td>0.4</td>
</tr>
<tr>
<td>AF (%)</td>
<td>2 (10%)</td>
<td>8 (13.7%)</td>
<td>0.2</td>
</tr>
<tr>
<td>DM (%)</td>
<td>3 (15%)</td>
<td>9 (15.5%)</td>
<td>0.2</td>
</tr>
<tr>
<td>obesity (%)</td>
<td>3 (15%)</td>
<td>12 (20.1%)</td>
<td>0.09</td>
</tr>
</tbody>
</table>

Comparisons were performed utilizing Chi-squared tests for proportions and non-paired t-test for age. When subjects were assessed by the ESC criteria of a VO2 max of less than 25 mls/kg/min being considered abnormal, the subjects were predominantly female with a trend towards obesity.
Table 3.4 Demographics according to age and gender matched VO2 max

<table>
<thead>
<tr>
<th></th>
<th>Vo2 max &gt;25mls/kg/min</th>
<th>Vo2 max 70-85% predicted</th>
<th>P value</th>
<th>Vo2 max &lt; 70%</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>age, (%)</td>
<td>67 +/-6</td>
<td>70 +/-6</td>
<td>0.09</td>
<td>72 +/-12</td>
<td>0.02</td>
</tr>
<tr>
<td>gender, F (% female)</td>
<td>8 (40%)</td>
<td>15 (75%)</td>
<td>0.02</td>
<td>6 (75%)</td>
<td>0.09</td>
</tr>
<tr>
<td>MI (%)</td>
<td>1 (5%)</td>
<td>4 (20%)</td>
<td>0.15</td>
<td>0 (0%)</td>
<td>0.5</td>
</tr>
<tr>
<td>IHD (%)</td>
<td>4 (20%)</td>
<td>6 (30%)</td>
<td>0.4</td>
<td>3 (37.5%)</td>
<td>0.3</td>
</tr>
<tr>
<td>HT (%)</td>
<td>7 (35%)</td>
<td>10 (50%)</td>
<td>0.4</td>
<td>4 (50%)</td>
<td>0.5</td>
</tr>
<tr>
<td>AF (%)</td>
<td>2 (10%)</td>
<td>3 (15%)</td>
<td>0.6</td>
<td>3 (37.5%)</td>
<td>0.08</td>
</tr>
<tr>
<td>DM (%)</td>
<td>3 (15%)</td>
<td>5 (25%)</td>
<td>0.4</td>
<td>4 (50%)</td>
<td>0.05</td>
</tr>
<tr>
<td>obesity (%)</td>
<td>3 (15%)</td>
<td>6 (30%)</td>
<td>0.6</td>
<td>2 (25.5%)</td>
<td>0.5</td>
</tr>
</tbody>
</table>

P values in Table 3.4 were the difference between the group with a VO2 max > 25mls kg/min and the groups with a VO2 max < 70%, age and gender predicted, corrected, as well as the group with mild cardiac limitation with a VO2 max between 85-70% predicted, corrected for multiple comparison using a Bonferroni correction.

Individuals whose CPEX data were interpreted as indicative of physical deconditioning (n=24) were omitted from the analysis of Table 3.4.

When subjects were assessed by an age and gender matched nomogram for an abnormal VO2 max, patients with more severe the cardiac limitation tended to be older with a greater prevalence of diabetes and a trend towards an increased prevalence of atrial fibrillation, compared with those displaying a normal VO2 max or those with lesser degrees of objective exercise impairment on CPEX.

3.6 Baseline echo characteristics

The baseline echocardiographic variables are described in Table 3.5. The LV ejection fraction as expected is well above 50%, which is the cut-off we have used for normal in our study. The average left atrial area is surprisingly above the normative values described in common practice, although the average age our population would be significantly older than the population the normative values would be based on.
Table 3.5  Baseline echo characteristics: Entire group (n=1744)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ejection fraction</td>
<td>58 +/- 10.3%</td>
</tr>
<tr>
<td>Left ventricular end diastolic diameter (mm)</td>
<td>4.4 +/- 1.0</td>
</tr>
<tr>
<td>Left atrial volume (mls/m2)</td>
<td>37 +/- 24</td>
</tr>
<tr>
<td>Left atrial area (cm2)</td>
<td>24.4 +/- 14</td>
</tr>
<tr>
<td>Left ventricular hypertrophy (%)</td>
<td>206/1744 (11.8%)</td>
</tr>
<tr>
<td>Deceleration time (MS)</td>
<td>214 +/- 75</td>
</tr>
<tr>
<td>E/E'(lateral)</td>
<td>8.0 +/- 4.3</td>
</tr>
<tr>
<td>E/E'(sep)</td>
<td>9.9 +/- 4.1</td>
</tr>
<tr>
<td>Mitral valve (m/s propagation velocity)</td>
<td>50 +/- 33</td>
</tr>
<tr>
<td>Mitral A-pulmveina (ms)</td>
<td>42 +/- 4.2</td>
</tr>
</tbody>
</table>

3.7  Statistical analysis

SPSS (version 21.0, SPSS Inc., Chicago, Illinois) was used for statistical analyses. Continuous variables were expressed as median within an interquartile range. All tests of proportion utilized chi-squared comparisons. Two-sample comparisons were performed using an unpaired t-test for normally distributed variables and Wilcoxin test for skewed parameters. The Pearson coefficients for linear and Spearman coefficients for nonlinear correlations were used where appropriate. Regression analyses and curve fitting were performed to determine exact relations. Those parameters for which P < 0.05 values applied on univariate analysis were evaluated via backwards stepwise multiple logistic regression. A value of p < 0.05 was considered to be statistically significant in all analyses. Multiple comparisons were performed with a one way Anova with a Bonferroni correction.

Data were expressed as mean +/- mean (interquartile range) throughout.
Clinical, echocardiographic and exercise predictors of dyspnoea in the community

Exertional dyspnoea is the predominant symptom of HFpEF and echocardiography is the most readily available clinical tool in diagnosing HFpEF. In this chapter we evaluate the implications of dyspnoea with and without an impaired performance on cardiopulmonary exercise testing (CPEX) regarding resting echocardiographic findings for measures of LV diastolic function.

4.1 Introduction

The diagnostic criteria for heart failure with preserved ejection fraction (HFpEF) were proposed in 2007 by the Heart Failure and Echocardiography Associations of the European Society of Cardiology (Paulus et al. 2007). The diagnosis of HFpEF requires the following conditions to be satisfied:

- signs or symptoms of heart failure
- normal or mildly abnormal systolic LV function
- evidence of diastolic LV dysfunction.

Normal or mildly abnormal systolic LV function implies both an LVEF $\geq 50\%$ and an LV end-diastolic volume index (LVEDVI) $<97 \text{ mL/m}^2$. Diagnostic evidence of diastolic LV dysfunction can be obtained invasively (LV end-diastolic pressure $>16 \text{ mmHg}$ or mean pulmonary capillary wedge pressure $>12 \text{ mmHg}$) or non-invasively by tissue Doppler (TD) ($E/E'$ of $>15$). If TD yields an $E/E'$ ratio suggestive of diastolic LV dysfunction ($15 < E/E' < 8$), additional non-invasive investigations are required for diagnostic evidence of diastolic LV dysfunction. These can consist of a blood flow Doppler of the mitral valve or pulmonary veins, echo measures of LV mass index or left atrial volume index or electrocardiographic evidence of atrial fibrillation.

Thus the ESC criteria are based on resting diastolic function. However, more recent studies (Phan et al. 2009; Holland 2011) suggest that HFpEF might be a dynamic disorder with exercise-induced changes in diastolic and systolic function. Furthermore, signs such as lung crackles and peripheral oedema have usually been considered as non-specific in diagnosing heart failure. This
raises the question of the usefulness of resting diastolic measures in diagnosing the cause of dyspnoea in a community population, where exertional breathlessness would be the main symptom, as opposed to orthopnea, paroxysmal nocturnal dyspnoea or ankle swelling.

The extent of correlation between abnormalities in exercise physiology and those in resting diastolic measures described above has not been extensively explored to date.

1.1.1 Evaluating abnormalities in exercise physiology

We chose CPEX as the modality for evaluating abnormalities in exercise physiology. In the ESC guidelines on diagnostic criteria for HFpEF as proposed by Paulus et al. 2007 (described above), the use of CPEX was suggested as a means of establishing a cardiac, rather than other cause, of limitation of exercise, and as a surrogate for the signs and symptoms of heart failure, which is the first prerequisite for the diagnosis of HFpEF. A cut-off of a peak VO2 max of less than <25ml/kg/min at a RER of 1 was suggested as a means of determining cardiac limitations.

However, peak VO2 declines with age and is lower in women than in men (Guazzi et al. 2012). A fixed cut-off may therefore be inappropriate. There is a literature on normative values for peak VO2 by age and gender (Schneider 2013). In the age group represented in the current community study (mean age >69.3+/-8.3), a peak VO2 of < 25mls/kg/min could be within the normal range.

Furthermore, peak VO2 is simply a measure of exercise capacity. It provides no information regarding the cause of exercise limitation, although lung disease can be inferred as the cause of exercise limitation on the basis of a low ventilatory reserve calculated by the maximum voluntary ventilation (MVV) at peak exercise, as well as arterial oxygen desaturation below 90% at peak exercise. The absence of a low ventilatory reserve and arterial oxygen desaturation below 90% do not distinguish between cardiac limitation and deconditioning. Whilst imperfect, this distinction can be made on the basis of the VE/VCO2 slope and the VO2 at anaerobic threshold.

In cardiac limitation, the anaerobic threshold is also usually <40% of the predicted VO2 max, whilst for deconditioning, it is above 40% predicted peak VO2 (Wasserman K 1999; Milani, Lavie and Mehra 2004).
1.1.2 Correlation of abnormal exercise physiology with diastolic parameters

In the studies reported in this chapter, we began by first evaluating the nexus between the presence of the various resting echo-based criteria of diastolic dysfunction and the subjective presence of life style limiting dyspnoea as reported by the population cohort described in the last chapter. We then explored the extent of the correlation between abnormal exercise physiology and its contribution to the diastolic parameters described above.

For the purpose of comparison, the subjects were stratified according to a VO2 max at an RER of at least one.

- Normal exercise performance was defined as a VO2 max of > 25mls/kg/min
- Comparator groups were:
  - VO2 max < 25 (despite limitations to the pathological implications of this classification because of lack of age-adjustments)
  - VO2 max < 85% predicted of age and gender matched normative values (Schneider 2013; McDonough, Kusumi and Bruce 1970; Bruce et al. 1985).

Subjects were also evaluated for deconditioning as described previously, and not included in the analysis if they met the criteria for physical deconditioning.

4.2 Methods

4.2.1 Study population

Subjects aged ≥ 60 were randomly selected from the community to undergo screening as summarised in Chapter 3. Of these 1833 individuals, those with LV systolic dysfunction were excluded from the analysis, as we were interested in those with a preserved ejection fraction.

4.2.2 Statistical analysis

Statistical analyses were described in Chapter 3.

4.3 Results

4.3.1 Subject demographics

Overall, subjects characteristics and subsequent analysis of those with dyspnoea versus asymptomatic individuals were described in Chapter 3. On the basis of univariate comparisons, the female gender, increasing age, and presence of diabetes and hypertension were all correlates of dyspnoea, as was obesity and current smoking. Among the dyspnoeic population, there was a
substantial proportion of individuals with atrial fibrillation, previous myocardial infarction and/or angina pectoris.

Echocardiographic parameters were compared between the dyspnoeic and non-dyspnoeic individuals. Results are shown in Table 4.1.

<table>
<thead>
<tr>
<th>Table 4.1 Echo characteristics</th>
<th>Dyspnoea</th>
<th>No dyspnoea</th>
<th>pvalue</th>
</tr>
</thead>
<tbody>
<tr>
<td>ejection fraction</td>
<td>56 +/- 10.3%</td>
<td>59 +/- 11.2%</td>
<td>0.12</td>
</tr>
<tr>
<td>LVEDD(mm)</td>
<td>4.5 +/- 0.7</td>
<td>4.4 +/- 0.6</td>
<td>0.09</td>
</tr>
<tr>
<td>LA(mls/m2)</td>
<td>48 +/- 24</td>
<td>33 +/- 22</td>
<td>0.002</td>
</tr>
<tr>
<td>LA(cm2)</td>
<td>24.4 +/- 14</td>
<td>23 +/- 15</td>
<td>0.4</td>
</tr>
<tr>
<td>LVH(%)</td>
<td>31/204(14%)</td>
<td>175/1458(12%)</td>
<td>0.16</td>
</tr>
<tr>
<td>DT(ms)</td>
<td>215 +/- 75</td>
<td>211 +/- 56</td>
<td>0.36</td>
</tr>
<tr>
<td>E/E’ (Lateral)</td>
<td>8.9 +/- 4.3</td>
<td>7.7 +/- 3.6</td>
<td>0.001</td>
</tr>
<tr>
<td>E/E’ (Sep)</td>
<td>10.8 +/- 4.1</td>
<td>9.3 +/- 3.6</td>
<td>0.001</td>
</tr>
<tr>
<td>mitral valve(m/s propagation velocity)</td>
<td>47 +/- 33</td>
<td>53 +/- 30</td>
<td>0.018</td>
</tr>
<tr>
<td>mitral A-pulmveina(ms)</td>
<td>40 +/- 4.2</td>
<td>43 +/- 1.6</td>
<td>0.2</td>
</tr>
</tbody>
</table>

In accordance with the selection criteria, mean LVEF was normal and did not differ according to symptomatic status. However, the main difference between echocardiographic findings in the presence and absence of dyspnoea were related to the parameters of diastolic LV function, with E/E’ mitral valve propagation velocity and (indexed) LA volumes all trending towards abnormal values in the dyspnoeic individuals. The echocardiographic variables are discussed further in the following subsection.

4.3.2 Implications of diastolic dysfunction: Correlation with presence of symptoms

The first objective of the current analysis was to determine whether the presence of dyspnoea corresponded closely to either the presence of ‘abnormal diastology’ and/or the extent of abnormal diastology, either individually or cumulatively.

Extent of abnormal diastology, either individually or cumulatively. As regards the variously proposed measures of diastolic dysfunction, neither deceleration time nor mitral A-pulm vein A interval varied according to symptomatic status. The proportion of patients with LVH did not vary between groups.
- Left atrial volume and E/E’ (irrespective of site) were potentially useful univariate discriminators, with differences of 10-35% between groups.

- A preliminary analysis utilized a receiver operator curve (ROC) construction for both E/E’ septal and lateral: dyspnoea relationship.

- The area under the curve for E/E’ septal (Figure 4.1a) was 0.59 and the area under the curve for E/E’ lateral was 0.5 (Figure 4.1b). The sensitivity and specificity of E/E’ to predict dyspnoea were 60% and 55% respectively.

---

**Figure 4.1a**  
Area under the curve of 0.59 P<0.0001  
E/E’(s)>9 predicts dyspnoea with sensitivity of 60% specificity of 55%

**Figure 4.1b**  
Area under the curve of 0.57 P=0.0002  
E/E’(L)>8 predicts dyspnoea with a sensitivity of 60% and specificity of 54%
A strong correlation between E/E’ septal and lateral was observed, as indicated by the $R^2$ value of 0.51 with a p value of $<0.001$ (Figure 4.2a) in all patients, and by the $R^2$ value of 0.5 and a p value of $<0.001$ in patients who were dyspnoeic (Figure 4.2b).

This would suggest that E/E’ septal and lateral could be used interchangeably, but also established that the extent of E/E’ evaluation in general represented a poor predictor of the presence of dyspnoea in isolation.
For secondary analysis, individual abnormal diastolic parameters were assessed qualitatively.

On the basis of established criteria for abnormality (Paulus 2007), the following parameters were chosen for Chi squared analysis:

- $E/E'$ > 11: data only from lateral walls were utilized to avoid unnecessary multiple comparisons.
- LA volume was > 40mls/m2.
- Atrial fibrillation was present.

On this basis, data are summarized in Tables 4.2(a), (b) and (c).

Table 4.2(a) Chi squared analysis for the presence of an $E/E'$ >11 in patients with and without dyspnoea

<table>
<thead>
<tr>
<th>Dyspnoea * $E/E'(L)$&gt;11 crosstabulation</th>
<th>E/E(L)’2</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td></td>
<td></td>
</tr>
<tr>
<td>absent (0)</td>
<td>count</td>
<td>1347&lt;sub&gt;a&lt;/sub&gt;</td>
</tr>
<tr>
<td></td>
<td>percentage</td>
<td>88.6%</td>
</tr>
<tr>
<td>present (1)</td>
<td>count</td>
<td>174&lt;sub&gt;a&lt;/sub&gt;</td>
</tr>
<tr>
<td></td>
<td>percentage</td>
<td>81.7%</td>
</tr>
</tbody>
</table>

Chi-squared tests

<table>
<thead>
<tr>
<th></th>
<th>Value</th>
<th>df</th>
<th>Asymp. Sig. (2-sided)</th>
<th>Exact Sig. (2-sided)</th>
<th>Exact Sig. (1-sided)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pearson Chi-square</td>
<td>8.352&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1</td>
<td>.004</td>
<td></td>
<td></td>
</tr>
<tr>
<td>continuity correction&lt;sup&gt;b&lt;/sup&gt;</td>
<td>7.719</td>
<td>1</td>
<td>.005</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

This Chi-squared analysis confirmed that $E/E'$ values were significantly higher in the presence of dyspnoea. Significantly more subjects with dyspnoea had an $E/E'$>11 (18.3%) compared with 11.4% of the asymptomatic patients. However, a substantial proportion of dyspnoeic patients had a $E/E'$<11 [Table 4(b)].
Table 4.2(b)  Chi squared analysis of the presence of atrial fibrillation: Comparisons between dyspnoeic and non dyspnoeic patients

<table>
<thead>
<tr>
<th>Dyspnoea * AF crosstabulation</th>
<th>AF</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Dyspnoea absent (0)</td>
<td>count</td>
<td>1465a</td>
</tr>
<tr>
<td></td>
<td>percentages</td>
<td>96.3%</td>
</tr>
<tr>
<td>Dyspnoea present (1)</td>
<td>count</td>
<td>191a</td>
</tr>
<tr>
<td></td>
<td>percentages</td>
<td>89.7%</td>
</tr>
</tbody>
</table>

Value | Df | Asymp. Sig. (2-sided) |
---    | --- | ---------------------|
Pearson Chi-square | 18.635<sup>a</sup> | 1 | .000 |
continuity correction | 17.151 | 1 | .000 |

More subjects with atrial fibrillation (10.3%) were present in the dyspnoeic group than among asymptomatic individuals. Thus the analysis once more confirmed the association of AF with dyspnoea, while suggesting that the finding would have little clinical utility as a discriminator in isolation.

Table 4.2(c)  Chi squared analysis for the presence of LA dilatation : comparisons between dyspnoeic and non dyspnoeic individuals

<table>
<thead>
<tr>
<th>Dyspnoea * LA dilatation crosstabulation</th>
<th>LADilatation</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Dyspnoea absent (0)</td>
<td>count</td>
<td>1112a</td>
</tr>
<tr>
<td></td>
<td>percentages</td>
<td>76.3%</td>
</tr>
<tr>
<td>Dyspnoea present (1)</td>
<td>count</td>
<td>133a</td>
</tr>
<tr>
<td></td>
<td>percentages</td>
<td>67.5%</td>
</tr>
</tbody>
</table>

Value | df | Asymp. Sig. (2-sided) |
---    | --- | ---------------------|
Pearson Chi-square | 7.234<sup>a</sup> | 1 | .007 |
Continuity correction | 6.768 | 1 | .009 |

Again, despite the significant association of dyspnoea with atrial dilatation as revealed by the chi squared analysis, the actual proportions of subjects with dilatation were 33% and 24% respectively, suggesting lack of utility of the measures as a univariate discriminator.
The findings therefore precipitated a detailed quantitative examination of the frequency distribution of abnormal diastolic function parameters among dysnoeic and non dysnoeic individuals, as outlined below.

Figure 4.3 illustrates the result of the analysis of the frequency distribution of E/E’ values between the dysnoeic and asymptomatic groups.

Although there was a greater percentage of subjects in the dysnoeic group with higher E/E’, the overall distribution of values was similar to the asymptomatic group. These data therefore emphasize the lack of utility of this parameter in isolation for clinical diagnostic purposes.

We then explored the utility of combining diastolic parameters (similar to the ESC criteria) to investigate if a combination of diastolic abnormalities was more prevalent in the dysnoeic group. We used the two parameters which were significantly different in the univariate analysis between the dysnoeic and asymptomatic groups, E/E’ and LA volumes. E/E’ of more than 11 on the lateral wall and/or a LA volume > 40mls/m2 were considered evaluated, as described above. Figure 4.4 illustrates the percentage of the asymptomatic and dysnoeic population with a combination of diastolic abnormalities.
For this analysis the majority of individuals in both groups had no diastolic abnormalities, or just a single diastolic parameter that was abnormal. However, when the diastolic abnormalities were combined, there was a significantly larger proportion of individuals in the dyspnoeic group. This suggests that although E/E’ and LA dilatation may be poor univariate discriminators, combining the abnormalities may prove a better discriminator of dyspnoea. However, the utility of this approach is limited by the small proportion of dyspnoeic individuals (approximately 12%) who have both left atrial enlargement and abnormally elevated E/E’.

Finally, a multivariate analysis using the risk factors for dyspnoea in Table 4.3, as well as echocardiographic parameters that were significant in the univariate analysis or trending to significance, namely, E/E’ and LA volumes and mitral inflow propagation velocity, was undertaken. The results revealed that the presence of diabetes was the only multivariate predictor of dyspnoea and that there was also a (non-significant) trend for a similar association in the presence of obesity (Table 4.3). Noticeably, E/E and LA volumes ceased to be predictors in the multivariate model.
Table 4.3 Multivariate predictor of dyspnoea

<table>
<thead>
<tr>
<th>Coefficients³</th>
<th>Unstandardized coefficients</th>
<th>Standardized coefficients</th>
<th>t</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model</td>
<td>B</td>
<td>Std. Error</td>
<td>Beta</td>
<td></td>
</tr>
<tr>
<td>DM</td>
<td>.667</td>
<td>.185</td>
<td>.667</td>
<td>3.606</td>
</tr>
<tr>
<td>obesity</td>
<td>.333</td>
<td>.185</td>
<td>.333</td>
<td>1.803</td>
</tr>
</tbody>
</table>

Dependent variable: Dyspnoea

4.3.3 Correlation between abnormal exercise physiology and resting diastolic abnormalities: Does VO2 max reflect diastolic function?

For the next part of the study, we explored the putative correlation between integrity of exercise physiology and resting diastolic abnormalities on echocardiography with the aims of:

- investigating if the relationship between dyspnoea and abnormal exercise physiology
- determining whether abnormalities of exercise physiology can be predicted by resting diastolic abnormalities on echocardiography.

We initially categorized the dyspnoeic individuals who underwent metabolic exercise testing on the basis of the ESC criteria of < 25mls/kg/min implying cardiac limitation, but inadequately corrected for age and gender, as previously discussed. The characteristics of the individuals had been described previously in Chapter 3.

58 dyspnoeic individuals were identified with a VO2 max of less than 25mls/kg/min and a RER of > 1. Twenty patients with dyspnoea had a VO2 max of >25mls/kg/min and a RER of > 1. In accordance with the selection criteria, the mean LVEF was normal in both groups (64.1 +/- 6 and 63.2 +/- 6.6 in dyspnoeic and asymptomatic individuals). There were no significant differences in LVEF.

In order to compare VO2 values with E/E’, overall correlations were first sought. As shown in Figure 4.5, there was a significant (R² = 0.064, p=0.04) inverse correlation, with increasing VO2 max correlating with decreasing E/E’ values. However, this correlation was statistically weak.
Next, the extent of differences in E/E’ mean values between subjects according to the VO2 max values was evaluated. The mean values of E/E’ were 8.5 +/-3.25 and 7.21+/−2.75 respectively for individuals with a VO2 max < 25mls/kg/min and more than or equal to 25mls/kg/min (P value=0.02). Thus the presence of even a borderline decrease in VO2 max values corresponded statistically to increased E/E’.

However, the central issue to be evaluated was whether VO2 max < 25mls/kg/min was strongly associated with abnormal values of E/E'(L),(defined as E/E’>11). A ROC analysis was performed (Figure 4.6) and revealed that:

- at the chosen value of E/E’>11 there was a sensitivity and specificity of 31% and 71% respectively
- the optimal discriminating capacity for VO2 max: E/E’(L) comparisons were about 9.5 with a sensitivity and specificity of 60 and 61% respectively.

Therefore, based on this analysis, the association between a VO2 max < 25mls/kg/min and E/E’ was clinically limited as a discriminator of abnormal exercise physiology.
We subsequently evaluated if an abnormal VO₂ correlated with the full ESC criteria (for diastolic abnormalities as outlined in the introduction section of this chapter). Among dyspnoeic individuals, we compared the group with a VO₂ max of <25mls/kg/min with the group >25mls/kg/min (Table 4.4).

<table>
<thead>
<tr>
<th>VO₂ &lt; 25mls/kg/min</th>
<th>ESC</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>absent</td>
<td>.00</td>
<td>1.00</td>
</tr>
<tr>
<td>count</td>
<td>17</td>
<td>3</td>
</tr>
<tr>
<td>percentage</td>
<td>85.%</td>
<td>15%</td>
</tr>
<tr>
<td>present</td>
<td>36</td>
<td>22</td>
</tr>
<tr>
<td>count</td>
<td>62.1%</td>
<td>37.9%</td>
</tr>
<tr>
<td>percentage</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Thus, the presence of a VO₂ max <25mls/kg/min plus reported dyspnoea corresponded in 38% of cases to diastolic dysfunction (ESC echo criteria), whereas with VO₂ max >25mls/kg/min, still 15% of subjects had abnormal diastolic function. These data therefore demonstrate that VO₂ max <25mls/kg/min is statistically associated with abnormal diastolic function, but that association is relatively weak.
4.3.4 Beyond a single VO2 max cut off: Does stratification of VO2 max according to age and gender norms improve the correlation with resting diastolic abnormalities?

As described in Chapter 3, we subsequently classified subjects undergoing metabolic exercise testing further into those with true cardiac limitation based on age and gender matched nomograms for VO2 max, as well as other physiological parameters on CPEX testing, such as the VE/VCo2, VO2 at anaerobic threshold and the breathing reserve. The characteristics of these subjects are described in Chapter 3.

The objective of the analysis in this chapter was to evaluate if refining the definition of cardiac limitation on exercise physiology would improve the correlation with parameters of resting diastolic abnormalities on echocardiography.

For this purpose, we performed the analysis by dividing the subjects into three groups:

- cardiac limitation by CPEX meeting all criteria as with a age/gender adjusted VO2 max < 85%. (n=28) (Group A)
- VO2 max < 25mls/kg/min but not truly cardiac limited- either deconditioned, VO2 max > 85% predicted or lung limited. (n=30) (Group B)
- healthy controls with a normal VO2 max from the community cohort (n=34) (Group C).

For the first analysis we compared E/E'(L) between the three groups.

| Table 4.5 Comparisons of E/E'(L) between groups |
|-----------------|---------|---------|
| Group A         | 28      | 9.14    | 4.07    |
| Group B         | 29      | 7.94    | 2.03    |
| Group C         | 34      | 7.02    | 2.47    |
| Total           | 91      | 7.90    | 3.07    |

We performed a one way ANOVA with a Bonferroni correction for multiple analysis between groups. ANOVA revealed significant heterogeneity between groups (p=0.015), while Bonferroni comparisons with Group C (normal controls) revealed that Group A (p=0.038) but not group B (p=0.26) differed significantly from normal.

We subsequently performed a ROC analysis to evaluate if E/E'(L) would perform effectively as a discriminator of an abnormal VO2 (Group A) from subjects in Groups B and C (Figure 4.7).
(Area under the curve of 0.71; P value of 0.007; E/E’ (L)> 11 predicts cardiac limitation with a sensitivity of 45% and a specificity of 85%.)

As shown in Figure 4.7, an E/E’(L) of more than 11, is quite specific for cardiac limitation but not very sensitive.

Finally we compared how well the groups met the ESC criteria in terms of resting diastolic abnormalities (Table 4.9).

**Table 4.9  Presence of ESC criteria in the different groups**

<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group B</th>
<th>Group C</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>absent</td>
<td>12</td>
<td>21</td>
<td>30</td>
</tr>
<tr>
<td>present</td>
<td>16</td>
<td>10</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>28</td>
<td>30</td>
<td>34</td>
</tr>
</tbody>
</table>

These data suggest that:

- Among **Group A** (individuals who met all exercise based criteria for HFpEF) approximately 58% would be classified as HFpEF on echo based criteria.
- Among **Group C** (individuals whose exercise performance is completely normal), still 7% would be classified as HFpEF on echo based criteria.
- Among **Group B** (individuals whose exercise performance was abnormal but not diagnostic of cardiac based limitation), still 33% would be classified as HFpEF.

Differences between groups were evaluated statistically by a Chi-squared test with Bonferroni correction. Results were:
- **Group A versus C**: p< 0.001. This basis of comparison demonstrates a highly significant difference between these diametrically opposite groups.

- **Group B versus C**: p=0.06. There is a borderline significant difference between subjects with a ‘non’ cardiac limitation and normals.

The observed results suggest that fully characterizing abnormalities in cardiac physiology based on age and gender matched nomograms and excluding patients who are just deconditioned results in a better correlation with resting diastolic abnormalities of relaxation/filling on echocardiography.

### 4.4 Discussion

A critically important issue regarding the diagnosis of heart failure of all types is that most forms of diagnostic imaging are performed while patients are at rest, yet most patients develop symptoms primarily on exertion. The condition of HFpEF provides an excellent example of this: the presence of abnormalities of left ventricular relaxation on resting echocardiography constitutes a relatively subtle finding, whereas symptoms associated with exertion are often severe. Technical limitations have essentially prevented the widespread use of truly simultaneous exercise and imaging, and this problem extends most importantly to the technique of magnetic resonance spectroscopy (MRS), where it has not proved practicable to date to quantify myocardial energetic impairment during exercise (Phan et al. 2009).

The other critically important issue is that the predominant symptom of HFpEF is that of exertional breathlessness, a symptom that is difficult to quantify clinically and remains a subjective assessment. The clinical signs of heart failure, such as inspiratory crackles on auscultation of the chest, as well as swelling of the ankles are relatively non specific. Symptoms with relatively definitive implications, such as orthopnoea, are usually absent in HFpEF.

The first part of this study therefore initially evaluated the nexus between a subjective, but lifestyle limiting assessment of dyspnoea, and resting measures of diastolic abnormalities on echocardiography, as these measures form the cornerstone for the diagnosis of HFpEF in current diagnostic algorithms.

The main findings from the first part of the study were that the prevalence of resting diastolic abnormalities among dyspnoeic individuals was significantly greater for those in the
asymptomatic cohort. However, the degree of difference between the two groups was such that individual diastolic abnormalities were not strongly associated with symptomatic status.

We next evaluated the potentially incremental impact of the presence of multiple diastolic abnormalities in predicting the presence of dyspnoea. The findings were that the presence of dual parameters of diastolic dysfunction occurred approximately six times more frequently among dyspnoeic subjects, but only about 10% of dyspnoeic subjects exhibited this anomaly.

Hence, this association is only a useful discriminator between groups when present.

A multi-variate analysis of all the clinical risk factors of HFpEF and the relevant diastolic abnormalities confirmed the above findings in that a history of diabetes was the only significant predictor of dyspnoea in this analysis, and there were no echocardiographic parameters of significance in the final analysis.

These findings tend to emphasize that resting abnormalities of left ventricular relaxation/filling may not be closely related to determinants of exercise performance. Apart from the fact that impaired myocardial energetics would have primary impact during exertion, there is a consideration of the potential effect of variable skeletal muscle dysfunction on exercise performance.

Diabetes has not previously been identified as a common basis for dyspnoea in the absence of hypertension or ischemia. In theory, diabetes may be associated with a cardiomyopathy characterized by relatively normal resting left ventricular systolic function, which would conform with the definition of HFpEF. (Dhalla 1998). However, under these circumstances it is likely that such cases would have been characterized by abnormal VO2 max values. The association with dyspnoea may also reflect the emergence of abnormal physiology only during exertion, for example due to impaired glucose utilization. However, the current study lacks mechanistic data to identify such putative means of association.

In the second part of the study, a number of aspects of the relationship of exercise performance and echocardiographic measures at rest for patients with putative HFpEF were evaluated – a further example of an attempt to reconcile exercise versus resting data. The two testing modalities being compared were ‘standard’ for HFpEF:
CPEX testing, subject to some caveats, can be used to detect involuntary limitation of VO2 max, and can be categorized to attribute such anomalies to cardiac limitation or otherwise.

Echocardiographic analysis of ‘abnormal diastology’ utilizing parameters such as E:E’ is in widespread clinical use, and provides a reasonably reproducible measurement (Nagueh et al. 2009). It was shown in the previous subsection that E/E’(L) and E/E’ (S) could be used interchangeably with reasonable concordance.

Nevertheless, the central dilemma remains. It has never been shown that E:E’ (or any other echocardiographic measurement) is closely predictive of the extent of cardiac-based impairment of exercise capacity, despite correlating with exercise intolerance in general (Ha et al. 2005).

For the second part of the studies we tested the correlation of VO2 max and E/E’ (L) and the concordance of the severity of abnormalities. Whilst there certainly is a negative relationship, with an abnormal VO2 reflecting a higher resting E/E’, the correlation is not linear. This is reflected in the area under the curve for VO2 max to predict an abnormal E/E’(L).

We initially used the ESC definition of an abnormal VO2 max of less than 25mls/kg/min, with all its imperfections of being inadequately corrected for age and gender and not interpreted in conjunction with other CPEX parameters that help distinguish deconditioning and lung limitation from cardiac limitation.

The next part of the study was to evaluate whether an abnormal VO2 max(<25mls/kg/min) predicted abnormal diastology as outlined by the current echocardiographic guidelines from the European Society. The results would suggest that an abnormal VO2 max does not closely predict abnormal diastology, as only about 37% of patients with cardiac limitation on metabolic exercise testing met the criteria for the diagnosis. Specificity of the association also has to be questioned since about 14% of patients with a VO2 max > 25mls/kg/min met the echo criteria for HFpEF.

In the final part of the study we used an age and gender nomogram for the interpretation of VO2 max data and used a diagnostic algorithm that incorporated measures such as VE/VCO2, VO2 at the anaerobic threshold and breathing reserve, which have been described in Chapter 3.

Using the above measures, the subjects with an abnormal VO2 max were reclassified to cardiac limited or limited due to other non cardiac causes of dyspnoea. An increased specificity of diastolic measures was demonstrated in predicting cardiac limitation by CPEX testing. About
60% of patients in the cohort with cardiac limitation on this basis also satisfied the full ESC echo based criteria for HFpEF, a proportion greater than that reported in most recent publications (Borlaug 2011). According to the data analysis, a E/E’(L)> 12 at rest almost certainly means a diagnosis of HFpEF, although a value less than 12 does not exclude cardiac limitation by strict CPEX criteria.

There are a number of limitations in this study including the small sample size of dyspnoeic subjects with proven cardiac limitation and the incomplete CPEX testing of all patients. However, the results indicate that there is ultimately a correlation of resting diastolic measures on echocardiography and cardiac limiting exercise physiology. A way forward would either be to identify a test on exertion that is able to be used for most or all patients, even the physically disabled, possibly utilizing a combination of treadmill and cycle CPEX testing, or to improve the sensitivity of resting diastolic parameters. The newer echocardiographic modalities, such as speckle tracking, offer the promise of improved sensitivity to the indicators of HFpEF.

Nevertheless, the current data suggest that the logistic limitation of performing echocardiography at rest does not totally preclude its utility as a component of diagnosis of HFpEF.
chapter 5

Is the ejection fraction in HFpEF ‘truly’ preserved? Defining the contribution of subtle systolic dysfunction to the pathophysiology of HFpEF

In this chapter we explore the contribution of subtle left ventricular systolic function abnormality to the pathophysiology of HFpEF. Having established its contribution, we aim to evaluate its potential significance in overcoming limitations in the diagnostic algorithms of HFpEF, as demonstrated in Chapter 4.

5.1 Introduction

The pathophysiology of HFpEF is thought to involve a combination of diastolic and also potentially subtle systolic dysfunction. The postulated mechanisms of HFpEF include defects of calcium handling (Zile and Brutsaert 2002), impairment of relaxation and energetics (Phan et al. 2009), as well as inflammation and scarring of the myocardium, which all to some extent involve a combination of diastolic and systolic abnormalities (Paulus and Tschope 2013). The concomitant subtle systolic functional abnormalities are not usually quantified and never thought of as being ‘primary’. Nevertheless HFpEF is probably a mixture of both diastolic and systolic abnormalities, as well as energetic impairment, all accentuated with exercise.

The left ventricular ejection fraction (LVEF) has traditionally been used as a method for assessing LV systolic function, as well as a prognostic tool in patients with known or suspected heart disease. The heart is a complex organ that undergoes cyclical changes in multiple dimensions that result in the ejection of blood (Sengupta et al. 2006). LVEF, irrespective of the imaging method, is unable to give precise information on each individual dimension. LVEF is also a sum contribution of multiple regions and therefore does not provide information on regional systolic dysfunction (Abraham, Dimaano and Liang 2007). It is also dependent on the pre and after load (Braunwald E. 1992).

In essence, LVEF offers an approximate estimation of global systolic function and is presently used to divide patients with chronic heart failure into two distinct types – systolic heart failure and diastolic heart failure – now referred to as heart failure with preserved ejection fraction (HFpEF)
and heart failure with reduced ejection fraction (HFrEF), respectively. There has been much debate regarding this LVEF-based bimodal view (Paulus et al. 2007; Sanderson 2007), particularly as there is no pathophysiological basis to support the concept that systolic dysfunction should be absent in HFpEF. Both conditions present with similar symptoms (Bhatia et al. 2006), display similar mortality risks (Owan et al. 2006), and, importantly, both demonstrate systolic and diastolic abnormalities. Given these conditions, it is evident that to state that systolic function is entirely normal in patients with ‘normal’ LVEF is completely misleading, since LVEF is not precise in assessing mildly impaired systolic function compared to investigative measures such as tissue Doppler imaging (TDI) (Sanderson 2007).

TDI as has been described in Chapter 2, measures the longitudinal function of the left ventricle as opposed to the radial function as measured by the ejection fraction. Longitudinal function is usually affected early in pathophysiological conditions affecting the left ventricle, whilst the radial function remains relatively preserved.

A number of studies that have shown that ventricular long axis function is not normal in HFpEF (Yip et al. 2002; Yu et al. 2002; Nikitin 2002). Ventricular long axis systolic motion can be assessed by TDI by determining the peak systolic velocity in the ejection period measured at the mitral annulus (S’a) or at myocardial segments (S’m). Measured at the basal medial segment S’m, or the basal lateral segment S’(l) on the apical four chamber view, Sm has been shown to be significantly lower in patients with HFpEF than in age-matched controls (Yip et al. 2002), reflecting the fact that subtle abnormalities of systolic function are present in patients with HFpEF. Furthermore, ventricular long axis function is also reduced in LV hypertrophy and diabetes, conditions associated with HFpEF (Liu et al. 2001). Thus, isolated diastolic heart failure is uncommon and normal LVEF does not exclude LV systolic dysfunction.

There have, however, been other studies that have shown that peak (+) dp/dt, a measurement of cardiac contractility that is only mildly load dependent, is similar in patients with HFpEF and their age and gender matched controls (Baicu et al. 2005). Nevertheless peak (+) dp/dt is also subject to minor changes with increased afterload.
While HFpEF is a partial misnomer, the role of that component of ‘semi-concealed’ systolic dysfunction in the pathogenesis of symptoms is uncertain. The objectives of the current evaluation therefore were to:

- define the range of systolic dysfunction included in current HFpEF cohorts using ventricular long axis function (S’m and l)
- determine whether the systolic abnormalities bear a predictable relationship to
  - symptom severity
  - extent of diastolic dysfunction.

5.2 Method

The study population has previously been described in significant detail in Chapters 3 and 4. The echocardiographic assessment has also been previously discussed, along with the baseline echocardiographic characteristics in Chapter 3.

Subjects who underwent CPEX testing were grouped based on their performance using the ESC criteria initially and subsequently based on an age and gender matched nomogram as described in the Chapter 4. In addition, a group of patients from the cohort, who were asymptomatic and without traditional risk factors for HFpEF, also underwent metabolic exercise testing.

To evaluate the objectives of the study as outlined above, (that despite a preserved ejection fraction patients who are breathless had evidence of systolic impairment), the difference in both the basal septal and lateral ventricular long axis function Sm and Sm (l) and between those with dyspnoea and those without dyspnoea was measured. Both groups of patients had a preserved and similar LV ejection fraction by the Simpson’s method. Initially, a correlation between the ventricular long axis function and E/E’, which had previously been defined as a predictor of dyspnoea in Chapter 4, was established.

To address the next objective of the study (determining the relationship between severity of systolic abnormalities to symptom severity), the ventricular long axis function in patients with a cardiac limitation, as defined by an abnormal VO2 measured by CPEX, and the ventricular long axis function in patients with a normal VO2 was compared.
Finally, the clinical utility of combining systolic and diastolic impairment in both additive and multiplicative models was investigated in order to establish if this combination improved the ability to predict symptom severity and the extent of diastolic dysfunction.

5.2.2 **Statistical analysis**

The method of statistical analysis is described in detail in Chapter 3. *SPSS* (version 21.0, SPSS Inc., Chicago, Illinois) was used to conduct the analyses. The key aspects of the statistical methods used were:

- Continuous variables were expressed as the median with interquartile range. All tests of proportion utilized Chi-squared comparisons. Two-sample comparisons were performed using an unpaired *t* test for normally distributed variables and the Wilcoxon test for skewed parameters.
- The Pearson coefficients for linear and Spearman coefficients for nonlinear correlations were used where appropriate. Regression analyses and curve fitting were performed to determine exact relations. A value of *p* < 0.05 was considered to be statistically significant in all analyses. Multiple comparisons were preceded by a one way Anova and followed by Bonferroni correction.
- Data were expressed as mean +/- mean (interquartile range) throughout.

5.3 **Results**

5.3.1 **Establishing the presence of systolic abnormalities and correlations with diastolic abnormalities in a dyspnoeic cohort with preserved ejection fraction on echocardiography**

222 patients with dyspnoea and 1522 asymptomatic patients were identified from the original cohort. As noted previously, there was no significant difference in terms of ejection fraction and left ventricular end-diastolic diameter but there was a statistically significant difference in terms of ventricular long axis function in terms of both *S’*(m) and *S’*(l). The potential clinical utility of this difference was limited due to the small absolute difference (Table 5.1).

| Table 5.1  Comparisons of parameters of systolic function between dyspnoeic and asymptomatic individuals |
|---------------------------------|-----------------|---------------|-----|
|                                 | Dyspnoea        | No dyspnoea   | *p* value |
| ejection fraction              | 56+/-10.3%      | 59+/-11.2%    | 0.12 |
| LVEDD(mm)                      | 4.5+/-0.7       | 4.4+/-0.6     | 0.09 |
| *S’*(m) (cm/s)                 | 7.4+/-1.9       | 7.9+/-1.9     | 0.03 |
| *S’*(l) (cm/s)                 | 8.5+/-2         | 9.1+/-2       | 0.02 |
Subsequently a correlation between $S'(l)$ and $E/E'(L)$, as well as $S'm$ and $E/E'(S)$ was established, as $E/E'$ had previously been shown to be a univariate predictor of dyspnoea. (Figure 5.1a&b). Thus the extent of abnormalities of systolic function is directly related to that of diastolic dysfunction.

![Graph showing correlation between E/E'(L) and S'(L)](Figure 5.1a)

![Graph showing correlation between E/E'(S) and S'm)](Figure 5.1b)

5.3.2 Correlating abnormal exercise physiology, subtle left ventricular systolic abnormalities and diastolic abnormalities

We next compared the $S'(l)$ and $S'm$ values recorded for the group of dyspnoeic patients who had VO2 max of less than 25mls/kg/min with a group with a VO2 max of more than 25mls/kg/min. There were no significant differences between the groups. In both $S'(l)$ and $S'm$ with a mean $S'(l)$
of 8.5+/-2.6 (group <25mls/kg/min) versus 8.9+/-2.7 (group>25mls/kg/min) and a mean S’m of 7.4+/-1.69<25mls/kg/min) versus 7.8+/-1.7, (>25mls/kg/min) (p non significant for both).

However, the potential limitations of using VO2 max <25mls/kg/min as a criterion for ‘abnormal’ exercise physiology have already been discussed. Therefore, for the next part of the study we divided the patients into three groups, as defined in Chapter 4:

- cardiac limitation by CPEX meeting all criteria as with a age/gender adjusted VO2 max < 85%. (n=28) (Group A)
- VO2 max < 25mls/kg/min but not truly cardiac limited- either deconditioned, VO2 max > 85% predicted or lung limited. (n=30) (Group B)
- healthy controls with a normal VO2 max from the community cohort(n=34) (Group C).

Thus two hypothesis were tested:

- That Groups A and C would differ (primary hypothesis)
- That Groups B and C would differ

For the first analysis we compared S’m and S’(l) between the three groups (A, B and C).

### Table 5.2 Comparisons of S’m(cm/sec) between groups

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Mean</th>
<th>Std. Deviation</th>
<th>P values (vs Group C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A</td>
<td>28</td>
<td>7.0</td>
<td>1.5</td>
<td>0.007</td>
</tr>
<tr>
<td>Group B</td>
<td>29</td>
<td>7.8</td>
<td>1.7</td>
<td>0.47</td>
</tr>
<tr>
<td>Group C</td>
<td>34</td>
<td>8.1</td>
<td>1.6</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>91</td>
<td>7.6</td>
<td>1.6</td>
<td></td>
</tr>
</tbody>
</table>

We performed a one way ANOVA with a Bonferonni correction for multiple comparisons between groups. ANOVA revealed significant heterogeneity between groups, (p = 0.03), while Bonferroni comparisons with Group C (normal controls) revealed that only Group A (p = 0.007) differed significantly from normal.

### Table 5.3 Comparisons of S’(l)(cm/sec) between groups

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Mean</th>
<th>Std. Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A</td>
<td>28</td>
<td>8.5</td>
<td>2.6</td>
</tr>
<tr>
<td>Group B</td>
<td>30</td>
<td>8.9</td>
<td>2.7</td>
</tr>
<tr>
<td>Group C</td>
<td>34</td>
<td>9.9</td>
<td>2.9</td>
</tr>
<tr>
<td>Total</td>
<td>92</td>
<td>9.1</td>
<td>2.7</td>
</tr>
</tbody>
</table>
The one way ANOVA revealed no significant difference between groups with a p value of 0.12 between groups. Although there were similar differences in mean values between Group A (8.5 +/- 2.6) and Group C (9.9 +/- 2.9), to those seen for the S’m data (Table 5.2), the larger standard deviations in S’(l) compared to S’m, resulted in a statistically non significant difference between the groups. Given these data, S’m was used for subsequent analyses.

A ROC analysis to define a suitable cut-off for S’m in predicting cardiac limitation on CPEX was conducted (Figure 5.2) and revealed that the optimal discriminating capacity for S’m was a value of less than 6.5 (cm/sec) with a sensitivity of 43% and a specificity of 86% in predicting cardiac limitation by CPEX.

We then explored the utility of combining diastolic abnormalities and systolic left ventricular dysfunction (S’m < 6.5) to investigate whether the combination of abnormalities would improve discrimination between the three groups. Diastolic dysfunction was defined categorically according to the ESC criteria (Paulus 2007).
For this qualitative analysis, it can be seen that the extremes of the combination of abnormal/normal diastolic abnormalities, together with abnormal/normal S’m are potentially clinically useful in one respect – no subjects in group C had both abnormalities; while nearly 80% had neither. The positive predictive accuracy of combined negative criteria (differentiating Group C from A) using this method is therefore approximately 64%.

On the other hand, the proportion of subjects in Group A with ‘double positive’ data is only 40%, limiting the potential utility of this measure.

For a quantitative assessment of the additive analysis of diastolic and systolic abnormalities, we investigated the relationship between E/E’(S)-S’m and the age and the gender percentage predicted of VO2 max attained (Figure 5.4).
Figure 5.4  Correlation between E/E'(S) – S'm and age/gender adjusted predicted VO2 max
R value – 0.21 with a p value of 0.061

Thus, although there was a trend towards the expected negative correlation, the p value did not reach statistical significance. These data therefore suggest that additive interaction between echocardiographically defined diastolic and systolic dysfunction is a poor method of predicting the extent of exercise-associated limitation of cardiac performance.

Cardiac limitation on CPEX is not solely dependent on a VO2 max, but also on the VE/VCO2 slope and other parameters as described in Chapter 4; and therefore these factors have to be taken into account in the above analysis.

Having performed an additive model in terms of diastolic and systolic abnormalities, we next explored a multiplicative model. We divided E/E’(S) with S’m (E/E’(S)/S’m) and compared the results for the three groups (Table 5.4).

| Table 5.4  Comparisons of E/E’(S)/S’m between groups |
|-----------|-----------|-----------|----------------|
| Group A   | 28        | 1.8       | 0.9            | 0.034          |
| Group B   | 30        | 1.36      | 0.8            | 0.8            |
| Group C   | 34        | 1.25      | 0.7            |                |
| Total     | 92        | 1.45      | 0.8            |                |
We performed a one way ANOVA with a Bonferroni correction for multiple analysis between groups. ANOVA revealed significant heterogeneity between groups, \( p = 0.034 \), while Bonferroni comparisons with Group C (normal controls) revealed that Group A (\( p = 0.034 \)) but not group B (\( p = 0.8 \)) differed significantly from normal.

Given the significant difference in mean values, we explored the potential of this multiplicative model in predicting symptom severity in terms of a predictable relationship with percentage achieved of predicted VO2 max (Figure 5.5).

![Figure 5.5 Correlation between E/E'(S)/S'm and age/gender adjusted predicted VO2 max](image)

| R value - 0.2 and p value of 0.02 |

Although there was a statistically significant negative correlation, the potential clinical utility of this relationship appears to be limited, probably due to the substantial role of other factors involved in determining cardiac limitation apart from the VO2 max.

We then evaluated the discriminatory potential of this multiplicative model by performing a ROC analysis (Figure 5.6) of E/E'(S)/S’m to predict cardiac limitation by CPEX. The factors affecting the previous analysis were taken into account with this particular method.
Area under the curve of 0.81; P value of <0.001; E/E'(S)/Sm(S)> 1.42 predicts cardiac limitation with a sensitivity and specificity of 75 and 75% respectively.

Therefore, this multiplicative model of echocardiographic systolic and diastolic impairment measurement of E/E'(S)/Sm(S) arguably provided the best predictor of cardiac limitation by CPEX, compared to all previous models analyzed.

5.4 Discussion

Despite a relatively preserved ejection fraction in patients with HFpEF, the contribution of subtle systolic left ventricular dysfunction to its pathophysiology has been inadequately characterized in the past. One of the main reasons for this inadequacy has been the difficulty in identifying an appropriate modality to quantify the systolic dysfunction. In this study we used tissue Doppler imaging as the modality of choice to quantify and subsequently assess the relationships to diastolic abnormalities and symptom severity.

The advantages of tissue Doppler imaging (TDI) are that this technique is readily available, robust and reproducible. Strain imaging using either TDI, or more recently speckle tracking imaging, provides much greater precision of both global and regional LV function, both in systole and diastole (Mor-Avi et al. 2005).

TDI studies using annular or basal velocities are measurements of the longitudinal function of the ventricle. This motion of the mitral and tricuspid annulus – akin to a pumping action – is a major component of normal function in both left and right ventricles. The importance of this was confirmed in a recent study using magnetic resonance imaging (cMRI), which quantified the
percentage of the stroke volume due to longitudinal atrioventricular plane displacement (AVPD), and found that the percentage of the stroke volume explained by longitudinal motion was about 60% (Carlsson et al. 2007). The twisting motion of the heart pulls the mitral and tricuspid valve down towards the apex in systole, which involves the coordinated action of longitudinal, circumferential and radially orientated fibres (Greenbaum et al. 1981; Ingels et al. 1989).

Immediately after aortic valve closure, the myocytes begin to relax and untwisting starts using the energy stored during systole within ventricular and atrial myocytes and the interstitium. This energy creates the negative pressure gradient that produces the ventricular suction that is a vital process in the normal heart as it allows rapid filling at low pressures, and is even more important at higher rates during exercise (Cheng, Igarashi and Little 1992; Notomi et al. 2006).

After the LV pressure has fallen, the atrioventricular plane springs back to its equilibrium position moving around the column of blood passing through the mitral valve, thus aiding filling of the ventricle. By this simple mechanism, blood that was in the left atrium finds itself in the ventricle (Greenbaum et al. 1981). Movement of the annulus is therefore the primary contributor to LV pump function. This motion of the mitral annulus or AVPD also indirectly reflects the twist or torsion of the ventricle, and in a way integrates the function, not only of the longitudinal fibres but probably also the circumferential fibres to some extent. The fact that this is such a fundamental motion is probably why annular velocities are such powerful predictors of heart health outcomes, and why they are reduced early by a multitude of conditions affecting both the right and left ventricles.

Progress in TDI has allowed accurate quantitative assessment of cardiac systolic and diastolic function, which in turn provides independent prognostic information in major cardiac diseases, such as myocardial infarction, heart failure and hypertension (Yu et al. 2007). Peak myocardial early diastolic velocity measured at the mitral annulus (Ea) or at myocardial segments (Em), Sm, as well as measurement of transmitral to TDI early diastolic velocity ratio (E/E’), have consistently been shown to offer independent prognostic value in these conditions (Yu et al. above). For example, Wang et al. (Wang et al. 2003) demonstrated that mortality was significantly higher in a cohort of subjects (which included normals, as well as subjects with a
variety of cardiac diseases) when both Sm and Em were reduced, with hazard ratios of 7.5 and 5.3 respectively, whereas LVEF was not significant.

Similar results were found in a cohort of heart failure patients (Wang et al. 2005a) and hypertensive subjects with LVH (Wang et al. 2005b). In another study of 185 patients with HF and LVEF <45% over a median follow-up of 32 months, only mean colour Sm velocity (HR = 0.648 [95% confidence interval (CI) 0.460 to 0.912]; p = 0.013) and diastolic arterial pressure (HR = 0.966 [95% CI 0.938 to 0.994]; p = 0.016) were independent predictors of outcome (Nikitin et al. 2006). In all these studies, TDI measurements provided better prognostic power than LVEF. Furthermore, annular velocities are technically easy to measure using modern echocardiographic machines and quicker than calculating the LVEF by the standard Simpson’s method.

Recently, Svealv, Olofsson and Andersson (2008) have shown that in heart failure patients the simple mitral annular systolic amplitude is strongly associated with mortality or transplantation over a 10 year follow-up and is more powerful than short axis measurements or LVEF. Although many echocardiographic variables were associated with 10 year mortality in the univariate analysis, in the multivariable Cox regression analysis only long axis measurements (not LVEF) retained an independent prognostic value.

In the current study, an attempt has been made to elucidate further the extent of the relationship between systolic and diastolic impairment in a community cohort with a preserved left ventricular ejection fraction and predominantly exertional dyspnoea by using TDI. The research has shown that dyspnoea is related to both systolic and diastolic impairment. This accords with the ongoing theories on the pathophysiology of HFpEF, which have been outlined previously in Chapter 2. It has also been established that there is a significant correlation between the degree of systolic and diastolic impairment in these patients.

The benefits of measuring TDI, as described above, would seem to indicate that it is possible to quantify the extent of systolic impairment and, although limited, predict the extent of dyspnoea. By analysing the relative contributions of both diastolic and systolic impairment in both additive and multiplicative models, we have established incremental discriminatory capabilities of resting echocardiographic parameters in predicting abnormalities in VO2 max as well as other parameters.
of abnormal exercise physiology. It is perhaps useful to reflect that there is increasing evidence that impaired myocardial energetic status plays an important pathophysiological role in HFpEF (Phan et al, 2009). That being the case, it is not unreasonable that both the extent of diastolic and systolic functional changes at rest may represent an integrated predictor of impairment of exercise performance.

However, it remains to be determined what pathological processes are best quantified by the combination of systolic and diastolic functional deficit. Possibilities include energetic impairment and/or degree of myocardial fibrosis.

Having established the link between systolic and diastolic impairment in the sample cohort, it is clear that further studies using more sophisticated methods for quantifying early systolic impairment using speckled tracking are needed to try to overcome the limitations of TDI described above. A significantly larger cohort of patients to undergo metabolic exercise testing is also required to ensure an adequate sample size to fully examine the relationship between exercise limitation and the abnormalities identified in systole and diastole despite a preserved ejection fraction.
Chapter 6

Conclusions and future directions

6.1 Review of the research

There has been expanding interest on all aspects of HFpEF over the last couple of decades. However, the progress in terms of understanding the epidemiology, pathophysiology, diagnosing the condition, as well as treatment, have lagged behind advances in our understanding of systolic heart failure.

The theories regarding pathophysiology continue to evolve, but have not had unequivocal support in a unifying and all-inclusive theory. It may well be that it does not exist due to the fact that the syndrome includes a constellation of various pathophysiological mechanisms, united by a common symptom of exertional dyspnoea and a preserved ejection fraction.

A method of diagnosis, which ideally would include robust criteria, easy to use and readily available investigational tools, as well as widespread acceptance, has not been readily identified despite reams of literature in this area. The difficulty in diagnosis has led to the inaccuracies and subsequent variations in the epidemiology studies associated with this diagnosis. Treatment outcomes for HFpEF have unfortunately failed to keep pace with the positive outcomes achieved in the intervention studies related to systolic heart failure, perhaps because of our current limited knowledge of its epidemiology, pathophysiology and diagnosis.

It was in response to the paucity of available knowledge that the current research was undertaken, with an emphasis on revisiting the basics in terms epidemiology and the various components that make up the diagnosis of HFpEF.

The first study described in this thesis (Chapter 4) revisited the widely held notion that patients with HFpEF were more likely to be female, overweight, diabetic, hypertensive and in atrial fibrillation and whether there was a simple diagnostic tool to identify this cohort as having a cardiac cause of dyspnoea. Using univariate analysis to examine the correlates of dyspnoea in a community population over the age of 60, however, the current research disproved this notion. The main echocardiographic parameters that were significantly different between the dyspnoeic and non-dyspnoeic group were that of E/E’ and LA volumes. Using multivariate analysis,
however, only diabetes and obesity and LA volumes were predictors of dyspnoea. Nevertheless, the study showed that E/E’ measured at the septum and lateral wall could be used interchangeably. There has been debate in the literature as to the ideal method for obtaining this measurement. Arguably a large population study such as this was required to put the debate to rest.

The outstanding conclusion from the first study was that resting diastolic parameters on echocardiography were neither sensitive nor specific enough for the diagnosis of what is predominantly a syndrome that is present upon exertion, and diagnostic modalities that included an exercise component had to be explored in refining that diagnosis of HFpEF.

In the next section of Chapter 4), we investigated the utility of cardiopulmonary exercise testing (CPEX) as the diagnostic modality that included an exercise component. The European Society of Echocardiography (ESE) guidelines suggest CPEX as a means of confirming a cardiac cause of dyspnoea.

An abnormal VO2, as defined by the ESC guidelines, (as less than <25mls/kg/min), was assumed, to reflect, in general, a higher E/E’ at rest on echocardiography. However, an abnormal VO2 predicted abnormal diastology in only 37% of the population.

The reason for the counter-intuitive results of the study was the lack of complete data for CPEX testing on all dyspnoeic patients for a variety of reasons. If the study were to be repeated there would be various strategies attempted to try to ensure the majority of dyspnoeic patients would undergo a cardio-pulmonary test, including the use of a bicycle method for those unable to undergo treadmill testing.

Unfortunately, the initial decision to recruit 2000 patients for the study had been based on a sample size calculation extrapolated from the ECHOES study performed in the same region. It transpired, however, that twice the number of patients would have needed to be recruited in order to attain an ideal sample size. Future epidemiological studies should recruit a sample size of about 5000 patients (Mahadevan et al.2012).
The second possible explanation for the results of the study was that an abnormal VO2 is age and gender dependant and not the only criteria for defining cardiac limitation. These issues were further addressed in Chapter 4.

The ideal cut-offs for CPEX were examined. There has been literature in terms of an age and gender matched cut-off for defining cardiac limitation. Through the analysis of VE/VO2 slopes, there has also been work done in distinguishing ‘true’ cardiac limitations from deconditioning, which will also present with an abnormal VO2 max. Using a 85% predicted cut-off of previously published age and gender matched VO2 max values, as well as analysing the VE/VCO2 slope generated in each study, it was found that only about half the previously abnormal studies were ‘truly’ cardiac limited.

The role of a subtle systolic abnormality in the pathophysiology HFpEF has been actively debated in a number of contradictory studies. In Chapter 5 the relationship between subtle abnormalities and HFpEF was examined further in a community setting where most patients presented with stage C heart failure symptoms but had not necessarily had a hospital admission with heart failure. The investigation, using a readily available, robust and reproducible technique with tissue Doppler imaging, demonstrated that there was certainly a subclinical systolic dysfunction not reflected in the ejection fraction. We showed an inverse correlation between the extent of systolic impairment and the degree of cardiac limitation on CPEX, especially in a multiplicative model of both systolic and diastolic abnormalities.

In a multiplicative model the combined systolic and diastolic parameter of (E/E’/S’m,) provided the best sensitivity and specificity. The small sample size involved in the study was a limitation, but the general consensus from the study was that resting echocardiographic measures should not be marginalised and should be reassessed with the current available technology, such as speckle tracking, where a combination of systolic and diastolic abnormalities should be incorporated into an algorithm to predict cardiac pathophysiology as the cause of abnormal exercise physiology.
6.2 Future directions

Future directions are considered in three different areas:

- epidemiology and primary prevention of HFpEF
- the diagnostic algorithms
- The impact of both of the above on treatment and management of HFpEF.

From the first study it was clear that further emphasis should be placed on Stage A of the disease process for HFpEF, concentrating on reducing the incidence and subsequently the prevalence of diabetes and obesity (with its correlates, hypertension and obstructive sleep apnoea). These two conditions were identified in the multivariate analysis as the strongest correlates of dyspnoea, the main symptom of HFpEF.

The prevalence of ‘true’ HFpEF was in the region of 1.3 to 2.3% of the population cohort. The fact that not all dyspnoeic patients were cardiac limited, as demonstrated in Chapter 5, would explain the variations in the prevalence of HFpEF in the published epidemiological studies. The variations are also linked to the varying diagnostic criteria used. The standardization of the diagnostic criteria, an objective evidence of dyspnoea and a standard cut-off, as well as a uniform method of measuring an ejection fraction are all ingredients for an accurate epidemiological study.

An ideal diagnostic algorithm should be robust, reproducible, easy to use and reflect the underlying pathophysiology of the condition being investigated. One of the main shortcomings of the reported studies was the failure to use BNP and NT-Pro BNP in the diagnostic algorithms. Although there was a plan to measure BNP and NT-Pro BNP at rest and after exercise, there were insufficient samples to make definitive conclusions. In forthcoming studies this parameter will be included as BNP and NT-Pro BNP have been included in the algorithm for diagnosing HFpEF in the ESC consensus statement.

The importance of an exercise component to the diagnostic algorithm has already been explored. The two modalities that have to be investigated further are cardiopulmonary exercise testing and exercise echocardiography. Further research is required in relation to age and gender matched normative values for both sedentary and active subjects for CPEX testing. There also has to be an attempt to modify exercise protocols by combining the use of treadmill and cycle, so that patients with physical limitations can also be included in assessment. Although the described studies have
not addressed exercise stress echocardiography, there have been publications with regards to its feasibility and usefulness. It still has not gained widespread acceptance in everyday clinical practice, however, probably due to limited expertise, as well as the inability of patients to undergo the exercise protocol due to physical limitations.

Improving the sensitivity of resting diastolic echocardiographic measurements seems to be required. The reported studies have demonstrated its specificity in patients with ‘true’ HFpEF. The research group of which I am a member (Phan et al. 2009) has previously demonstrated and published findings about exercise related changes in LV relaxation and a reduced cardiac energetic reserve in patients with HFpEF. The findings were based on investigations using magnetic resonance spectroscopy with the cohort already identified in the studies described in this thesis. Newer echocardiographic developments such as speckle tracking would enable the quantification of suction, an energy dependent process in diastology. This would need to be explored in future studies in keeping with the assertion that diagnostic tools should be based on the pathophysiology of the condition being investigated.

In the study reported in Chapter 5, a subtle systolic impairment in patients with HFpEF was identified, as was impairment in LV contractile function during exercise (Phan, et al 2009). This relationship could be further elucidated with speckle tracking and global longitudinal strain (GLS). GLS has demonstrated superior prognostic value over ejection fraction predicting adverse events in a number of clinical situations (Kalam, Otahal and Marwick 2014,, Stanton, Leano and Marwick 2009). Further validation studies would be required in HFpEF patients, correlating exercise parameters to resting GLS.

Therapeutic trials involving HFpEF should include the above recommendations in terms of diagnosis for patient selection. The method of patient selection was never more evident than in the TOPCAT study. There was a reduction in hospitalization in the treatment group but a sub group analysis suggested the method of patient selection might have resulted in more significant benefits, possibly even a mortality benefit (Pitt et al. 2014).
References


Yu et al. (*J Am Coll Cardiol*. 2007 May 15;49(19):1903-14)


Addenda & corrigenda
Addenda and corrgenda

The two reviewers of this thesis have made a number of suggestions regarding alterations and inclusions in order to improve its impact. The response to these suggestions is encapsulated in the current section.

Initially, it must be stated that Reviewer 2 requested an alteration in title of the thesis from ‘The epidemiology, diagnosis and pathophysiology of heart failure and preserved ejection fraction (HFpEF) in an elderly community cohort’ to ‘Mechanisms of dyspnea and poor exercise tolerance in a representative cohort of elderly patients with a relatively normal ejection fraction on echocardiography’: the modified title is now in place.

As regards other alterations:

Reviewer 1

1 Terminology for condition studied.
   The reviewer makes the point that in most series thus far reported, patients with left ventricular ejection fractions as little as 40% have been included. Therefore I acknowledge that ‘diastolic heart failure’ is a better descriptive term.

2 Other community studies.
   We regret the omission of data from

   i A paper published within the Copenhagen City Study by Mogelvang et al (Circ 2009 May 26;119(20): 2679-85), which demonstrated in a population of 1036 patients randomly selected from the general population, with ages varying from 20 to 93 years, that tissue Doppler velocity parameters were able to predict mortality. This was despite a relatively preserved ejection fraction on echocardiography.

   ii From the same Copenhagen City study, Mogelvang et al (Eur Heart Journal 2009;Mar 30(6): 731-9) also demonstrated cardiac dysfunction in patients with documented ischemic heart disease, hypertension and diabetes, as identified by tissue Doppler imaging, despite a relatively normal ejection fraction on conventional echocardiography.
Finally Moglevang et al (J of Cardiac Failure 2009 Aug 15(6):489-95) correlated the cardiac dysfunction demonstrated by tissue Doppler imaging with elevated plasma pro-B-Type natriuretic peptide concentrations.

and acknowledge that all of these may be relevant to the current thesis.

3 **Energetics/rate of recoil.**

This area was omitted in the early stages of the thesis (but not around page 96).

We wish to insert the following as an item of addendum after page 20:

During exercise, the systolic phase of the cardiac cycle results in more forceful contraction which enhances early diastolic myocardial elastic recoil, due to the greater systolic shortening associated with exercise. This results in enhanced diastolic filling (Little WC et al, 1994).

The energy of the elastic recoil is stored in titin and the extra-cellular matrix (ECM). The early stages of diastolic heart failure are postulated to be associated with inco-ordinate systolic function, which may lead to reduced early diastolic filling.

This is discussed further on page 96.

4 **Impairment of atrial function.**

As pointed out by Reviewer 1, we wish to add that atrial function is abnormal on exercise and that this was demonstrated by Tan et al (Heart 2010;96:1017-23), where it was established that patients with heart failure and normal ejection fraction had a larger left atrial volume index on exercise, as well as an impaired left atrial functional reserve. The left atrial functional reserve was measured using early and late mitral annular velocities during rest and exercise. These correlated with systolic and diastolic ventricular abnormalities on exercise.

5 **Potential impact of exercise echocardiography.**

I agree that lack of exercise echocardiography data is one of the substantial limitations of the work.
6 Numbers incorrect.
   i Subjects screened: 1833 individuals were screened
   ii Subjects with cardiac origin of dyspnea: We agree that the study endpoints are based on small numbers, but the underlying message of the heterogeneity of the cause of dyspnea could be extrapolated back to the whole community.

7 Propagation velocity.
   It is indeed interesting that propagation velocity correlated with dyspnea. The reason that is was not considered further was mainly its lack of clinical application in the current European and American Society of Echocardiography guidelines. Mottram and Marwick (Mottram, Heart 2005 May 91(5):681-95) have previously published the fact that the propagation velocity is less reliable in small hypertrophied ventricles (the majority of patients in this community study) due to the preload dependence of the measured variable.

8 Importance of pulmonary pressures and RV function.
   It is clear from the work of Lam CS et al (JACC, 2009 53:1119-26), that variability in right sided haemodynamic status may be a further source of differential symptomatic status in this patient population. Right heart pressures were attempted for all subjects in this study but RV function was not quantified objectively.

   This would certainly be an interesting follow up study to evaluate the impact of these two parameters on symptoms in this population.

9 Mention of abstracts/publications.
   We regret the omissions of the publications listed below, which were a body of work that followed on from our initial study, and we would now like to mention:
   i As suggested in our conclusion, exercise echocardiography was subsequently used to unmask the complex abnormalities of both systolic and diastolic abnormalities in the pathophysiology of heart failure with a normal ejection fraction by Tan et al (JACC, 2009 Jun 30,54(1):36-46). They established that 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 (p < 0.001). In diastole, patients had reduced and delayed untwisting, reduced left ventricular suction at rest and on
exercise, and higher end-diastolic pressures. Mitral annular systolic and diastolic velocities, systolic left ventricular rotation, and early diastolic untwist on exercise correlated with peak VO(2)max.

ii  Tan et al (Eur J Heart Failure 2011, Sept;13(9):953-960), established a further simple parameter on exercise echocardiography, using MAPSE at rest and on exercise correlates well with more sophisticated measurements of ventricular function in HFpEF patients. It is potentially a useful and easily acquired measurement, especially on exercise, for the diagnosis of HFpEF with an the area under the receiver operating characteristic curve for MAPSE was 0.655 (confidence interval 0.540-0.770) at rest and 0.901 (confidence interval 0.835-0.967) on exercise, to differentiate between patients and controls.

10  The importance of speckle tracking on echocardiography.
We had commented on the importance of speckle tracking on echocardiography to correlate with the reduced cardiac energetic reserve and systolic abnormalities that had been previously demonstrated in patients with HFpEF.

We therefore would like to acknowledge that the use of speckle tracking in this group of patients was addressed by Tan et al (JACC, 2009 Jun 30, 54(1):36-46), as described above in section (9)(i).

There was a further publication by Kraigher-Krainer et al, (JACC 2014:63:447-456). They established that, compared to both normal controls and hypertensive heart disease patients, the HFpEF patients demonstrated significantly lower longitudinal strain (LS) (-20.0 ± 2.1 and -17.07 ± 2.04 vs. -14.6 ± 3.3, respectively, p < 0.0001 for both) and circumferential strain (CS) (-27.1 ± 3.1 and -30.1 ± 3.5 vs. -22.9 ± 5.9, respectively; p < 0.0001 for both). Lower LS was modestly associated with higher NT-proBNP, even after adjustment for 10 baseline covariates including LVEF, measures of diastolic function, and LV filling pressure (multivariable adjusted p = 0.001).

11  Reference list
We regret the omissions and the reference list has been updated with the following references:

Page 96: Yu et al (J Am Coll Cardiol. 2007 May 15;49(19):1903-14)


12 Duplication of verbiage, page 96

I was not previously aware that the draft manuscript which I quoted has now been published. In essence, the verbiage used here is my own.

The final publication was Sanderson JE; Left and right ventricular long axis function and prognosis. *Heart* 2008; 94:262-263.

Reviewer 2

I acknowledge that a more appropriate title for the thesis would be *Mechanisms of dyspnoea and poor exercise tolerance in a representative cohort of elderly patients with a relatively normal ejection fraction on echocardiograph.*

This has been changed in the revised version.

As regards the failure of the body of the thesis to address adequately the epidemiology of the process, I agree that there are limitations here. Rather than re-cast the work to adequately deal with all epidemiology issues, the charge in title will eliminate this need. However, it must be stated that an adequate understanding of the epidemiology of HFnEF remains an important clinical priority.