CLINICAL CHARACTERISTICS OF PATIENTS WITH HEART FAILURE AND PRESERVED LEFT VENTRICULAR SYSTOLIC FUNCTION: A DESCRIPTIVE COHORT STUDY AND COMPARISON WITH HEART FAILURE AND REDUCED SYSTOLIC FUNCTION

A thesis by

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Submitted for the degree of Doctor of Medicine

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September 2006

Acknowledgements

I am greatly indebted to Professor J.J.V McMurray both for the opportunity to perform this study, and for his expert advice, encouragement and forebearance throughout.

I am grateful to the British Heart Foundation, without which, this work would not have been possible.

I would like to acknowledge the help of Mrs Esther Rooney and Mrs Eileen Lundmark, without whom the acquisition of the echocardiography data would not have been possible. I would also like to thank Dr Ian Morton for his assistance with the analytical biochemistry and Mr Jim Christie, whose help with the database was invaluable. Dr Pardeep Jhund assisted me with some of the more complicated statistical analyses, for which I am very grateful.

I would also like to thank Dr Susan Lynch, Dr Rachel Myles and Dr Matthew Walters and many other close friends and colleagues for their help, patience and support over the years.

I dedicate this thesis to my Dad whom I will always miss and to my Mum for always being there.

Declaration

The work described in this thesis was carried out while I was employed as a Clinical Research Fellow in the University Division of Cardiovascular and Medical Sciences at the Western Infirmary, Glasgow.

Echocardiography was performed by Ms Eileen Lundmark and Doppler echocardiography was performed by Mrs Esther Rooney. The more complex statistical analyses were supervised by Dr Pardeep Jhund of the University of Glasgow. The biochemical assays were performed by Dr Ian Morton.

I carried out the remainder of the work myself. The writing of the thesis was entirely my own work.

This work has been presented at various national and international meetings including the European Society of Cardiology in 2003, 2004 and 2005; the Scottish Society of Experimental Medicine in 2004; the British Society of Cardiology in 2004; and the American College of Cardiology in 2004.

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Presentations to Learned Societies

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Aug 2004 **European Society of Cardiology**

Neurohumoral correlates of markers of collagen turnover in heart failure with preserved systolic function (HF-PSF).
Selected for ESC Highlight Session.
K Hogg, E Rooney, J McMurray

May 2004 **British Cardiac Society**

What proportion of patients with heart failure and preserved systolic function has an elevated BNP concentration? (Further increase in numbers and more detailed information on baseline characteristics including a comparison of subjects with normal and an elevated BNP concentration)
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March 2004 **American College of Cardiology**

What proportion of patients with heart failure and preserved systolic function has an elevated BNP concentration? (Increased numbers and information on baseline characteristics)
K Hogg, E Rooney, J McMurray

Aug 2003 **European Society of Cardiology**

What proportion of patients with heart failure and preserved systolic function has an elevated BNP concentration?
K Hogg, E Rooney, J McMurray

Poster Presentations

Sept 2005 **European Society of Cardiology**

Prognostic importance of plasma natriuretic peptide concentrations in patients with heart failure and preserved systolic function.
Hogg K, Rooney E, O'Hara E, McMurray J

Jan 2004 **Scottish Society of Experimental Medicine**

Patients with heart failure and preserved systolic function – what proportion has an elevated BNP concentration?
Hogg K, Rooney E, McMurray J

List of Abbreviations

HF	Heart failure
NHS	National Health Service
HF-RSF	Heart failure with reduced systolic function
HF-PSF	Heart failure with preserved systolic function
LV	Left ventricule/left ventricular
LVEF	Left ventricular ejection fraction
FS	Fractional shortening
LVWMI	Left ventricular wall motion index
CHS	Cardiovascular Health Study
IN-CHF	Italian Network on Congestive Heart Failure
NYHA	New York Heart Association
QoL	Quality of life
MI	Myocardial infarction
CHD	Coronary heart disease
CVD	Cerebrovascular disease
LVH	Left ventricular hypertrophy
AF	Atrial fibrillation
DM	Diabetes mellitus
eGFR	Estimated glomerular filtration rate
ACE-I	Angiotensin converting enzyme inhibitors
βB	Beta blocker
CCB	Calcium channel blocker
LA	Left atrium
DT	Deceleration time

ANP	Atrial natriuretic peptide
BNP	B-type natriuretic peptide
CNP	C-type natriuretic peptide
DNP	D-type natriuretic peptide
Pro-ANP	Precursor protein of ANP
NPR	Natriuretic peptide receptor
C-GMP	Guanosine 3',5'-(cyclic) phosphate
LVEDP	Left ventricular end diastolic pressure
NT-proBNP	N-terminal prohormone B-type natriuretic peptide
RI	Radioimmunoassay
PIIINP	Aminoterminal propeptide of type III procollagen
ECM	Extracellular matrix
MMP	Matrix metalloproteinase
TIMP	Tissue inhibitors of metalloproteinase
TGF-B	Transforming growth factor-B
CXR	Chest radiograph
ECG	Electrocardiogram
LVSD	Left ventricular systolic dysfunction
LBBB	Left bundle branch block
Hb	Haemoglobin
WCC	White cell count
CRP	C-Reactive protein
TFT	Thyroid function test
WHO	World Health Organisation
MDRD	Modified Diet in Renal Disease

FBC	Full blood count
COAG	Coagulation screen
U&E	Urea and electrolytes
LFT	Liver function test
LVSF	Left ventricular systolic function
VHD	Valvular heart disease
LVIDS	Left ventricular internal diameter in systole
LVIDD	Left ventricular internal diameter in diastole
IVSDS	Interventricular septum diameter in systole
IVSDD	Interventricular septum diameter in diastole
LVPWS	Left ventricular posterior wall in systole
LVPWD	Left ventricular posterior wall in diastole
RVEDD	Right ventricular end-diastolic diameter
HF-IPSF	Heart failure with isolated preserved systolic function
IVRT	Isovolumetric relaxation time
PFT	Pulmonary function test
FEV_1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
VC	Vital capacity
ISD	Information and Statistics Division
HR	Heart rate
PAD	Peripheral arterial disease
COPD	Chronic obstructive pulmonary disease
IHD	Ischaemic heart disease
SBP	Systolic blood pressure

DBP	Diastolic blood pressure
HF +ve	Heart failure score positive
HF –ve	Heart failure score negative
PND	Paroxysmal nocturnal dsypnoea
JVP	Jugular venous pressure
S3	Third heart sound
RR	Respiratory rate
CABG	Coronary artery bypass graft
LTOT	Long term oxygen therapy
BMI	Body mass index
MCV	Mean cell volume
ALP	Alkaline phosphatase
AST	Aspartate aminotransferase
GGT	Gamma glutamyl transpeptidase
ARB	Angiotensin receptor blocker
LAD	Left axis deviation
RBBB	Right bundle branch block
RVH	Right ventricular hypertrophy
RAD	Right axis deviation
LOL scores	Cantrils Ladder of Life scores
CHARM	Candesartan in heart failure assessment of reduction in morbidity and mortality
DHF	Diastolic heart failure
dp/dt	Maximum rate of pressure decline
tau	Time constant of relaxation
DD criteria	Diastolic dysfunction criteria

ROC	Receiver operator curve
AUC	Area under the curve
IQR	Inter-quartile range
NP	Natriuretic peptide
TFG	Tissue growth factor
IGF	Insulin-like growth factor
BFGF	Basic fibroblast growth factor
Ang II	Angiotensin II
TNFα	Tissue necrosis factor alpha
HCM	Hypertrophic cardiomyopathy
BP	Blood pressure
RAAS	Renin aldosterone angiotensin system
SCDHeFT	Sudden cardiac death in heart failure trial
BBB	Bundle branch block
ARR	Aldosterone to renin ratio
I-PRESERVE	Irbesartan in heart failure with preserved systolic function
PEP-CHF	Perindopril for elderly people with chronic heart failure
EPHESUS	Eplerenone post-acute myocardial infarction heart failure efficacy and survival study
TOPCAT	Trial of aldosterone antagonist therapy in adults with preserved ejection fraction congestive heart failure

Summary

Heart failure is a common disorder, which is increasing in prevalence worldwide. It carries a significant burden in terms of both morbidity and mortality, and in terms of both economic and social cost. Recent advances in pharmacological and device therapy have lead to a reduction in the morbidity and mortality associated with heart failure with reduced left ventricular systolic function. No such therapeutic strategies have been forthcoming for patients with heart failure and preserved left ventricular systolic function (HF-PSF), resulting in static mortality rates, and, in the context of our ageing population, an escalating problem.

At the time of starting this work, the syndrome of heart failure with preserved systolic function was a neglected area in clinical cardiovascular research. The aim of this study was to improve our understanding of this condition by investigating the prevalence of HF-PSF in a cohort of patients admitted to hospital with heart failure, examining their clinical characteristics and determining their prognosis.

Until recently, there have been relatively few data concerning the prevalence of HF-PSF. However, the indications are that it is a common condition and this is corroborated by my findings, that around half of all patients admitted with heart failure have preserved left ventricular systolic function.

By comparing the detailed clinical characteristics of patients with HF-PSF to those of patients with reduced systolic function, this study has provided a number of important insights into this common syndrome. Patients with preserved systolic function heart failure tend to be older, and are more likely to have a history of hypertension. These are findings have now become well established in the HF-PSF literature.

In relation to comorbidity, I specifically examined the prevalence of chronic obstructive pulmonary disease (COPD) in the subset of my study patients with HF-PSF, with a view to determining if they may have been misdiagnosed. On the contrary, while few patients had both a normal BNP and abnormal PFTs, a significant number of those patients with HF-PSF who had previously received a clinical diagnosis of COPD, actually had normal spirometry but an elevated BNP. This rather suggests that they may have been misdiagnosed with COPD, when in fact, they were suffering from HF-PSF. The importance of the interplay between COPD and HF is increasingly recognised, and these results serve to underline the need for further study in this area.

In addition to the idea that HF-PSF was merely misdiagnosis, until recently conventional expectations were that HF-PSF would produce a mild version of the clinical syndrome. However, in this study I found that patients with HF-PSF did indeed display markers of severe and complicated heart failure. The majority were classified as Killip IIA or greater on admission to hospital, and the majority had moderate renal dysfunction.

This suggestion that HF-PSF is not a benign condition is borne out by the mortality data from this study. All-cause mortality in the HF-PSF group, although lower than that for heart failure with reduced systolic function, was significant, with a case fatality rate of 37% after three years. This high mortality rate underscores the need for effective treatments for patients with HF-PSF.

Before we can develop such treatments, we need to understand the aetiology of the condition. Comparatively little is known about the aetiology of heart failure in the context of preserved, as opposed to reduced systolic function. Left ventricular diastolic dysfunction has received

much attention as a potential mechanism, whereby reduced LV compliance impairs left ventricular filling and therefore reduces stroke volume. However, in a practical clinical context, there has been much debate regarding the assessment of diastolic function, for which there is no concensus method. In this study, I compared a number of different echocardiographic criteria and found a wide variation in the estimated prevalence of diastolic dysfunction.

Natriuretic peptides have recently revolutionised the diagnosis and risk stratification of patients with heart failure and reduced systolic function. BNP and its precursor, NT pro BNP have also been found to have prognostic significance in patients with HF-PSF. In this study I determined normal ranges of natriuretic peptides from an age-matched local population and applied these to my cohort. BNP and NT-pro BNP were elevated in both types of heart failure, and although absolute levels were higher in patients with reduced systolic function, a significant majority of the HF-PSF group had elevated natriuretic peptide levels. This constitutes biochemical evidence of left ventricular compromise in these patients, despite the fact that systolic function is preserved.

Aminoterminal propeptide of type III procollagen (PIIINP) is a novel marker of myocardial fibrosis, a process which has been implicated in left ventricular remodelling, and may therefore be important in the aetiology of heart failure with either reduced or preserved systolic function. In my examination of PIIINP levels in this cohort of patients, the majority of patients with HF-PSF also had an elevated PIIINP, supporting a possible causative role for myocardial fibrosis in the development of HF-PSF.

In summary, this thesis describes the detailed characterisation of the syndrome of heart failure with preserved left ventricular systolic function, through the examination of the clinical, biochemical and echocardiographic indices and long term follow-up of a cohort of patients hospitalised for heart failure. I have shown that this is a common condition which results in significant mortality. The findings of this work are consistent not only with the hypothesis that heart failure with preserved systolic function is a well-defined clinical entity in its own right, but also that it is a major public health issue both now and for years to come.

CHAPTER ONE

INTRODUCTION

1.01 The burden of heart failure

Heart failure (HF) is now fully recognised as a major public health problem[1;2]. It has been estimated that there are nearly 23 million people with HF worldwide[1]. HF is an escalating public health problem, particularly in industrialised countries, due to the ageing population. In the UK, the overall incidence of HF has been estimated to be 3-20 cases per 1,000 population, rising to more than 100 cases per 1,000 in those aged 65 years and older[3]. HF produces significant mortality and morbidity, in the recent Sudden Cardiac Death in Heart Failure Trial (SCD HeFT), patients in the placebo arm were on best medical therapy, and the mortality was 36.1% at 5 years or 7.2% per year[4]. These combined mean that management of heart failure is a considerable financial burden to the National Health Service (NHS). This cost is relatively easy to assess in terms of the number of hospital admissions, which are increasing, with 20-30% of HF patients being hospitalised[3]. In the UK, almost 2% of the entire NHS budget is spent on caring for patients with HF[3]. Estimates of HF spending from the US are of the order of 15-40 billion dollars per annum[5;6]. Significant healthcare spending is only a part of the problem posed by the high prevalence of HF. Much of the long-term care afforded to patients disabled by HF is provided by family and extended family members. It is clear that the burden of HF borne by society as a whole is extensive, and has far reaching consequences.

1.02 Heart Failure with preserved left ventricular systolic function

Until recently the medical profession have focused on diagnosis and treatment of HF caused by reduced left ventricular systolic function (HF-RSF). The concept of HF with preserved left ventricular systolic function (HF-PSF) was initially developed in the 1970's[7], following the clinical observation that a number of patients had a heart failure syndrome but without

depressed left ventricular (LV) function. Over the past decade there has been a growing interest in HF-PSF[8-12].

1.02.1 Prevalence of heart failure with preserved systolic function

Epidemiological studies estimate the proportion of patients with clinical HF who have preserved LV systolic function to be 40%-71% (with a mean of 56%). However, there was wide variation with respect to sample size, and the age range of individuals studied[13]. This may go some way to explaining the wide variation in recorded prevalence. These studies also used different criteria to define HF in general and HF-PSF in particular. The definitions of HF in these studies varied from utilising the diagnosis of a single physician, to using epidemiological questionnaires (e.g. Framingham score). The echocardiographic tools employed to assess LV function varied from qualitative assessment of left ventricular ejection fraction (LVEF), to quantitative measurements such as fractional shortening (FS), wall motion score or LVEF (ie. by Simpson's rule). There were also differences in the thresholds used for dividing "reduced" from "preserved" systolic function. For example, the most commonly used method was FS. This method measures systolic function at the base of the heart and can be normal in patients with apical hypokinesis, in whom the LVEF would be expected to be reduced. The Copenhagen[14] and Vasteras[15] studies highlight how very different proportions of patients with HF-PSF may be calculated depending on whether a left ventricular wall motion index (LVWMI) of >1.5 or >1.7 is used as a cut-point. To further illustrate this point, in the Cardiovascular Health Study (CHS), 80% of patients had an LVEF >0.45, but only 55% had an LVEF >0.55[16]. What these studies highlight is that there is currently no accepted binary division between preserved and reduced systolic function. What this leaves us with is an uncertain "grey area" where, depending on the investigator these patients could be classified as having either reduced or preserved systolic function[13].

The above findings are supported by observations from large-scale studies such as the Improvement Programme in Evaluation and Management of Heart failure (IMPROVEMENT-HF) study[17], which was undertaken in primary care in 15 member countries of the European Society of Cardiology, and also the Italian Network on Congestive Heart Failure (IN-CHF) study, conducted in out-patients in 133 out of 192 Italian cardiology centres[18].

1.02.2 Incidence of heart failure with preserved systolic function

There are two prospective studies which aim to identify the relative incidence of reduced and preserved systolic function within the HF population[19;20]. In the Olmsted study, 216 patients with new HF were identified over a 12 month period. Of these, 137 (63%) had had a recent echocardiographic assessment of LV function recorded as LVEF. HF-PSF was defined as LVEF $\geq$ 50%, and a further subdivision was made according to the presence or absence of valvular heart disease (isolated PSF). Fifty-nine (43%) had HF-PSF, and five of these had significant valve disease, leaving fifty-four (39%) with a diagnosis of HF with isolated PSF. In the Bromley Heart Failure study, all local primary care physicians were asked to refer new cases of HF to a specialised clinic and all patients who had a hospital admission for HF were also included. Over a 14 month period, 332 new cases of HF were identified, and 310 (93%) had an echocardiogram. By echocardiographic criteria, 16% had HF-PSF, and 84% had HF-RSF[13]. Again, we see a wide variation in estimated incidence of HF-PSF.

1.02.3 Preserved systolic function in patients hospitalised for heart failure

Since 2000 there have been a limited number of studies published on hospitalised cohorts of patients with HF-PSF (Table 1.1). These heterogeneous studies range from a small single-centre study with a majority of African-American patients, to a large sample of Medicare beneficiaries in the USA, to a countrywide epidemiological survey from France. Full

information on the assessment of LV function is lacking in many of these studies. However, the proportion of patients with PSF was lower than in the population studies, ranging from 24%-55% (mean 41%). This is consistent with evidence, which will be discussed later in this Chapter, that patients with HF-PSF have less severe symptoms and are therefore less likely to require in-patient treatment. The patients in these studies were less likely to have a prior history of hospitalisation for HF. As seen in the population studies, a greater proportion of patients with HF-PSF were female. Masoudi *et al* confirmed that female gender was an independent predictor of PSF in patients with HF[21]. The recent Euro Heart Failure survey of over 11,000 hospital discharges from 115 hospitals in 24 European countries supports these findings[22]. Only 28% of women with HF had an LVEF of <0.40, compared to 51% of men. Patients with HF-PSF were also older, though the relationship between age and PSF appears to be less strong than that between PSF and female gender[21]. Berry *et al* recently published results from over 500 emergency admissions with heart failure based on the discharge letter and prescription. Of these, 29% had HF-PSF (LVEF >0.40) and 62% of these were female compared to 45% of the HF-RSF group[23].

Table 1.1 Prevalence of heart failure with preserved left ventricular systolic function: hospitalisation cohort studies[13].

first author/ country	Year of publication	n=*	design	criteria for preserved LV systolic function	preserved/ total (%)	female % (P/R)	mean age** (P/R)	AA % (P/R)
Philbin (USA-MISCHF Registry)[26]	2000	1291 (2906)	MISCHF registry, DRG 127, LV function assessment within 6 months of discharge, numeric LVEF available	echo/RNVG/other LVEF ≥50%	312/1291(24)	70/50	75/74	4/3†
Malki (USA-Detroit)[27]	2002	187 (?)	prospective, clinical & radiologic pulmonary congestion, echo. within 6 months	echo LVEF ≥ 50%	57/187(30)	63/46	69/65	60/79
Dauterman (USA-California)[28]	2002	782 (1720)	retrospective chart review, Medicare ≥ 65 yrs, CXR cardiomegaly/pulmonary oedema, LV function measurement, No C/I to ACE-I	echo/RNVG/other LVEF ≥ 40% or qualitative LV assessment	238/438(54)	69/49	-	15/14***
Ahmed (USA-Alabama)[29]	2002	438 (1091)	Medicare ≥ 65 years, clinical score, LV function measurement	LVEF >40% or qualitative LV assessment	430/782(55)	69/49	-	14/19
Cohen-Solal (France)[30]	2000	739 (1058)	prospective, national epidemiological survey, Framingham criteria clinical diagnosis	echocardiographic/RNVG/ other LVEF, echo LVEF > 40%	200/438(46)	51/29	76/71	-
Varela-Roman (Spain)[31]	2002	229 (301)	prospective, Framingham criteria, LV function assessment within 2 weeks	echo LVEF ≥ 50%	66/229(29)	64/33	67/66	-
Tsutsui (Japan)[32]	2001	172 (236)	retrospective chart review, Framingham criteria, deaths excluded, Echo LVEF	echo LVEF >50%	61/172(35)	51/33	69/68	-
Thomas (USA-Chicago)[33]	2002	225 (282)	prospective, consecutive admissions over 4 months, Framingham criteria	qualitative echo LVEF ≥ 45%	104/225(46)	56/35	59/54	ǂ
Masoudi (USA-Medicare)[34]	2003	19,710 (33,814)	Medicare (≥65 years) sample April 1998-March 1999	LVEF ≥50% or qualitatively normal LV systolic function, past history of CHF or radiographic evidence	6,700/19,710 (35)	79/49	80/78	9/10
Smith (USA-Connecticut)[35]	2003	413	prospective, consecutive admissions, 1996-1998, NHANES criteria	echo/RNVG/other LVEF ≥ 40%	200/413 (48)	63/35	73/70	21/25†
Gustafsson (Denmark)[36]	2003	5491	randomised controlled trial, admissions with CHF 1993-1996	echo WMI > 1.6 (approximates to LVEF > 48%)	2218/5240 (42)	49/33	73/71	-
Varadarajan (USA-California)[37]	2003	2,258	retrospective chart review, 1990-1999, echocardiogram	echo LVEF ≥ 55%	963/2258 (43)	3/97	70/71	11/10

* number with LVEF measurement (total number in cohort); ? it is unclear whether whole cohort had a LVEF measurement

** years

*** non-white

† non-caucasian

ǂ 75% overall

P/R Preserved/reduced LV systolic function

AA African/American

MISCHF Management to Improve Survival in Congestive Heart Failure

LVEF left ventricular ejection fraction

RNVG radionuclide ventriculogram

CXR chest X-ray

USA United States of America

ESC European Society of Cardiology

DRG diagnosis related group

LV left ventricular

1.02.4 Clinical characteristics of patients with HF-PSF

A comparison of the demographic characteristics of HF patients with reduced and preserved systolic function will provide important insights into HF-PSF. Only three of the prevalence studies discussed earlier, specifically cite the separate figures for men and women. Consistently across these studies the proportion of women with HF-PSF exceeds that of men. Consistent with this, in a case control study from Framingham 73% of the 33 women and 33% of the 40 men had HF-PSF[8].

Few studies have consistently reported the frequency of characteristic symptoms of HF such as dyspnoea at rest or on exertion, orthopnoea or paroxysmal nocturnal dyspnoea (PND), or signs such as an elevated jugular venous pressure (JVP), pedal oedema and pulmonary crepitations on auscultation. The two studies which have done this, have shown that signs and symptoms were similar in patients with HF-PSF compared to those with HF-RSF. The exception to this was the presence of a 3rd heart sound which was more common in HF-RSF[24;25]. Philbin *et al*[26] and Varela-Roman *et al*[27] found that patients with HF-PSF were less likely to be in a high New York Heart Association (NYHA) class. This finding was confirmed in the IN-CHF study[18]. Smith *et al*[28] recently reported that severe dyspnoea was less common in patients with HF-PSF. Philbin *et al*[26] measured quality of life (QoL), using the Ladder of Life scoring system. The mean score was 6.5 for HF-RSF and 6.4 for HF-PSF and these results were almost identical to those from Jaarsma *et al*[29] who used the same QoL questionnaire. Other studies, using both a general QoL questionnaire and a disease-specific questionnaire such as the Minnesota Living with Heart Failure Questionnaire, have shown that QoL is lowest in those with HF-RSF but that QoL is lower with either types of HF than that which would be expected in the general population[30].

In four studies reporting length of hospital stay in the two types of HF, there was little difference. In one study, the duration of stay was 11 days in both groups[31]. Other studies have reported, for HF-PSF and HF-RSF, in-patient stays of 7.5 versus 7.9 days[26], 6.1 versus 7.0 days[32], and 5.2 versus 5.9 days[24]. In more detailed analyses, however, both Philbin *et al* and Malki *et al* found that length of stay did increase with worsening LV systolic function[24;26].

1.02.5 Concomitant medical pathology in HF-PSF

Much of the information regarding concomitant cardiac problems comes from hospitalisation cohort studies. Myocardial infarction (MI) or any evidence of previous coronary heart disease (CHD) is less commonly found in those with HF-PSF. However, evidence of CHD in HF-PSF is more common than in age and gender-matched controls[8]. Other evidence of atherosclerotic disease, such as peripheral arterial disease or cerebrovascular disease (CVD) was also less common in HF-PSF, compared with HF-RSF. These findings were corroborated by the IN-CHF study[17]. Masoudi *et al* demonstrated that CHD independently predicted patients less likely to have PSF in patients hospitalised with HF[21].

Conversely, a history of hypertension was more common in patients with HF-PSF[33;34], a finding again supported by the IN-CHF study[18]. Masoudi *et al* also found that a history of hypertension was an independent predictor of PSF in patients hospitalised with HF[21]. In association with this finding, left ventricular hypertrophy (LVH) was more commonly found in HF-PSF[26] with the exception of the study by Thomas *et al*[25].

The incidence of atrial fibrillation (AF), was more common in HF-PSF, occurring in one-quarter to one-third of patients. In the IN-CHF study, 16% of the HF-RSF patients had AF

compared with 25% of the HF-PSF patients (defined as LVEF >45%)[18]. Masoudi *et al* demonstrated that AF was an independent predictor of PSF in patients hospitalised with HF[21]. The question of whether AF is a primary cause or secondary problem in HF-PSF remains unanswered[13].

It has been previously speculated that diabetes mellitus (DM) is more common in HF-PSF. DM has been found to be more common in both types of HF compared with the general population. However, this co-morbidity has not been found to be more frequent in patients with PSF, with the exception of the Strong Heart Study[35]. It should be noted however, that Redfield *et al* found that DM was a risk factor for the presence of diastolic dysfunction[36]. Chronic pulmonary disease was more common in patients with PSF, raising a concern of misdiagnosis[37].

To date, there has been no clear evidence that there is a significant difference in renal function, as measured by serum creatinine or by creatinine clearance, between the two types of heart failure. In a recent study, Berry *et al* confirmed that the renal function was impaired but comparable between the two types of HF. As serum creatinine concentration can be an inaccurate measure of renal function, especially in the elderly this study confirmed the comparable renal function using estimated glomerular filtration (eGFR)[23].

1.02.6 Medical Treatment

Studies to date have documented a wide variation in the medications taken by HF patients with RSF and PSF. Angiotensin converting enzyme inhibitors (ACE-I) and digoxin were used less frequently in patients with PSF[38]. Beta-blocker (βB) use was higher in the PSF group, although these studies were generally before the benefits of βB in HF-RSF were

accepted. Findings from the IMPROVEMENT-HF[17] and IN-CHF[18] registries were consistent with the above. Calcium channel blocker (CCB) use was also higher in the PSF group, perhaps reflecting the view that these agents may be useful in this subset of patients and harmful in those with HF-RSF[39]. In the IN-CHF registry, 23% of patients with an LVEF >45% were taking a CCB compared to 8% of those with HF-RSF[18].

1.02.7 Economic considerations

There are few formal cost studies dealing with the specific problem of HF-PSF. However, some crude estimates of cost can be inferred from the rate of hospitalisation, which accounts for most of the overall cost of HF to health care systems. This is cost is primarily driven by the length of stay. As discussed above, approximately 40% of patients hospitalised with HF have PSF and the length of stay in hospital is very similar to those with HF-RSF. Therefore, approximately 40% of the overall cost of HF is probably accounted for by patients with HF-PSF. Some support for this conclusion comes from Philbin *et al*, who calculated the mean hospital charge for both types of HF to be approximately $8,600[26].

1.02.8 Morbidity and mortality

If we use figures for mortality and repeat hospital admissions to estimate prognosis, then studies indicate that the prognosis for patients with HF-PSF is poor. In the Helsinki Ageing Study, four-year mortality in individuals free of HF was 30%. In those with HF of any type the mortality rate was 46%, in those with HF-PSF the mortality rate was 43% and in those with HF-RSF the mortality rate was 54%[40]. In the Cardiovascular Health Study (CHS), the 6.4-year mortality rate in subjects without HF was 16% compared to 45% in those with HF. Mortality rate was 87 per 1000 patient years in subjects with HF-PSF, 115 in those with HF and borderline systolic function, and 154 in subjects with HF and reduced systolic function[41].

These figures are similar to the overall five-year mortality rate of 65% in the Olmsted County incidence study[19]. In this study, the age and gender-adjusted mortality rates in those with HF were higher than those without HF, but there was no significant difference between patients with PSF and those with RSF. Patients with HF-RSF in the Framingham study with had an annual mortality rate of 18.9% compared with 4.1% in age and gender-matched controls (over 6.2yrs). In patients with HF-PSF the annual mortality was 8.7% compared to 3% in matched controls. In an adjusted analysis, patients with both types of HF had four times the risk of death compared with age and gender-matched controls. The median survival in patients with reduced systolic function was 4.3 years, and in those with HF-PSF it was 7.1 years[8]. Redfield *et al* recently demonstrated the importance of diastolic dysfunction with regard to prognosis within this population and the authors concluded that mortality increases with increasing diastolic dysfunction[36]. Hospital cohort studies show that patients with HF-PSF have a better survival at all time points from admission. However, patients with HF-PSF still have a high mortality following admission to hospital, with rates of 40-50% after four to five years of follow-up, and the annual death rate is similar to that in the Framingham study[8]. Gustafsson *et al* also demonstrated that survival decreases with worsening systolic function in a graded way[42]. The IN-CHF registry has reported 1-year mortality data for out-patients with HF. For those with LVEF <35% the 1-year mortality was 18.9%, where LVEF was greater than 45% 1-year mortality was 8.9% and for those with an LVEF between 35% and 45% 1-year mortality was 11.5 %[18].

In terms of hospital readmissions, the Olmsted County incidence study showed that for those with HF-RSF, over a five year period 10% were never hospitalised, 41% were hospitalised once, and 49% were hospitalised twice or more. These proportions for patients with PSF were 24%, 51%, and 25% respectively. Thus patients with RSF had more hospital

admissions[19]. The CHS also reported the risk of non-fatal MI and stroke[41]. In subjects without HF these were 10.9 and 12.5 per 1,000 patient-years at risk respectively. These rates increased to 23.3 and 27.5 in patients with HF-PSF, 37.7 and 50.7 in those with HF and borderline systolic function but dropped to 19.4 and 45.2 in subjects with HF-RSF. There is no obvious explanation for the latter finding. In hospital cohort studies, overall the rates of readmission for HF-PSF are very high, 15 – 25% of patients are readmitted with an exacerbation of HF within six months and one-third within a year. Approximately 45-60% are readmitted within one year for any cause[13]. It is clear that with both types of heart failure there is a poor prognosis. This is highlighted in the findings of Philbin *et al*[26], who showed that the six-month rate of death or readmission was 50% in patients with HF-PSF and 52% in patients with HF-RSF.

1.03 Pathophysiology of heart failure with preserved systolic function

It is now accepted that HF with preserved, as opposed to reduced systolic function is a separate clinical entity. What is more controversial is the nature of the underlying pathological change. For the majority of patients, this is presumed to be diastolic dysfunction[43;44].

1.03.1 Left ventricular diastolic function

Normal LV diastolic function may be clinically defined as the capacity of the left ventricle to receive a filling volume which will result in an adequate stroke volume at low pressures[45].

There are two main pathophysiological processes which produce diastolic dysfunction. These are impaired LV relaxation and increased LV stiffness[9;46]. Zile *et al* assessed the diastolic properties of the LV in 47 patients who had HF-PSF. All had impaired relaxation and

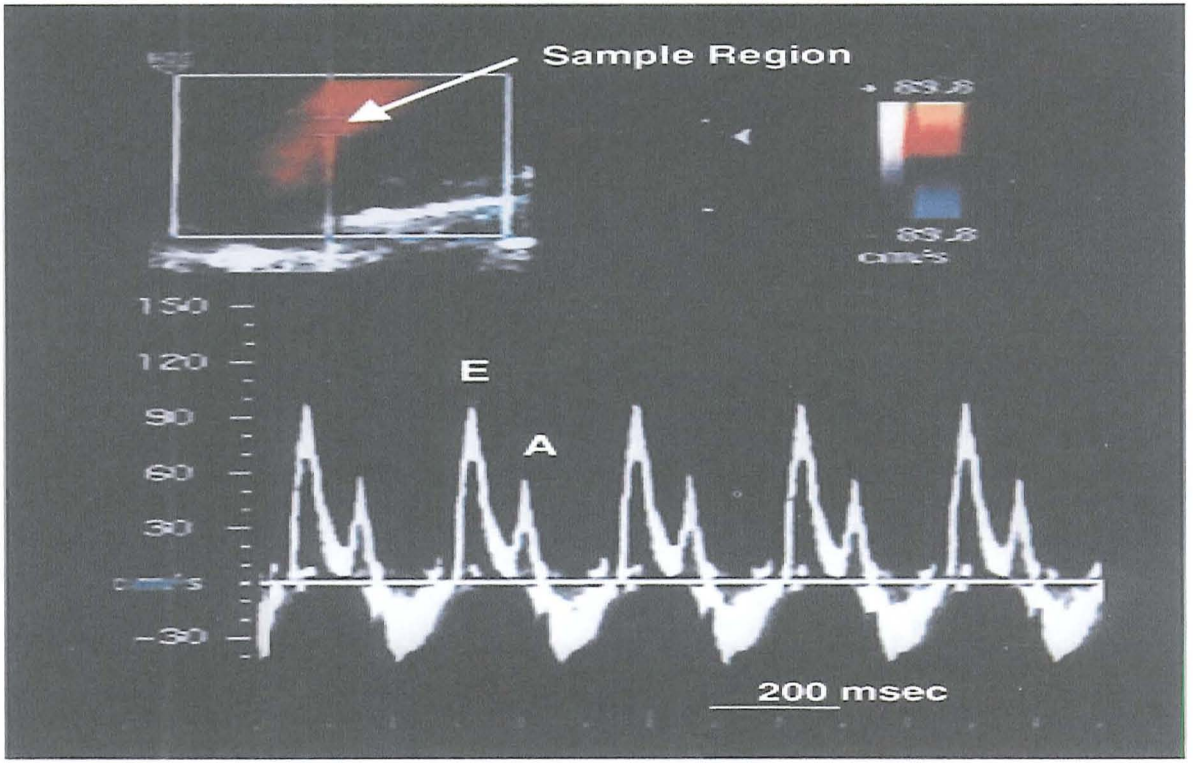
increased left ventricular chamber stiffness when compared to a control group. The authors concluded that the signs and symptoms of HF in patients with preserved systolic function are caused by abnormalities in diastolic function. It is thought that these abnormalities in diastolic function make patients susceptible to sodium retention, neurohormonal activation, increased venous tone or increased arterial stiffness, all of which can result in pulmonary oedema. Also, increased LV stiffness means that the ventricle is unable to accept venous return adequately, without high diastolic filling pressures. High filling pressures result in decreased lung compliance, which increases the work of breathing and contributes to breathlessness[43].

Patients with HF-PSF are often found to have impaired exercise tolerance. This is also thought to be due to increased LV stiffness. In addition to the effect on filling pressures described above, the stiff ventricle operates on a flat portion of the Frank-Starling curve. Consequently, these patients have little or no increase in stroke volume on exercise. Overall, during exercise, the stiff ventricle is unable to fill properly or to increase its stroke volume and therefore the cardiac output does not increase, producing symptoms on exercise[43]. There are limitations to the non-invasive assessment of the pathophysiology of HF-PSF, however, the work done to date suggests that impaired diastolic function causes the signs and symptoms of HF. This is an area where more work is required, and tools such as cardiac MRI may provide more specific information in the future.

1.03.2 Echocardiography and diastolic dysfunction

Spectral Doppler echocardiography, particularly of the mitral inflow, is widely used for the non-invasive assessment of diastolic filling of the left ventricle[47]. The normal mitral inflow is biphasic (Figure 1.1).

Figure 1.1 Mitral inflow pattern



The mitral inflow velocity trace reflects the relative driving force across the mitral valve. When pulsed wave Doppler is sampled from the level of the tips of the mitral valve leaflets, the measured peak velocity is indicative of the relative instantaneous change in pressure between the left atrium (LA) and the LV after the opening of the mitral valve.

The E velocity is the peak early filling velocity, and is influenced by the LA pressure at mitral valve opening, LA compliance, the pressure gradient between the LA and LV, and the rate of ventricular relaxation[47]. The rate of decrease of velocity following the E peak is measured as the deceleration time (DT). The initial slope is extrapolated to baseline, and the DT is the interval between the peak E velocity and the intersection of the slope with the baseline. The DT depends on the rate of increase in LV pressure in early diastole, after it has reached its nadir, and is a measure of the effective chamber compliance of the LV[47]. The A velocity measures mitral inflow during atrial contraction. As LA contraction usually occurs after relaxation is completed, the peak velocity depends on LV chamber compliance as well as the volume and contractility of the LA. Normal mitral inflow velocities vary with loading conditions, age and heart rate. In a normal middle-aged subject the E velocity is larger than the A velocity, and the DT is approximately 200 +/- 40ms.

Diastolic function has been categorised into:

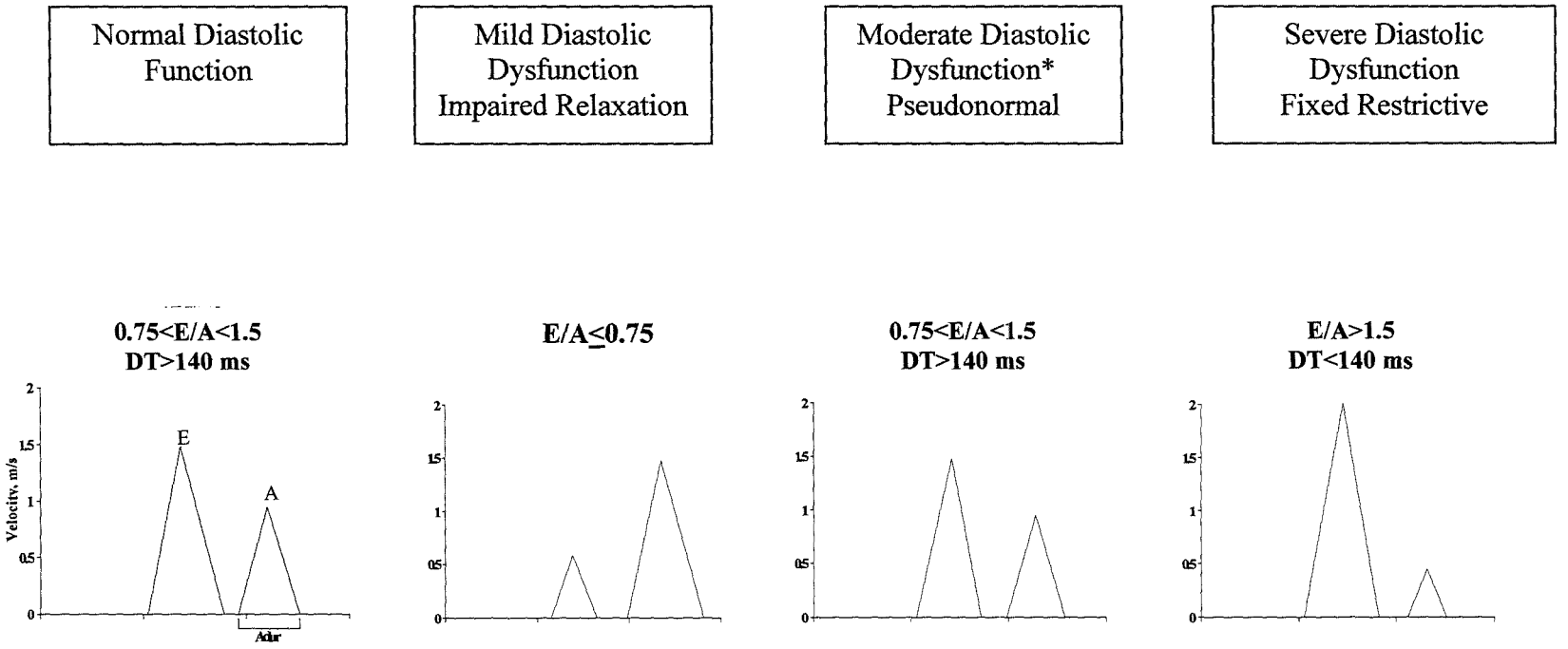
1) Normal
2) Mild dysfunction – Impaired relaxation without evidence of increased filling pressures
3) Moderate dysfunction – Impaired relaxation associated with elevated filling pressures or pseudonormal filling
4) Severe dysfunction – Reduction in compliance or restriction of the LV

Pseudonormal filling is as a normal resting mitral inflow pattern, but E/A ratio reversal on Valsalva manoeuvre.

Impaired LV relaxation produces specific changes in the mitral inflow Doppler trace. As there is slower reduction in the rate of decrease of the LV pressure, and the duration of relaxation is prolonged into mid or late diastole. This results in a lower initial driving force across the mitral valve producing a low peak E velocity. The prolonged duration of ventricular relaxation results in prolongation of the DT. There is a subsequent increase in mitral inflow during atrial contraction, because of higher atrial preload, resulting in a higher peak A velocity. To summarise impaired LV relaxation is indicated by a low peak E velocity, a high peak A velocity and a prolonged DT on spectral Doppler of mitral inflow[47].

As the diastolic dysfunction progresses, the peak A velocity increases and becomes greater than the peak E velocity, termed E/A reversal. When LV restriction is also present there is E/A reversal and a shortened deceleration time (Figure 1.2).

Figure 1.2 Mitral inflow criteria for classification of diastolic function (adapted from Redfield *et al*[36])



1.03.3 Natriuretic Peptides

In the early 1980s de Bold *et al* observed that extracts of atrial tissue infused into rats caused a massive diuresis. From this work came the isolation of atrial natriuretic peptide (ANP), the first in the family of natriuretic peptides[48]. A decade later the second member of the family was described, B-type natriuretic peptide (BNP). Since the 1980's four different natriuretic peptides have been described: ANP, BNP, C-type natriuretic peptide (CNP) and D-type natriuretic peptide (DNP). They all contain a characteristic 17 amino-acid ring structure, formed by an disulfide bridge between two cysteine residues[49]. The amino- and carboxy-terminal tail varies between the different peptides: ANP has a 28 amino acid polypeptide, BNP a 32 amino acid polypeptide, CNP a 53 amino acid polypeptide and DNP a 38 amino acid polypeptide[50]. They all exist as pro-hormones with relatively high molecular weight, which are cleaved to active moieties before release into the circulation[51].

The ANP and BNP precursor peptide genes are located in tandem on the distal short arm of chromosome 1[52]. The CNP precursor peptide gene is localized on chromosome 2[52]. The gene encoding the DNP precursor peptide has not as yet been cloned[53].

The precursor protein of ANP (pro-ANP) is a 126 amino-acid molecule. It is proteolytically cleaved to a 98 amino acid fragment and a 28-carboxy-terminal fragment, which constitutes biologically active ANP[54]. In the normal human adult heart, the atria are the main source of ANP[50].

BNP will be discussed in detail later in this chapter.

CNP is expressed primarily in the central nervous system and in vascular tissues, but unlike ANP and BNP is nearly non-existent in cardiac tissue[55]. Despite this, CNP does play an important role in cardiovascular physiology, as it is a potent vasodilator, as well as being an inhibitor of smooth muscle proliferation and endothelial migration[56].

DNP is a 38 amino acid peptide and is the most recently discovered of the natriuretic peptides. Originally isolated from the venom of the green mamba snake (*Dendroaspis Angusticeps*)[57]. Currently there are little data regarding DNP in humans. Some authors suggest that DNP is a primitive cardiac natriuretic peptide and is an evolutionary precursor of ANP and BNP[53;58].

There are three known natriuretic peptide receptors (NPR): NPR-A, NPR-B and NPR-C. These mediate the physiological effects of the natriuretic peptides. Each receptor contains a single transmembrane domain and an extracellular binding domain[59]. NPR-A and NPR-B are structurally similar with 44% homology in the ligand-binding extracellular domain[60]. ANP and BNP bind preferentially to NPR-A which then dimerizes and uses the chloride ion to hold itself in the "open" position. The receptor is linked to a guanosine 3',5'-(cyclic)phosphate (c-GMP)-dependent intracellular signalling cascade, which mediates most of its biological activities[61]. Mice lacking functional NPR-A exhibit hypertension, cardiac hypertrophy and dilatation and premature sudden death[62]. It has been demonstrated that BNP has a ten-fold lower affinity for NPR-A compared with ANP[63]. This has led to speculation that an additional BNP-specific cGMP coupled receptor may play a role in its functioning[64]. Both NPR-A and NPR-B are found in adrenal glands and kidney but NPR-A is most abundant in large blood vessels, whereas NPR-B is most abundant in the pituitary gland[51]. NPR-B has a low affinity for ANP and BNP but is activated by CNP[61;64].

In contrast to NPR-A and B, NPR-C uses a G-protein coupling system for intracellular signalling to mediate its physiological effects[61]. NPR-C is found in vascular endothelium, smooth muscle, cardiac muscle, adrenal and kidney[65]. As demonstrated in NPR-C knockout mice, its function is to clear ANP, BNP and CNP[66]. These molecules are internalised in a receptor vesicle and enzymatically degraded, following which the receptor returns to the cell surface[50]. This receptor binds all three natriuretic peptides, having the highest affinity for ANP, followed by CNP then BNP[67]. This accounts for the longer half-life of BNP compared with ANP in humans[61].

There are two mechanisms of clearance of natriuretic peptides. As described above, NPR-C - mediated endocytosis followed by lysososomal degradation. Natriuretic peptides are also degraded by neutral enodpeptidase[49]. The relative importance of each mechanism is not yet clear. Renal pathways play a lesser part in clearance of CNP[56]. Some investigators believe that lysosomal degradation is the main process, while others believe that the increase in natriuretic peptides in heart failure saturates receptors, and the enzymatic degradation process takes over[68].

Regulation of natriuretic peptide release at a cellular level is controlled predominantly by the degree of stretch of the atria and ventricles. Increased wall stretch can act directly or via local paracrine factors such as endothelin-1[69], nitric oxide[56], and angiotensin II[70] to increase natriuretic peptide levels. Other stimuli include tachycardia[71] and glucocorticoids[72], both of which contribute to induction of cardiac BNP mRNA in overt heart failure[56]. The trigger for ANP release is primarily raised atrial transmural pressure. It has been demonstrated that ANP gene induction occurs days after the increase in atrial pressure[73]. This relatively slow induction of ANP allows for its storage in granules and periodic release[74].

Experimental data suggests that ANP is released in heart failure regardless of severity and occurs even in compensated heart failure when hypertrophy is present but LV end diastolic pressure (LVEDP) is normal[75]. The trigger for BNP release is a combination of pressure and volume overload. This is illustrated by the correlation seen between LV chamber size[76], LVEDP[77], and plasma BNP concentration. BNP gene activation is seen within hours of increased chamber pressure, BNP is not stored in granules, but instead released in bursts[78]. In contrast with ANP, BNP is only induced in heart failure when the LVEDP is elevated[75].

Natriuretic peptides act on the kidney at the level of the glomerulus and collecting ducts to stimulate natriuresis and diuresis. At the glomerulus they cause afferent arteriolar dilation with efferent arteriolar vasoconstriction which consequently increases the glomerular filtration rate (GFR)[79]. In the collecting duct, their effect is to decrease sodium reabsorbtion, thereby increasing sodium excretion[80]. Both ANP and BNP inhibit the secretion of renin, angiotensin II and aldosterone[81]. Experimental studies have shown that BNP acts a cardiomyocyte-derived anti-fibrotic factor, and therefore may be a local regulator of ventricular remodelling[61]. Both ANP and BNP have inhibitory effects on the sympathetic nervous system[50].

Table 1.2 summarises the main characteristics of the natriuretic peptides discussed above.

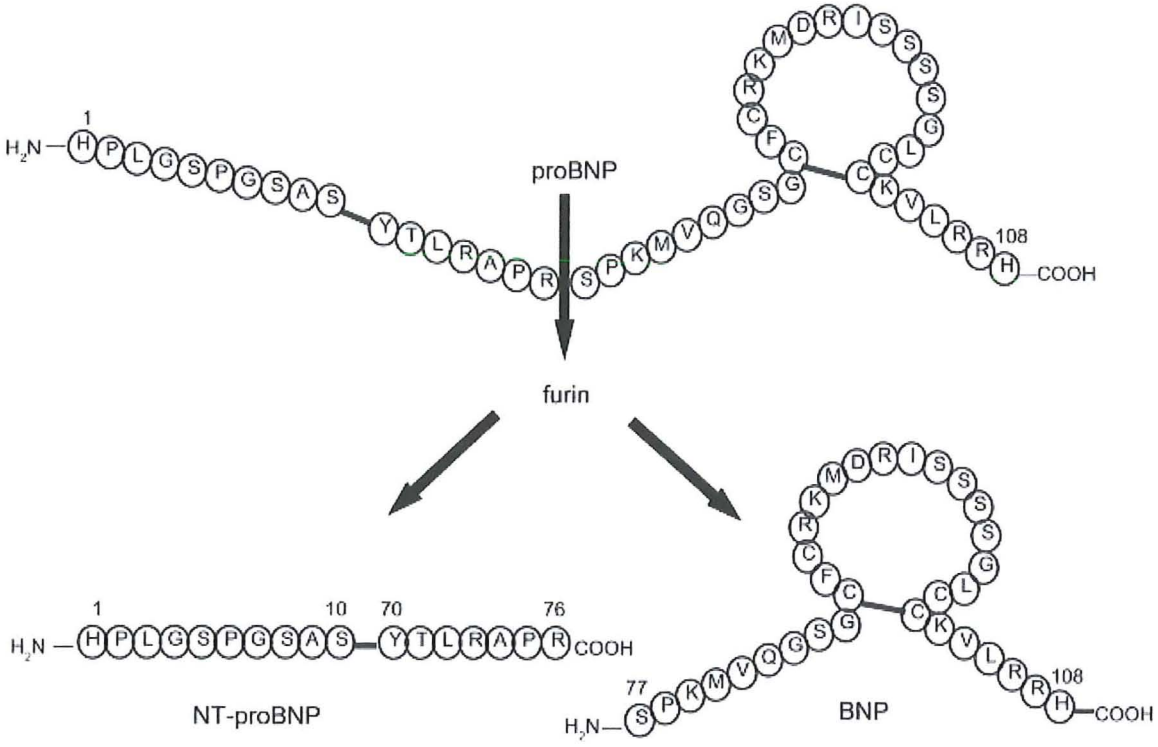
Table 1.2 Characteristics of the natriuretic peptides (Adapted from Vanderheyden *et al*[58])

	ANP	BNP		CNP	DNP
		BNP	**NT-proBNP**		
Components	Ct-ANP(28 AA)	BNP(32 AA)	Nt fragment (1-76) NT-proBNP (1-108)	CNP-22 CNP-53	
Hormonally active	Nt-ANPt (98 AA) Endocrine / paracrine	Endocrine / paracrine	NT-proBNP (1-108)	CNP-53 paracrine	
Genesis	Cleavage from pro-ANP	Cleavage form pro-BNP	Release from ventricular myocytes	Cleavage from pro-CNP	
Half-life		20 min	120 min		
Clearance mechanism	Neutral endopeptidase Clearance receptor NPR-C	Neutral endopeptidase Clearance receptor NPR-C	Renal clearance	Neutral endopeptidase Clearance receptor NPR-C	unk
Approved cutoff for CHF diagnosis	unk	100 pg/ml	Age <75 years: 125 pg/ml	-	-
Tissue distribution	Cardiac atria and ventricles	Brain Cardiac ventricles Myocardial fibrosis	Brain Cardiac ventricles Myocardial fibrosis	Brain, ovary, uterus Testis epididymis	Snake venom

Ct = carboxy-terminal Nt = amino-terminal AA = aminoacid Unk = unknown

BNP, and more recently NT-proBNP have been recognised to be of particular importance in heart failure. As described above, the predominant source of BNP in humans is the ventricular myocardium[78;82]. BNP is released in bursts as a 108 amino acid prohormone which is then cleaved to form biologically active BNP, a 32 amino acid molecule and the 76 amino acid molecule, NT-proBNP. Figure 1.3 summaries this process.

Figure 1.3 Structure and formation of BNP and NT-proBNP (adapted from Hall et al[83])



Circulating BNP has the characteristic natriuretic peptide ring structure with an amino-terminal tail of nine amino acids, and a carboxy- tail of six amino acids[51].

In normal subjects, the plasma concentrations of BNP and NT-BNP are similar. The half-life of BNP and NT-proBNP in blood are approximately 22 minutes and 120 minutes respectively. This suggests that they could be used to reflect pulmonary capillary wedge pressure changes every two and 12 hours respectively[84]. In patients with LV systolic dysfunction both BNP and NT-proBNP are elevated, however, increases in NT-proBNP are two-to ten-fold greater than increases in BNP. The explanation for this is unknown. Both BNP and NT-proBNP can be measured by radioimmunoassay (RI). The combination of its longer half-life and greater increases in heart failure, may make NT-proBNP a better marker of heart failure[85].

The accuracy of the natriuretic peptides as markers of cardiac function, is influenced by renal function, gender and age. There is a correlation between BNP and estimated GFR, such that BNP rises as GFR falls ($r = -0.20$). This implies that a higher value for the upper limit of normal is required when using BNP in the diagnosis of HF if GFR is reduced. However, BNP does maintain a high level of diagnostic utility despite this[86]. NT-proBNP has a stronger correlation with with GFR than BNP ($r = -0.60$) and is influenced by the normal age-related decline in renal function. For example, an eGFR less than 60ml/min/1.73m^2, which is common in elderly patients, may make the detection of HF using NT-proBNP less accurate[87]. In this context, some authors have suggested that NT-proBNP specifically reflects cardio-renal rather than cardiac function[85].

Redfield *et al* demonstrated than in normal subjects with no known cardiovascular disease or detectable structural heart disease, plasma BNP concentrations were higher in females and correlated positively with increasing age. The authors suggest that the increased BNP found in females may be due to oestrogen status, as BNP levels were higher in women on hormone replacement therapy preparations. Interestingly, it has also been speculated that diastolic dysfunction and ventricular stiffening is more common in women[88-90].

The mechanism of the increase in BNP with age is not known, however, the LV does stiffen with age, which would be expected to stimulate BNP production[88]. Regardless of mechanism, Redfield *et al* demonstrated than the effect of age and gender on BNP was independent of atrial volume, LV dimension and LV mass. They concluded that both gender and age should be taken into account when interpreting BNP concentrations on a diagnostic basis[90].

The New York Heart Association (NYHA) functional classification system for heart failure correlates well with symptoms and mortality. BNP levels also correlate with NYHA class.
For some time it has been accepted that BNP levels are elevated in patients with heart failure due to impaired LV systolic function[91-93]. BNP is also raised in those with asymptomatic LV systolic dysfunction[92-94]. More recently NT-proBNP has been shown to be elevated in patients with heart failure, post-MI LV systolic dysfunction and asymptomatic LV dysfunction[95-97].

Breathlessness is a common problem in patients presenting to casualty. Differentiating between respiratory and cardiovascular causes of breathlessness is often problematic. Davis *et al* reported the usefulness of BNP in distinguishing between HF and chronic obstructive pulmonary disease in this setting. BNP concentrations of greater than 22pg/ml predicted the

presence of HF with a sensitivity of 93% and a specificity of 90%[98]. Subsequent studies have confirmed the ability of BNP to accurately predict the presence of HF in a breathless patient (area under the ROC being 0.97)[99]. The role of BNP in identifying dyspnoea due to HF was specifically addressed in the Breathing Not Properly Multinational Study. This was a multicentre prospective study of 1586 patients presenting with acute dyspnoea. BNP was measured in the Accident and Emergency Department. BNP levels were significantly higher in those with HF (either HF-RSF or HF-PSF)[100].

The most important feature of BNP as a diagnostic tool in HF, is its high negative predictive value (NPV). Cowie *et al* demonstrated a negative predictive value of 97%, indicating a role for BNP as a "rule out" test[101].

It has also been suggested that BNP could be used to guide treatment in HF. Patients who are admitted with fluid overload, are found to have a high BNP (a so-called "wet BNP"), and this level falls as they are rendered euvolaemic (or "dry BNP"). This could be used as a guide for timing discharge from hospital. Patients in whom the BNP remains high despite euvolaemia often have a poor prognosis[88]. Both BNP and NT-proBNP concentrations have been positively correlated with worse prognosis. Omland *et al* were the first to report that an elevated plasma BNP concentration taken on day three post-MI, was an independent predictor of cardiovascular death[102].

Subsequent studies have corroborated this finding. Richards *et al* demonstrated that BNP and NT-proBNP are the most sensitive predictors of poor outcome and have the highest NPV for mortality post MI when compared with other natriuretic peptides[95]. Others have confirmed the association of elevated NT-proBNP and a poor outcome post-MI, both in terms of death

and subsequent LV systolic dysfunction[96]. Tsutamoto *et al* have shown that BNP is superior to ANP in determining prognosis and that BNP is an independent predictor of mortality[103]. Richards *et al* showed that NT-proBNP is similarly effective at predicting adverse outcome in patients with ischaemic LV systolic dysfunction, without prior MI[104]. Even in unselected population studies, it has been shown that an elevated BNP concentration is an independent predictor of four year all-cause mortality. It has also been shown to be a useful prognostic marker in the elderly[105]. Recently, Gardner *et al* demonstrated that NT-proBNP concentration is an independent predictor of both mortality alone or a combined endpoint of death or urgent transplantation in patients with advanced heart failure referred for consideration of cardiac transplantation[106]. Berger *et al* have also demonstrated that elevated BNP concentrations are a predictor of sudden cardiac death in heart failure[107].

Most of the work on natriuretic peptides has been done in patients with heart failure and reduced LV systolic function. Less is known about natriuretic peptide levels in patients with heart failure and preserved systolic function. The introduction to Chapter five outlines the evidence to date.

1.03.4 Aminoterminal propeptide of type III procollagen (PIIINP) as a marker of myocardial collagen turnover in heart failure

The myocardial extracellular matix (ECM) is the connective tissue skeleton of the heart and plays a key role in cardiac function. It is a fibrillar network which determines the structure, tensile strength and stiffness of the tissue. It is therefore a major determinant of diastolic function. In myocardium, the main types of collagen are I and III. The extracellular matrix is known to be dynamic. The controlling mechanisms are complex, but are principally mediated by matrix metalloproteinaeses (MMPs), which are involved in the degradation of the ECM

and are thought to be a key component of myocardial matrix remodelling[108]. The MMPs are a family of functionally related zinc-containing endoproteinases. Myocardial MMPs are produced by fibroblast-like cells and cardiomyocytes[109]. There are four main groups: collagenases, gelatinases, stromelysins, and membrane-type. The first group includes MMP-1 (interstitial collagenase), MMP-8 (neutrophil collagenase) and MMP-13 (collagenase-3), all of which cleave fibrillar collagens (type I, II and III). These collagen form fibrils which are tightly opposed and highly cross-linked, and are thus extremely resistant to cleavage by most proteinases. Recent evidence has suggested that the substrate-based classification of MMPs is not useful, as there is cross-linkage in action between the four groups. For example, gelantinases are thought to play an important role in cleavage of interstitial collagens as well as gelatins, and therefore play a more important role in ECM remodelling than was first appreciated[110-112]. The regulation of ECM degradation by MMPs is achieved through regulation of MMP expression, and by specific endogenous MMP inhibitors called tissue inhibitors of metalloproteinases (TIMPs). MMP inhibition by TIMPs occurs following binding at the zinc binding site of the active MMP. There are other naturally occurring inhibitors of MMPs such as alpha-macroglobulin which is a large (750kDa) protein produced by the liver[108].

Individual myocyte function is preserved during the ageing process, however, myocytes are replaced by ECM, in particular by collagen deposition, and this contributes to the ventricular dilatation and reduction in LV function seen with ageing[113;114].

Cardiac fibrosis is defined as an increase in the concentration of matrix collagens in the interstitium, but also involves a change in the type of collagen found[115;116], its organisation[117;118], cross-linkage[119;120], and denaturation[117;118]. Cardiac fibrosis in

hypertrophied hearts develops in two distinct phases[121]. Firstly, there is a reactive accumulation of connective tissue in the interstial space due to *de novo* synthesis of collagen. This fibrogenesis occurs without loss of parenchyma. Secondly, there is a adaptive process where parenchymal cells are lost and replaced by fibrotic tissue. The accumulation of collagen fibrils in the interstitial space has been attributed, at least in part, to growth factors produced in response to mechanical load. Stimulators of local collagen biosynthesis include agents such as platelet-derived growth factor (PDGF), transforming growth factor-B (TGF-B), angiotensin II, aldosterone and endothelin[122;123].

Type III collagen is a major constituent of developing granulation tissue[124-126]. The aminoterminal propeptide of type III procollagen (PIIINP) is an extension peptide of the type III procollagen, which is cleaved off during the conversion from type III procollagen to type III collagen[127]. As a consequence, PIIINP reflects enhanced collagen turnover and therefore, myocardial fibrosis[128;129]. There is accumulating evidence that serum PIIINP and MMP concentrations can be used as markers of myocardial remodelling. This comes mainly from studies on patients following MI or with dilated cardiomyopathy (DCM). Elevated serum PIIINP is associated with LV dilatation and depressed ejection fraction, as well as with a restrictive LV filling pattern. Elevated PIIINP concentrations in these clinical settings are also associated with a worse prognosis[129-133].

Only a few studies have examined the relationship of PIIINP to diastolic function using echocardiography. Poulsen *et al* studied the relationship between PIIINP and LV function in patients presenting with a first acute MI. The authors concluded that the PIIINP concentrations measured in the sub-acute phase of MI related, in the long-term, to detrimental changes in LV systolic function. Those with higher PIIINP concentrations were more likely

to have a restrictive LV filling pattern, which is associated with increased LVEDP. This could either be due to increased myocardial stiffness or increased LV volume. In this particular group, the restrictive LV filling pattern is more likely to be due to increased LV volumes[129]. This relationship was also observed recently by Rossi *et al*[131], who examined out-patients with dilated cardiomyopathy. To date, serum PIIINP concentrations have not been described in patients with HF-PSF.

1.03.5 Renin and aldosterone

The renin-angiotensin-aldosterone system (RAAS) is one of the main physiological systems involved in mediating the pathology of heart failure. HF causes over-activation of the RAAS and aldosterone excess. Aldosterone increases renal reabsorption of sodium ions in exchange for potassium and hydrogen ions. This in turn leads to sodium retention and expansion of the extracellular volume, with eventual impairment of haemodynamic responses and a fall in cardiac output. A cycle is then established, whereby the resultant reduction in renal perfusion causes further activation of the RAAS, leading to further compromise of cardiac function, along with secondary hyperaldosteronism and hypokalaemia.

The first work to explore the role of aldosterone as a cause of cardiac fibrosis was by Karl Weber in 1988. This has lead to the key concept, that aldosterone can cause cardiac fibrosis, independent of its effect on blood pressure or on the development of ventricular hypertrophy.

Plasma aldosterone and renin concentrations have not been described in patients with HF-PSF.

1.04 Aims of study

It is clear from the above discussion that HF-PSF is an important cause of morbidity and mortality, but that this complex clinical entity is, as yet, poorly understood. Establishing exactly what constitutes HF-PSF requires comprehensive study of such patients and their outcomes. At the time of starting this study, the majority of data regarding clinical characteristics and long- term adjusted mortality rates were derived from out-patient populations, and there was limited prospective data from hospitalised cohorts. Another major limitation of the published work at that time, was that there was little focus on elucidating the relevant pathophysiological processes in HF-PSF. No study had prospectively investigated both indices of diastolic function and natriuretic peptides in the same cohort of patients with HF-PSF. No studies had documented PIIINP or renin and aldosterone levels in such patients.

This study aims to define a cohort of patients hospitalised for heart failure, to characterise them using clinical, echocardiographic and biochemical variables and to compare the characteristics of patients with reduced and preserved systolic function. This study also aims to determine mortality rates and independent predictors of mortality in both groups of heart failure patients.

CHAPTER TWO

METHODS

2.01 Patient population

All patients were recruited from the Western Infirmary which is a community hospital for north-west Glasgow, with a catchment area of approximately 250,000. Patients are admitted to the hospital either by self referral to the Accident and Emergency Department or directly from their General Practitioner for review by the medical receiving team. All patients admitted to the Medical Admissions Unit are assessed by a senior member of the medical receiving team. A provisional diagnosis and treatment plan is initiated by the senior medical physician, and then reviewed by the medical consultant at 12 hourly intervals. The working diagnosis and continuing management plan are implemented following this review.

All patients admitted to the Medical Admissions Unit were screened for clinical evidence of heart failure such as shortness of breath, basal lung crepitations, peripheral oedema or treatment with intravenous diuretics on admission. Patients fulfilling any of these clinical features were approached to enter the study. Patients who agreed to enter the study signed a written consent form and were given written confirmation pertaining to the study as agreed with the North Glasgow Ethics Committee (see appendix 1). Patients who were clinically too ill to formally consent or those with documented dementia were not approached to enter the study. If, at this initial meeting, it was felt that the patient had an element of cognitive impairment then the patient was not asked to enter the study.

Patients who met the inclusion criteria and who consented to enter the study were then assessed for clinical evidence of heart failure using the three heart failure scoring systems: the Boston score[134], the NHANES score[135] and the Framingham score[136] (see appendix 2). For the purposes of this study a patient was deemed to have heart failure if they scored positively in any one of these scoring systems.

All three of the heart failure scoring systems use a combination of physical and radiographic assessment, along with objective measures of ventricular performance and an estimate of exercise capacity. Each of these variables has limitations when used independently[137]. Consequently, combinations of these have been developed as scoring systems and have been used in epidemiological studies and clinical trials. Both the Framingham and NHANES scores were developed for use in large epidemiological studies and the Boston score was validated to assess the degree of HF in cardiovascular medication trials.

It has previously been established that the Boston heart failure score has a sensitivity of 0.50[138] and a specificity of 0.78 to detect a left ventricular ejection fraction $\leq$ 40% and a sensitivity of 0.90 for identifying a pulmonary wedge pressure of 12mmHg or more in patients undergoing non-emergency right heart catheterisation[139]. The Boston score comprises three sections: clinical symptoms, clinical signs and chest radiograph (CXR) appearances. A maximum score of 4 can be obtained from each section to give a total score out of 12. Scores of less than 5 suggest that HF is not present, a score of between 5 and 8 indicate possible HF and a score of 8 or more suggests definite heart failure.

The Framingham HF score has both a sensitivity and specificity of 0.63 for the detection of a left ventricular ejection fraction $\leq$ 40%[138]. This score is divided into major and minor criteria. HF is defined as present when either two major criteria or one major and two minor criteria are met.

The NHANES score is based on the same principles as the other two scores and includes clinical, symptomatic and CXR criteria. A score of greater than 3 is suggestive of heart failure. In a study comparing six heart failure scores including NHANES the authors found

that all the scores were similar in terms of their capability to detect HF. All the scores had a high sensitivity for the detection of definite heart failure and a lower sensitivity for detection of possible heart failure[140].

It is important to note that these HF scoring systems have all been validated in assessing HF with reduced ejection fraction. Their sensitivity and specificity to detect HF with preserved EF is unknown.

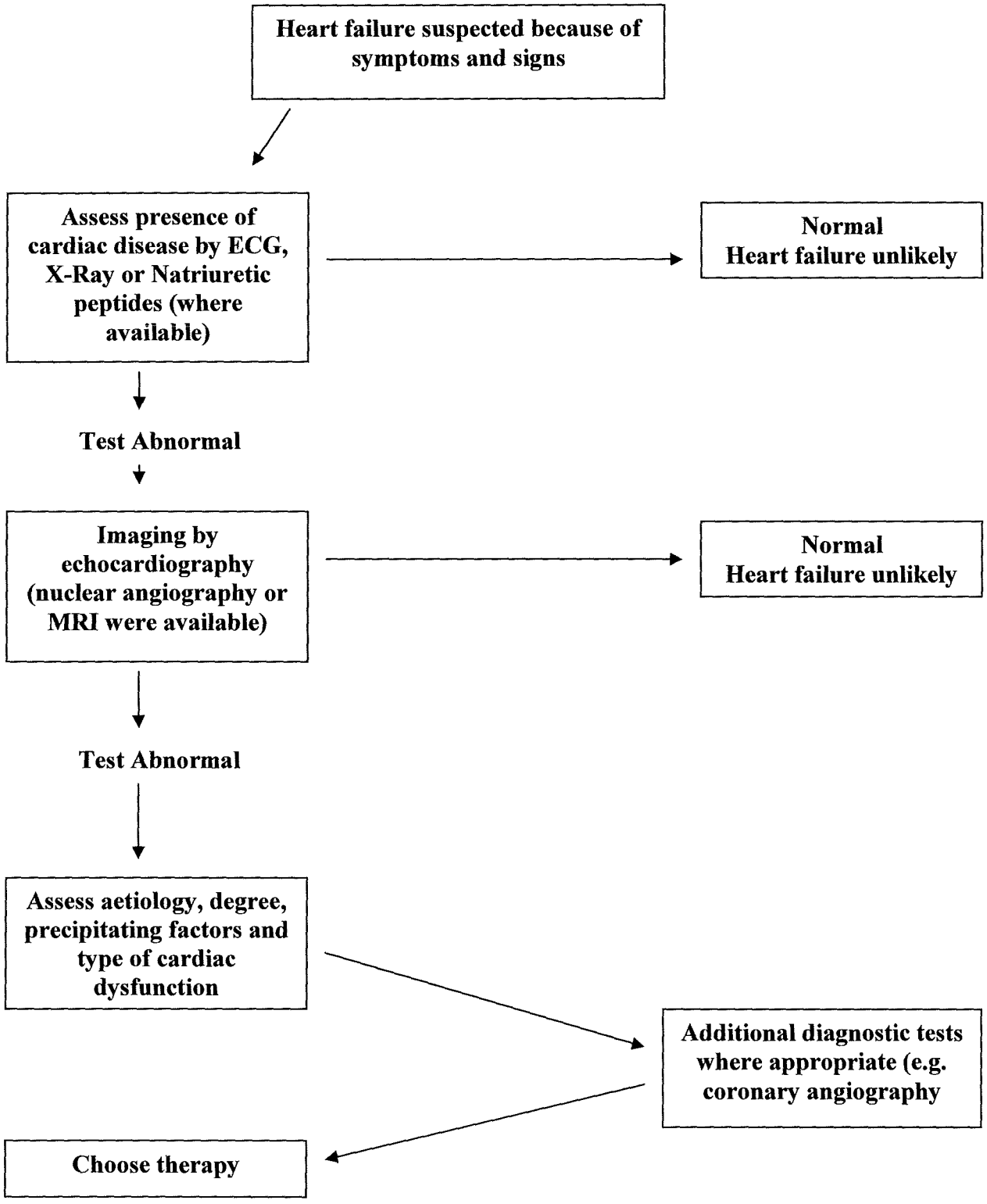
For this study, the clinical assessment comprised: a detailed cardiovascular and medical history with systematic documentation of the presence or absence of symptoms of HF, a clinical examination for signs of HF, a record of the patients cardiorespiratory parameters as well as electrocardiogram (ECG) and CXR findings from admission (see Appendix 3).

Specific information was recorded from the ECG of each patient including heart rate and rhythm, and the presence or absence of: atrioventricular block; bundle branch block; mean QRS axis deviation; ventricular hypertrophy; ST segment deviation; T-wave inversion; pathological Q-waves and QT interval prolongation (see Appendix 4). All patients had a CXR on admission.

It is well established that both ECG and CXR play an important role in the diagnosis of heart failure. This is outlined in the European Society of Cardiology Task Force for the diagnosis and treatment of chronic heart failure diagnostic algorithm (Figure 2.1)[141]. These HF guidelines were the most up to date at the time of starting the study in 2002. Since then they have been updated[142].

ECG abnormalities are common in patients with heart failure. The negative predictive value of a normal ECG to exclude left ventricular systolic dysfunction (LVSD) is greater than 90%[143-146]. Likewise, the presence of either anterior Q-waves or left bundle branch block (LBBB) in patients with ischaemic heart disease are good predictors of decreased LV ejection fraction[147]. The presence of ECG signs of atrial stretch or left ventricular hypertrophy can be associated with both systolic and diastolic dysfunction but have a relatively low predictive value. For the purposes of this study, left ventricular hypertrophy by ECG was based on either the Sokolow and Lyon criteria (S V_1 + R V_5 or V_6 > 35 mm) or the Cornell criteria (S V_3 + R avL > 28mm [men] and S V_3 + R avL > 20 mm [females]). The ECG is also particularly important for the detection of arrhythmias which may contribute to or exacerbate heart failure. The diagnostic power of ECG abnormalities is markedly increased when used in combination with clinical signs and symptoms of heart failure[141].

Figure 2.1 Algorithm for the diagnosis of heart failure[159]



Those patients in whom the initial clinical assessment revealed evidence of heart failure then underwent objective assessment of heart failure severity. This was achieved using the New York Heart Association (NYHA) and Killip classification system for HF. Patients were asked at the time of admission about their symptoms in the weeks prior to admission. These symptoms were given an NYHA class (Table 2.1). The severity of heart failure at presentation based on clinical examination findings was given a Killip score (Table 2.2)[142].

Table 2.1 NYHA classification of heart failure

NYHA Class	Definition
I	No limitation. Ordinary physical activity does not cause undue fatigue, dyspnoea or palpitations
II	Slight limitation of physical activity. Comfortable at rest but ordinary activity results in fatigue, dyspnoea or palpitations
III	Marked limitation of physical activity. Comfortable at rest but less than ordinary activity results in symptoms
IV	Unable to carry out any physical activity without discomfort. Symptoms of heart failure are present at rest and made worse by any type of activity

Table 2.2 Killip classification of heart failure

Killip classification	Description
I	No heart failure
II a	Heart failure. Basal lung crepitations
II b	Heart failure. Basal to mid zone lung crepitatons
III	Frank Heart failure. Lung crepitations throughout lung fields
IV	Cardiogenic shock

2.02 Blood sampling and biochemical analyses

The European Society of Cardiology Task Force also recommends various laboratory investigations as part of the evaluation of heart failure: serum haemoglobin (Hb), white cell count (WCC), platelets, electrolytes, creatinine, glucose, hepatic enzymes and urinalysis should be carried out. They also recommend that additional tests are considered, including C-reactive protein (CRP), thyroid function (TFT), serum uric acid, and cardiac enzymes or troponin to exclude myocardial infarction[141].

Anaemia may exacerbate existing heart failure or may develop as a result of heart failure. Regardless of aetiology the presence of anaemia in heart failure is associated with a worse prognosis[148-150]. For the purposes of this study the World Health organisation (WHO) criteria for anaemia were used. These define anaemia as Hb < 12g/dL in both males and females[151]. A raised haematocrit suggests the possibility of other pathologies for breathlessness such as respiratory disease.

In the context of heart failure, an elevated serum creatinine is usually caused by either primary renal disease, as a result of reduced cardiac output or by drug treatment. The relationship between heart failure and renal dysfunction is complex, primary renal failure often results in fluid overload, producing clinical signs very similar to those found in heart failure. Also, heart failure and renal dysfunction often coincide because of common underlying diseases such as diabetes and hypertension, or because increasing age is associated with both heart failure and a reduction in GFR. Heart failure associated with a low cardiac output can cause renal dysfunction by producing chronic renal hypoperfusion. In addition, many of the agents available for the treatment of heart failure can have deleterious effects on renal function. ACE-inhibitors, angiotensin receptor blockers, aldosterone antagonists and

diuretics all have the potential to impair renal function, particularly when used in combination, as is often necessary for optimal heart failure treatment. As an absolute serum creatinine is not a comparative marker of renal function between individuals, in this study renal function was assessed using estimated glomerular filtration rate (eGFR). This was calculated using the Modified Diet in Renal Disease (MDRD) formula[152;153], a validated measure of renal function. The value for eGFR is calculated as follows:

eGFR (mL/min/1.73m^2) = 186 x (plasma creatinine) $^{-1.154}$ x (age)$^{-0.203}$ x 0.742 if female.

Renal function as measured by eGFR was then categorised using the National Kidney Foundation classification[153]. Renal function was classed as normal if the eGFR was $\geq$ 90 mL/min/1.73m^2. Impairment of renal function was defined as mild (eGFR 60 - < 90 mL/min/1.73m^2), moderate (eGFR $\geq$ 30 $\leq$ 60 mL/min/1.73m^2) or severe (eGFR < 30mL/min/1.73m^2)[154].

Liver function may become deranged in HF as a consequence of hypoperfusion. Urine analysis can be useful to detect proteinuria and glycosuria indicating the possibility of underlying renal dysfunction or diabetes which may complicate heart failure. Thyrotoxicosis causing rapid atrial fibrillation can present as heart failure, especially in the elderly. Hypothyroidism can also present as heart failure. Hyponatraemia and renal dysfunction in the context of heart failure indicate a poor prognosis[141].

In this study all patients had blood samples taken at the time of admission for routine haematological and biochemical analyses including full blood count (FBC), coagulation screen (COAG), urea and electrolytes (U&E), glucose, thyroid function (TFT), liver function (LFT) and Troponin I. The routine blood samples were taken and analysed in the hospital biochemistry and haematology laboratories on the day of venesection. Troponin I was

measured using an ADVIA Centaur analyser (Bayer Diagnostics), which employs a chemiluminescent assay. A positive troponin was taken to be one greater than or equal to 0.2μg/L.

In addition, four further study-specific blood samples were taken within 24 hours of admission. These were taken to provide serum to measure BNP, NT-proBNP, PIIINP, aldosterone and renin. All serum samples were taken from the anticubital fossa with the patient in the supine position for a minimum of 10 minutes prior to venesection. While each patient was being entered into the study the blood samples were stored in the ward fridge. All study-specific blood samples were then taken directly to the research laboratory in the Western Infirmary and spun directly at 4°C in a centrifuge for 15 minutes at 3000 rpm. The supernatant was removed and put into separate freezer containers labelled with the patient subject number and stored in the freezer at -20°C until the assays were analyzed in batches of approximately 100 samples.

Plasma BNP was measured using the Shionoria immunoradiometric kit (Schering CIS, West Sussex, England). It has a within-assay and between-assay confidence variable (CV) of 3.7% and 7.5% respectively. The normal range for BNP quoted from the radioimmunoassay kit in subjects aged 55-74 years is 3.2 – 91pg/ml. Work carried out on a local healthy population identified the 95th percentile at 61.3pg/ml for those aged 55-69 years and 67.6pg/ml for those aged 70 years and over. For the purposes of this study, an elevated BNP value was taken to be one greater than the 95th percentile for the relevant age group[155].

The Roche Elecsys proBNP (Roche Diagnositics, East Sussex, England) Immunoassay was used to analyse NT-BNP (proBNP). Roche claim equivalence with the Biosite Triage BNP

test. The Elecsys method used was an electrochemiluminescent immunoassay on an Elecsys 2010 autoanalyser. This has a within-assay and between-assay CV of 2.7 and 3.2% respectively. The measuring range of the assay is 5 – 35,000 pg/ml. The analytical sensitivity of the assay is 5pg/ml. The diagnostic information quotes the cut-off for patients younger than 75 years to be 125 pg/ml and 450pg/ml for those 75 years and older. From work conducted on a healthy population, the following 95th percentile figures were established as normal ranges dichotomised for age and sex (Table 2.3)[156]. An elevated NT-proBNP was taken to be a value greater than the 95th percentile for each age and sex category.

Table 2.3 95th percentile according to age and sex of NT-proBNP for a healthy population

	NT-proBNP concentration pg/ml			
Age (years)	≤ 64	65-69	70-74	≥ 75
Female	213.4	314.2	338.5	355.3
Male	122.6	112.6	236	295.7

A commercially available kit, UniQ PIIINP radioimmunoassay (Quidel (UK) Ltd, licensed from Orion Diagnostic) was used for PIIINP analysis. This has a within- and between-assay precision of 7% and 6.5% respectively. Table 2.4 details the reference intervals supplied by the manufacturer.

Table 2.4 Serum PIIINP reference intervals

	Adults
Number of subjects	232
Mean	3.7 ug/L
Reference Interval	2.3 – 6.4 ug/L
0.90 Confidence interval for lower reference limit	1.9 – 2.6 ug/L
0.90 Confidence interval for upper reference limit	5.5 – 6.7 ug/L

Normal ranges from the literature using the same immunoradiometric assay at the time of setting up the study, estimate the upper limit of normal to be 4.5μg/L. For the purposes of this study an elevated PIIINP was taken to be a value greater than 4.5μg/L[129;131;132;157].

Aldosterone was measured using a commercially available Coat-A-Count assay (Euro/DPC, Ltd, Gwynedd, Wales)[158]. This is a solid-phase radioimmunoassay designed for the quantitative measurement of aldosterone levels in unextracted serum. A minimum of 200uL of sample is required. The assay is based upon aldosterone-specific antibody immobilised to the wall of a polypropylene tube. ^{125}I-labelled aldosterone competes for antibody sites with aldosterone in the patients sample for a fixed time. The tube is decanted to separate bound from free aldosterone, and the radiolabelled aldosterone is then counted in a gamma counter. The amount of aldosterone present is then determined from a calibration curve. The within-assay and between-assay CV are up to 5.4 and 15.7% respectively. An elevated aldosterone concentration was again defined as greater than the 95th percentile of a local healthy population. Consequently, for purposes of this study an elevated aldosterone concentration was taken to be one greater than 20ng/dL.

Plasma renin concentrations were measured using an in-house assay with a CV of < 3.5%. The expected normal range is 5-50uU/ml[159]. For the purposes of this study an elevated plasma renin concentration was taken to be a value greater than 50uU/ml.

The radioimmunoassays above were completed by Dr Ian Morton who was blinded to clinical details, including LV systolic function. The results were recorded on a Microsoft Excel spreadsheet separate from any other clinical details or patient identifiers.

2.03 Echocardiography

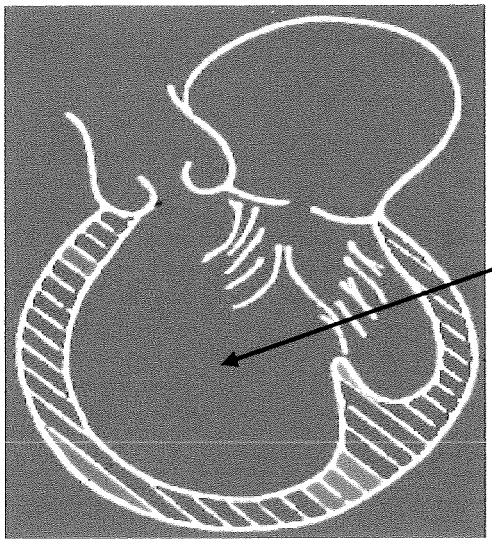
The use of echocardiography as an objective measure of cardiac dysfunction is necessary for the diagnosis of heart failure[141]. All patients had a departmental echocardiogram usually within 48 hours of admission. Often this was an investigation which was clinically indicated as part of their admission to hospital and was therefore outwith the study protocol. In these instances a copy of the echocardiogram report was obtained. Otherwise an echocardiogram was requested as part of the study protocol. These echocardiograms were conducted by a single operator, who is a British Society of Echocardiography trained senior cardiac technician within the cardiology department. The echo machine used was an Acuson Sequoia C256, which is the machine used for all such studies within the Western Infirmary. For the examination patients were positioned in the left lateral decubitus position.

The primary function of this echo was to make an assessment of left ventricular systolic function (LVSF) and to establish any structural abnormalities such as valvular heart disease (VHD) or wall motion abnormalities. A qualititative assessment of overall LVSF (preserved or reduced function) was made. Such qualitative assessment has previously been shown to correlate closely with formal echocardiographic and radionuclide measurement of left

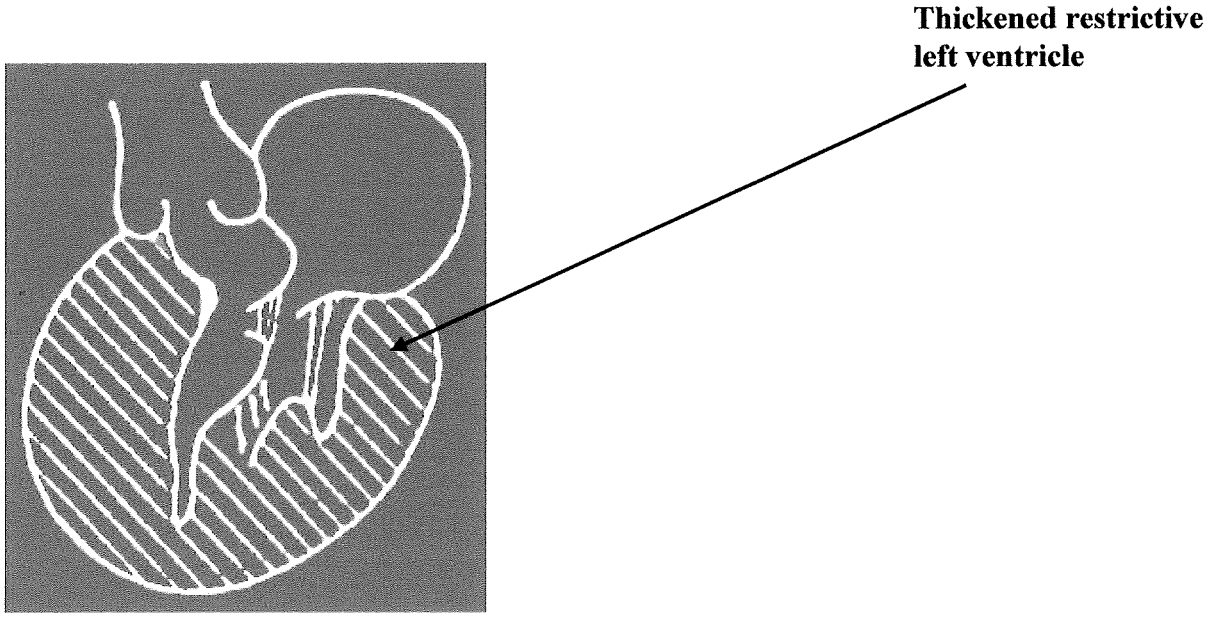
ventricular ejection fraction[160-162]. It is however, known that using this method standardisation among different observers is difficult to obtain[163]. Therefore, in this study, a single experienced operator and a single reporter conducted all echocardiographic examinations. Those with reduced LVSF were further classified into borderline, mild, mild-moderate, moderate, moderate-severe and severe left ventricular dysfunction. Only patients with normal left ventricular systolic function were classed as having preserved LVSF. Figure 2.2 is an illustration of the echocardiographic appearances of the two types of HF.

Figure 2.2 Diagramatic echo image of:

A) LV systolic dysfunction



B) Preserved systolic function with left ventricular hypertrophy



In addition to assessment of LVSF further recordings were taken where images allowed. In the parasternal long axis view (in cm): left atrial diameter, right ventricular diameter, LV internal diameter in systole (LVIDS) and diastole (LVIDD), inter-ventricular septum diameter in systole (IVSDS) and diastole (IVSDD), LV posterior wall in systole (LVPWS) and diastole (LVPWD). In the apical four-chamber view: mitral inflow maximum velocity (m/s), mitral valve pressure-half time (m/s), aortic valve outflow maximum velocity (m/s), aortic valve gradient (mmHg), and estimated peak pulmonary artery pressure (mmHg).

For this study, significant valvular incompetence was defined as mitral or aortic regurgitation classified as more than mild. Aortic stenosis was defined as significant when the aortic gradient was greater than 50mmHg. Significant mitral stenosis was defined as a mitral valve pressure-half time greater than 100m/s.

Using the heart failure classification scores the patients were divided into two groups: those in whom heart failure was present (HF-positive) and those in whom heart failure was not present (HF-negative). The HF-positive group were further subdivided using a combination of ECG and echocardiography:

1. Reduced systolic function (+/- significant valve disease) – HF-RSF
2. Preserved systolic function (HF-PSF)
    - HF-PSF + significant valvular heart disease (VHD) + atrial fibrillation (AF)
    - HF-PSF + significant valve disease (no AF)
    - HF-PSF + AF (no valve disease)
    - 'Isolated' HF-PSF (no valve disease / no AF)

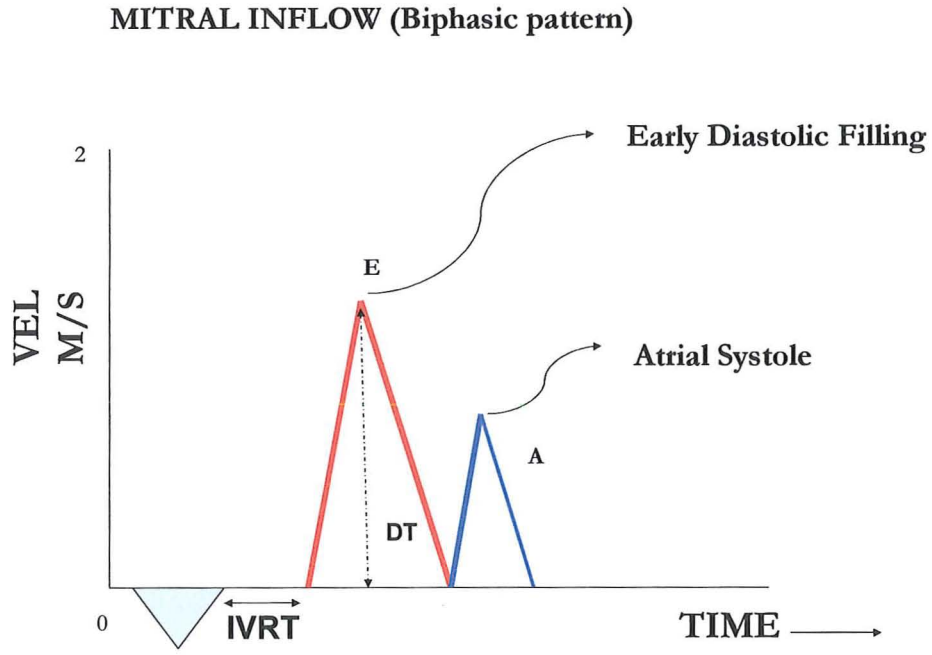
Patients in the HF-RSF and HF-PSF group with significant valve disease or AF had no further investigations requested as part of the study unless they were clinically indicated. All of those patients were given cardiology clinic appointments if clinically indicated and not already been arranged as part of their discharge plan.

2.04 Echocardiography and Doppler indices of diastolic dsysfunction

Patients with isolated HF-PSF (HF-IPSF) returned for follow-up and Doppler echocardiography within 1 month of discharge. This echocardiogram was performed again by a single operator, who is a British Society of Echocardiography trained senior cardiac technician. These examinations were carried out on an Accuson 128XP machine normally used for out-patient echocardiography.

During this echocardiogram the same standard measurements described above were repeated. In addition, pulsed wave Doppler was performed across the mitral valve in the apical four-chamber view, to measure the mitral E-wave, mitral A-wave, mitral E/A ratio, isovolumetric relaxation time (IVRT) and deceleration time (DT) [Figure 2.3].

Figure 2.3 Biphasic mitral inflow pattern and indices of diastolic function



Vel = Velocity
IVRT = Interventricular relaxation time
DT = Deceleration time

Where possible, on completion of the echocardiogram patients were asked to perform a Valsalva manoeuvre by blowing against a fixed syringe. Measurements of the E-wave, A-wave and E/A ratios were repeated during the Valsalva. It has been demonstrated that measurements taken during Valsalva can be used to differentiate pseudonormal diastolic function from normal. Patients with pseudonormal diastolic function will show reversal of a normal resting mitral valve inflow pattern during Valsalva[164].

Seven criteria for diastolic dysfunction were identified using a Medline search. Doppler data from patients in this study with HF-IPSF were used and compared against all 7 criteria. Details of each criteria are described below.

1) **Krishnaswamy criteria**[165]**:** Diastolic dysfunction was grouped by three categories i) pseudonormal pattern, ii) impaired relaxation and iii) restrictive pattern.

Impaired relaxation	E/A < 1 + DT > 240msec in patients < 55yrs
	E/A < 0.8 + DT > 240msec in patients ≥ 55yrs
Restrictive pattern	E/A > 1.5 + DT < 150msec
Pseudonormal	E/A > 1 + DT > 240msec with confirming evidence of either:
	Pulmonary vein diastolic flow
	Abnormal IVRT
	Left atrial enlargement
	Left ventricular hypertrophy

2) **Lubien criteria**[166]**:** Diastolic dysfunction was classified into 3 criteria

Impaired Relaxation E/A ratio < 1 or DT > 240ms in patients < 55yrs

E/A ratio < 0.8 + DT > 240ms in patients ≥ 55yrs

Pseudonormal E/A ratio of 1 – 1.5 + DT > 240ms

Confirmation included: PVd/PVs > 1.5 or IVRT < 90msec

or

Reversal of E/A ratio (to < 1.0) by Valsalva

Restrictive pattern DT < 160ms + ≥ 1 or the following:

Left atrial size > 5cm

E/A > 1.5

IVRT < 70ms

PVd / PVs >1.5

Pulmonary A-wave reversal duration exceeding forward mitral A-wave duration

3) **Redfield criteria**[36]**:** Diastolic function was categorised according to the progression of diastolic dysfunction

i) Normal

ii) Mild (impaired relaxation) E/A ≤ 0.75

iii) Moderate (pseudonormal) 0.75 < E/A < 1.5 + DT > 140ms

iv) Severe (restrictive filling) E/A > 1.5 + DT < 140ms

4) Cohen criteria[167]:

i) Impaired relaxation E/A ratio < 1, DT > 220ms, IVRT > 100ms

ii) Pseudonormalisation E/A ratio > 1 < 2,

DT > 150 < 220ms,

IVRT > 60 < 100ms

iii) Restrictive filling: E/A ratio > 2, DT < 150ms, IVRT < 60ms

5) **European Working Group criteria[168]:**

i) Signs and symptoms of congestive heart failure

and

ii) Normal or mildly reduced left ventricular systolic function

and

iii) Evidence of abnormal left ventricular relaxation

IVRT (<30yr) > 92ms, IVRT (30-50yr) >100ms, IVRT (> 50yr) > 105ms

and / or

iv) Slow early left ventricular filling

E/A (< 50yr) < 1.0 and DT (< 50yr) > 220ms

or

E/A (> 50yr) < 0.5 and DT (> 50yr) > 280ms

6) **Chen criteria[169]:** i) Abnormal relaxation E/A < 0.75

ii) Restrictive pattern E/A > 1.5 and / or DT < 160 ms

7) Zile criteria[170]:

i) Abnormal diastolic function E/A ratio < 1.0 or > 1.5

DT < 160 or > 280ms

IVRT < 60 or > 105 ms

LV mass was estimated from the M-mode measurements of the LV in diastole. The American Society of Echocardiography recommends that a correction factor was used when calculating LV mass from diastolic measurements therefore the following formula for LV mass used[164]:

LV mass (g) = 0.8 x (1.04 x ((LVIDD + IVSDD + LVPWD)^3 – LVIDD^3) + 0.6g

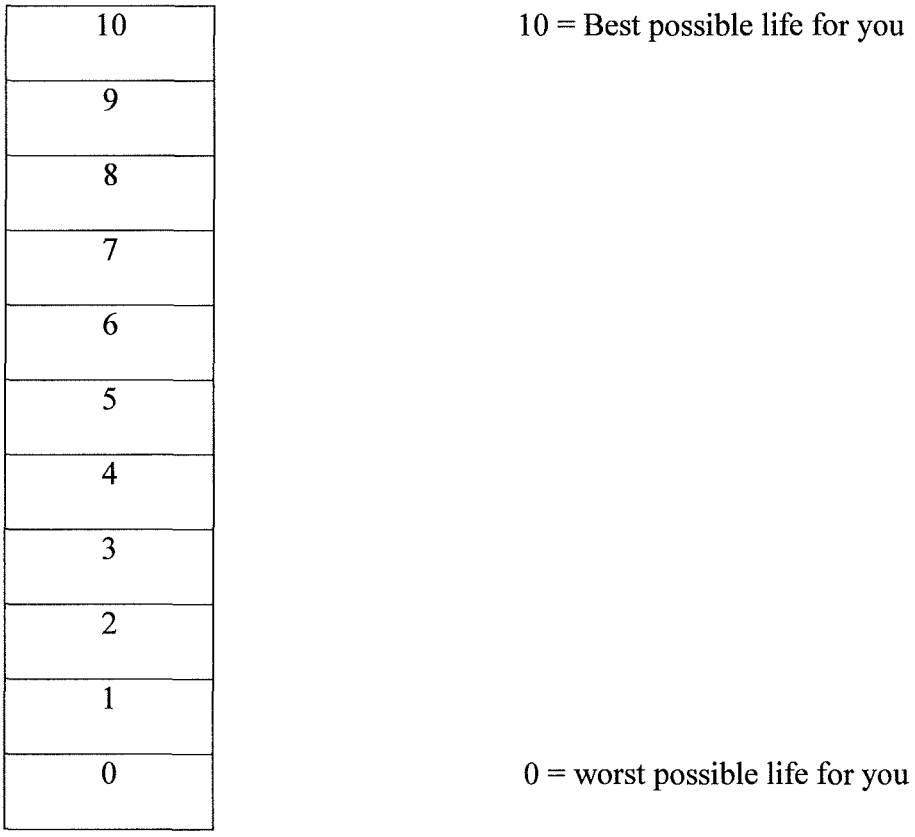
Where possible, all patients with HF-PSF underwent pulmonary function testing (PFT). The primary aim was to identify patients with significant pulmonary disease which may account for their symptoms. Pulmonary disease is a frequent cause of admission to hospital and often the symptoms and signs can mimic those of heart failure. Likewise, patients with pulmonary disease often have co-morbidity, including heart failure and this must not be overlooked[171]. The measurements taken included: forced expiratory volume in one second (FEV_1), forced vital capacity (FVC), FEV_1/FVC ratio, and vital capacity (VC). The PFTs were reported by a respiratory physician blinded to clinical details. For the study, PFTs were recorded as being normal or abnormal.

For the purposes of the study the patients with HF-PSF were reviewed on one occasion following discharge and further follow-up or investigations were arranged as was clinically indicated.

2.05 Quality of Life

Quality of Life (QoL) was measured in all patients using the Cantril Ladder of Life scoring system. This instrument has been used in various cardiovascular studies and is considered to be a valid measure of "global well-being"[172;173]. Figure 2.4 illustrates the Ladder of Life scoring system. Patients were given envelopes containing the scoring system and asked to score how they had been feeling in the weeks prior to admission. The envelopes were then sealed and returned.

Figure 2.4 Cantrils Ladder of Life



2.06 Follow-up

Once recruitment was complete the patient identifiers were sent to the Information and Statistics Division (ISD) in Edinburgh for flagging in order to obtain mortality follow up data. ISD linked my database by probability matching, to information held by the General Registrar's Office for Scotland on in-hospital and out-of hospital deaths.

2.07 Statistical analyses

All study data were entered into an Access database (2000) created specifically for the study. Minitab (version 13) statistical package was used for all basic statistical analyses and SPSS (version 12) was used for mortality analyses.

Survival time was calculated from date of screening (earliest date 1st November 2002) until death or censoring at 1st March 2006. Crude case fatality was calculated for follow-up using the actuarial life table method. Fatality was calculated separately for heart failure groups. This method accounts for the date of death and the different follow-up periods for each individual.

Kaplan-Meier survival curves were constructed to illustrate the survival experience of the individuals according to heart failure group. Curves were compared using the log rank test. This involves calculating the observed and expected number of deaths in both groups at separate time intervals and summing these. The Kaplan-Meier survival method was used to determine median survival. This could only be calculated in the groups in which 50% of the individuals had suffered the event of interest i.e. all-cause death.

Cox regression analysis was used to determine factors associated with all-cause mortality. The model adjusted for the following variables: smoking, age, eGFR, Hb, HR, AF, DM,

hypercholesterolemia, PAD, COPD, IHD, CVD, HF group (PSF vs. RSF), NYHA class III, NYHA class IV, bundle branch block, SBP, DBP, BNP and sex (male vs. female).

The model was built by entering the variables that were available from this study that had previously been shown to predict all cause mortality in the CHARM cohort[174]. As no significant departure from linear trend was found, age, eGFR, Hb, HR, SBP, DBP and BNP were modelled as continuous variables. For each variable entered into a model, the lowest class was set at unity. For NYHA class, class I and class II were combined for reasons of power (there were very few with class I heart failure). After fitting the final model, the assumptions were checked. The assumptions underlying a Cox proportional hazards model are:

1. Proportional hazards, the ratio of hazard functions for two individuals with different covariates does not vary with time.

2. Linearity, the relationship between the covariates and the hazard function should be linear in the log space.

3. Survival times should be independent, as should survival times and censoring times and the censoring should not be affected by the covariates.

These were checked by looking at log minus log plots for each categorical covariate in the model, which should demonstrate parallel lines if the hazards are proportional. In addition visual inspection of the Kaplan Meier curve confirmed that the proportional hazards assumption was met. All mortality analyses were carried using SPSS statistical package.

CHAPTER THREE

CLINICAL CHARACTERISTICS OF PATIENTS WITH HEART FAILURE AND PRESERVED SYSTOLIC FUNCTION

3.01 Introduction

At the time of starting this study only 2 previous authors had reported any of the clinical characteristics of patients with HF-PSF[24;25]. This Chapter aims to describe in detail the clinical characteristics of a cohort of patients with HF-PSF and to make comparisons with HF-RSF.

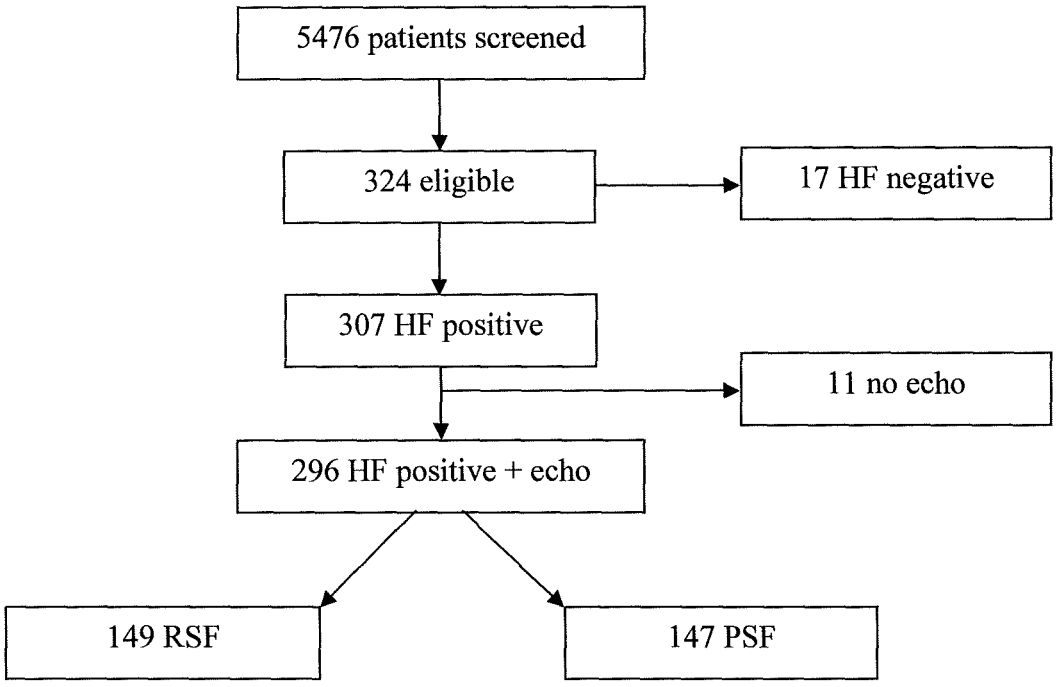
3.02 Results

3.02.1 Study population

Recruitment for the study took place over a 21 month period from November 2002 to July 2004. During this period, 5476 acute medical admissions were screened for clinical evidence of heart failure (HF). Details of recruitment to the study are described in Chapter 2. Of the 5476 patients screened, 324 patients were eligible and agreed to enter the study.

Of the 324 patients recruited, 307 had clinical evidence of HF, defined as a positive score on at least one of the three HF scores (HF +ve). 17 patients were considered to have no clinical evidence of HF (HF –ve), as they did not score positively on any of the HF scoring systems. Of the 307 patients with clinical evidence of HF, 296 had an echocardiogram. In the 11 cases where an echocardiogram was not available, this was either because the patient was too unwell to attend the echocardiography department or because the patient died prior to their echocardiogram being carried out. Of the 296 patients who had clinical evidence of HF and an echocardiogram, 149 had reduced LV systolic function (HF-RSF) and 147 had preserved systolic function (HF-PSF). This chapter will describe and compare the clinical characteristics of these two groups of patients with HF (Figure 3.1).

Figure 3.1 Patient groups



3.02.2 Demographics

The two groups of patients had similar demographic characteristics (See Table 3.1). Their mean ages were similar, as was the proportion of patients aged 75 years or over in each group. The only significant difference between the two groups was that there was a higher proportion of female patients in the HF-PSF group (66% vs. 46%, $p < 0.0001$). The majority of patients in each group were Caucasian.

Table 3.1 Demographic characteristics of patients with HF-RSF and HF-PSF

	HF-RSF (n = 149)	HF-PSF (n = 147)	p value
Age (years) mean (SD)	76 (10)	75 (10)	0.593
n (%)			
≥ 75years	91 (61)	84 (57)	0.491
Female	69 (46)	97 (66)	<0.0001
Caucasian	146 (98)	146 (99)	0.318

3.02.3 Signs and symptoms of heart failure

Table 3.2 shows the symptoms and signs of HF present on admission in each group. These data were collected prior to the echocardiogram being performed.

An assessment of the severity of HF before admission was made using the NHYA classification. The severity of HF on admission was assessed using the Killip classification (both described in Chapter 2). With respect to pre-admission functional limitation, a higher proportion of patients in the HF-RSF group had at least moderately severe HF (NYHA class III/IV). However, the proportion of patients with at least moderately severe HF on admission (Killip class ≥ IIA) was not significantly different between the two groups (p = 0.223). In both groups, more than two-thirds of patients were in Killip class IIA or higher at the time of admission. Tables 3.3 and 3.4 show the individual NYHA and Killip classification scores for both types of HF.

The symptoms of HF reported by patients in the two groups were generally similar, whether or not systolic dysfunction was present. However, a higher proportion of the group with HF-RSF, reported PND and orthopnoea, though the difference from those with HF-PSF was not statistically significant ($p=0.064$ and $p=0.062$ respectively). Otherwise, similar proportions reported reduced exercise tolerance, ankle swelling, general fatigue and leg fatigue. Weight loss was reported too infrequently to perform statistical analysis.

In terms of distinguishing clinical signs, a higher proportion of patients with HF-RSF group had an elevated jugular venous pressure (JVP) (60% vs. 43% in the group with HF-PSF). Otherwise, a similar proportion of patients in each group with had crepitations, sacral oedema, peripheral oedema and wheeze. The mean respiratory rate (RR) was elevated in both types of HF, with no significant difference between the groups. The presence of a third heart sound (S3), hepatomegaly or ascites occurred in too few patients to perform statistical analysis though each appeared to be slightly more common in the patients with HF-RSF.

Table 3.2 Comparison of signs and symptoms of heart failure in HF-RSF / HF-PSF

(n) %	RSF (n = 149)	PSF (n = 147)	p value
HF Classifications			
NYHA class III/IV	90 (60)	64 (44)	0.003
Killip class ≥ IIA	124 (83)	115 (78)	0.223
Clinical data			
RR breaths pm, mean (SD)	21 (7.8)	21 (7.7)	0.370
HR bpm, mean (SD)	92 (26)	89 (25)	0.305
Signs			
Raised JVP	90 (60)	63 (43)	0.002
3rd HS	6 (4)	2 (1)	N/A
Crepitations	126 (85)	119 (81)	0.410
General wheeze	38 (26)	44 (30)	0.394
Sacral oedema	12 (8)	5 (3)	0.083
Peripheral oedema	86 (58)	84 (57)	0.920
Ascites	3 (2)	1 (0.6)	N/A
Hepatomegaly	4 (3)	2 (1)	N/A
Symptoms			
Orthopnoea	89 (60)	72 (49)	0.062
PND	62 (42)	46 (31)	0.064
Reduced ex tolerance	130 (87)	134 (91)	0.277
Reported ankle swelling	98 (66)	97 (66)	0.969
General fatigue	115 (77)	111 (76)	0.735
Leg fatigue	67 (45)	63 (43)	0.715
Weight loss	7 (5)	3 (2)	N/A

NYHA = New York Heart Association, RR = respiratory rate, pm = per minute, HR = heart rate, bpm = beats per minute, JVP = jugular venous pressure, HS = heart sound, PND = paroxysmal nocturnal dyspnoea, ex tolerance = exercise tolerance.
P value N/A = where the size of the group was too small to accurately perform statistical analysis.

Table 3.3 NYHA scores

NYHA score n (%)	HF-RSF (n = 149)	HF-PSF (n = 147)
I	1	0
II	57 (38)	83 (56)
III	47 (32)	37 (25)
IV	44 (30)	27 (18)

Table 3.4 Killip Scores

Killip score n (%)	HF-RSF (n = 149)	HF-PSF (n = 147)
I	1	0
II	23 (15)	32 (22)
IIa	65 (44)	68 (46)
IIb	19 (13)	24 (16)
III	41 (28)	23 (16)
IV	0	0

3.02.4 Heart Failure scores

Each subject was screened for clinical evidence of HF using the three scoring systems described in Chapter 2. There was a small number of patients who scored positively for only one HF score and negatively in the other two. The table below shows their distributions according to HF scores (Table 3.5).

Table 3.5 Distribution of isolated positive HF scores

Heart Failure score	HF-RSF (n = 149)	HF-PSF (n = 147)
Boston	3	4
NHANES	2	7
Framingham	0	0

These patients accounted for only 3% of those with HF-RSF. The proportion was slightly higher in the HF-PSF group, but still accounted for only 7% of patients. These cases were split between the Boston and NHANES scoring systems. As described in Chapter 2, the Boston score is divided into possible and definite heart failure. All four patients who scored positively for the Boston score but negatively for the others, were classified as probable heart failure. All four patients also had other potential causes for their symptoms, such as chronic obstructive pulmonary disease, atrial fibrillation or valvular heart disease. Seven patients with HF-PSF scored positively for HF with the NHANES instrument and negatively with the other scoring systems. Of these, only two had no other clinical explanation for their presenting symptoms. The other five patients were either smokers, had atrial fibrillation/flutter or were clinically obese. In both groups, no patient scored positively with the Framingham system without also scoring positively in at least one other scoring system. Table 3.6 summarises the distribution of patients scoring positively for one, two or all three HF scores. A significantly higher proportion of patients with HF-RSF scored positively for all three HF scores than in the HF-PSF group ($p<0.001$). However, nearly four-fifths of the patients with HF-PSF showed concordantly positive results.

Table 3.6 Summary of HF scores

No. positive HF Scores n (%)	HF-RSF (n = 149)	HF-PSF (n = 147)	p value
1	5 (3)	11 (7)	N/A
2	9 (6)	25 (17)	N/A
3	135 (91)	111 (76)	<0.0001

p values N/A = where the size of the group was too small to accurately perform statistical analysis.

3.02.5 Co-morbidity

With respect to co-morbidity, there were four main differences between the two groups (Table 3.7). Firstly, a significantly higher proportion of patients with HF-RSF had valvular heart disease, compared to those with HF-PSF (45% vs. 24%, $p<0.0001$). Secondly, within the HF-RSF group there was a higher proportion of patients with a prior history of peripheral arterial disease (PAD) (12% vs. 5%, $p=0.02$). Thirdly, there was a higher proportion of patients with a prior history of hypertension in the HF-PSF group compared with the HF-RSF group (56% vs. 38%, $p=0.001$). Finally, nearly half of the patients with HF-RSF (47%) had a prior diagnosis of HF, compared to 16% of those with HF-PSF ($p<0.0001$). Of note, there were no significant differences between the two groups in terms of prevalence of other relevant co-morbidities, particularly ischaemic heart disease (IHD) and diabetes mellitus (DM). Atrial fibrillation (AF) was also present in similar proportions in both groups.

Table 3.7 Co-morbidity in HF-RSF and HF-PSF

n (%)	HF-RSF (n=149)	HF-PSF (n=147)	p value
Ischaemic heart disease*	86 (58)	78 (53)	0.42
Cerebrovascular disease**	28 (19)	29 (20)	0.84
Peripheral arterial disease	18 (12)	7 (5)	0.02
Diabetes mellitus	32 (21)	26 (18)	0.41
Hypertension	56 (38)	83 (56)	0.001
Hypercholesterolaemia	45 (30)	38 (26)	0.40
Atrial Fibrillation	44 (30)	42 (29)	0.86
Valve Disease	67 (45)	36 (24)	<0.0001
Prior diagnosis of HF***	70 (47)	23 (16)	<0.0001
Current smoker	29 (19)	34 (23)	0.41
Ex-smoker	54 (36)	52 (35)	0.88

*Ischaemic heart disease was defined as a history of angina, previous myocardial infarction or previous CABG
**Cerebrovascular disease was defined as a history of previous cerebrovascular accident, transient ischaemic attack or previous carotid endarterectomy.
***HF=Heart Failure

Chronic obstructive pulmonary disease (COPD) was considered to be present when there was a documented diagnosis in the medical records, or if the patient was prescribed inhalers, long term oxygen therapy (LTOT) or regular nebulised bronchodilators or if there was evidence of COPD on pulmonary function testing (PFT). COPD was common in both types of HF but was more common in those with HF-PSF (p=0.022). This is discussed fully in Chapter 8.

3.02.6 Admission clinical data

Clinical findings on admission were very similar between the two groups of patients with HF (Table 3.8).

Table 3.8 Admission clinical data

Mean (SD)*	HF-RSF (n = 149)	HF-PSF (n = 147)	p value
SBP (mmHg)	141 (32.9)	145 (29.5)	0.195
DBP (mmHg)	78 (19.4)	78 (17.6)	0.969
HR (bpm)	92 (26)	78 (17.6)	0.969
RR (bpm)	21 (7.8)	21 (7.7)	0.370
Urea	11.8 (9.7)	8.6 (5)	<0.0001
Creatinine (μmol/L)	136 (54)	114 (52)	0.001
eGFR (ml/min/m^2)	47 (17.6)	54 (16.8)	0.001
Hb (g/dL)	12.41 (2)	12.51 (2)	0.662
BMI (kg/m^2)	28 (5.4)	29 (5.8)	0.285
Anaemia n (%)	59 (40)	53 (36)	0.529
Troponin +ve, n (%)	61 (41)	30 (20)	<0.0001

* except anaemia and troponin
SBP = systolic blood pressure, DBP = diastolic blood pressure, HR = heart rate, RR = respiratory rate, eGFR = estimated glomerular filtration rate mL/min/1.73m^2 [186 x (Plasma creatinine) $^{-1.154}$ x (age)$^{-0.203}$ x 0.742 if female], Troponin +ve = positive troponin, BMI = body mass index , Anaemia = WHO classification of anaemia (Hb<12 g/dL for males and females)

Renal function was worse in the group with HF-RSF, when using either serum creatinine (136 μmol/L ± 54) or eGFR (47 ml/min/m^2 ± 52) as the measure (p = 0.001 in both cases). In both groups, the mean eGFR equated to "moderate" renal dysfunction according to the National Kidney Foundation classification of kidney disease (described in Chapter 2)[154]. In both

groups, two-thirds or more of patients had at least moderate renal dysfunction (eGFR < 60mL/min/m^2). Plasma urea concentrations were also significantly higher in HF-RSF compared to those with HF-PSF ($p < 0.0001$) [Table 3.9].

Table 3.9 Comparison of range of eGFR in HF-RSF and HF-PSF

eGFR mL/min/m^2	HF-RSF (n=149)	HF-PSF (n=147)
n (%)		
≥ 90	0 (0)	3 (2)
60-89	37 (25)	47 (32)
30-59	87 (58)	90 (61)
0-29	25 (17)	7 (5)
<60	112 (75)	97 (66)

eGFR = estimated glomerular filtration rate

One significant difference in the admission clinical data between the two groups was the higher proportion of patients with HF-RSF who had a raised troponin (41% vs. 20% in the group with HF-PSF, $p<0.0001$).

Values for routine haematological investigations carried out on admission are presented in Table 3.10. The findings were very similar in both groups. The mean platelet count was higher in patients with HF-PSF group, compared to those with HF-RSF though the mean value in both groups was within the normal range. A similar proportion of patients in each group were anaemic (see Table 3.8).

Table 3.10 Routine haematology

Mean (SD)	HF-RSF (n = 149)	HF-PSF (n = 147)	p value
Hb (g/dL)	12.41 (2)	12.51 (2)	0.66
MCV (fl)	92 (10)	91 (6.9)	0.76
WCC $x10^9$ (cells/L)	9.1 (3.3)	9.5 (3.2)	0.31
Lymphocytes $x10^9$ (cells/L)	1.37 (1.1)	1.3 (0.9)	0.83
Neutrophils $x10^9$ (cells/L)	6.9 (2.7)	7.2 (3.1)	0.32
Platelets $x10^9$ (cells/L)	252 (90)	276 (107)	0.04

Hb = haemoglobin, MCV = mean mean cell volume, WCC = white cell count

Table 3.11 shows the results of the routine biochemical investigations carried out in the two groups. Renal function, as measured by median serum urea and creatinine concentration, was worse in the patients with HF-RSF ($p < 0.0001$). That group also had a significantly higher median random serum glucose concentration ($p = 0.023$) and a higher median level of serum bilirubin ($p = 0.045$), AST ($p = 0.046$) and GGT ($p = 0.011$), compared to the group with HF-PSF. There was also a trend towards a higher median serum CRP concentration in the group with HF-RSF, though the difference was not statistically significant. Conversely, mean cholesterol level was significantly lower in the group with HF-RSF (4.2 mmol/L), compared to the group with HF-PSF (4.8 mmol/L, $p = 0.011$), as was the median serum albumin, 39 g/L in HF-RSF compared to 40 g/L in those with HF-PSF ($p=0.024$).

Table 3.11 Routine biochemistry

Median (IQR)	HF-RSF (n = 149)	HF-PSF (n =147)	p value
Sodium (mmol/L)	140 (137-142)	140 (138-142)	0.19
Potassium (mmol/L)	4.3 (3.9-4.7)	4.2 (3.9-4.5)	0.06
Urea (mmol/L)	9.5 (6.6-13.1)	7.5 (5.5-10.1)	<0.0001
Creatinine (μmol/L)	124 (102-155)	104 (89-120)	<0.0001
Cholesterol (mmol/L)	4.2 (3.5-5.1)	4.8 (3.7-5.6)	0.01
Glucose (mmol/L)	6.7 (5.5-9.0)	6.0 (5.5-7.6)	0.02
*Random glucose > 11mmol/L n (%)	21 (14%)	11 (7%)	0.05
Bilirubin (μmol/L)	14 (11-22)	13 (10-18)	0.05
ALP (u/L)	196 (150-259)	197 (159-246)	0.79
AST (u/L)	26 (20-40)	25 (19-34)	0.05
GGT (u/L)	40 (22-72)	31 (18-55)	0.01
Albumin (g/L)	39 (36-41)	40 (38-42)	0.02
CRP (mg/L)	19 (8-60)	13 (6-42)	0.08

* median (IQR) except n (%) random glucose >11 mmol/L
ALP = alkaline phosphatase, AST = aspartate aminotransferase, GGT = gamma glutamyl transpeptidase, CRP = C-reactive protein

For logistical reasons it was not possible to calculate body mass index (BMI) for all patients, however, with the available data there was no significant difference in mean BMI between the two groups. In both groups the mean BMI was at the upper limit of the range defined by the WHO as "overweight" (BMI 25-29.9)[175;176].

3.02.7 Cardiovascular medications

Table 3.12 compares the cardiovascular medications being taken by each group on admission. These were very similar in the two groups, with the exception of ACE-I. A higher proportion of patients with HF-RSF were taking an ACE-I compared to those in the group with HF-PSF (45% and 31% respectively).

Table 3.12 Admission cardiovascular medications

Medication n (%)	HF-RSF (n = 149)	HF-PSF (n = 147)	p value
Antiplatelet	90 (60)	78 (53)	0.225
Diuretics	106 (71)	98 (67)	0.455
Spironolactone	12 (8)	3 (2)	N/A
ACE-I	67 (45)	46 (31)	0.016
ARB	12 (8)	8 (5)	0.378
B Blocker	54 (36)	48 (33)	0.543
Digoxin	22 (15)	20 (14)	0.793
Vasodilators	51 (34)	62 (42)	0.144
Statin	60 (40)	50 (34)	0.284

ACE-I = Angiotensin converting enzyme inhibitor
ARB = Angiotensin receptor blocker
Vasodilators = Calcium channel blocker, nitrates, and nicorandil
P value N/A = where the size of the group was too small to accurately perform statistical analysis.

3.02.8 Electrocardiographic findings

Table 3.13 illustrates that a significantly higher proportion of patients with HF-RSF (79%) had an abnormal ECG at the time of presentation compared to patients with HF-PSF (63%) [p=0.002]. However, it should be noted that nearly two-thirds of patients with HF-PSF also had an abnormal ECG. A significantly higher proportion of patients with HF-RSF had left bundle branch block (LBBB) (29%), left axis deviation (LAD) (21%) or left ventricular hypertrophy (LVH) (25%) compared to those with HF-PSF: 12% (p<0.0001), 12% (p=0.046) and 14% (p = 0.16), respectively.

Table 3.13 ECG findings

ECG features n (%)	HF-RSF (n=149)	HF-PSF (n=147)	p value
SR	94 (63)	101 (69)	0.25
AF	44 (30)	42 (29)	0.25
LBBB	40 (27)	13 (9)	<0.0001
RBBB	8 (5)	3 (2)	N/A
LVH	35 (23)	18 (12)	0.01
RVH	2 (1)	1 (0.7)	N/A
ST Elevation	19 (13)	29 (20)	0.10
ST Depression	19 (13)	29 (20)	0.10
T Inversion	30 (20)	25 (17)	0.49
Q waves	15 (10)	7 (5)	0.08
RAD	6 (4)	3 (2)	N/A
LAD	31 (21)	18 (12)	0.05
Abnormal ECG	117 (79)	92 (63)	0.002

HR = Heart rate, SR = Sinus rhythm, LBBB = Left bundle branch block, RBBB = Right bundle branch block, LVH = Left ventricular hypertrophy, RVH = Right ventricular hypertrophy, RAD = Right axis deviation, LAD = Left axis deviation. P value N/A = where the size of the group was too small to accurately perform statistical analysis.

3.02.9 Quality of life

Quality of life (QoL), as measured by the Cantril Ladder of Life (LOL) questionnaire, was reduced in both groups compared to what would be expected in healthy age and sex matched individuals. There was no statistically significant difference in QoL between the two groups, mean LOL score being 4.6 (2.5) in the group with HF-RSF and 5.0 (2.6) in the patients with HF-PSF (p=0.162).

3.02.10 Comparison of clinical characteristics of HF-RSF and HF-isolated preserved systolic function (HF-IPSF)

In the HF-PSF group 41% of patients had either valvular heart disease, AF or both, which could have accounted for their symptoms and signs of HF. Therefore, I defined a group of patients with clinical HF, preserved systolic function who did not have significant valvular heart disease or AF. For the purposes of this thesis, this group is referred to as HF with isolated preserved systolic function (HF-IPSF), and I have compared their characteristics with those of patients with HF-RSF (Table 3.14 A-D).

Mean ages in the two groups were similar, but a significantly higher proportion of patients with HF-IPSF were female ($p<0.0001$). With respect to cardiovascular co-morbidities, the only significant difference between the two groups was that a higher proportion of patients in the isolated PSF group had a history of hypertension (58% vs. 38%, $p = 0.002$). A significantly higher proportion of patients with isolated PSF had COPD, either as a primary or additional diagnosis (47% vs. 30% in the group with RSF, $p = 0.01$).

Functional limitation, as measured by NYHA class, was significantly worse in patients with HF-RSF when compared with those with HF-IPSF. More patients with HF-RSF described PND (42% vs. 28%, $p < 0.030$) or orthopnoea (60% vs. 43%, $p = 0.012$). The presence of reduced exercise tolerance, ankle swelling, general fatigue and leg fatigue was reported in similar proportions in both types of heart failure. A similar proportion of patients in each group were classified as having moderately severe HF on admission, as determined by Killip class of IIA or greater ($p = 0.117$). With regard to the findings on clinical examination, the only significant difference between the two groups was the higher proportion of patients with HF-RSF which had an elevated JVP (60% vs. 42%, $p = 0.005$).

Patients with HF-RSF were more likely to score positively in all three HF scoring systems, however, the majority of patients with isolated PSF did show concordant positive results across all three scoring systems.

There were no significant differences in the clinical findings on admission, with the exception of heart rate, which was higher in the group with HF-RSF ($p = 0.004$). A similar percentage of patients were anaemic in both groups. Renal function was significantly worse in the HF-RSF group, as measured by both serum creatinine concentration ($p = 0.002$) and eGFR ($p = 0.001$). Again, in both groups the mean eGFR equated to moderate renal dysfunction according to the National Kidney Foundation criteria for renal function. In both the HF-RSF and isolated PSF groups the majority of patients (75% and 60%) had moderate renal dysfunction (eGFR $< 60ml/min/m^2$). A significantly smaller proportion of patients with isolated PSF had a positive troponin at the time of admission, compared to those with HF-RSF ($p < 0.0001$). Patients with HF-RSF were more likely to have an abnormal ECG on admission ($p = 0.029$), though two-thirds of patients in the HF-IPSF group did have an abnormal ECG. Admission cardiac medications were similar between the two types groups, again with the exception of ACE-I medications which were more commonly prescribed in the HF-RSF group ($p = 0.026$).

QoL scores were again reduced compared with the general population and there was no significant difference in mean (SD) LOL scores between the two groups: HF-RSF 4.6 (2.5) and isolated PSF: 5.0 (2.4), $p = 0.23$.

Table 3.14 Summary comparison of clinical characteristics of HF-RSF/HF-IPSF

A) Demographics and cardiovascular risk factors

	HF-RSF (n=149)	HF-IPSF (n=86)	p value
Age (yrs) mean (SD)	76 (9.5)	73 (10.1)	0.092
n (%)			
Female	69 (46)	60 (70)	<0.0001
IHD	86 (58)	48 (56)	0.777
CVD	28 (19)	15 (17)	0.795
PAD	18 (12)	5 (6)	0.088
DM	32 (21)	20 (23)	0.753
HBP	56 (38)	50 (58)	0.002
Hypercholesterolaemia	45 (30)	25 (29)	0.855
COPD	44 (30)	40 (47)	0.010

IHD = ischaemic heart disease, CVD = cerebrovascular disease, PAD = peripheral arterial disease, DM = diabetes mellitus, HBP = hypertension, COPD = chronic obstructive airways disease

Table 3.14 Summary comparison of clinical characteristics of HF-RSF / HF-IPSF

B) Clinical Recordings

Mean (SD)	HF-RSF (n=149)	HF-IPSF (n=86)	p value
SBP (mmHg)	141 (33)	144 (30)	0.390
DBP (mmHg)	78 (19)	77 (17)	0.540
HR (bpm)	92 (26)	83 (20)	0.004
RR (breaths pm)	21 (7.8)	21 (9.3)	0.607
Creatinine (μg/L)	136 (54)	112 (56)	0.002
EGFR (ml/min/m^2)	47 (18)	55 (17)	0.001
Hb (g/dL)	12.4 (2)	12.5 (2)	0.685
LOL scores	4.6 (2.5)	5.0 (2.4)	0.233
n (%)			
Anaemic	59 (40)	31 (36)	0.588
Troponin +ve	61 (41)	14 (16)	<0.0001
Abnormal ECG	117 (79)	56 (65)	0.029
Concordant HF scores	135 (91)	61 (71)	<0.0001

SBP = systolic blood pressure, DBP = diastolic blood pressure, HR = heart rate, RR = respiratory rate, eGFR = estimated glomerular filtration rate, LOL scores = Ladder of Life scores

Table 3.14 Summary comparison of clinical characteristics of HF-RSF/HF-IPSF

C) Clinical signs and symptoms

n (%)	HF-RSF (n=149)	HF-IPSF (n=86)	p value
NYHA III/IV	90 (60)	39 (45)	0.021
Killip ≥ IIA	124 (83)	64 (74)	0.117
Elevated JVP	90 (60)	36 (42)	0.005
Lung crepitations	126 (85)	65 (76)	0.102
Peripheral oedema	86 (58)	50 (58)	0.950
Sacral oedema	12 (8)	2 (2)	N/A
Wheeze	38 (26)	26 (30)	0.439
PND	62 (42)	24 (28)	0.030
Orthopnoea	89 (60)	37 (43)	0.012
Reduced ex tolerance	130 (87)	76 (88)	0.799
Reported ankle oedema	98 (66)	60 (70)	0.526
General fatigue	115 (77)	68 (79)	0.735
Leg fatigue	67 (45)	36 (42)	0.643

JVP = Jugular venous pressure,
PND = paroxysmal nocturnal dyspnoea,
Ex tolerance = exercise tolerance
p value N/A = where the size of the groups are too small to perform accuracte statistical analysis

Table 3.14 Summary comparison of clinical characteristics of HF-RSF / HF-IPSF

D) Cardiovascular medications on admission

n (%)	HF-RSF (n=149)	HF-IPSF (n=86)	p value
Anti-platelet	90 (60)	45 (52)	0.268
Diuretics	106 (71)	52 (60)	0.123
Spironolactone	12 (8)	1 (1)	N/A
ACE-I	67 (45)	26 (30)	0.026
ARB	12 (8)	4 (5)	N/A
β-Blocker	54 (36|)	25 (29)	0.280
Vasodilator	51 (34)	34 (40)	0.381
Statin	60 (40)	31 (36)	0.564

ACE-I = ACE inhibitor, ARB = Angiotensin receptor blocker, B-Blocker = beta blocker
p value N/A = where the size of the groups are too small to perform accuracte statistical analysis

3.03 Discussion

This Chapter describes the detailed clinical characteristics of a cohort of patients hospitalised for heart failure. The first and most striking finding is the prevalence of heart failure with preserved left ventricular systolic function, which accounted for around half of all heart failure admissions studied. This is similar to the recent Euroheart Failure Survey[177] where over 6000 patients were studied and almost 50% were found to have HF-PSF. Two studies published during the time of writing showed that 47% and 31% of patients with HF had preserved systolic function[178;179]. Both of these studies defined HF-PSF as having clinical HF with an ejection fraction > 50%. Although the current study did not measure ejection fraction we did use a single experienced operator to provide a quantitative assessment of LV systolic function and previous work has shown that there is a good correlation between this method and ejection fraction[160]. These prevalence figures underline the importance of HF-PSF, which has emerged as a recognised clinical entity over the last decade[13].

One major drawback of prior studies was the lack of systematic data regarding patients with HF-PSF. This study has addressed this deficit by gathering detailed clinical information and comparing patients with HF-PSF to those with heart failure and reduced systolic function.

This comparison clearly shows that there are many similarities between patients with heart failure and reduced or preserved systolic function. Age was similar between the two groups, as were relevant cardiovascular comorbidities such as the presence of ischaemic heart disease or atrial fibrillation. Importantly, symptoms and signs of heart failure were broadly comparable between the two groups, and there was no difference in the proportion of patients presenting in each group with moderate to severe heart failure. This suggests that heart failure is a clinical syndrome which exists across a spectrum of normal and impaired LV systolic function.

This study has highlighted a number of important differences, which may improve our understanding of HF-PSF. Firstly, a higher proportion of patients with HF-PSF were female. Owan *et al*[178] and Bhatia *et al*[179] also found that HF-PSF was more common in females in their recent publications. It is not entirely clear why HF-PSF is more common in women.

Another notable difference between the two groups is the higher prevalence of hypertension in the HF-PSF group. This may reflect an important aetiological factor in HF-PSF, which is widely thought to be due to left ventricular diastolic dysfunction. Increased afterload in systemic hypertension induces compensatory LV hypertrophy, which in turn can cause abnormalities in diastolic function. The findings from this study therefore corroborate evidence from previously published studies. Hypertension must now be regarded as a risk factor for this type of HF[18;21;33;34;178;179].

The incidence of hypertension increases with age in both sexes however, more so in women. In men the incidence of hypertension increases with age from 3.3% per year at ages 30-39 to 6.2% at ages 70-79 and in women from 1.5% at ages 30-39 to 8.6% at ages 70-79[180;181]. It is therefore possible that as the incidence of hypertension is higher in older women compared with older men, that this accounts for some of the increased prevalence of HF-PSF in women. Another possibility is that women are more susceptible to the presence of hypertension and the consequential remodelling process that results in the development of HF. More detailed imaging techniques such as tissue Doppler echocardiography and cardiac MRI may provide further insight into the diastolic function of this group.

Renal function was worse in those patients with HF-RSF. However, it is interesting to note that a significant proportion of patients with HF-PSF also had significant renal dysfunction. This may be due to coincident cardiorenal disease, or it may reflect that there are similar levels of renal dysfunction as a consequence of the syndrome of heart failure, regardless of the presence of systolic dysfunction. This would again tend to suggest that systolic dysfunction is not a pre-requisite for severe or complicated heart failure.

As would be expected, a higher proportion of patients with HF-RSF had an elevated troponin, although this finding was present in a significant minority of the HF-PSF group. Though the cause of an elevated troponin was not specifically addressed in this study, potential explanations include; myocardial ischaemia, pulmonary embolism, renal impairment, sustained tachyarrhythmia, heart failure itself, or a combination of these. It is interesting to speculate that myocardial ischaemia or tachyarrhythmias could be causing heart failure requiring hospitalisation, without any apparent compromise of LV systolic function. It is also possible that either of these may cause transient LV systolic dysfunction which is not present

when echocardiography is performed some time after admission. Underlying abnormalities in diastolic function may result in these patients being more susceptible to events such as myocardial ischaemia or tachyarrhythmias, resulting in clinical heart failure. Therefore it would seem that echocardiography at the time of admission may provide useful insights into the roles of systolic and diastolic dysfunction in heart failure.

Interestingly, less than half of the patients with HF-RSF were taking an ACE-I at the time of admission. Just under a half of patients with HF-RSF had a prior diagnosis of HF from the medical records. However, it is still not clear whether the low rate of ACE-I use in those patients with HF-RSF was because their LV dysfunction was new or previously undiagnosed. However poor compliance with medications or lack of adherence to HF guidelines may also have been important factors.

The mean LOL scores for both groups were very similar to those found by Luttik *et al* in a population of NYHA class III or IV HF patients (4.6 ± 2.6)[172]. Ormel *et al* reported higher mean LOL scores of 7.9 from a healthy elderly Dutch population[182], this underlines that the social impact of symptomatic heart failure is not limited to HF-RSF.

The CHARM-Preserved trial randomised a similar population to that which I have defined here as HF-PSF[183]. If we use the CHARM-Preserved population as a reference, there are many similarities between the population described in this study and the one described in CHARM-Preserved. The majority of my patients with HF-PSF were female, and they were more likely than those with HF-RSF to have a history of hypertension. The majority (56%) of patients with HF-PSF in our study had NYHA class II symptoms, similar to those in CHARM-Preserved (61%)[183]. The mean age of the patients with HF-PSF in my study is

slightly higher than in CHARM-Preserved, at 75 years. 29% of patients in CHARM preserved had atrial fibrillation[183]. The same proportion of patients in my study also had atrial fibrillation.

This Chapter illustrates that approximately one-third of all patients admitted with clinical HF and preserved systolic function did not have either VHD or AF to account for their signs and symptoms. Comparing this group to those with HF-RSF produced a very similar set of conclusions to the comparison of HF-PSF and HF-RSF. This is extremely important as it supports the view that heart failure with preserved systolic function exists as a clinical entity in its own right, and is not merely an expression of other co-morbidity.

CHAPTER FOUR

ECHOCARDIOGRAPHIC FINDINGS

4.01 Echocardiography and diastolic dysfunction

Echocardiography has played a major role in the development of the diagnosis of "diastolic heart failure" (DHF). Patients with breathlessness are frequently referred for echocardiography, and with the finding of preserved LV systolic function they are often given a diagnosis of diastolic heart failure.

The European Cardiology Society state that a diagnosis of DHF requires:

1) clinical symptoms of heart failure

2) demonstration of an ejection fraction $\geq 50\%$

3) demonstration of diastolic dysfunction

Diastole encompasses the relaxation and filling phases of the cardiac cycle, between closure of the aortic valve, when LV pressure falls below aortic pressure, and closure of the mitral valve[45]. Diastole has both active and passive components[45;46], and can be divided into four phases:

- Isovolumetric relaxation
- Early rapid LV filling
- Diastasis
- Late LV filling due to atrial contraction (atrial systole)

Isovolumetric relaxation: the period occurring between the end of LV systolic ejection (aortic valve closure) and the opening of the mitral valve, when LV pressure falls and LV volume remains constant. This is mainly active LV relaxation[45].

Early rapid LV filling: this phase begins when the LV pressure falls below the left atrial pressure and the mitral valve opens. During this period the blood has an acceleration which is directly related to the aorto-ventricular pressure gradient and therefore reduces as this gradient equalises[45]. This is an active process involving the use of energy by the myocardium.

Diastasis: When left atrial and ventricular pressures are almost equal, LV filling is maintained by pulmonary venous flow. During diastasis, the left atrium acts as a passive conduit[45].

Atrial systole: LV filling is completed by left atrial contraction. This phase ends with mitral valve closure[45].

There is no single measurement of overall diastolic function. The most clinically relevant indices of diastolic function are:

- Ventricular relaxation
- Myocardial or chamber compliance
- Filling pressures

Left ventricular isovolumetric relaxation occurs during the interval between aortic valve closure and mitral valve opening. Abnormal relaxation results in prolongation of the isovolumetric relaxation time and a slower rate of decline in the ventricular pressure. There is consequently a reduction in the early peak filling, because of the reduced pressure difference between the atrium and the ventricle when the atrioventricular valve opens. Measures of left ventricular relaxation include:

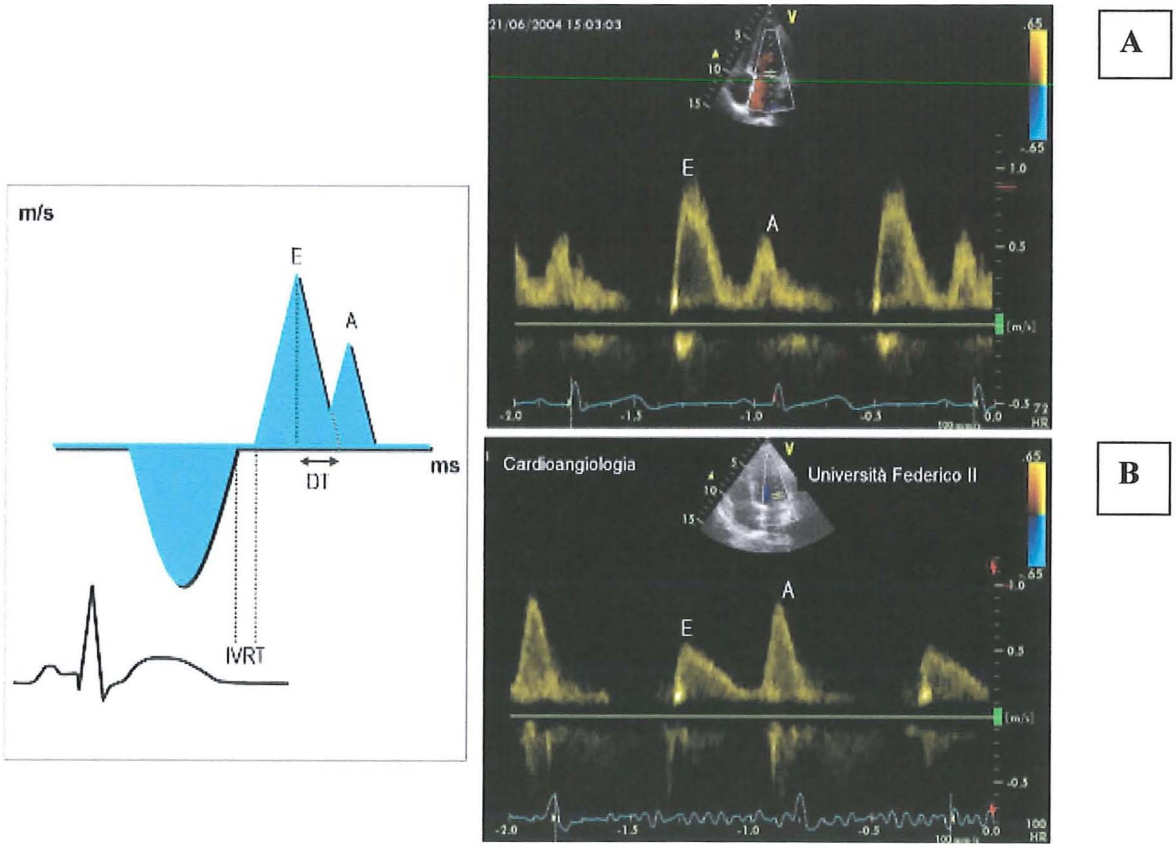
- Isovolumetric relaxation time (IVRT)
- The maximum rate of pressure decline (-dP/dt)
- Time constant of relaxation (tau or t)

There are relatively simple spectral Doppler measurements that can be made during routine echocardiography, that have been advocated as indices of diastolic function[184]. Spectral Doppler measurements of LV diastolic filling velocities correspond closely with ventricular filling parameters measured by cardiac catheterisation. Doppler measurements recorded in the current study, as described in Chapter 2, were mitral E-wave velocity (m/s), mitral A-wave velocity (m/s), mitral E/A ratio, mitral inflow deceleration time (ms) and IVRT (ms). These measurements are made in the apical four-chamber view which allows alignment of the ultrasound beam with mitral inflow. Pulsed-wave Doppler is placed in the mitral inflow at the level of the mitral valve tips. The normal mitral inflow Doppler pattern is shown in Figure 4.1a.

In the normal mitral inflow Doppler pattern, there is a brief interval between aortic valve closure and the onset of ventricular filling, and this is called the isovolumetric relaxation time (IVRT). Immediately following mitral valve opening, there is rapid acceleration of blood flow from the atrium to the ventricle. In young healthy individuals the early peak filling velocity reaches 0.6 to 0.8 m/s around 90-110ms after the onset of flow[164]. This early filling is shown by the E-wave of the mitral inflow Doppler signal and its maximum velocity reflects the maximum pressure gradient between the atrium and ventricle. After this, flow decelerates rapidly, in normal individuals the deceleration is 4.3 to 6.7 m/s[164]. Deceleration time (DT) is defined as the interval from the peak E-wave to where a line following the initial deceleration slope intersects with the baseline. In normal individuals this ranges from 140 to 200ms[164].

This is followed by a period of minimal flow (diastasis). Then, with atrial contraction, left atrial pressure again exceeds ventricular pressure, resulting in a second velocity peak in the mitral inflow signal (A-wave). The peak velocity of the A-wave typically ranges from 0.19 to 0.35 m/s in young normal individuals[164] (Figure 4.1a).

Figure 4.1 (A) Normal pattern and (B) Abnormal pattern of left ventricular diastolic filling recorded with pulsed-wave Doppler



Adapted from Galderisi *et al*[45]

Diastolic dysfunction has two main components:

1) Impaired left ventricular relaxation

2) Impaired left ventricular compliance

Impaired relaxation is characterised by a classical pattern of reduced early diastolic filling and an increased atrial contribution to total LV filling. Impaired relaxation is shown on the mitral inflow Doppler by:

- Reduced E-wave velocity
- E/A ratio < 1
- Prolonged IVRT
- Prolonged DT

If LV compliance is decreased (a "stiff ventricle"), as the LV fills, the diastolic pressure rises rapidly giving a high E-wave velocity, followed by a steep deceleration slope. The atrial contribution to filling is relatively small because it occurs on a steep portion of the pressure-volume curve. In addition, the LV pressure in end-diastole is typically elevated resulting in a reduced atrio-ventricular pressure gradient following atrial systole.

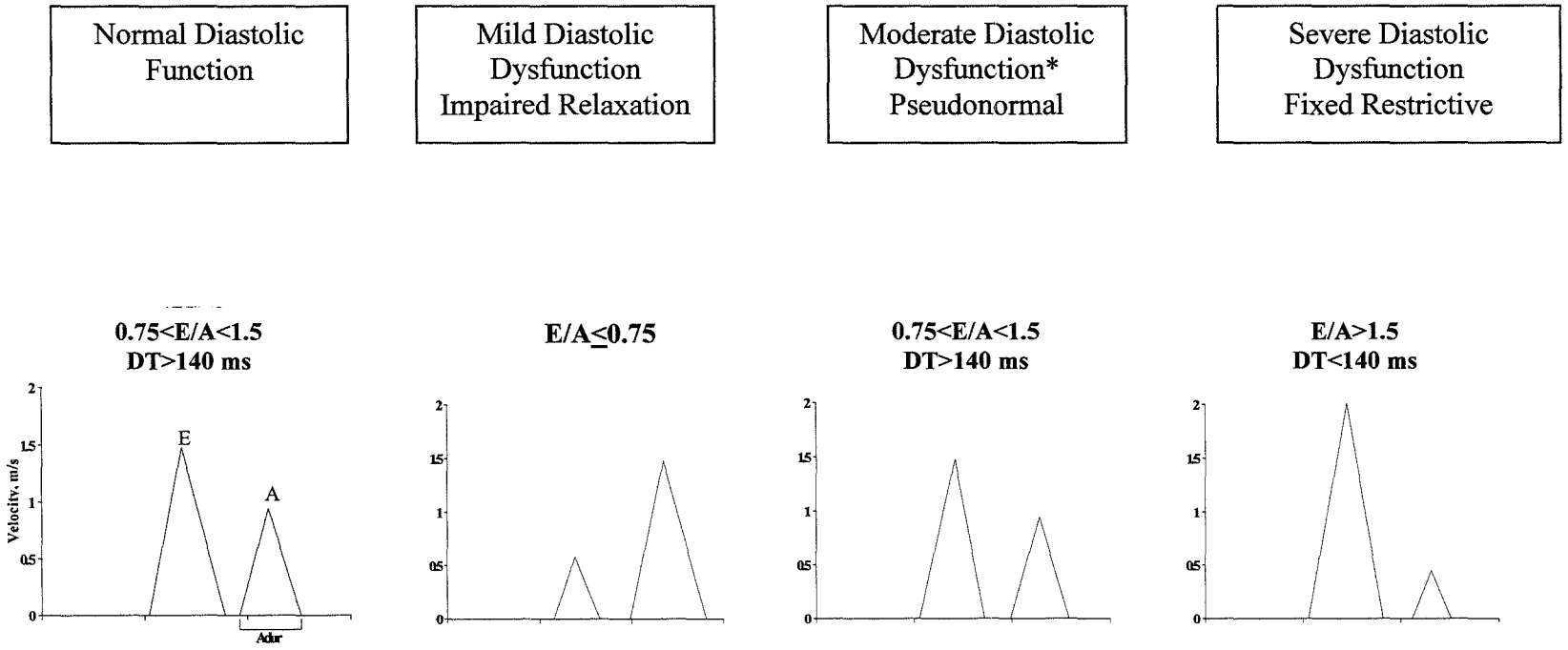
Reduced compliance is associated with:

- Increased E-wave velocity
- E/A ratio > 1
- Reduced IVRT
- Decreased DT

One of the main difficulties with echocardiographic assessment of diastolic function is that there are many different criteria for the diagnosis of diastolic dysfunction. This was illustrated by Petrie *et al,* who applied the most common criteria for diastolic dysfunction to consecutive patients with suspected HF. They found up to a 16-fold difference in the prevalence of diastolic dysfunction, depending on which measure was used, indicating very poor concordance between the different measures for diagnosing diastolic dysfunction[184].

However, Redfield *et al*[36] provide a useful explanation of the different patterns of mitral inflow and their relationship to diastolic function. Diastolic dysfunction was categorised as mild, moderate or severe. Mild diastolic dysfunction was defined as impaired relaxation without increased filling pressures. Moderate diastolic dysfunction was defined as impaired relaxation associated with moderate elevation in filling pressures or pseudonormal filling. Severe diastolic dysfunction was defined as advanced reduction in compliance or restriction of the left ventricle (Figure 4.2).

Figure 4.2 Doppler criteria for classification of diastolic dysfunction (adapted from Redfield et al[36])



4.02 Results

4.02.1 Basic echocardiographic measurements

Patients were categorised into HF-RSF and HF-IPSF as documented in Chapter 2. As described previously, those with HF-IPSF did not have significant valve disease or atrial fibrillation.

Basic echocardiographic measurements of left atrium and left ventricle were recorded for all patients within 48 hours of admission. All patients had qualitative assessment of LV function and quantitative assessment of valvular function. In some studies imaging windows were limited and it was therefore not possible to make formal measurements of atrial or ventricular dimensions. Table 4.1 shows left atrial and ventricular dimensions.

Table 4.1 Left atrial and left ventricular dimensions: HF-RSF and HF-PSF

Echo parameters Mean (SD)	HF-RSF (n=149)	HF-PSF (n=147)	p value
LA diameter[†]	n=96 4.5 (0.8)	n=92 4.3 (0.9)	0.098
LVSDD[‡]	n=83 1.04 (0.3)	n=90 1.2 (0.3)	0.003
LVIDD[††]	n=94 5.8 (0.9)	n=90 4.6 (0.8)	<0.0001
LVIDS[‡‡]	n=51 4.9 (1)	n=28 3.1 (0.7)	<0.0001
LVPWD[†††]	n=81 0.96 (0.2)	n=89 1.02 (0.2)	0.045
LV mass[‡‡‡]	n=80 226 (69)	n=88 186 (62)	<0.0001

[†]Left atrial diameter (cm)
[‡] Interventricular septum diameter in diastole (cm)
[††]Left ventricular internal diameter in diastole (cm)
[‡‡] Left ventricular internal diameter in systole (cm)
[†††]Left ventricular posterior wall diameter in diastole (cm)
[‡‡‡] Left ventricular mass

Table 4.1 illustrates that the HF-RSF group had increased LV diameter and greater LV mass compared with the HF-PSF group. The septum and posterior wall were thicker in the HF-PSF group. There was no significant difference in the left atrial size between the two groups. Table 4.2 details these parameters when the HF-RSF group is compared to the HF-IPSF group.

Table 4.2 Left atrial and left ventricular dimensions: HF-RSF and HF-IPSF

Echo parameters Mean (SD)	HF-RSF (n=149)	HF-IPSF (n=86)	p value
LA diameter[†]	n=96 4.5 (0.8)	n=51 3.9 (0.6)	<0.0001
IVSDD[‡]	n=83 1.04 (0.3)	n=52 1.13 (0.2)	0.031
LVIDD[††]	n=94 5.8 (0.9)	n=53 4.6 (0.7)	<0.0001
LVIDS[‡‡]	n=51 4.9 (1)	n=5 3.2 (0.7)	0.003
LVPWD[†††]	n=81 0.96 (0.2)	n=52 0.97 (0.2)	0.846
LV mass[‡‡‡]	n=80 226 (69)	n=52 175 (57)	<0.0001

[†]Left atrial diameter (cm)
[‡] Interventricular septum diameter in diastole (cm)
[††]Left ventricular internal diameter in diastole (cm)
[‡‡] Left ventricular internal diameter in systole (cm)
[†††]Left ventricular posterior wall diameter in diastole (cm)
[‡‡‡] Left ventricular mass

Table 4.2 illustrates that the HF-RSF group had significantly larger left atrial and ventricular dimensions and also had greater left ventricular mass compared with the HF-IPSF group. The HF-IPSF group did have significantly thicker left ventricular septum compared with the HF-RSF group.

4.02.2 Echocardiographic measures of diastolic function

The patients in the HF-IPSF group had a further echocardiogram specifically to assess parameters of diastolic function, and these are shown in Table 4.3. As it is not possible to achieve satisfactory imaging windows in all patients, not all measurements have been recorded for every patient.

Table 4.3 Parameters of diastolic function in patients with HF-IPSF

	n	Mean	SD
LA systole	51	3.9	+/-0.6
RVEDD	30	2.9	+/-0.4
IVRT	63	108	+/-25
DT	57	216	+/-63
		Median	**IQR**
E velocity	64	0.69	0.6-0.9
A velocity	63	0.82	0.66-1.0
E/A velocity	63	0.79	0.69-1.0
E velocity (Valsalva)	13	0.53	0.4-0.6
A velocity (Valsalva)	13	0.7	0.54-1.13
E/A ratio (Valsalva)	13	1.0	1.0-1.0

RVEDD = right ventricular end-diastolic diameter, IVRT = isovolumetric relaxation time,
DT = decleration time

4.02.3 Criteria for diastolic heart failure

Using a Medline literature search, seven different sets of criteria for the diagnosis of diastolic dysfunction were identified and the HF-IPSF group was categorised according to each one separately (Table 4.4). The 7 criteria for diastolic dysfunction used were those of Krishnaswamy *et al*[165], Lubien *et al*[166], Redfield *et al*[36], Cohen *et al*[167], European Working Group criteria (EWGR)[168], Chen *et al*[169], and Zile *et al*[170].

Table 4.4 Comparison of median natriuretic peptide concentrations between positive and negative criteria for diastolic dysfunction

Doppler criteria (n)	Median (IQR) BNP pg/ml	p value	Median (IQR) NT-proBNP pg/ml	p value
Krishnaswamy +ve (n=17)	120 (52-250)	0.148	1223 (446-3856)	0.068
Krishnaswamy –ve (n=48)	74 (33-223)		610 (129-1871)	
Lubien +ve (n=14)	105 (47-686)	0.175	669 (417-7839)	0.189
Lubien –ve (n=49)	77 (33-205)		660 (134-2078)	
Redfield +ve (n=24)	85 (39-289)	0.647	933 (254-2323)	0.949
Redfield –ve (n=18)	131 (46-250)		931 (167-3576)	
Chen +ve (n=34)	115 (48-340)	0.054	1180 (405-3576)	0.007
Chen –ve (n=31)	47 (27-152)		410 (106-878)	
Cohen +ve (n=18)	63 (43-262)	0.792	595 (144-1457)	0.895
Cohen –ve (n=47)	120 (32-232)		769 (165-2508)	
EWGR* +ve (n=32)	60 (38-205)	0.227	591 (129-1280)	0.325
EWGR* –ve (n=33)	144 (35-256)		1010 (173-3039)	
Zile +ve (n=67)	84 (37-256)	0.921	748 (144-2496)	0.718
Zile –ve (n=4)	115 (53-138)		598 (173-2308)	

*European Working Group

There was no significant difference in the natriuretic peptide concentrations between those who scored positively or negatively in each individual diastolic dysfunction score (Table 4.4). The only exception to this was the Chen criteria where there was a significantly higher median BNP and NT-proBNP concentration in those who had diastolic dysfunction as classified by this score compared to those who did not ($p=0.054$, $p=0.007$ for BNP and NT-proBNP respectively).

As discussed in Chapter 2, many of these Doppler criteria differentiate diastolic dysfunction into impaired relaxation (mild), pseudonormal (moderate) and restrictive (severe) diastolic dysfunction patterns. The following Figures (4.3 - 4.9) illustrate the relationship between mild, moderate and severe diastolic dysfunction and BNP for each diastolic dysfunction criteria. Three of the criteria (Cohen, EWGR and Zile) reported only the presence or absence of diastolic dysfunction.

Figure 4.3 **Median BNP concentrations using the Krishnaswamy criteria for diastolic dysfunction**

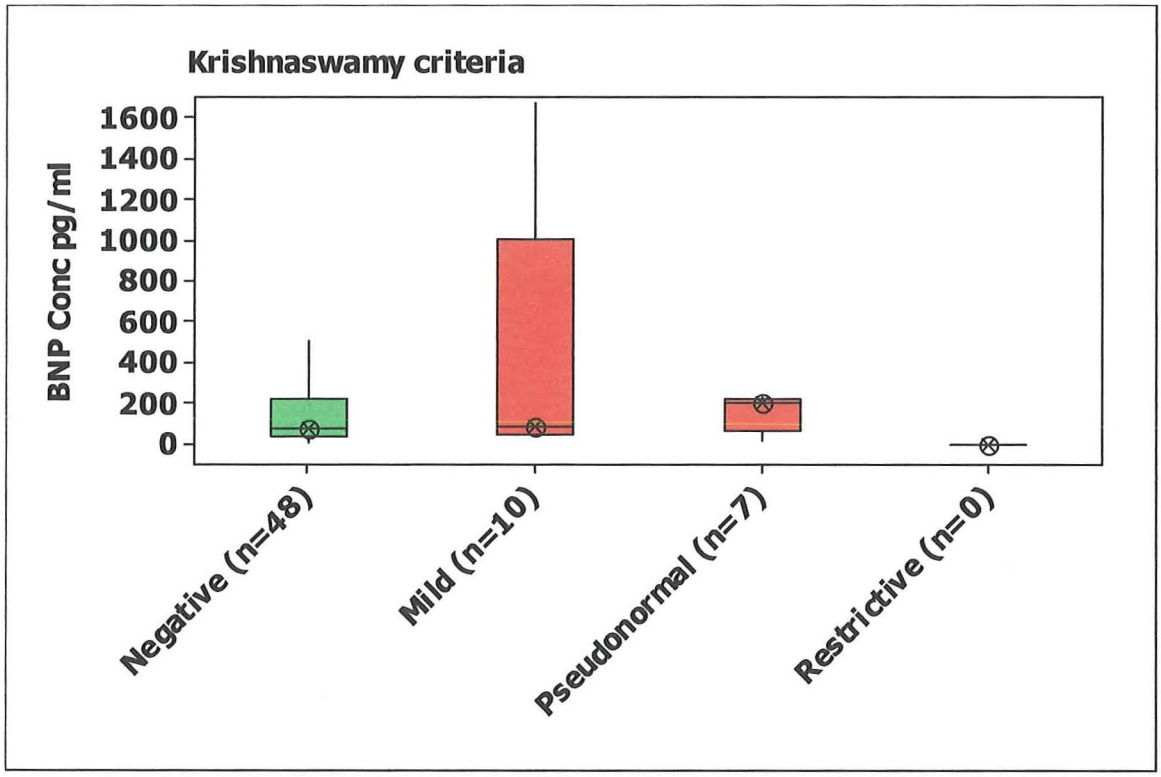


Figure 4.4 **Median BNP concentrations using the Lubien criteria for diastolic dysfunction**

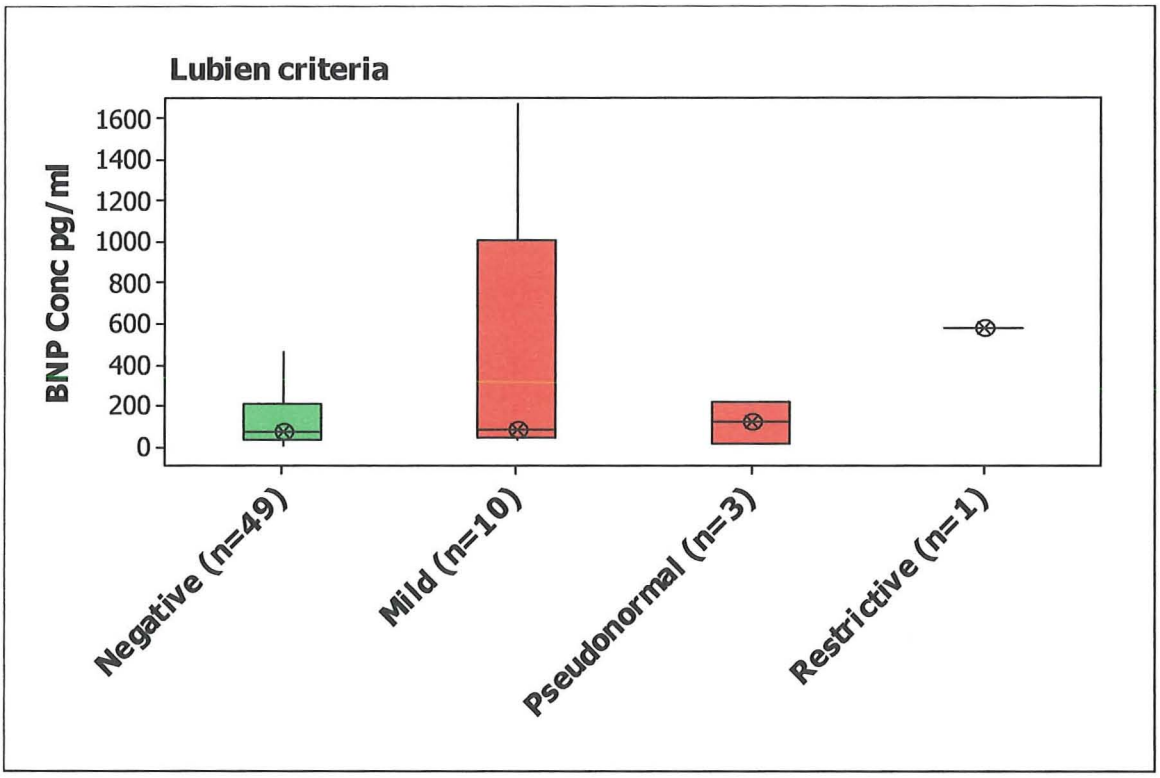


Figure 4.5 **Median BNP concentrations using the Redfield criteria for diastolic dysfunction**

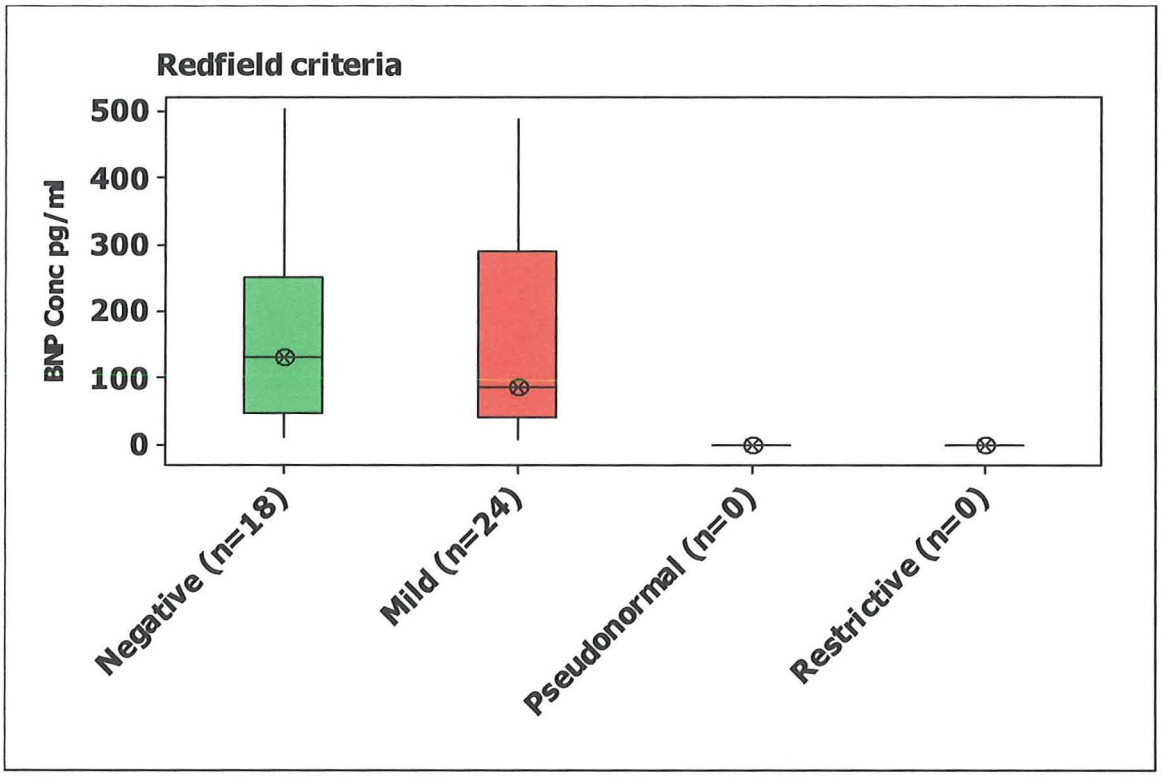


Figure 4.6 **Median BNP concentrations using the Cohen criteria for diastolic dysfunction**

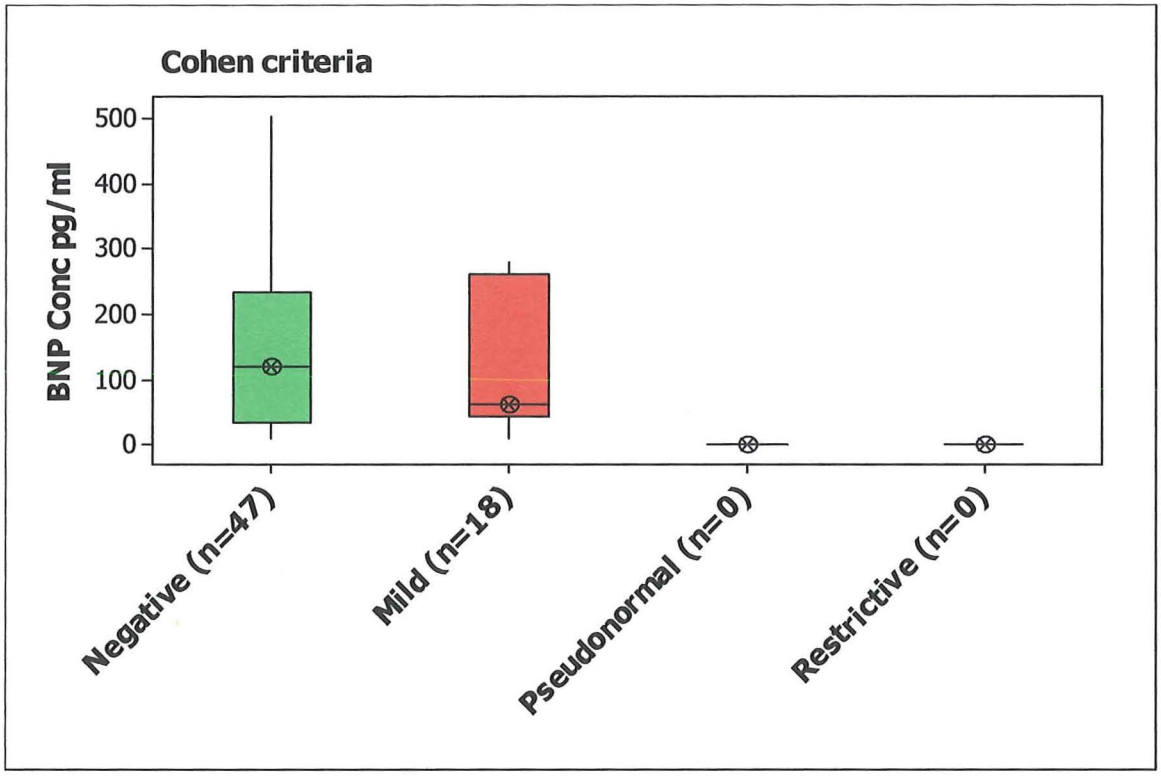


Figure 4.7 **Median BNP concentrations using the Chen criteria for diastolic dysfunction**

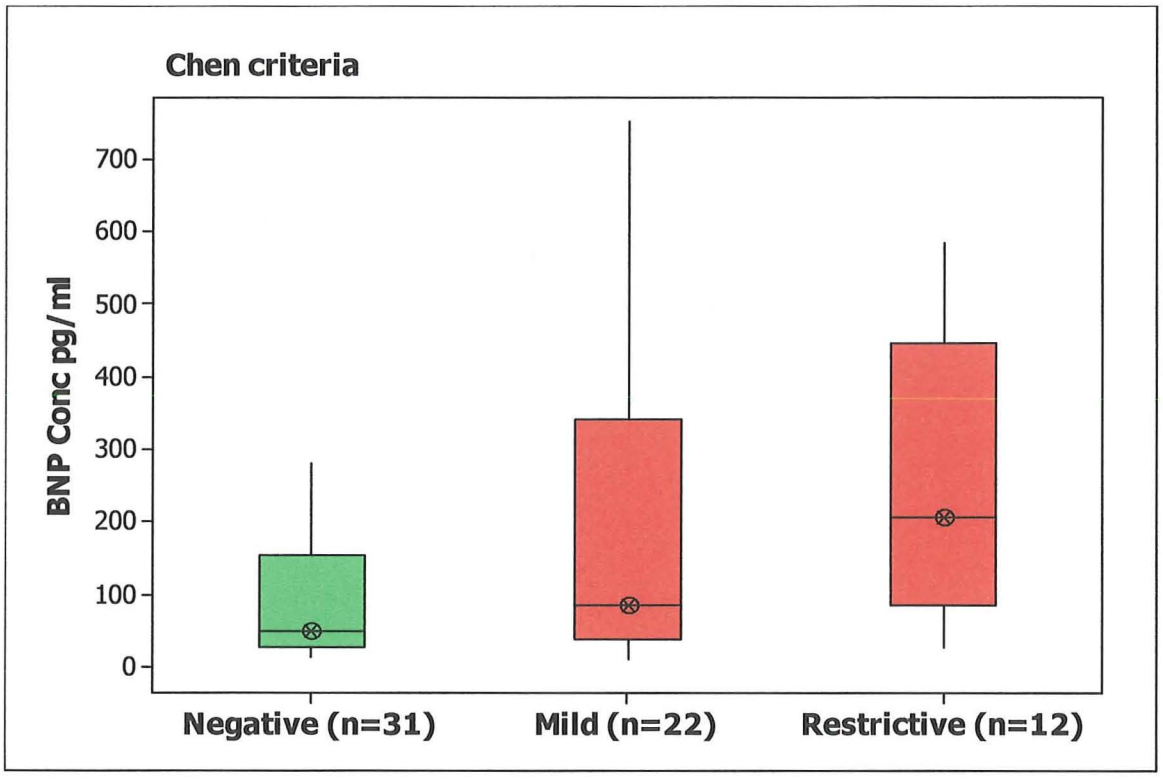


Figure 4.8 **Median BNP concentrations using the European Working Group criteria for diastolic dysfunction**

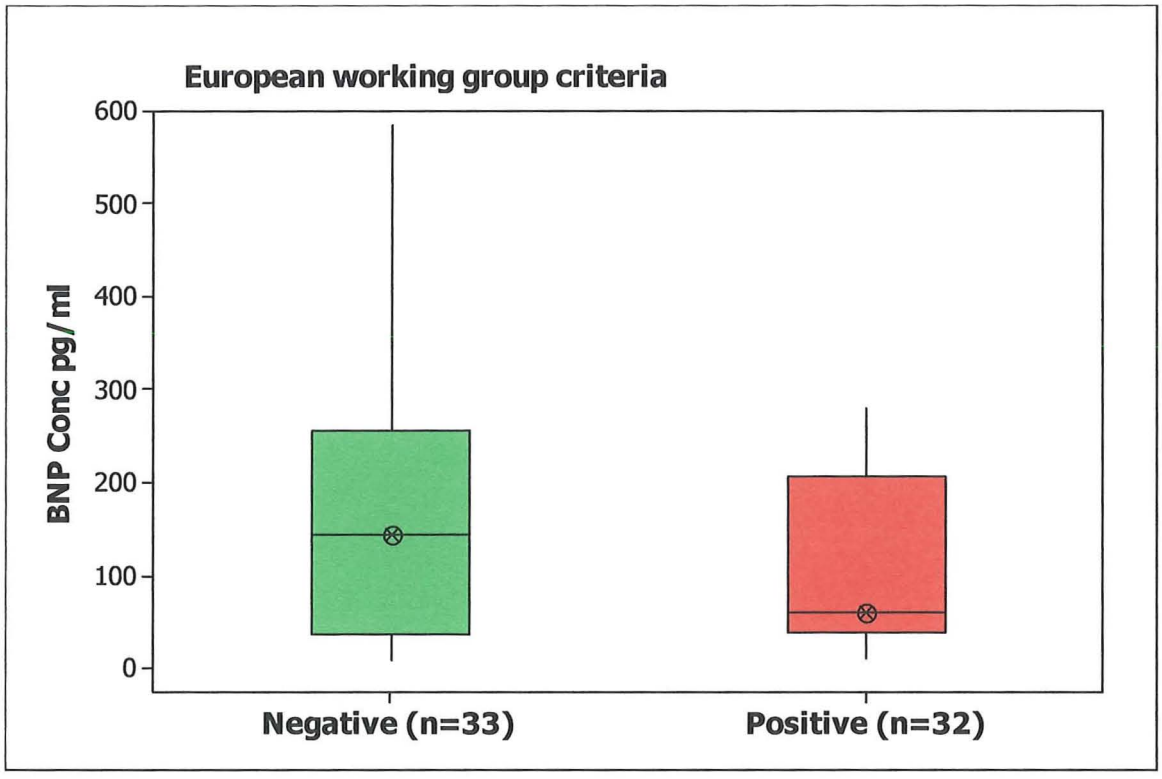
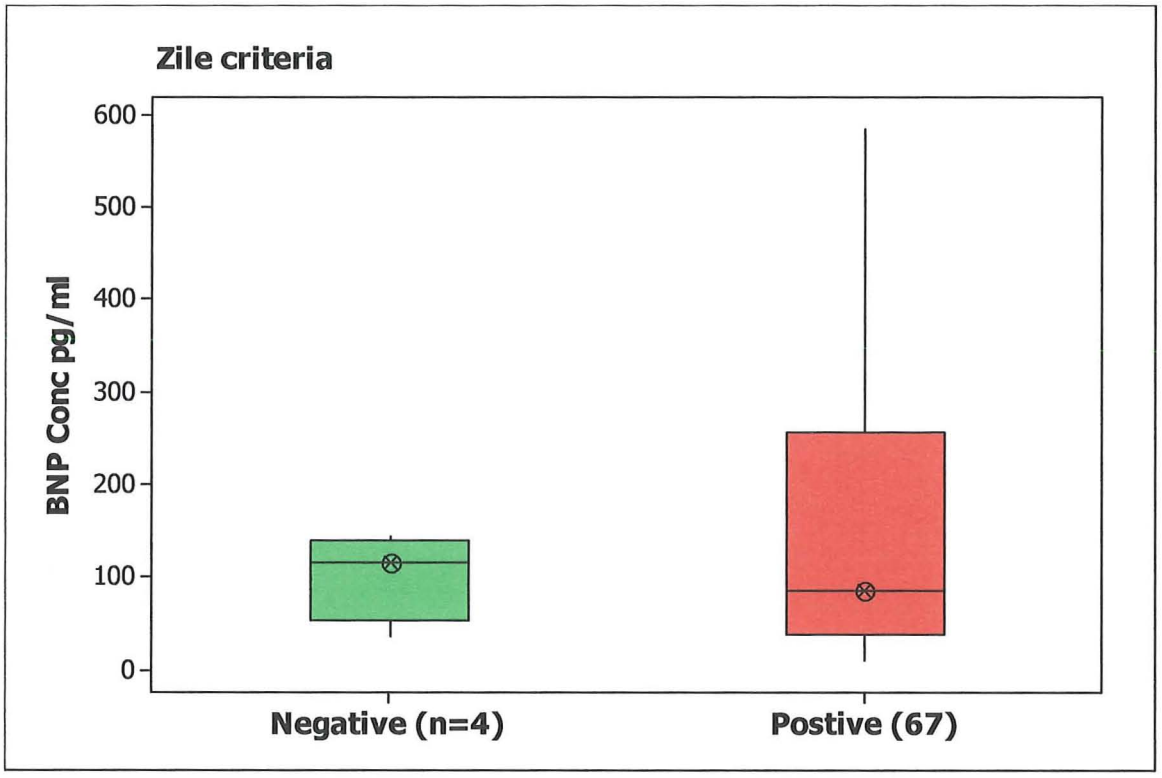


Figure 4.9 Median BNP concentrations using the Zile criteria for diastolic dysfunction



These Figures show that for those criteria that differentiate between mild, moderate and severe diastolic dysfunction, BNP concentrations become higher as the diastolic dysfunction gets worse. The exception to this was with the Redfield criteria, presumably because no patients were classified as having either pseudonormal or restrictive diastolic dysfunction.

Table 4.5 shows the number of positive diastolic Doppler criteria and corresponding natriuretic peptide concentrations. There did not appear to be any correlation between the number of Doppler indices of diastolic dysfunction and the median BNP or NT-proBNP concentrations (Table 4.5).

Table 4.5 Diastolic Doppler criteria and natriuretic peptide concentrations

No. of DD criteria +ve	n	Median (IQR) BNP pg/ml	Median (IQR) NT-proBNP pg/ml
1	13	120 (27-355)	567 (114-3723)
2	12	133 (42-455)	792 (123-4946)
3	22	57 (29-209)	422 (137-1503)
4	6	60 (16-812)	796 (122-14052)
5	2	40 (n/a)	878 (n/a)
6	0	N/A	N/A

Of the HF-IPSF group who had satisfactory Doppler measurements taken, only three subjects did not score positively for diastolic dysfunction on any criteria. Table 4.6 shows the proportions of patients with diastolic dysfunction as classified by each diastolic Doppler criteria.

Table 4.6 Proportion of patients with diastolic dysfunction according to different criteria

Diastolic dysfunction criteria	n (%)
Krishnaswamy	17 (26)
Lubien	14 (22)
Redfield	24 (57)
Chen	34 (52)
Cohen	18 (28)
European Working Group	32 (49)
Zile	67 (94)

For each set of criteria, all the diastolic parameters had to be measured in order for the criteria to be applied. This was not always possible, particularly as most of the patients in the study were elderly and might therefore be expected to have some difficulty with manoeuvres such as Valsalva. Of the 86 patients with HF-IPSF, 74% had all measurements of diastolic function recorded.

Table 4.6 illustrates that there is poor concordance between different criteria for diastolic dysfunction in our population. The rates of diastolic dysfunction varied from 22% - 94% depending on the criteria used.

4.03 Discussion

The echocardiographic data from this study show that those patients with either HF-PSF or HF-IPSF have significantly increased interventricular septum diameter when compared with those with HF-RSF. This would be consistent with a higher proportion of these patients having a prior history of hypertension and is in turn recognised to be associated with diastolic dysfunction[169]. These patients also differed from those with HF-RSF in that the median LV diameters were not increased in those with HF-PSF or HF-IPSF.

I did not find that the different published echocardiographic criteria were useful in determining which patients had diastolic dysfunction. There was a wide variation in the estimated prevalence of diastolic dysfunction in this cohort, depending on the set of criteria used. There was also no correlation between the presence of the individual echocardiographic criteria for diastolic dysfunction and natriuretic peptide concentrations. Of the seven diastolic criteria used only the Chen criteria showed higher median natriuretic peptide concentrations in those with diastolic dysfunction, compared to those without. There was no obvious reason as to why the Chen criteria should show this relationship which was not seen with the other criteria. The Chen criteria did show that BNP concentrations were higher when more severe diastolic dysfunction was present. Therefore I feel that this study suggests that the use of standard diastolic Doppler echocardiography with currently available criteria is not sufficient to diagnose clinically relevant diastolic dysfunction. There does appear to be an association between worsening diastolic dysfunction and rising BNP, which supports the idea that elevated BNP broadly represents functional LV compromise.

However, this does not mean that echocardiography has no place in the diagnosis of diastolic dysfunction. Since this study was started newer techniques, such as tissue Doppler

echocardiography have been developed to evaluate LV filling dynamics. The tissue velocity measured during early filling (E') can be considered to be a surrogate marker for tau (the time constant of relaxation during the active component of diastole), as it is primarily determined by the expansion of the left ventricle during relaxation. Therefore, the ratio of peak early transmitral flow velocity (E) to the peak early myocardial tissue velocity (E/E') is frequently cited as evidence of myocardial diastolic dysfunction. This ratio reflects the LA pressure elevation compared with the degree of tau prolongation[185].

Although newer echocardiographic techniques such as tissue Doppler will improve our non-invasive assessment of diastolic function, the problem still remains that these measurements do not provide direct pathophysiological insights into the mechanisms responsible for causing the volume overload in patients with HF. It is possible that imaging modalities such as cardiac MRI may be able to provide more detailed information regarding the true pathophysiology of this cohort of HF patients.

CHAPTER FIVE

NATRIURETIC PEPTIDES

5.01 Introduction: Natriuretic peptides and HF-PSF

Plasma concentrations of B-type natriuretic peptide (BNP) and its precursor, NT-proBNP are known to be increased in patients with reduced LV systolic function, regardless of the presence or absence of symptoms of heart failure[92;186]. It is also clear that plasma concentrations of both peptides are positively correlated with the severity of heart failure[95;98;103;105;165;187-194]. BNP independently predicts morbidity and mortality in asymptomatic reduced LV systolic function, and in mild to moderate HF-RSF[104;195;196]. In addition, BNP has been shown to be a strong and independent predictor of sudden death in patients with HF[107]. NT-proBNP has also been shown to be an independent predictor of mortality[106;197] or decompensated HF following myocardial infarction[118], and in patients with chronic HF-RSF of ischaemic aetiology[104].

Data on the predictive value of natriuretic peptides in patients with HF-PSF are more limited. Studies have shown that BNP is elevated in patients with HF-PSF in the non-emergency setting[165;166;198-201].

Maisel *et al* were one of the first groups to demonstrate that BNP can reliably rule out the presence of abnormal LV systolic or diastolic function on echocardiography[202]. Lubien *et al* confirmed these findings in patients with preserved systolic function but abnormal diastolic function[166]. They demonstrated that BNP concentrations accurately predicted the presence of abnormalities in diastolic function on echocardiography, regardless of the presence of symptoms of HF. In that study, diastolic dysfunction was classified as impaired relaxation, pseudonormal filling or restrictive filling, as discussed in Chapter 4. The mean BNP concentration was highest in those with restrictive filling patterns. The authors concluded that, although BNP could not be used to differentiate between systolic and diastolic

dysfunction, BNP concentrations within normal limits in the setting of preserved systolic function may be able to rule out clinically significant abnormalities in diastolic function. BNP concentrations in those with preserved systolic function correlated with the presence of diastolic dysfunction. The authors calculated an area under the receiver operator curve (ROC) of 0.92 which is comparable to those for currently used screening tools such as prostate-specific antigen (which has an area under the curve (AUC) of 0.94 for prostatic cancer detection) and superior to some others, for example cervical smears (AUC = 0.7) and mammography (AUC= 0.85)[166;203-205].

Krishnaswamy *et al* took this concept a stage further, and hypothesised that as BNP reliably predicts the presence of systolic or diastolic LV dysfunction, a normal BNP concentration may preclude the requirement for echocardiography[165]. They demonstrated that BNP concentrations were higher in those with echocardiographic abnormalities. The BNP concentrations were highest in those with both systolic and diastolic dysfunction. Patients with systolic dysfunction had higher BNP concentrations than those with diastolic dysfunction. Of those with diastolic dysfunction, a restrictive filling pattern was associated with the highest BNP concentrations. The authors concluded that it was not possible to differentiate between systolic and diastolic dysfunction using BNP alone, but that an elevated BNP concentration in the context of preserved systolic function indicates the presence of diastolic dysfunction[165].

Similar findings have been demonstrated in the emergency setting. The Breathing Not Properly Multinational study recruited patients presenting with shortness of breath to hospital emergency departments and reported that HF-PSF was common in this group. When they examined BNP, they found higher concentrations in patients with HF compared to those

without HF. Once again, BNP alone could not differentiate between HF-RSF and HF-PSF, however, the authors concluded that a low BNP concentration in the setting of breathlessness had a negative predictive value of 96%. They therefore suggested that BNP should not be a surrogate for echocardiography but could be used in conjunction with clinical findings to aid diagnosis and further management[100].

More recently, Dahlstrom *et al* reported that patients with restrictive or pseudonormal filling patterns had higher BNP concentrations and consequently that BNP could be used as a marker for the presence of these abnormalities. However, they found that patients with relaxation abnormalities, who accounted for the majority of their cohort, had low BNP concentrations. The authors therefore argued that low BNP concentrations in the context of HF-PSF could not be used to rule out the presence of diastolic dysfunction, as mild diastolic dysfunction in the form of impaired relaxation was not associated with an elevated BNP in their study[206].

Hypertension is a major risk factor for diastolic heart failure, as it can result in left ventricular hypertrophy (LVH) which can result in reduced compliance[8;19]. *In vitro* studies have shown a close relationship between BNP and cardiomyocyte hypertrophy[207;208]. Of particular interest, was the finding that adaptive hypertrophy alone did not promote ventricular BNP production in Dahl salt-sensitive hypertensive rats, and that BNP was only elevated in the presence of maladaptive LV hypertrophy with fibrosis, which caused overt symptomatic DHF. Yamaguchi *et al* demonstrated elevated BNP concentrations may be a hallmark in patients with, or at risk of developing, diastolic heart failure among subjects with preserved systolic function independent of LV hypertrophy[209].

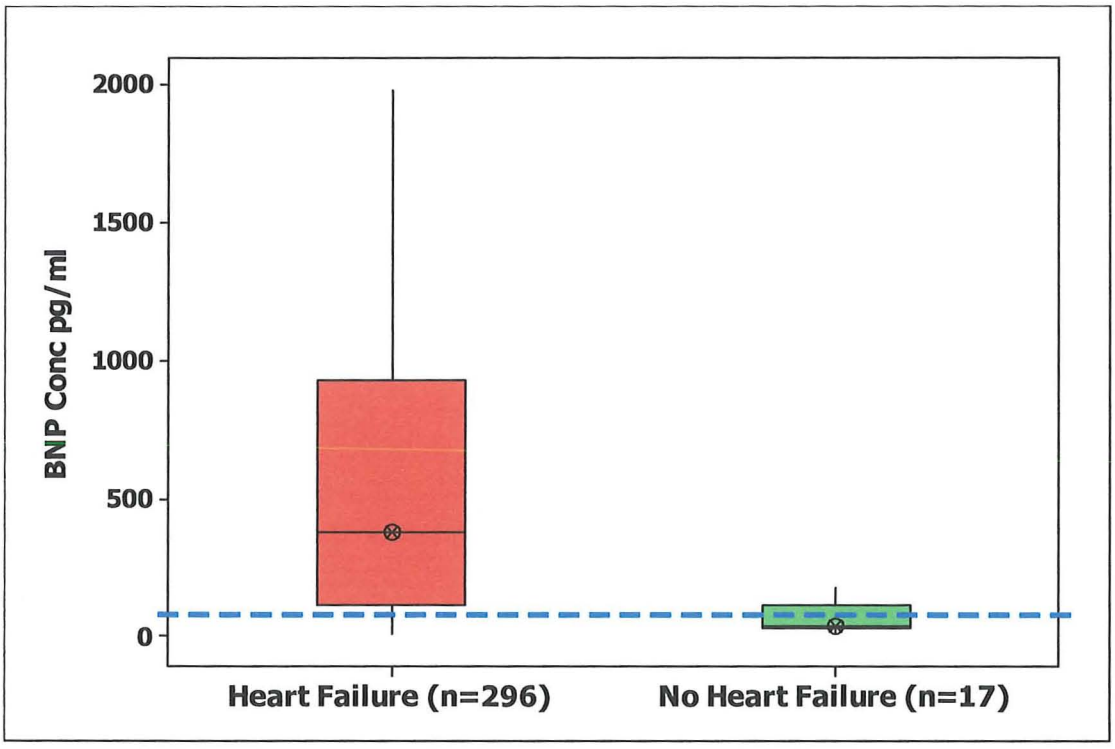
5.02 Results

5.02.1 Comparison of natriuretic peptide levels in HF-RSF and HF-PSF

As described in the Chapter 2, both BNP and NT-proBNP plasma concentrations were measured in all patients.

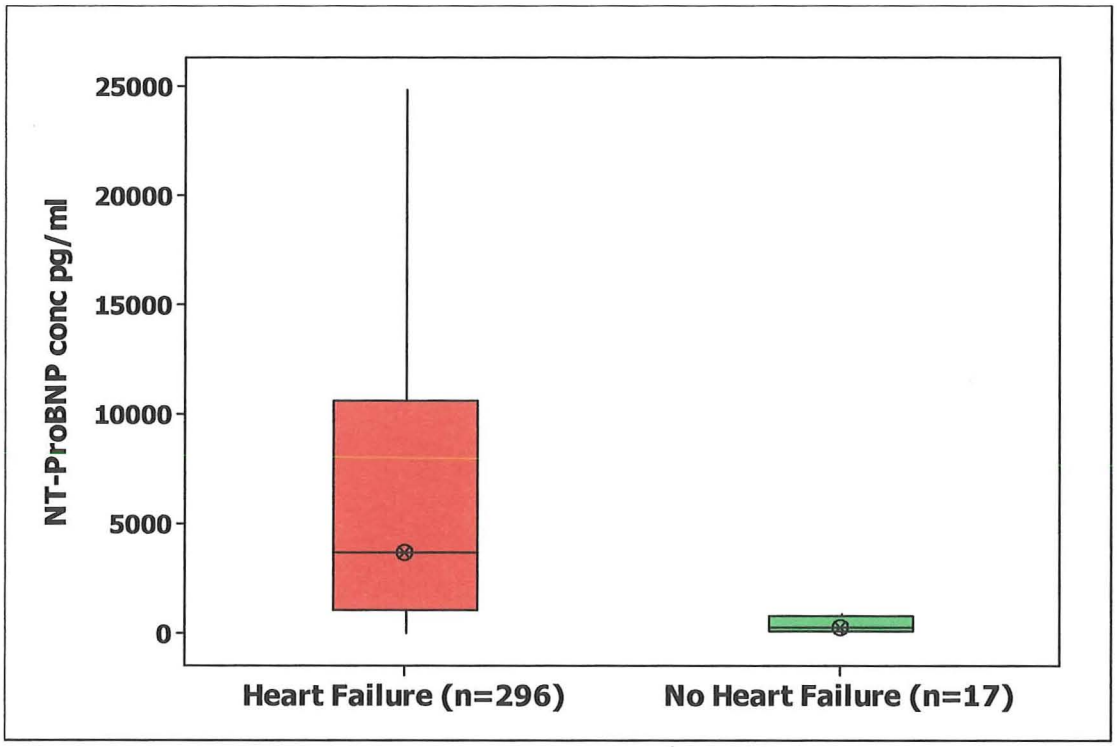
A small number of patients (n=17), were recruited into the study but did not have clinical evidence of heart failure when assessed using the heart failure scores. Significantly higher median concentrations of both BNP and NT-proBNP were found in those with clinical evidence of heart failure. Median BNP was 371 pg/ml (IQR:114-920 pg/ml) and median NT-proBNP was 3624 pg/ml (IQR: 1047-1059 pg/ml) in patients with clinical evidence of heart failure, as compared to a median BNP of 36 pg/ml (IQR: 28-116 pg/ml) [Figure 5.1] and median NT-proBNP of 234 pg/ml (IQR: 1047-10593 pg/ml) in those with no evidence of heart failure ($p<0.0001$) [Figure 5.2].

Figure5.1: Comparison of median BNP concentrations in patients with or without clinical heart failure



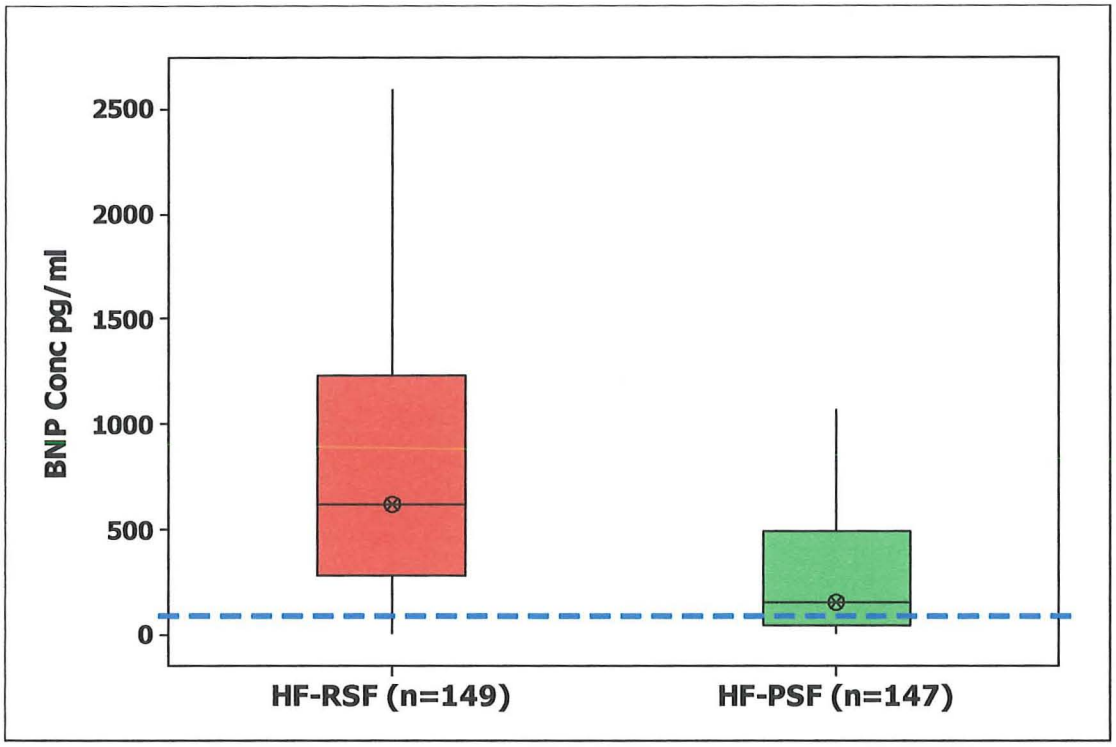
Upper limit of normal

Figure 5.2 **Median NT-proBNP concentrations in patients with and without clinical heart failure**



As described in Chapter 2, those patients with clinical evidence of HF were divided into two groups according to the initial echocardiogram, either reduced (HF-RSF) or preserved systolic function (HF-PSF). The following two figures illustrate the differences in the median BNP and NT-proBNP concentrations found between these two groups.

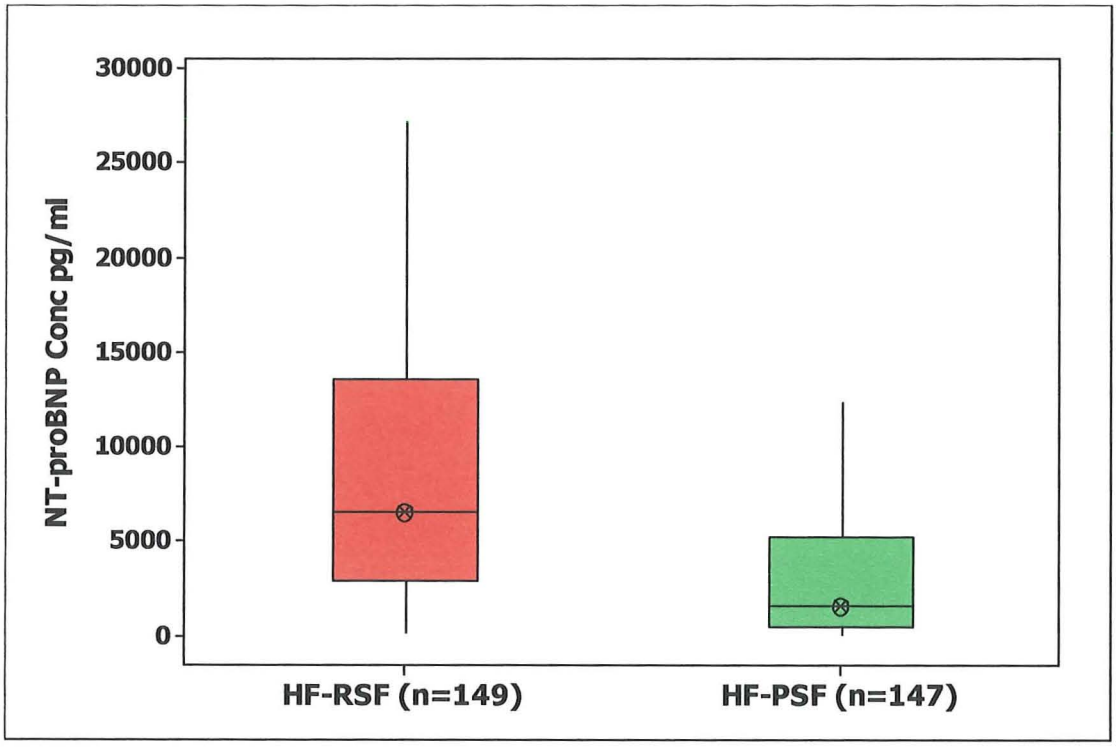
Figure 5.3 Median BNP concentrations in patients with HF-RSF and HF-PSF



Upper limit of normal

There is a significantly higher median BNP concentration in those with HF-RSF at 621 pg/ml (IQR: 287-1228 pg/ml) compared to 158 pg/ml (49-488 pg/ml) in the HF-PSF group ($p < 0.0001$) [Figure 5.3].

Figure 5.4 Median NT-proBNP concentrations in patients with HF-RSF and HF-PSF



Again, the median concentration of NT-proBNP is significantly higher the HF-RSF group at 6507 pg/ml (IQR: 2888 – 13,523), compared with the HF-PSF median value of 1541 pg/ml (IQR: 410-5223 pg/ml) ($p<0.0001$) [Figure 5.4].

As described in Chapter 2, the upper limit of normal for natriuretic peptide concentrations were taken as the 95th percentile of a local healthy population. Figures 5.5 - 5.6 illustrate the

proportion of patients in each group that have an elevated natriuretic peptide concentration i.e. have biochemical evidence of LV compromise.

Figure 5.5 Percentage of patients in each group with an elevated BNP concentration

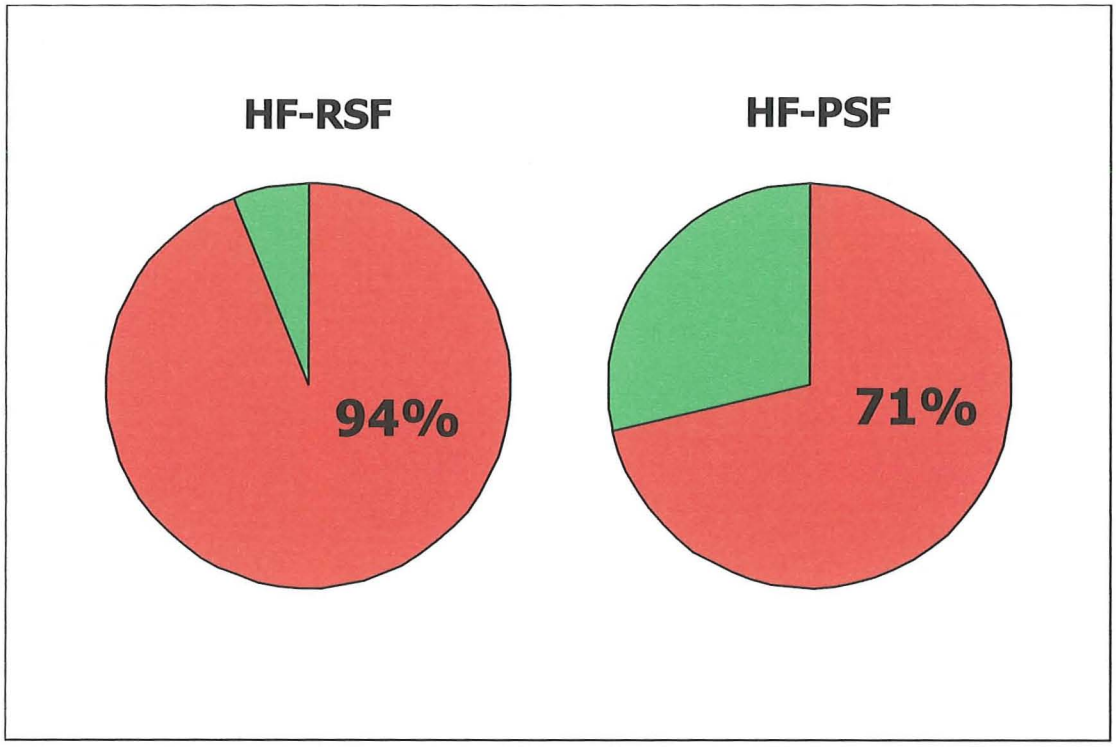
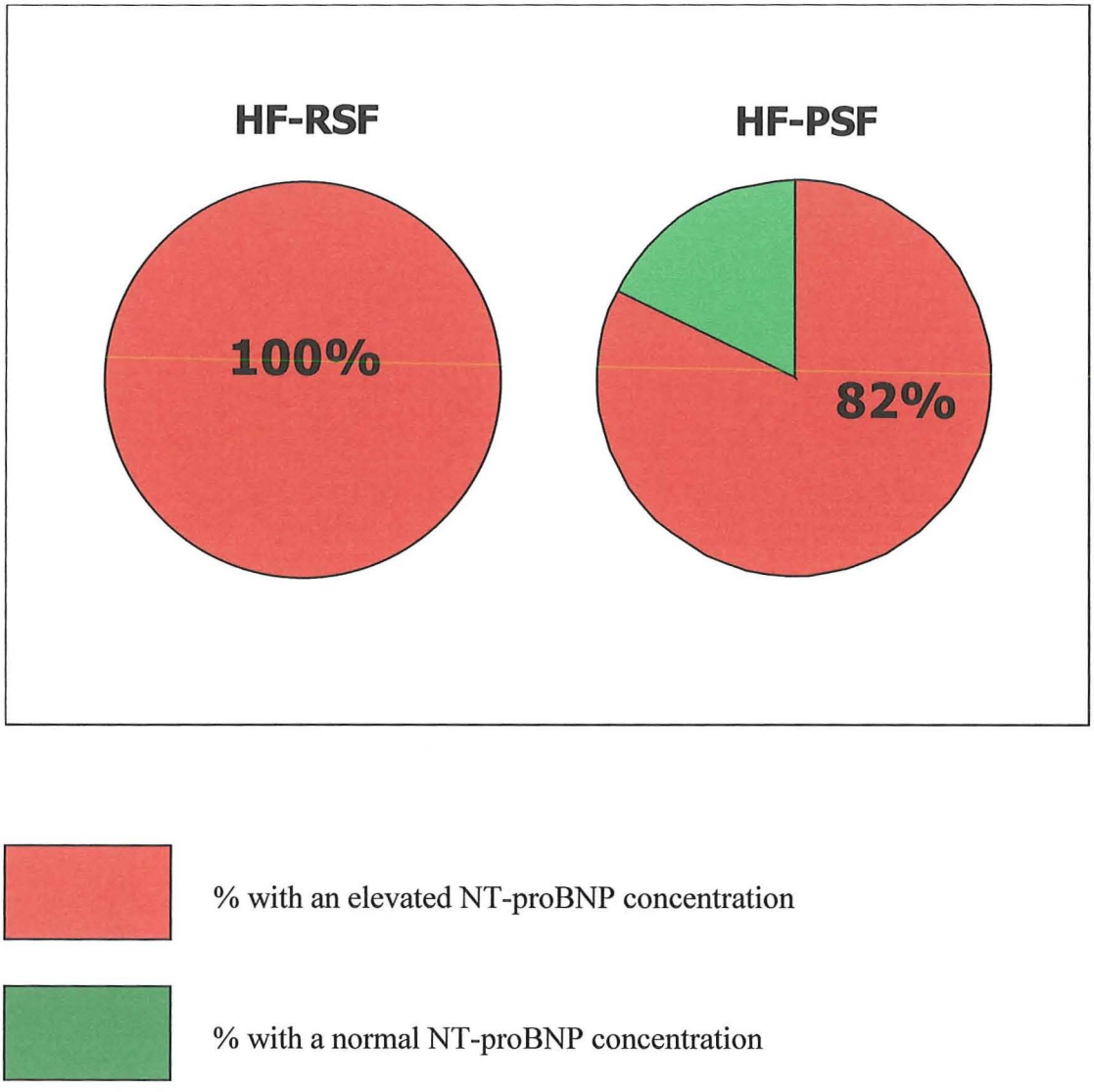


Figure 5.6 Percentage of patients in each group with an elevated NT-proBNP concentration



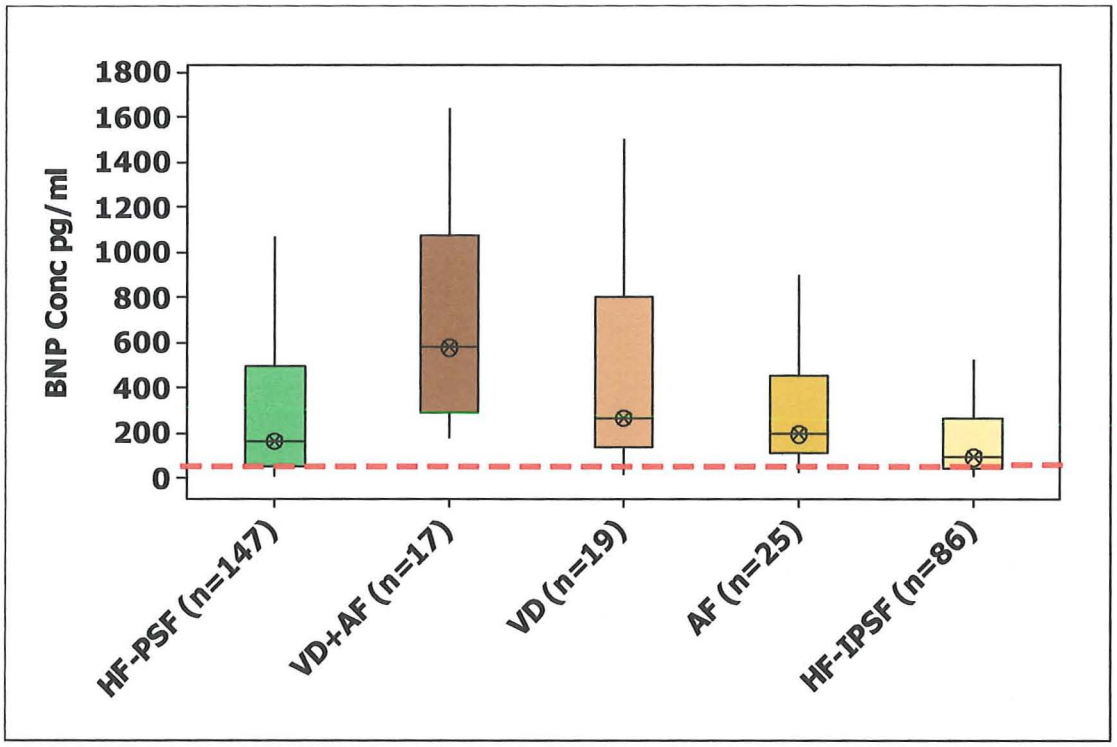
It is clear that nearly all patients with HF-RSF have an elevated BNP and NT-proBNP (94% and 100% respectively). In the HF-PSF group, 71% of patients had an elevated BNP and 82% of patients had an elevated NT-proBNP. These percentages are significantly less than

those in the HF-RSF group ($p<0.0001$), but still represent well over two-thirds of the patients in the HF-PSF group.

5.02.2 Influence of valve disease or atrial fibrillation on natriuretic peptides in HF-PSF

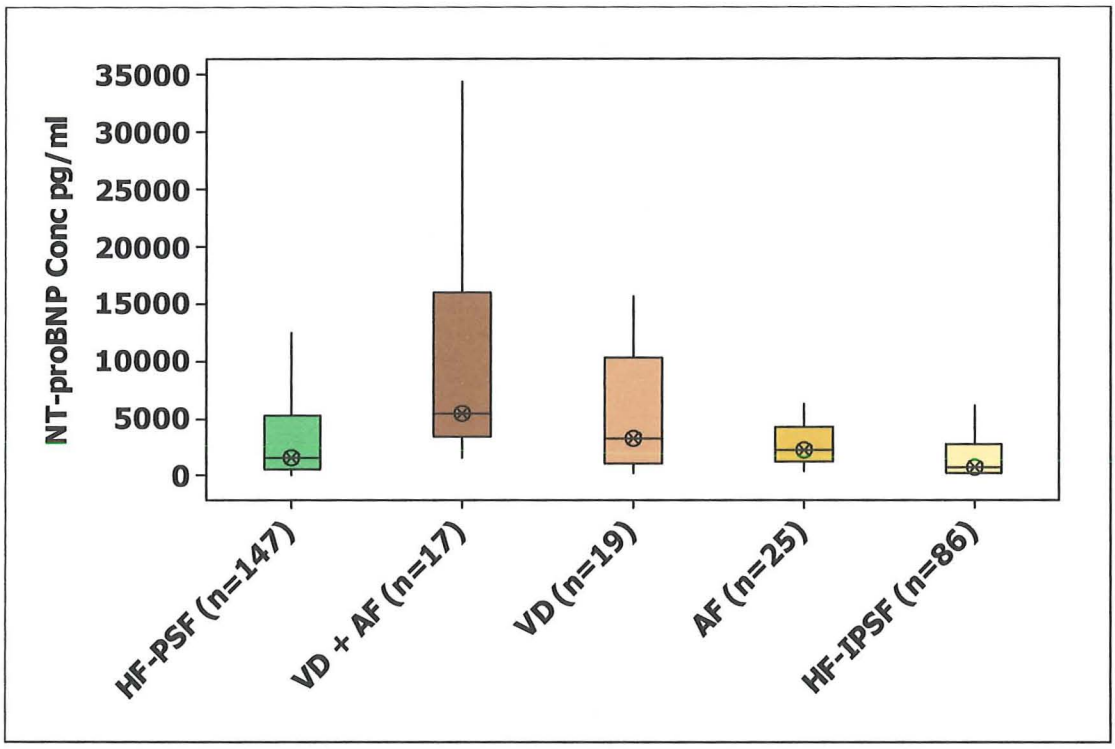
In HF-PSF the presence of valve disease or atrial fibrillation (AF) results in higher BNP and NT-BNP concentrations. As shown in Figures 5.7 and 5.8 the highest median BNP and NT-proBNP concentrations were found in those with both valve disease and atrial fibrillation (BNP 578 pg/ml [IQR: 284-1070 pg/ml], NT-proBNP 5354 pg/ml [IQR: 3300-16,025 pg/ml]). The presence of valve disease alone had a more profound effect on natriuretic peptide concentrations (median BNP 265 pg/ml [IQR: 130-798 pg/ml], median NT-proBNP 3101 pg/ml [IQR: 1049-10,180 pg/ml]) than the presence of atrial fibrillation alone (median BNP 193 pg/ml [IQR: 109-450] pg/ml, median NT-proBNP 2176 pg/ml [1187-4127 pg/ml]). The lowest median BNP and NT-proBNP concentrations were found in those with HF-PSF but without valve disease or atrial fibrillation (median BNP 92pg/ml [IQR: 37-259pg/ml], median NT-proBNP 649pg/ml [IQR: 174-2596pg/ml]). However, in this group, 56% had an elevated BNP concentration and 71% had an elevated NT-proBNP concentration without VHD or AF to account for the elevation in natriuretic peptides.

Figure 5.7 **Effect of valve disease or atrial fibrillation on BNP concentrations in HF-PSF**



HF-PSF = All heart failure with preserved systolic function
VD + AF = HF-PSF including those with valve disease and atrial fibrillation
VD = HF-PSF with valve disease but no atrial fibrillation
AF = HF-PSF with atrial fibrillation but no valve disease
HF-IPSF = HF-PSF with no valve disease or atrial fibrillation

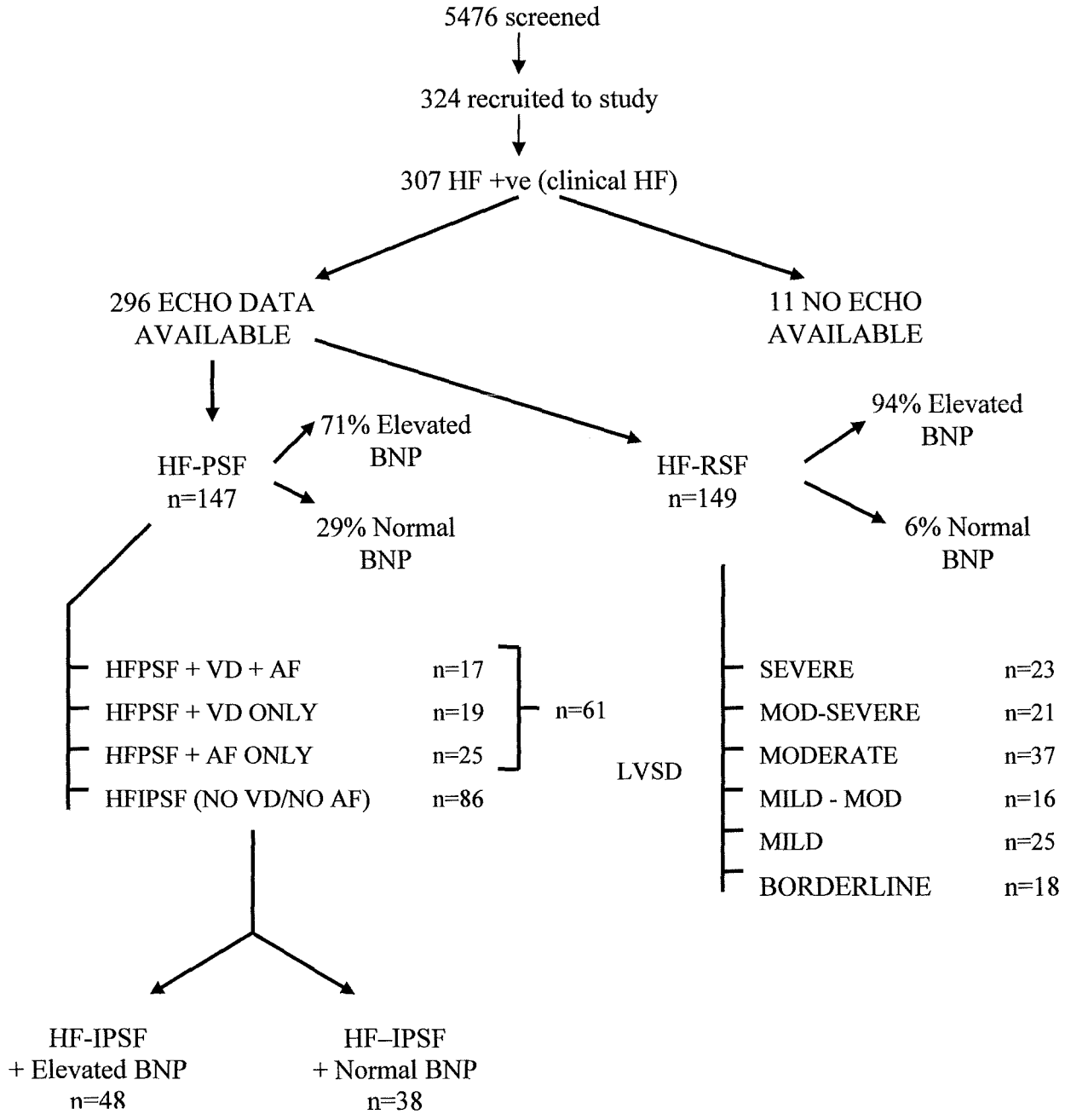
Figure 5.8 Effect of valve disease or atrial fibrillation on NT-proBNP concentrations in HF-PSF



HF-PSF = All heart failure with preserved systolic function
VD + AF = HF-PSF including those with valve disease and atrial fibrillation
VD = HF-PSF with valve disease but no atrial fibrillation
AF = HF-PSF with atrial fibrillation but no valve disease
HF-IPSF = HF-PSF with no valve disease or atrial fibrillation

For further analysis I have used BNP as the marker of LV compromise because it is my view that as the upper limits of normal were obtained locally, they are more reliable for the population being studied. 41% of patients with HF-PSF have VHD, AF or both which could account for their symptoms and signs of HF and could also contribute to the elevated natiuretic peptide concentrations. If we examine only those with HF-IPSF then we can use elevated BNP concentrations to highlight which of these patients has biochemical evidence of LV compromise. Figure 5.9 illustrates the subsets of patients within the study.

Figure 5.9 Subsets of patients recruited



I have now isolated a group of patients without VHD or AF who have clinical evidence of HF, with preserved LV systolic function by echocardiography, but biochemical evidence of LV compromise. This group accounts for 16% of all patients recruited with clinical evidence

of heart failure, and 33% of all those with HF-PSF. Tables 5.1-5.6 compare the clinical characteristics of this group of patients to those who have HF-IPSF but a normal BNP.

Table 5.1 Clinical characteristics of patients with HF-IPSF and elevated or normal BNP concentrations

	HF-IPSF and elevated BNP (n=48)	HF-IPSF and normal BNP (n=38)	p value
Age (yrs) mean (SD)	74 (10.7)	72 (9.3)	0.33
Female n (%)	38 (79)	22 (58)	0.03
BMI mean (SD)	29.2 (5.9)	29.5 (5.1)	0.87
SBP (mmHg) mean (SD)	143 (31)	145 (29)	0.75
DBP (mmHg) mean (SD)	77 (18)	77 (16)	0.90
RR (breaths pm) mean (SD)	20 (5)	22 (13)	0.56
HR (bpm) mean (SD)	84 (20)	82 (20)	0.62
Creatinine (μmol/L) median (IQR)	103 (82-129)	102 (89-110)	0.69
eGFR median (IQR)	50 (83-129)	57 (49-67)	0.08
Hb (g/dL) mean (SD)	12.1 (2.1)	13 (1.5)	0.02
Troponin positive n(%)	14 (29)	0	<0.001
Abnormal ECG n (%)	37 (77)	19 (50)	0.01
Ladder of life score mean (SD)	4.7 (2.3)	5.3 (2.6)	0.27

BMI = Body mass index, SBP = systolic blood pressure, DBP = diastolic blood pressure, RR = respiratory rate, HR = heart rate, eGFR = estimated glomerular filtration rate, Hb = haemoglobin

Table 5.2 Symptoms and signs of patients with HF-IPSF and elevated or normal BNP concentrations

n (%)	HF-IPSF and elevated BNP (n=48)	HF-IPSF and normal BNP (n=38)	p value
Symptoms			
NYHA (III/IV)	24 (50)	23 (61)	0.33
Killip ≥ IIA	37 (77)	27 (71)	0.52
Paroxysmal nocturnal dsypnoea	14 (29)	10 (26)	0.77
Orthopnoea	23 (48)	14 (37)	0.30
Wheeze	13 (27)	13 (34)	0.48
Reduced exercise tolerance	42 (88)	34 (89)	0.78
Ankle swelling	36 (75)	24 (50)	0.24
Leg fatigue	20 (42)	16 (42)	0.97
Weight loss	2 (4)	0	N/A
General fatigue	40 (83)	28 (74)	0.28
Signs			
Raised JVP	27 (56)	9 (24)	0.001
3rd HS	0	0	N/A
Peripheral oedema	31 (65)	23 (61)	0.17
Sacral oedema	2 (4)	0	N/A
Ascites	0	0	N/A
Wheeze	8 (17)	5 (13)	0.65
Crepitations	38 (79)	27 (71)	0.39

Table 5.3 Comparison of NYHA scores in patients with HF-IPSF and elevated or normal BNP concentrations

NYHA Score n (%)	HF-IPSF and elevated BNP (n=48)	HF-IPSF and normal BNP (n=38)
I	0	0
II	24 (50)	23 (61)
III	15 (31)	7 (18)
IV	9 (19)	8 (21)

Table 5.4 Comparison of Killip scores in patients with HF-IPSF and elevated or normal BNP concentrations

Killip Score n (%)	HF-IPSF and elevated BNP (n=48)	HF-IPSF and normal BNP (n=38)
I	0	0
II	11 (23)	11 (29)
IIa	20 (42)	17 (45)
IIb	6 (13)	6 (16)
III	11 (23)	0
IV	0	0

Table 5.5 Co-morbidities of patients with HF-IPSF and elevated or normal BNP concentrations

n (%)	HF-IPSF and elevated BNP (n=48)	HF-IPSF and normal BNP (n=38)	p value
IHD	29 (60)	19 (50)	0.33
Hypertension	30 (63)	20 (53)	0.36
Hypercholesterolaemia	15 (31)	10 (26)	0.61
PAD	3 (6)	2 (5)	N/A
DM	13 (27)	7 (18)	0.34
CVD	11 (23)	4 (11)	N/A
COPD	24 (50)	16 (42)	0.46
Anaemic	22 (46)	9 (24)	0.03

IHD = ischaemic heart disease, PAD = peripheral arterial disease, DM = diabetes mellitus, CVD = cerebrovascular disease, COPD = chronic obstructive pulmonary disease

Table 5.6 Comparison of admission cardiovascular medications of patients with HF-IPSF and elevated or normal BNP concentrations

Medication n (%)	HF-IPSF and elevated BNP (n=48)	HF-IPSF and normal BNP (n=38)	p value
Antiplatelet	28 (58)	17 (45)	0.25
Diuretic	31 (65)	21 (55)	0.46
Spironolactone	1 (2)	0	N/A
ACE I	14 (29)	12 (32)	0.75
ARB	1 (2)	3 (6)	N/A
Statin	19 (40)	12 (32)	0.49
β-Blocker	15 (31)	10 (26)	0.67
Vasodilator	17 (35)	17 (45)	0.33
Digoxin	2 (4)	0	N/A

Tables 5.1-5.6 compare the clinical characteristics of those with HF-IPSF and an elevated BNP to those with a normal BNP. Mean ages in the two groups were similar (p=0.33). A higher proportion of patients with an elevated BNP were female (79% vs 58%, p=0.03). The mean haemoglobin was lower (p=0.02) and the proportion of anaemic patients higher (p=0.03) in the elevated BNP group. A significantly higher proportion of patients in the elevated BNP group had an abnormal ECG (p=0.01). In both groups, the median eGFR showed moderate renal dysfunction. There was a trend towards worse renal function in the elevated BNP group but this was not statistically significant. A higher proportion of patients with an elevated BNP also had a positive troponin (p<0.001). No patients in the group with HF-IPSF and a normal BNP had a positive troponin on admission.

Symptoms and signs were similar in both groups with the exception of an elevated JVP which was reported more commonly in the group with an elevated BNP concentration (p=0.001).

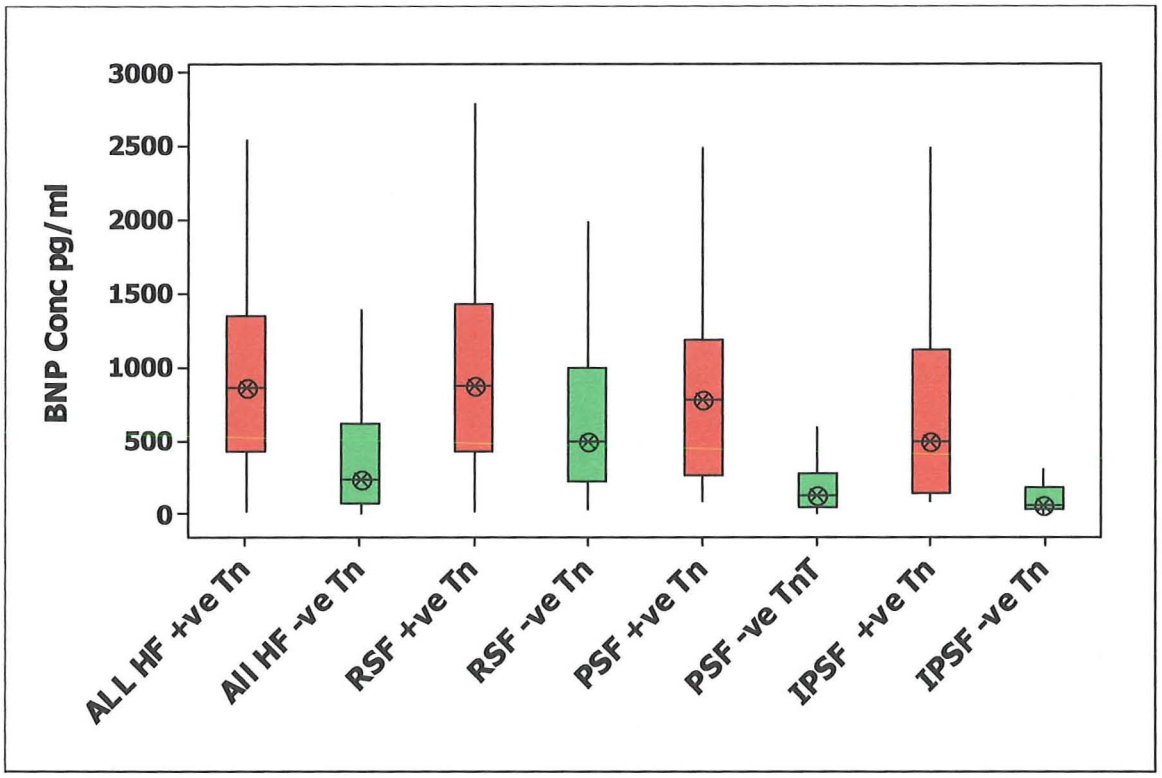
Similar proportions of patients in each group had an NYHA score of III/IV and a Killip score of ≥ IIA.

Similar cardiovascular co-morbidities were seen in both groups. A similar proportion of patients in each group had a prior history of COPD. Cardiovascular medications on admission were also similar between both groups.

5.02.3 Relationship between troponin and natriuretic peptide concentrations

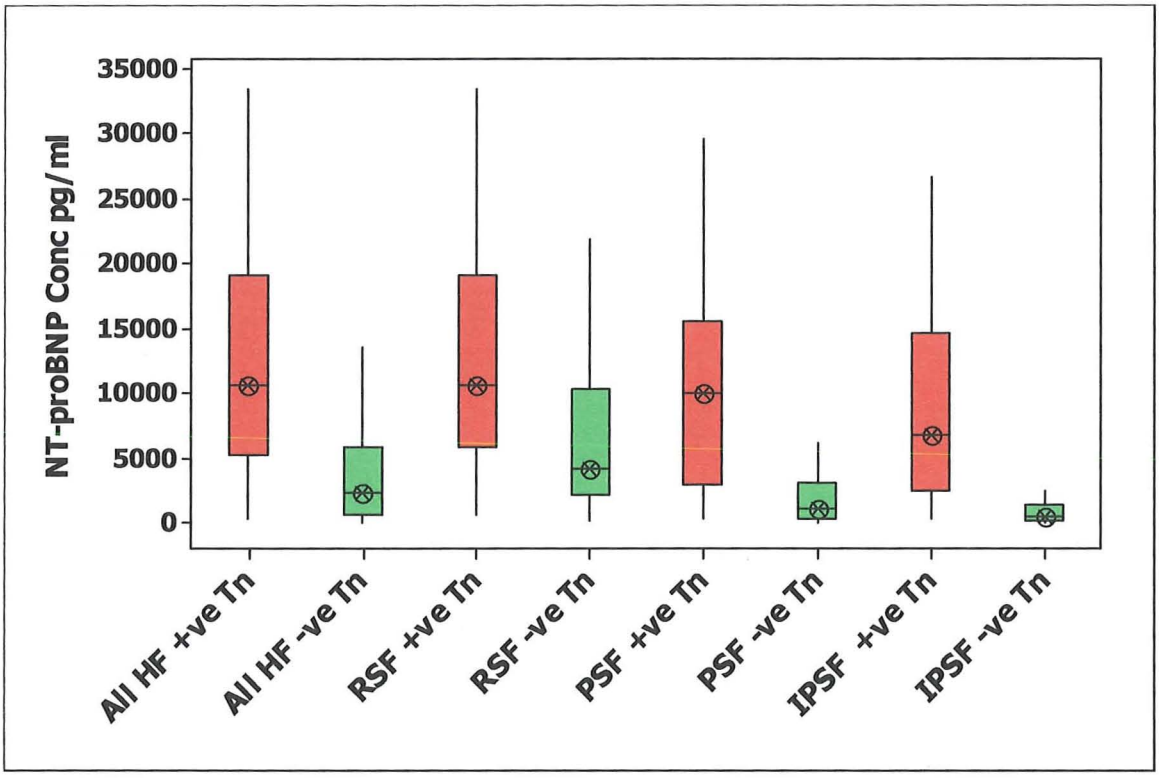
An elevated troponin I was taken to be one greater than or equal to 0.2μg/L (see Chapter 2). Figures 5.10 and 5.11 illustrate the similar relationship between elevated troponin and both BNP and NT-proBNP concentrations. I have divided the patients with clinical evidence of heart failure into four groups: All HF, HF-RSF, HF-PSF (including valve disease and AF) and HF-IPSF (no valve disease or AF) and compared the troponin and natriuretic peptide levels in each group. In each group the highest median BNP and NT-proBNP concentrations are found in those with elevated troponin levels on admission (Table 5.7). This is particularly prominent in the HF-IPSF group (median BNP 496pg/ml [IQR: 138-1,111pg/ml], median NT-proBNP 6,776 pg/ml [IQR:2435-14,653 pg/ml]). This is compared to the lower median BNP and NT-proBNP seen in those with negative troponin levels on admission (median BNP 61pg/ml [IQR: 33-178], median NT-proBNP 480pg/ml [IQR: 144-1,401pg/ml]). The differences in BNP and NT-proBNP concentrations between those with positive and negative troponin levels were significant ($p = 0.0001$ and $p < 0.0001$ respectively). Although it would seem that a positive troponin is associated with higher natriuretic peptide concentrations, only 16% of those with HF-IPSF had an elevated troponin at the time of admission, compared with 41% of the HF-RSF group.

Figure 5.10 Influence of positive troponin on BNP concentrations



+ve Tn = Positive troponin I
-ve Tn = Negative troponin I

Figure 5.11 Influence of positive troponin on NT-proBNP concentrations



+ve TnI = Positive troponin I
-ve TnI – Negative troponin I

Table 5.7 Influence of positive troponin on natriuretic peptide concentrations

	Median (IQR) BNP			Median (IQR) NT-proBNP		
	Troponin –ve	**Troponin +ve**	p value	**Troponin –ve**	**Troponin +ve**	p value
ALL HF (n = 307)	n=214 233 (72-610)	n=93 860 (431-1346)	<0.0001	n=214 2275 (563-5918)	n=93 10594 (5329-19107)	<0.0001
HF-RSF (n = 149)	n=88 498 (223-1000)	n=61 874 (431-1424)	<0.006	n=88 4177 (2243-10380)	n=61 10592 (5873-19206)	<0.0001
HF-PSF (n = 147)	n=117 124 (47-276)	n=30 784 (260-1188)	<0.0001	n=117 1045 (285-3057)	n=30 10028 (3027-15677)	<0.0001
HF-IPSF (n =86)	n=72 61 (33-178)	n=14 496 (138-1111)	0.0001	n=72 480 (144-1401)	n=14 6776 (2435-14653)	<0.0001

Of patients with HF-IPSF, the majority had a negative troponin on admission. Of these, 47% still have an elevated BNP and 65% an elevated NT-BNP concentration, and do not have valve disease, atrial fibrillation or positive troponin to account for the elevated natriuretic peptide concentrations.

5.02.4 Characteristics of patients with HF-IPSF and a negative troponin with elevated and normal BNP concentrations

Table 5.8 Summary of characteristics of patients with HF-IPSF and a negative troponin with elevated BNP or normal BNP concentrations

	Elevated BNP n = 34	Normal BNP n = 38	p value
Age (yrs) mean (SD)	75 (9.6)	72 (9.3)	0.313
Female n (%)	27 (79)	22 (58)	0.042
BMI mean (SD)	29.9 (6.6)	29.5 (5.2)	0.814
SBP (mmHg) mean (SD)	141 (29)	145 (29)	0.540
DBP (mmHg) mean (SD)	74 (16.3)	77 (15.5)	0.432
HR (bpm) mean (SD)	79 (17.8)	82 (20.4)	0.540
RR (breaths pm) mean (SD)	21 (5.5)	22 (12.8)	0.722
Creatinine (µg/L) mean (SD)	101 (81-134)	102 (89-110)	0.982
eGFR mean (SD)	54 (42-64)	57 (49-67)	0.209
Hb (g/dL) mean (SD)	11.8 (2.1)	13.0 (1.5)	0.008
Ladder of life score mean (SD)	5.1 (2.1)	5.3 (2.6)	0.683
NYHA (III/IV) n (%)	17 (50)	15 (39)	0.367
Killip Score ≥ IIa n (%)	25 (74)	27 (71)	0.814
n (%)			
Anaemic	17 (50)	9 (24)	0.017
IHD	23 (68)	19 (50)	0.122
DM	7 (21)	7 (18)	0.817
CVD	9 (26)	4 (11)	N/A
PAD	1 (3)	2 (5)	N/A
Hypertension	20 (59)	20 (59)	0.597
Hypercholesterolaemia	11 (32)	10 (26)	0.574
COPD	18 (53)	16 (42)	0.355
Abnormal ECG	26 (76)	19 (50)	0.015

BMI = body mass index, IHD = ischaemic heart disease, HBP = hypertension, PAD = peripheral arterial disease, DM = diabetes mellitus, CVD = cerebrovascular disease, COPD = chronic obstructive pulmonary disease, SBP = systolic blood pressure, DBP = diastolic blood pressure, RR = respiratory rate, HR = heart rate, eGFR = estimated glomerular filtration rate, Hb = haemoglobin.

Table 5.8 summarises some of the key characteristics of patients with HF-IPSF and a negative troponin on admission and compares those with elevated and normal BNP concentrations. The mean ages were similar in both groups, 75 (9.6) years in the elevated BNP group and 72 (9.3) years in the normal BNP group (p=0.313). A higher proportion of patients (79%) in the elevated BNP group were female (p=0.042). The two groups had a similar proportion of patients with NYHA class III/IV HF and with Killip scores ≥ IIA on admission. Both groups had comparable haemodynamic variables on admission. The cardiovascular risk factor profiles were also similar between the two groups. Renal function was similar in both groups and would be classed as moderate renal dysfunction. A similar proportion of patients in each group had COPD.

Half of the patients in the elevated BNP group were anaemic and the mean Hb was significantly lower in this group (Hb g/dL 11.8 +/- 2.1), compared with the normal BNP group where only 24% were anaemic (p=0.017). Over two-thirds of the patients with an elevated BNP concentration had an abnormal ECG on admission compared to 50% of those with a normal BNP concentration (p=0.015).

5.02.5 Relationship between natriuretic peptides and aminoterminal propetide of type III procollagen (PIIINP)

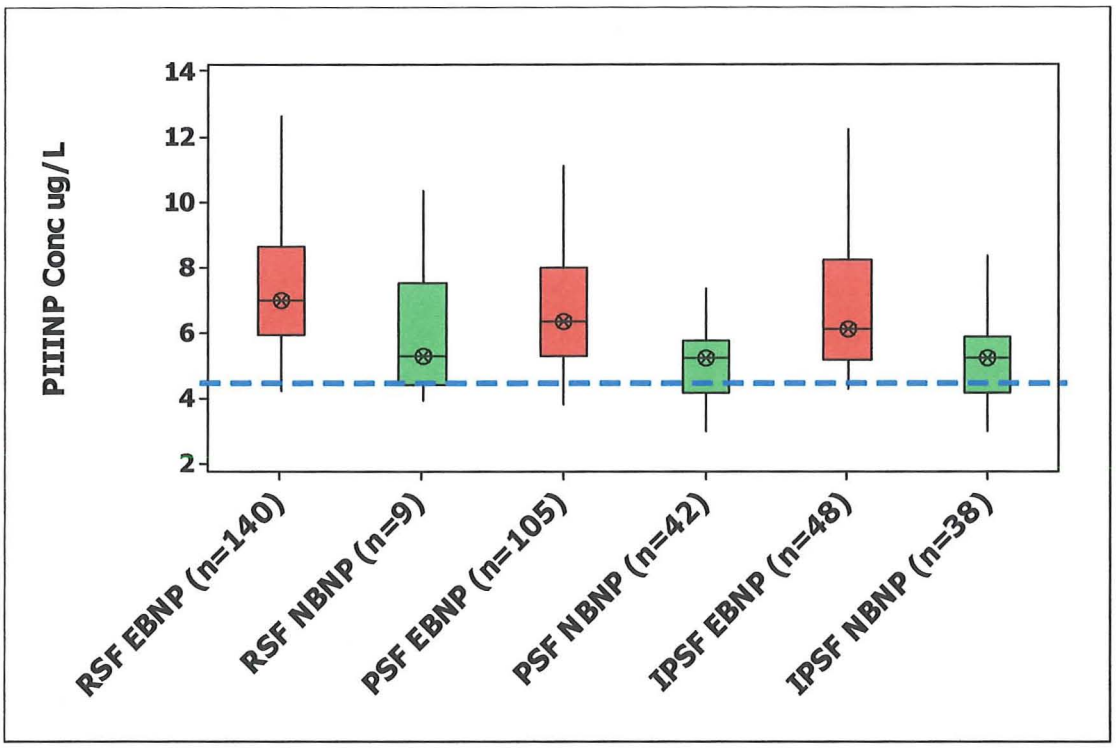
Table 5.9 compares the median PIIINP concentrations in patients with elevated and normal BNP concentrations in all types of HF. The upper limit of normal for PIIINP, described in Chapter 6, was 4.5μg/L.

Table 5.9 Median PIIINP concentrations in HF with elevated or normal BNP concentrations

	PIIINP (μg/L) Median (IQR)	p value
RSF + elevated BNP	7.0 (5.9-8.6)	
RSF + normal BNP	5.3 (4.4-7.5)	0.845
PSF + elevated BNP	6.4 (5.3-8)	
PSF + normal BNP	5.2 (4.2)	<0.0001
IPSF + elevated BNP	6.1 (5.1-8.2)	
IPSF + normal BNP	5.2 (4.2-5.9)	0.0001

The results from Table 5.9 are illustrated in Figure 5.12, and show that the median PIIINP concentrations are higher when BNP concentrations are elevated compared to those with normal BNP concentrations across all groups of HF patients. This difference was significant with the exception of the RSF group which only showed a trend towards a higher PIIINP concentration in the elevated BNP group.

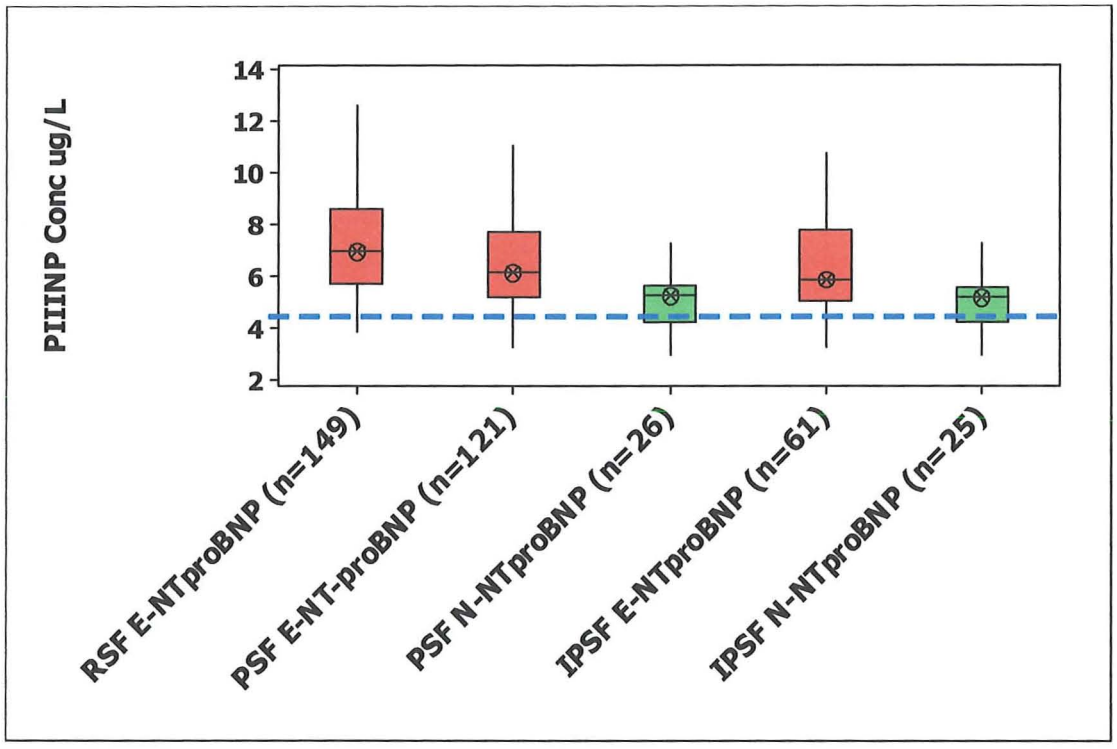
Figure 5.12 Median PIIINP concentrations according to type of HF and BNP concentration



EBNP = elevated BNP concentration
NBNP = normal BNP concentration

This pattern is replicated when comparing the median PIIINP concentrations in those with elevated and normal NT-proBNP concentrations. All patients in the HF-RSF group had an elevated NT-proBNP concentration, and the median PIIINP concentration was 7.0μg/L. In HF-PSF the highest median PIIINP concentrations were seen in those with elevated NT-proBNP concentrations: 6.2μg/L compared to 5.3μg/L in those with normal NT-proBNP concentrations (p=0.0003). This was also true for those with HF-IPSF and an elevated BNP (5.9μg/L) compared to those with a normal BNP concentration (p=0.006). This is illustrated in Figure 5.13.

Figure 5.13 Median PIIINP concentrations according to type of HF and NT-proBNP concentrations



Upper limit of normal

E-NT-proBNP = elevated NT-proBNP concentration
N-NT-proBNP = normal NT-proBNP concentration

5.03 Discussion

This examination of NP concentrations demonstrates that patients with clinical evidence of heart failure have higher NP concentrations than those without. The highest NP concentrations are found in those with HF-RSF, and nearly all patients in this group have elevated NP concentrations. These values are significantly higher than those found in the HF-PSF group. However, even in the HF-PSF group, approximately four-fifths of patients have NP concentrations above the upper limit of normal.

Previous studies have shown that the presence of valve disease correlates with higher NP concentrations[210-216], as may be expected due to the fact that most clinically significant valvular heart disease (VHD) will result in pressure or volume overload of the left ventricle. These findings have been reproduced in this study, where patients with VHD also had higher NP concentrations. The prognostic value of BNP in VHD remains to be established.

There is less literature on the association between AF and NP concentrations and this has largely remained controversial, with some authors reporting higher NP concentrations in the presence of AF, even in the absence of structural heart disease[217-219]. This study suggests that the presence of AF is indeed associated with higher NP concentrations. However, the exact mechanism by which the presence of AF, in the absence of structural heart disease, may influence NP concentrations remains unclear.

Those patients with HF-IPSF and an elevated BNP concentration were more likely to be female. Nearly half of these patients were anaemic and the median eGFR was in the moderate renal dysfunction range. These findings are similar to those discussed in Chapter 3, where I showed that HF-RSF was associated with significant renal dysfunction and anaemia. This

finding, that HF-IPSF is frequently associated with significant renal dysfunction and anaemia strongly suggests that HF-IPSF is not merely a benign manifestation of the heart failure syndrome, but rather is associated with similar complications to those found in HF-RSF.

One possible mechanism for the occurrence of heart failure with preserved systolic function, is transient LV dysfunction caused by a period of myocardial ischaemia, indicated by an elevated troponin. However, in this study, the majority of patients with HF-IPSF had a negative troponin but an elevated plasma BNP concentration. We have therefore identified a group of patients who have clinical evidence of heart failure, preserved systolic function, biochemical evidence of LV compromise, but without VHD, AF or myocyte necrosis to account for this. These patients undoubtedly have heart failure, in the presence of preserved LV systolic function, without a separate cardiac pathology which may be causing secondary heart failure. The cumulative results of this study, from detailed characterisation of heart failure patients, indicate that HF-PSF exists as a clinical entity in its own right.

Interestingly, this study also found that in patients with HF-IPSF, a positive troponin at the time of admission was associated with an elevated NP concentrations. No patients with HF-IPSF and a normal BNP had an elevated troponin. This co-distribution of troponin with BNP is relevant in the light of emerging evidence regarding the prognostic value of troponin in heart failure[220], and conversely, that BNP predicts outcome in acute coronary syndromes[221]. The interplay between these two biomarkers suggests that they represent related processes in the pathophysiology of heart failure, and this is an area which requires further study.

Evidence to suggest possible ventricular strain in patients with heart failure is found in the relationship between NP and PIIINP concentrations. PIIINP (examined in detail in Chapter 6)

is a recognised marker of increased collagen turnover[109;222] and has been shown to be elevated in association with cardiac pathology[129;223;224]. In addition, PIIINP is associated with a poor prognosis[129;225]. In this study, in both types of heart failure, the highest PIIINP concentrations were seen in those with elevated NP concentrations.

In summary, in this study I have identified a group of patients who have HF-PSF and elevated NP concentrations without an adequate alternative explanation for these findings. In the presence of preserved LV systolic function these patients have both clinical evidence of heart failure on validated scores, and objective biochemical evidence of left ventricular strain. Therefore, these patients may truly be said to have heart failure with preserved systolic function. Moreover, these patients do not appear to have a benign syndrome, but instead share markers of an adverse prognosis, such as elevated BNP, troponin or PIIINP and abnormal renal function, with patients with HF-RSF.

The focus of this study has been to characterise patients with HF-PSF and in this Chapter I have described their NP concentrations. However, my findings, that BNP and NT-proBNP are elevated in the majority of patients with positive heart failure scores, regardless of systolic function, also supports the developing role of BNP in the diagnosis of heart failure. Indeed, the diagnostic accuracy of BNP rises when patients with preserved systolic function are studied, and from this it has been suggested that, BNP may be superior to ejection fraction as a diagnostic and prognostic tool[226]. However, in routine clinical practice, the role of BNP is now clearly established as a diagnostic tool alongside echocardiography, and both should be performed in patients presenting with symptoms and signs compatible with heart failure[142].

CHAPTER SIX

AMINOTERMINAL PROPEPTIDE OF TYPE III PROCOLLAGEN

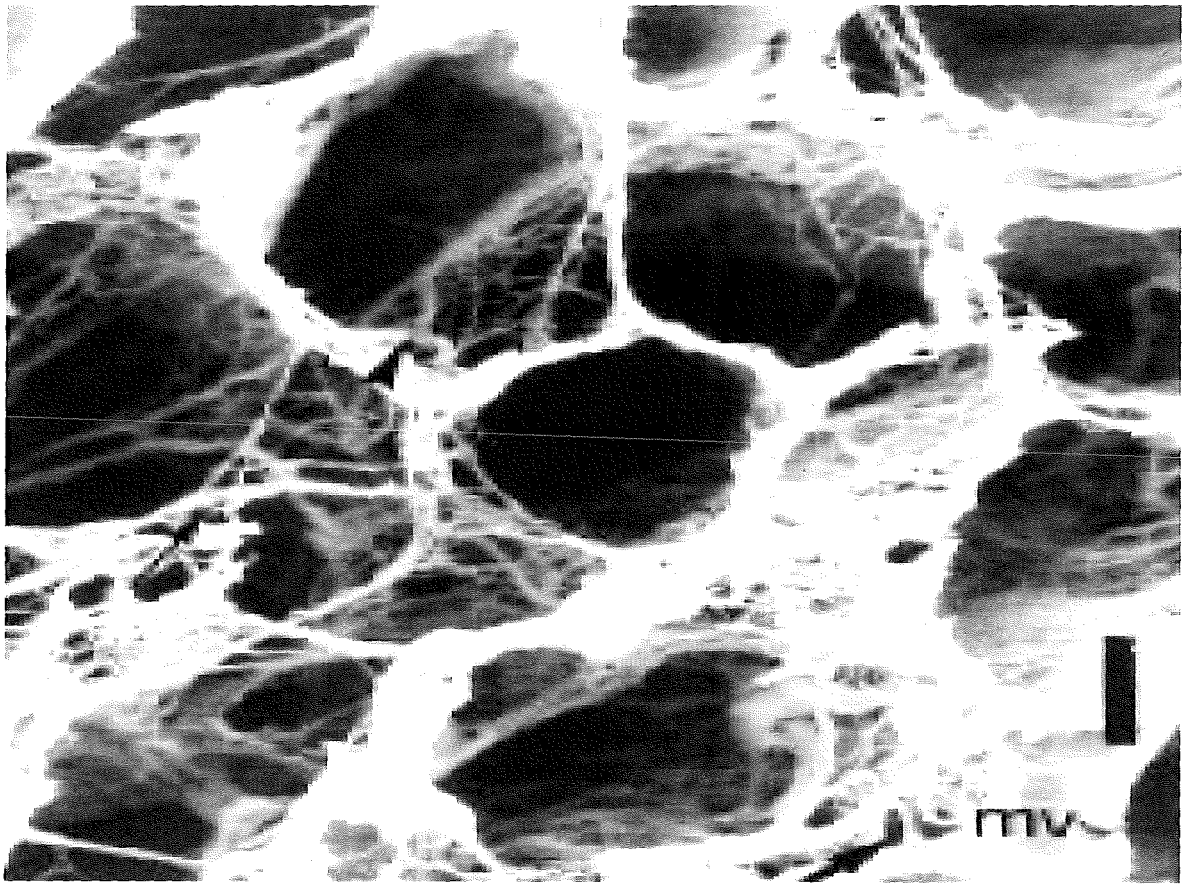
6.01 Introduction

6.01.1 Myocardial extracellular matrix

The myocardial extracellular matrix (ECM) is the connective tissue skeleton of the heart, and it plays a key role in cardiac function. It determines the structure of the myocardium and provides both the tensile strength and stiffness of the tissue. This is important for ventricular function through the transmission of myocyte generated ventricular force to the atria and ventricles. It also contributes to myocyte lengthening in diastole, and the ECM is therefore the main determinant of diastolic stiffness[227-229].

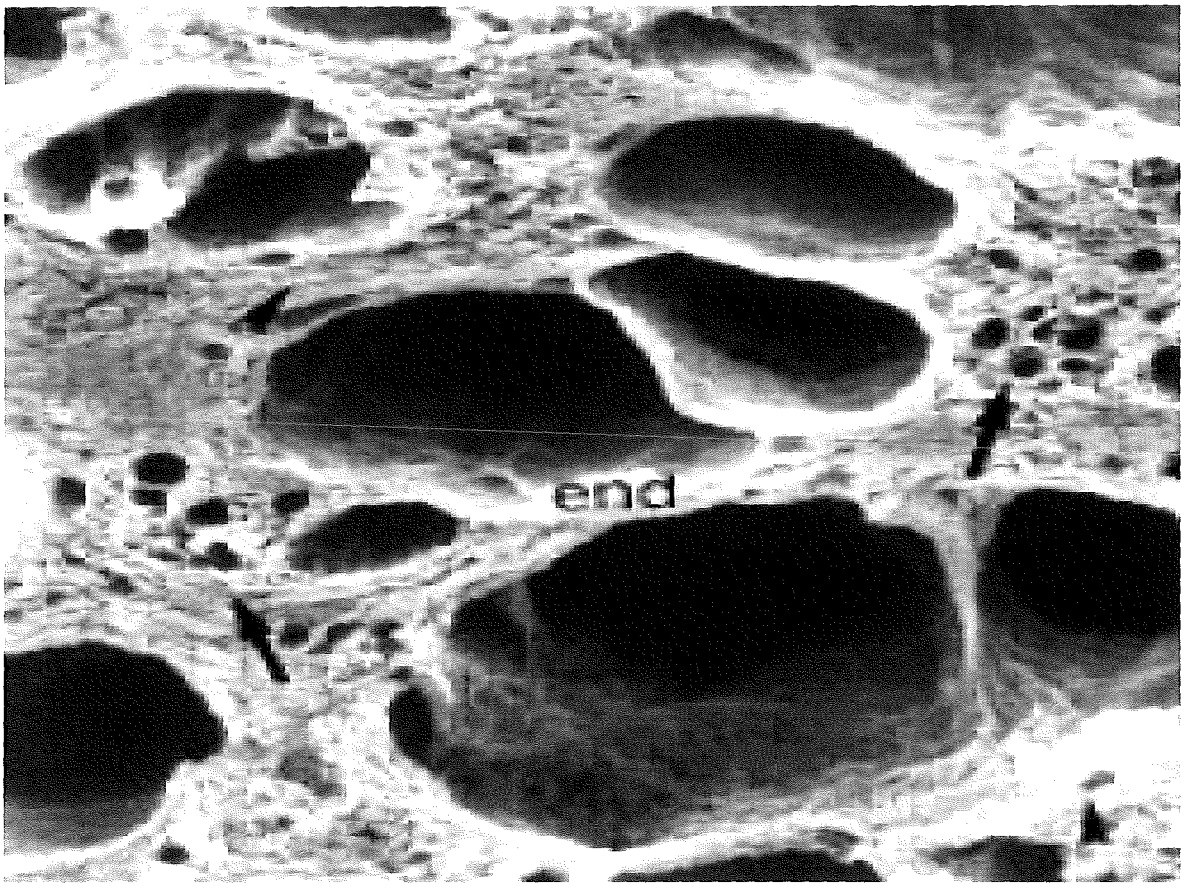
The myocardial ECM in the normal heart is a fibrillar network organised in a honeycomb pattern. It consists of collagen, basement membrane, fibronectin, proteoglycans, laminin, matrix metalloproteinases (MMPs) and growth factors. The ECM has three distinct components. The endomysium is a sheath of delicate reticular fibrils, which support and connect the individual myocytes. The endomysial weave envelops each myofibre, and is connected to adjacent myocytes by lateral struts. The perimysium is a connective tissue sheath which surrounds groups of myocytes. Collagen struts also connect myocytes to interstial microvessels and perimysial collagen fibrils[123] (see Figure 6.1).

Figure 6.1 Scanning electron microscopy of normal myocardial ECM



Adapted from Rossi *et al*[123]

Figure 6.2 Scanning electron microscopy of hypertrophied myocardial ECM



Adapted from Rossi *et al*[123]

More than simply a scaffold for cells, the extracellular matrix has dynamic properties and undergoes functional remodelling in disease states. Examples include: ventricular hypertrophy, dilated cardiomyopathy and remodelling following MI. ECM remodelling is an important part of LV remodelling, which plays a key role in the development of HF, regardless of aetiology[230] (see Figure 6.2).

6.01.2 Components of the ECM

Collagen types I and III are the most common, both in normal and diseased myocardium[230]. They are normally found together, but during a fibroproliferative response, the deposition of type III collagen precedes that of type I[231;232]. These collagen fibres ensure the structural integrity of the adjoining myocytes and provide the means by which myocyte shortening is translated into the generation of coordinated force. Collagen is also essential on a cellular level, as it forms part of the collagen-integrin-cytoskeleton which maintains alignment of the myofibrils within the myocyte. Collagen production is stimulated by growth factors such as transforming growth factor (TFG), insulin-like growth factor (IGF) and basic fibroblast growth factor (BFGF). Angiotensin II (Ang II) has also been shown to stimulate collagen gene expression and protein turnover in cultured cardiac fibroblasts[233]. Ang II also stimulates collagen synthesis and regulates collagen degradation in endothelial cells by attenuating interstial MMP-I activity, through activation of its tissue inhibitor[234-236].

Endothelin has been shown to mediate the effects of angiotensin II on cardiac fibroblasts. Endothelin is synthesized by both cardiomyocytes and fibroblasts and has been shown to stimulate collagen I and III synthesis[237]. In animal experimental models inhibition of endothelin has been shown to decrease left ventricular collagen accumulation[238].

Fibroblasts constitute the majority of non-myocyte cells in the heart. Cardiac fibroblasts increase their production of fibronectin and collagen when the heart is exposed to insults such as myocardial infarction (MI), pressure overload, or myocarditis[230;239;240]. Excess collagen deposition and the resultant cardiac fibrosis are implicated in increased tissue stiffness and diastolic dysfunction.

6.01.3 Myocardial extracellular matrix control mechanism

Matrix metalloproteinases (MMPs) are a family of functionally related enzymes that cleave ECM components resulting in collagen denaturation and degradation, and the synthesis of new fibrous tissue[241-248]. The MMPs are secreted by fibroblasts, smooth muscle cells and myocytes[249] as proenzymes (proMMPs), and are then activated by proteolytic cleavage to their active form. To date, 20 MMPs have been identified and work to identify others is continuing. The MMPs are differentiated by their structure and specificity: collagenase (MMP-1) which degrades fibrillar collagens; stromelysin (MMP-3) which degrades proteoglycans and glycoproteins; and gelatinases (MMP-2 and MMP-9) which degrade denatured collagens and basement membrane collagens[250].

The activity of the MMPs is regulated by a number of chemical agents, neurohormones and cytokines[243;246;248;249;251;252]. In most cases, the activation of proMMPs involves the "cysteine-switch" mechanism[253]. The active MMPs are then regulated by levels of TIMPs and α_2-macroglobulin, which inhibit MMP activity. The TIMPs inhibit MMPs directly, but also form complexes with proMMPs to modulate MMP activation[254]. The tight regulation of MMP-mediated collagen degradation appears to fail during the development of heart failure[255-257]. MMPs are thought to play a role in collagen synthesis, through the formation of matrikines[247;258] such as glycyl-histidyl-lysine, and by releasing biologically active growth factors which stimulate collagen production[259].

In rodents, heart failure can be induced by over-expression of tumour necrosis factor alpha (TNFα), the animals develop progressive ventricular hypertrophy and dilatation. These changes have been shown to be accompanied by a significant increase in MMP-2 and MMP-9 levels, an increase in collagen synthesis, deposition and denaturation, and a decrease in non-

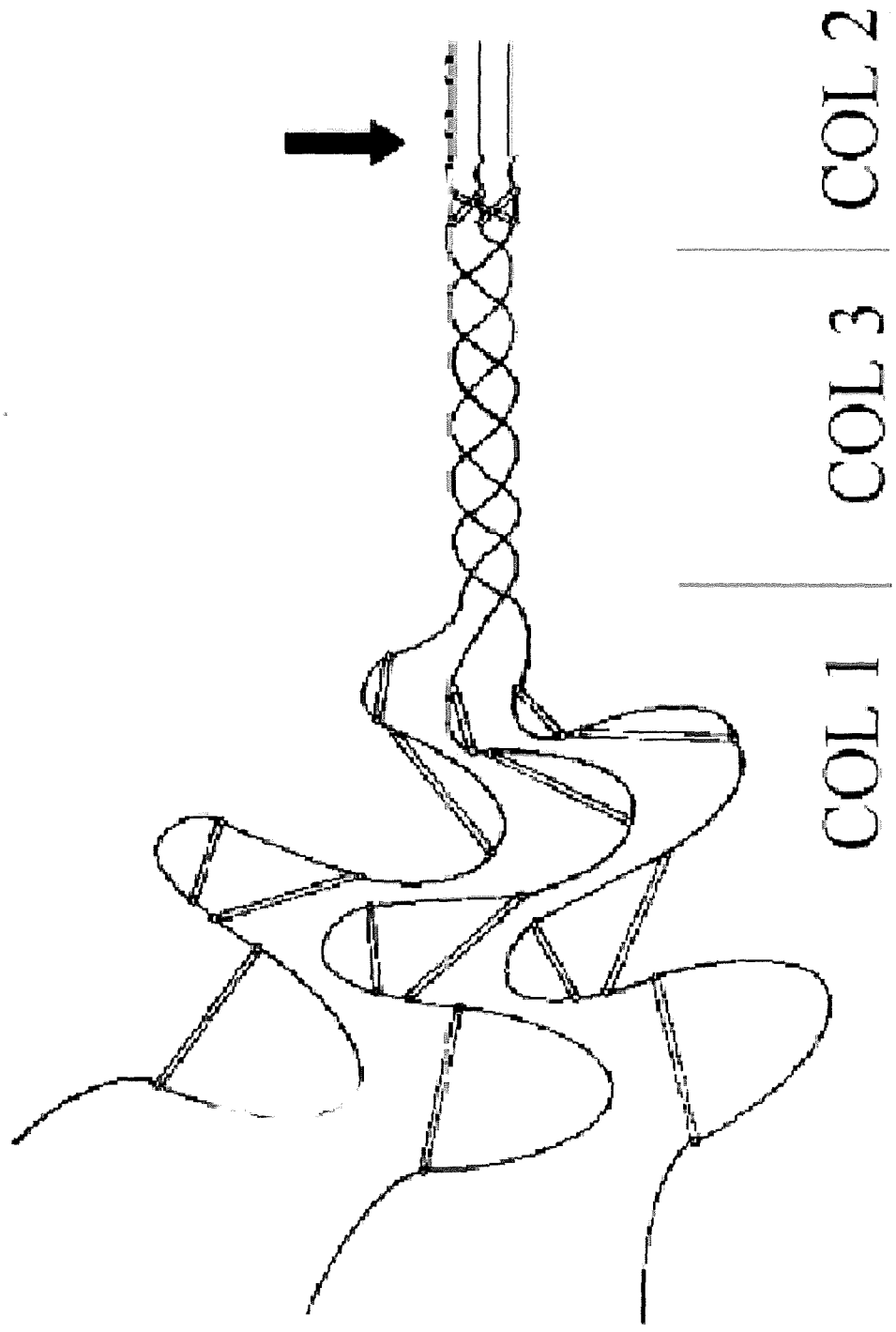
denatured soluble collagens[260]. The changes in the ECM of these rats were associated with marked diastolic dysfunction demonstrated by significantly reduced transmitral E/A ratio[260].

6.01.4 Aminoterminal propeptide of type III procollagen (PIIINP)

Type III collagen is a homotrimer of three α1 (III) chains, encoded by a single gene found on chromosome two (location q24.3-q31)[261]. Like the other fibrillar collagens, type III collagen is synthesised as a large precursor molecule (procollagen type III) with propeptides at each end. These propeptides are cleaved enzymatically during the extracellular processing of type III collagen. One of these propeptides, PIIINP, is cleaved by a specific N-proteinase during the formation of collagen type III.

PIIINP has a molecular weight of approximately 42,000 and consists of a cysteine rich globular domain (see Figure 6.3 col 1), a non-collagenous domain (see Figure 6.3 col 2) ending in the N-telopeptide and the 29 amino-acid triple-helical region (see Figure 6.3 col 3) which lies between col 1 and col 2. The cystiene-rich globular domain consists of five inter-chain disulfide bridges along with 79 amino acids. The non-collagenous domain is an area of 12 amino acids and is located in the carboxy-terminal region of the propeptide, and contains three interchain disulfide bonds. The PIIINP molecule is stabilised by these three interchain disulfide bridges. The melting temperature of the collagenous domain is 53°C and the refolding of the helix from the denatured peptides takes place extremely fast, mainly due to the disulfide bonds that already keep the three chains together[262]. Figure 6.3 is a diagrammatic illustration of the PIIINP molecule.

Figure 6.3 Diagramatic illustration of PIIINP molecule (modified from Risteli et al[263])



Circulating PIIINP is cleared by scavenger receptors located on hepatic endothelial cells. It has been postulated that tyrosine sulfation plays a role in the recognition of PIIINP by the scavenger receptors[263]. The amino-terminal component is renally cleared[264].

6.01.5 PIIINP as a marker of collagen synthesis

PIIINP is believed to reflect enhanced collagen turnover. In the rat heart, following induction of MI, degradation of collagen occurs at the infarct site at day one and two. Collagenolysis at the infarct site peaks at day seven, and then declines over the next 14 days. Over days three to five, accumulation of fibrillar collagen is seen. The synthesis of type III procollagen peaks after three weeks and appears to normalize after a period of months. This increased collagen turnover is reflected by an increase in serum PIIINP in the sub-acute phase of MI. In summary, this represents an initial increase in collagenolysis with an overlapping but prolonged increase in collagen synthesis[109].

Elevated PIIINP concentrations are associated with a poor prognosis in patients following MI[223]. Poulsen *et al* studied 47 consecutive patients admitted with their first acute MI. Using the same radioimmunossay (PIIINP-RIA Kit, Orion Diagnostics) as the current study, peak PIIINP concentrations measured on day four post MI were significantly higher compared to controls. PIIINP concentrations remained elevated during the first three months post MI[129]. The persistent elevation of PIIINP indicates a consistent increase in collagen synthesis during this time[265]. Patients with acute MI and an elevated PIIINP demonstrated significant LV dilatation and persistently depressed LVEF compared with patients with normal PIIINP following MI during the one year follow-up. In addition, Doppler analyses of transmitral and pulmonary venous flow indicated restrictive LV diastolic filling in those with higher PIIINP concentrations. A restrictive LV filling pattern is associated with increased LVEDP, which

can be due to increased myocardial stiffness or increased LV volumes[266]. As discussed above, these patients did develop LV dilatation. However, increased collagen deposition might also contribute to the development of restrictive filling. It has been shown that increased collagen deposition occurs not only at the infarct site, but also at remote sites in the ventricle, and this may be expected to increase myocardial stiffness[128]. Poulsen *et al* identified PIIINP > 5.0 μ/L and deceleration time ≤ 140ms (an indicator of restrictive LV filling, discussed in Chapter 4) as predictors of adverse clinical outcome[129]. A further study in patients following MI, demonstrated a positive correlation between PIIINP concentrations and infarct size, LVSD and the presence of coronary artery occlusion[132].

In left ventricular hypertrophy (LVH), collagen accumulation results in increased chamber stiffness and diastolic dysfunction[267]. Lombardi *et al* studied indices of collagen turnover in 36 patients with hypertrophic cardiomyopathy (HCM), which is characterised by: asymmetrical LVH: myocyte disarray; interstitial fibrosis; and increased arteriolar wall thickness. When compared with age and sex-matched controls, those with HCM had increased PIIINP levels. However, the authors did not find any correlation between PIIINP levels and the severity of LVH. An inverse relationship was found between PIIINP and LVEDD, thus serum PIIINP concentrations were higher in those with small ventricles, who would be expected to have restrictive defects in diastolic function[224].

6.01.6 Prognostic significance of PIIINP

Zannad *et al* reported on a sub-study of the Randomized Aldactone Evaluation Study (RALES) which examined the value of serological markers for cardiac ECM turnover as predictors of death and hospitalisation. They also assessed the effects of treatment with spironolactone on these markers and the interaction between spironolactone induced changes

in ECM turnover on mortality and morbidity[230]. All the patients in the RALES trial had severe HF. This was defined as NYHA class IV symptoms within the six months prior to randomisation and class III or IV symptoms at the time of randomisation, along with a depressed LVEF (<35%). Patients were randomised to receive conventional therapy with either placebo or spironolactone[268]. The baseline mean PIIINP concentration was 5.0 +/- 2.5 μg/L, which is well above the normal range (1.7-4.2μg/L)[264]. The baseline PIIINP concentration in this group was similar to those found in other studies of post-MI patients (5.08 +/- 0.36 μg/L)[132] and those with dilated cardiomyopathy (DCM) (6.1 +/- 0.4 μg/L)[225]. There was no difference in baseline median PIIINP concentration between the placebo and spironolactone arms. After six months, median PIIINP concentration was significantly lower in the spironolactone treated group. In this subgroup analysis, morbidity and mortality benefit was greatest in those with the highest PIIINP concentration.

Rossi *et al* studied patients with stable heart failure for at least six months and a diagnosis of DCM, in the presence of a depressed LVEF (< 45%)[131]. Those patients who also had severe diastolic dysfunction, as characterised by restrictive ventricular filling, had the highest PIIINP concentrations and the worst prognosis.

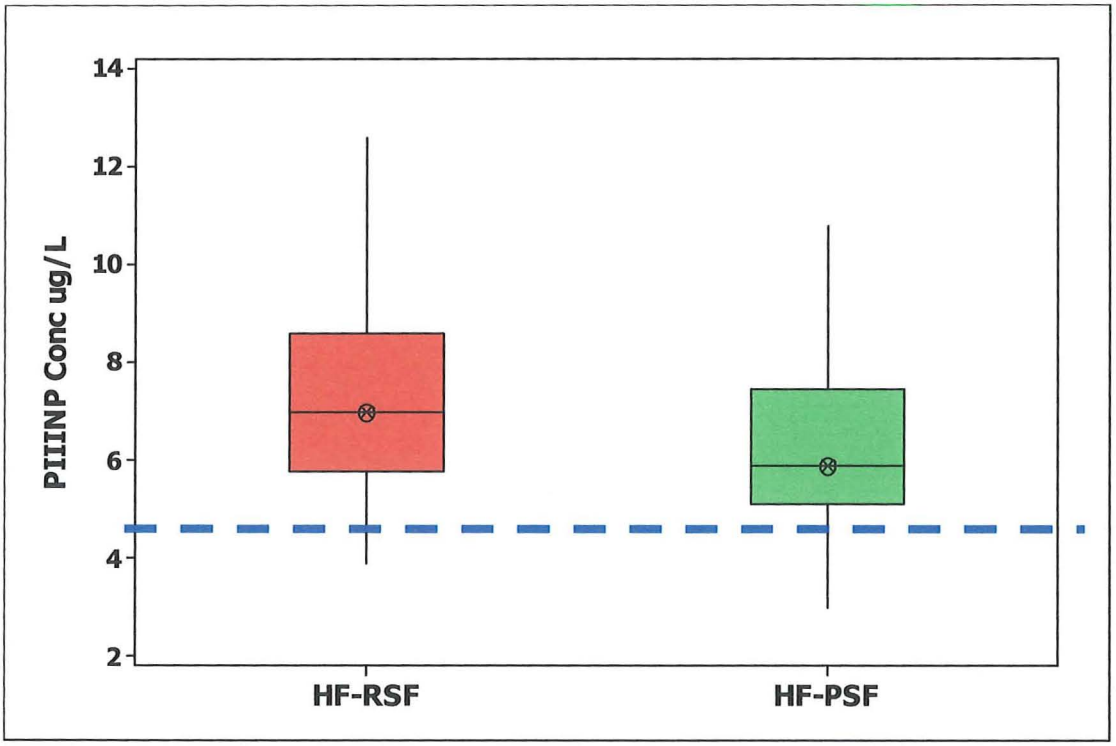
A recent study examined both natriuretic peptides and collagen markers after acute MI. Natriuretic peptides are anti-fibrotic and have been shown to be elevated following MI[50;93;95;269-271]. In this study natriuretic peptide elevation correlated positively with PIIINP concentration. The authors postulated that natriuretic peptides may be involved with PIIINP in the regulation of collagen formation during remodelling following MI[272].

6.02 Results

6.02.1 PIIINP concentrations in HF-RSF and HF-PSF

The median PIIINP concentrations are significantly higher in the HF-RSF group when compared with the HF-PSF group (7.0µg/L vs 5.9 µg/L, p=0.0001). This is shown in Figure 6.4.

Figure 6.4 Median PIIINP concentrations in HF-RSF and HF-PSF



Upper limit of normal

Figure 6.5 Proportion of patients with elevated PIIINP concentrations in HF-RSF and HF-PSF

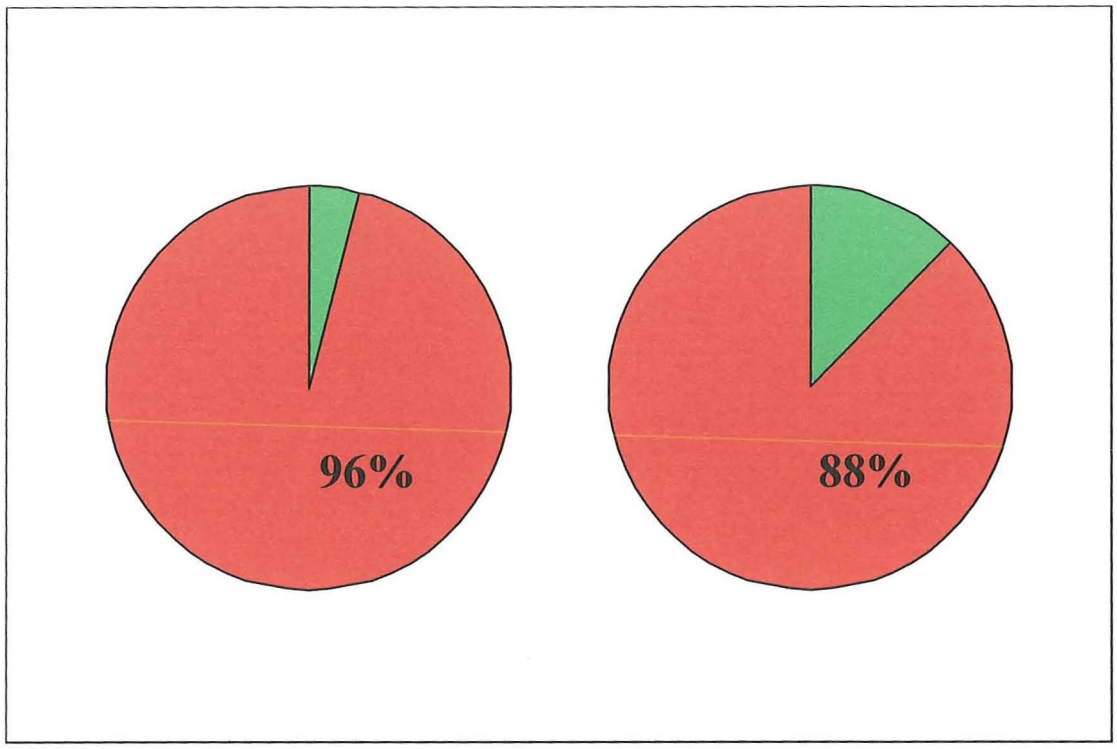
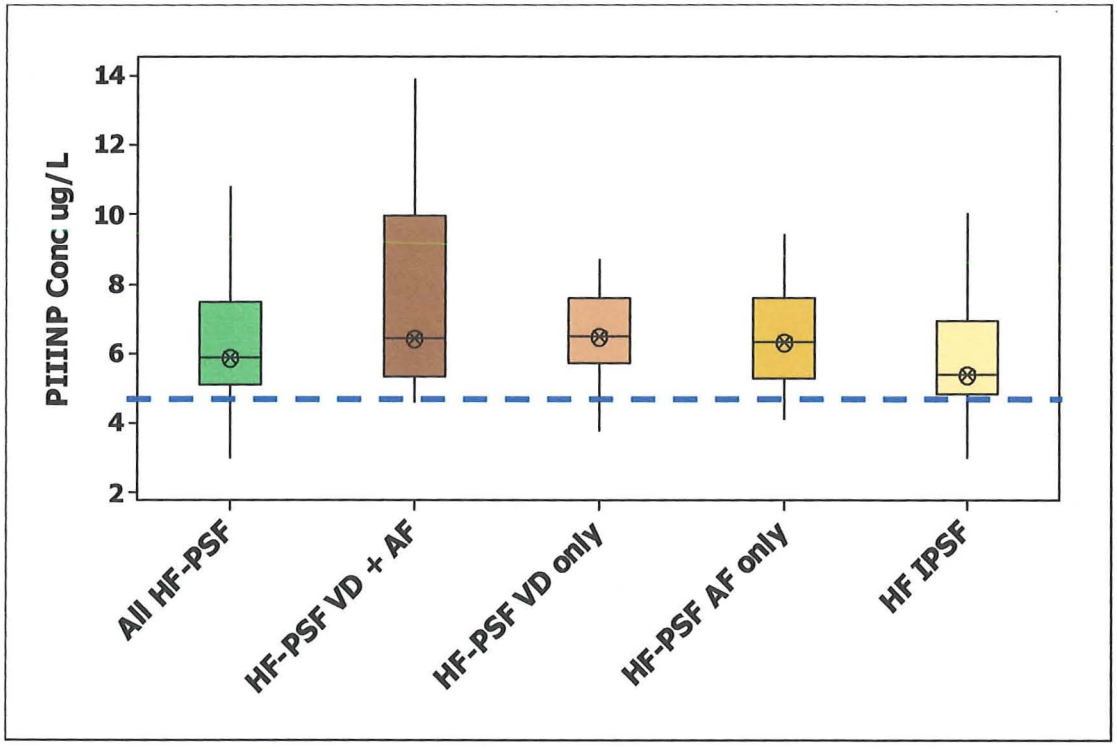


Figure 6.5 illustrates that the majority or patients in each group have an elevated PIIINP concentration. A significantly higher proportion of patients in the HF-RSF group have an elevated PIIINP concentration (96% vs 88%, p=0.009).

As described in Chapter 5, higher natriuretic peptide concentrations were associated with the presence of VHD and AF. Figure 6.6 illustrates that a similar relationship existed with

PIIINP concentration. There was a trend towards higher PIIINP concentrations in patients with VDH, AF or both compared to those with HF-IPSF (p=0.06).

Figure 6.6: Median PIIINP concentration and VHD or AF in HF-PSF

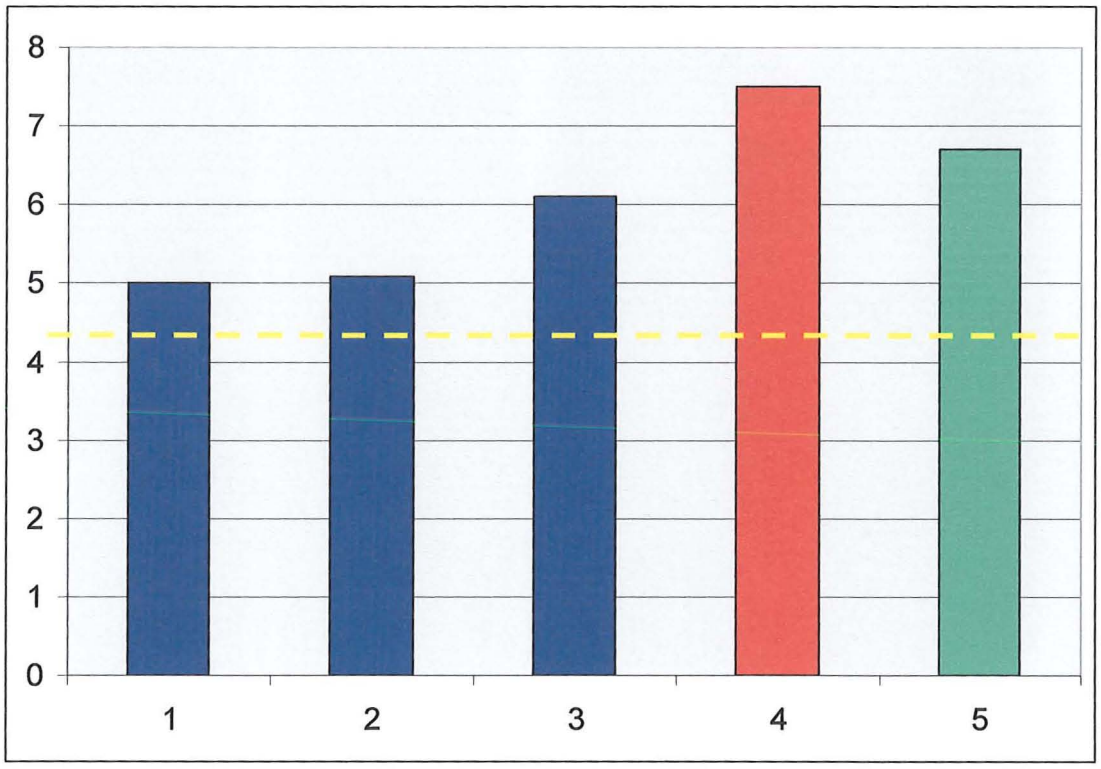


Upper limit of normal

6.02.2 Comparison of PIIINP levels in established cardiac pathology

Figure 6.7 compares the mean PIIINP concentration in the current study to those from previous studies using the same radioimmunoassay (Orion Diagnostics, Espoo, Finland).

Figure 6.7 Comparison of mean PIIINP concentrations



1 = Established heart failure[264]
2 = Post MI patients[132]
3 = Dilated cardiomyopathy[225]
4 = Current study HF-RSF
5 = Current study HF-PSF

Upper limit of normal

As discussed previously in this Chapter, these studies all required LVSD and included patients with severe HF (study 1 in Figure 6.7)[264], post-MI patients (study 2 in Figure 6.7)[132], and those with DCM (study 3 in Figure 6.7)[225]. In all groups, the mean PIIINP concentrations were above the upper limit of normal, including the patients in our study in both the HF-RSF and HF-PSF groups. Therefore, the mean PIIINP concentrations in the current study are in line with elevated PIIINP concentrations from previous studies with documented cardiac pathology.

6.03 Discussion

These results show that median PIIINP concentrations are elevated in both types of HF, and are significantly higher in HF-RSF. As would be expected, nearly all patients (96%) in the HF-RSF group had an elevated PIIINP concentration. This is in keeping with previous studies that describe a higher PIIINP concentration in patients with LVSD. In this study, the mean PIIINP concentrations are in fact slightly higher than those observed in other studies of HF with LVSD across a variety of aetiologies. This is possibly due to the fact that patients in this study were admitted with acute heart failure.

As well as reproducing the observation that PIIINP is elevated in the context of LVSD, we have demonstrated that the majority of patients with HF-PSF also have elevated PIIINP. This suggests that enhanced collagen formation is a feature both types of HF.

In conjunction with the results described in Chapter 5, I have found that there was an association between BNP and PIIINP in both groups of HF patients. The pathophysiological mechanism underlying this relationship has yet to be elucidated. It is possible that BNP acting as an anti-fibrotic agent is involved in the regulation of cardiac fibrosis for which PIIINP is a marker. Or it may be that both BNP and PIIINP are simply markers of this process. Investigation of this is beyond the scope of the current investigation, but is an important avenue for future research especially as recent studies have shown that PIIINP is a predictor of mortality in patients with HF-RSF[131;273]. Recently it has been suggested that traditional imaging techniques do not assess LV longitudinal systolic function[274]. Poulsen *et al* demonstrated that in patients with hypertension the longitudinal systolic LV function was in fact depressed when compared to controls. They also demonstrated that these patients had elevated PIIINP concentrations suggestive of myocardial fibrosis[274]. It is therefore possible

that the combination of more advanced imaging techniques with BNP and PIIINP concentrations may provide a more detailed understanding of the extent and effect of myocardial fibrosis in this cohort of HF patients.

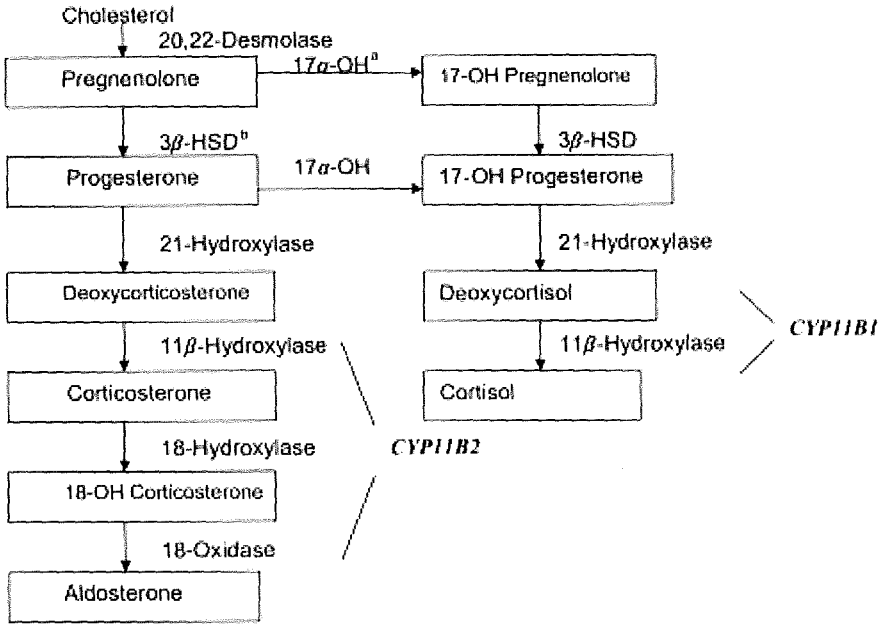
CHAPTER SEVEN

RENIN AND ALDOSTERONE

7.01 Introduction

Aldosterone is the principal mineralocorticoid hormone in humans, and is produced in the *zona glomerulosa* of the adrenal gland. The hormone is the product of a series of biosynthetic reactions, which are summarised in Figure 7.1[275]. Aldosterone is released from the adrenal cortex in response to an increase in the concentrations of angiotensin II, corticotrophin, catecholamines, endothelins and potassium[276;277].

Figure 7.1 Steroid biosynthetic pathway[275]



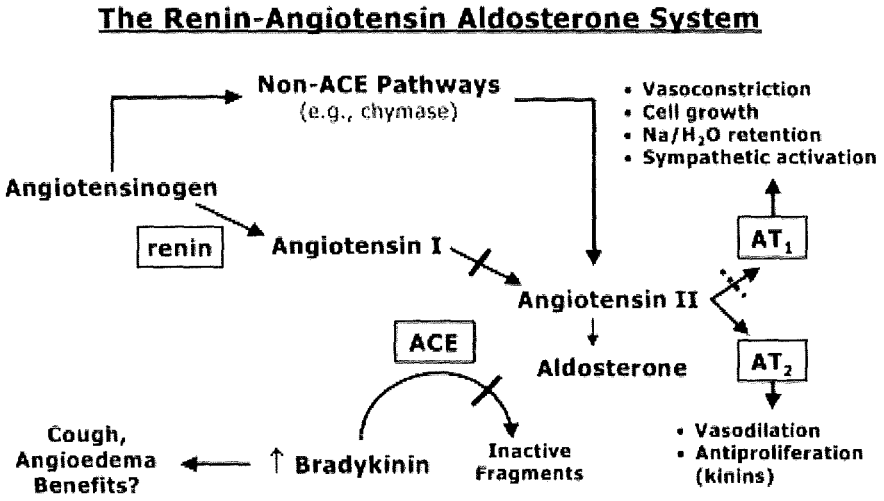
Angiotensin II and potassium are the principal regulators of aldosterone production. Angiotensin II stimulates aldosterone secretion in response to both sodium depletion and reduced extracellular fluid volume[278]. Even small increments in plasma potassium act as a powerful stimulus for aldosterone production[279].

The principal target organ for aldosterone is the kidney. However, mineralocorticoid receptors, which bind aldosterone, are also found in secretory epithelial sites in colon, sweat and salivary ducts, heart, brain, vascular smooth muscle, liver and peripheral blood leukocytes[275].

The best characterised physiological effect of aldosterone is to increase the reabsorption of sodium at the expense of potassium and hydrogen ions[278]. Aldosterone therefore affects blood pressure (BP) by plasma volume expansion and the associated increase in cardiac output. It is likely however, that aldosterone also regulates BP by mechanisms other than its action on sodium homeostasis. Evidence suggests that aldosterone binding to mineralocorticoid receptors in cardiac tissue regulates collagen formation[280]. It is possible that it may have a similar action on peripheral blood vessels, resulting in remodelling and an elevated BP. This is supported by evidence that aldosterone levels are inversely related to arterial compliance in essential hypertension[281].

Over the past two decades, a greater understanding of the importance of the renin-angiotensin-aldosterone system (RAAS) in cardiovascular disease has been achieved. Activation of the RAAS is associated with poor outcomes, especially in patients with hypertension and heart failure[276;277;282-286]. Aldosterone contributes to hypertension, and to the progression of both cardiovascular and renal disease. This occurs through sodium retention, an increase in magnesium and potassium loss, impairment of endothelial and baroreceptor function, reduction in vascular compliance, and promotion of cardiac and vascular fibrosis[276;282;286-290] (Figure 7.2).

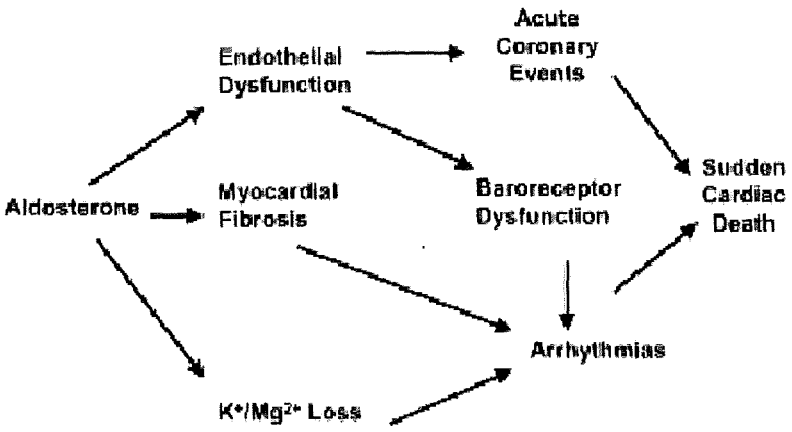
Figure 7.2 Renin-angiotensin-aldosterone system[291]



In HF, aldosterone release results in over-activation of the RAAS and further elevation of aldosterone levels. This leads to sodium retention, with resultant expansion of the extracellular volume, which leads to impaired haemodynamic responsiveness and a fall in cardiac output. Decreased renal blood flow stimulates the RAAS further, producing a vicious cycle, which results in secondary hyperaldosteronism and excessive sodium retention. Also, the electrolyte imbalances produced, in particular hypokalaemia and hypomagnesemia, increase the risk of sustained ventricular arrhythmias, which are a major cause of sudden cardiac death in heart failure[292;293].

More recent research has identified new pathophysiological mechanisms by which aldosterone could be expected to contribute to the progression of HF and increase the risk of sudden cardiac death[294] (Figure 7.3).

Figure 7.3 Mechanisms of promotion of sudden cardiac death by aldosterone[294]



A growing body of research suggests that aldosterone contributes to endothelial dysfunction[295-300]. The endothelium plays a critical role in the regulation of vascular tone, platelet aggregation, adhesion of leukocytes and the thrombotic cascade. Endothelial dysfunction is predictive of subsequent cardiovascular events[301].

Aldosterone also contributes to the progression of HF by promoting perivascular and interstitial myocardial fibrosis, by its action on cardiac mineralocorticoid receptors. *In vitro* experiments have reported that the administration of aldosterone to cardiac fibroblasts significantly enhances collagen synthesis[280;302;303]. This fibrosis reduces the flexibility of the myocardium, such that higher filling pressures are required, and therefore increases the likelihood of diastolic dysfunction. Structural remodelling of the interstitial collagen matrix, producing patchy myocardial fibrosis would also be expected to result in electrical inhomogeneity and therefore promote arrhythmia.

The first proof that the relationship between aldosterone and myocardial fibrosis was clinically important, came when it was shown that spironolactone reduced plasma levels of PIIINP in heart failure[304]. A comparison of patients with essential hypertension revealed that those with hyperaldosteronism had a higher LV mass index and alterations in myocardial texture which suggested increased collagen deposition, compared to those with normal aldosterone concentrations[305]. A further study, undertaken in patients with essential hypertension treated with an ACE-I, has reported that the LV mass index fell significantly only in patients in whom the aldosterone level was controlled, but remained unchanged in those with aldosterone escape[306].

Another potentially harmful effect of aldosterone is its ability to blunt the baroreflex response[307;308]. The normal baroreflex adjusts heart rate to normalise changes in BP. Aldosterone inhibits baroreflex sensitivity in healthy volunteers, independent of the attenuation of the baroreflex associated with angiotensin II[294].

Inhibition of the angiotensin-converting enzyme and antagonism of the angiotensin II receptor protect against vascular injury and end-organ damage. ACE-I mediated blockade of angiotensin II synthesis or angiotensin II receptor blockade lead to decreased synthesis of aldosterone. These decreases in angiotensin II and aldosterone are thought to be responsible for some of the cardioprotective effects of ACE-I or angiotensin II receptor blocker (ARB) treatment[276;277;286].

The data indicating a pathogenic role of aldosterone in HF have now been validated by two major prospective clinical trials. In the RALES study, 1663 patients with NYHA class III-IV HF were randomised to receive spironolactone (an aldosterone antagonist) or placebo[268]. The

trial was stopped early (mean follow up 24 months) after demonstrating a 30% reduction in mortality in the spironolactone group. This result was driven by a significant reduction in death due to progressive HF and sudden cardiac death. The spironolactone treated group also showed a significant improvement in HF symptoms, indicated by a reduction in NYHA class. The dose of spironolactone used in RALES (25-50mg/day) had no diuretic effect, as established by a sub-study where the sodium retention score was measured. The authors concluded that a cardio-protective effect of aldosterone blockade contributed to the reduction in mortality.

There are several potential explanations for the benefits of aldosterone blockade: aldosterone worsens endothelial function and so increases coronary events, and as discussed above it has arrhythmogenic effects[309]. Serological markers of cardiac collagen turnover (PICP, PINP, PIIINP) were analysed in a subgroup of the RALES study, to monitor the extent of tissue repair and fibrosis[157]. The levels of these markers decreased in the spironolactone group, but remained unchanged in the placebo cohort. This suggests that the benefit of aldosterone blockade is linked to the reduction in cardiac fibrosis. Interestingly, serum levels of all three procollagen markers were independently associated with risk of death, and the beneficial effects of spironolactone were predominantly seen among patients with the highest levels of procollagen markers. It is not yet clear whether aldosterone blockade is more effective in HF patients with higher plasma aldosterone levels[294].

The recent EPHESUS trial evaluated the use of the selective aldosterone blocker eplerenone in 6632 patients with acute MI complicated by LVSD and HF[310]. After a mean follow-up of 16 months, there was a 15% reduction in mortality compared to placebo and a 15% reduction in risk of hospitalisation for HF. The reduction in the primary endpoint was driven by a 21%

reduction in sudden cardiac death. The EPHESUS trial illustrated that the cardio-protective effect of aldosterone blockade is maintained even when patients are established on optimal therapy and close to the acute phase of MI[294].

7.02 Results

7.02.1 Renin and aldosterone concentrations

One of the major problems in measuring renin and aldosterone plasma concentrations is that many common cardiac medications influence the RAAS. In this study, the median plasma aldosterone concentrations were affected by the use of ACE-I, ARB and spironolactone. Table 7.1 and 7.2 show the median aldosterone concentrations in HF-RSF and HF-PSF dichotomised according to prescription of ACE-I, ARB or spironolactone. A higher median aldosterone concentration was found in HF-RSF (not taking ACE-I, ARB or spironolactone) compared to those with HF-PSF (not taking ACE-I, ARB or spironolactone) [p=0.026]. A higher proportion of patients in the HF-RSF (31%) had an elevated aldosterone concentration compared to those with HF-PSF. However nearly a one-fifth of the HF-PSF group also had an elevated aldosterone concentration and were not taking medications that influence the RAAS.

Table 7.1 Plasma aldosterone concentrations in patients with HF-RSF and HF-PSF

	HF-RSF (n=149)		HF-PSF (n=147)	
	Taking ACE-I / ARB No spiro (n=67)	Not taking ACE-I / ARB / spiro (n=71)	Taking ACE-I / ARB No spiro (n=52)	Not taking ACE-I / ARB / spiro (n=93)
Median (IQR) Aldo ng/dl	6 (3-11)	11 (7-24)	7 (3-13)	10 (4-16)
Elevated Aldo n(%)	5 (7)	22 (31)	4 (8)	16 (17)

Aldo = Aldosterone, spiro = spironolactone

Table 7.2 Plasma renin concentrations in patients with HF-RSF and HF-PSF

	HF-RSF not taking ACE-I / ARB/ Spiro (n=71)	HF-PSF not taking ACE –I / ARB / spiro (n=93)	p value
Median (IQR) renin μU/L	30 (17-109)	31 (13-59)	0.190
Elevated renin n (%)	28 (39%)	28 (30%)	0.224

Spiro = spironolactone

Median renin concentrations were analysed in the same way as shown in Table 7.2. There was no significant difference in the median renin concentration in HF-RSF and HF-PSF (not taking ACE-I, ARB or spironolactone) and a similar proportion of patients had elevated renin concentrations in each group. Only a few patients in both the HF-RSF (n=5) and HF-PSF (n=9) with elevated renin concentrations (not on ACE-I, ARB and spironolactone) were on a β-blocker.

7.02.2 Relationship between aldosterone and PIIINP

As already described in Chapter six and earlier in this Chapter, aldosterone can promote fibrosis and PIIINP is a marker of collagen formation, which occurs during fibrosis.

Table 7.3 shows the median PIIINP concentrations in HF-RSF and HF-PSF. In patients not taking medications that influence the RAAS, it is clear that higher PIIINP concentrations are seen in HF-RSF compared to those with HF-PSF.

Table 7.3 Median PIIINP concentrations in patients with HF-RSF and HF-PSF

	HF-RSF Median PIIINP µg/L	HF-PSF Median PIIINP µg/L	p
Taking ACE-I / ARB / spironolactone	6.9 (4.9-11.6)	5.0 (N/A)	0.28
Taking ACE-I / ARB Not taking spironolactone	6.6 (5.6-8.1)	6.2 (5.1-7.3)	0.07
Not taking ACE-I / ARB / spironolactone	7.2 (6.0-8.8)	5.8 (4.9-7.6)	0.0009

N/A = sample size too small for statistical analysis

Table 7.4 shows the median PIIINP concentrations in those patients with elevated aldosterone concentrations in both HF-RSF and HF-PSF not taking ACE-I, ARB or spironolactone.

Table 7.4 Median PIIINP concentrations in patients with HF-RSF/HF-PSF and elevated or normal aldosterone concentrations

	HF-RSF + elevated aldosterone	HF-RSF + normal aldosterone	p value
Median (IQR) PIIINP (µg/L)	6.6 (5.3-9.3)	7.4 (6.4-8.6)	0.565
	HF-PSF + elevated aldosterone	**HF-PSF + normal aldosterone**	
Median (IQR) PIIINP (µg/L)	5.9 (5.2-7.5)	5.8 (4.9-7.8)	0.909

In this study, patients with elevated plasma aldosterone concentrations did not have higher PIIINP concentrations. This finding was the same for both types of HF and there was also no significant difference in the PIIINP concentrations in those with elevated aldosterone concentrations in either HF-RSF or HF-PSF (p=0.237). This finding is in contrast to the

association, described in Chapter five, between elevated natriuretic peptide levels and elevated PIIINP.

7.03 Discussion

In patients not taking medications known to influence the RAAS (such as ACE-I, ARB and spironolactone), significantly higher median aldosterone and PIIINP concentrations were found in HF-RSF compared with HF-PSF. A higher proportion of patients with HF-RSF had elevated aldosterone concentrations. Renin concentrations were similar in both types of HF.

As has been discussed, the renin and aldosterone concentrations are difficult to interpret in isolation because of the influence of many common cardiovascular medications on the RAAS. I have tried to take this into account by further separating the two groups, into those who were taking ACE-I/ARB or spironolactone and those who were not.

It is important to appreciate, however, that other cardiac medications, such as diuretics and β-blockers also influence the RAAS. As less than one-fifth of the patients with clinical HF in this study were not on any medications which affect the RAAS, it is very difficult to interpret the significance of isolated renin and aldosterone measurements. Therefore, in future studies it would be beneficial to adopt measurements used in specialist hypertension practice for assessing aldosterone and renin, such as the plasma aldosterone to renin ratio (ARR). As a ratio, this provides an index of RAAS activation which is less influenced by the effects of medications on absolute renin or aldosterone concentrations.

Recently there has been increasing interest in aldosterone as a key cardiovascular hormone. Aldosterone excess results in hypertension and promotes collagen deposition in blood vessels,

thus enhancing vascular remodelling at the expense of vessel compliance. It has been shown that aldosterone excess in the presence of sodium chloride will stimulate perivascular and interstitial cardiac fibrosis and hypertrophy, independently of blood pressure. Treatment of severe heart failure with mineralocorticoid receptor antagonists such as spironolactone and eplerenone, significantly reduce mortality and morbidity, and this effect is also independent of any effect on blood pressure. Recently, animal models have shown that eplerenone can prevent and reverse mineralocorticoid induced fibrosis[311]. Given that fibrosis and hypertrophy are important pathological factors in the development of diastolic dysfunction, it may well be that RAAS over-activation is contributing to the development of HF-PSF. Results from this study would certainly seem to suggest that a proportion of patients with HF-PSF have RAAS over-activation. RAAS inhibition may therefore prove to be beneficial in HF-PSF. It may be that, in the future, measures of RAAS activation, such as ARR could identify those patients with HF-PSF who may benefit most from the early use of aldosterone antagonists.

CHAPTER EIGHT

HEART FAILURE AND CHRONIC OBSTRUCTIVE PULMONARY DISEASE

8.01 Introduction

The concern that patients thought to have heart failure in the context of preserved systolic function may have been misdiagnosed has been raised by a number of authors. One obvious cause of breathlessness that could be confused with heart failure is that arising as a consequence of chronic lung disease. Of course, it is also possible that both conditions might co-exist, especially given the role of smoking in causing both cardiac and pulmonary disease. No previous study has investigated the prevalence of chronic lung disease in patients with suspected heart failure and preserved systolic function.

8.02 Methods

A clinical diagnosis of chronic obstructive pulmonary disease (COPD) was defined as either: a past medical history of COPD or the prescription of bronchodilators, nebulisers or long term oxygen therapy (LTOT).

In order to further investigate the possibility of misdiagnosis, pulmonary function tests (PFTs) were requested in all patients with HF and preserved LV systolic function. The definition of COPD on spirometry was an FEV_1:FVC ratio less than 70[312].

PFTs were not requested, routinely, in patients with HF-RSF. For this reason, a comparison between HF-RSF and HF-PSF was only made using the "clinical" definition of COPD.

8.03 Results

8.03.1 Clinical COPD in HF-RSF and HF-PSF

Using the "clinical" definition of COPD, a significantly higher proportion of patients with HF-PSF had COPD (42%) than patients with HF-RSF (30%) [p=0.02].

8.03.2 Pulmonary function tests in HF-PSF

Nearly half (48%) of patients with HF-PSF had PFTs performed. Table 8.1 compares the key baseline characteristics of patients with HF-PSF; comparing those with and without PFTs. Most of the baseline characteristics were similar between those who had PFTs completed, compared with those who did not. The only exceptions were a greater mean age and higher median BNP and NT-proBNP concentrations in those patients for whom PFT data was not available.

Table 8.1 Clinical characteristics of patients with HF-PSF: PFTs recorded or not recorded

	HF-PSF + PFTs recorded (n=77)	HF-PSF + No PFTs recorded (n=70)	p value
Female n (%)	50 (65)	47 (67)	0.78
Age (yrs) mean (SD)	73 (9.3)	78 (10.9)	0.01
BNP (pg/ml) median (IQR)	113 (41-274)	259 (95-601)	0.01
NT-proBNP (pg/ml) median (IQR)	2552 (814-7890)	649 (183-2232)	0.001
Creatinine (µg/L) median (IQR)	104 (88-119)	104 (89-124)	0.76
eGFR (ml/min) (SD)	55 (16)	53 (18)	0.52
Hb (g/dL) mean (SD)	12.6 (2)	12.4 (2)	0.48
Anaemic n (%)	24 (31)	29 (41)	0.19
Positive troponin n (%)	14 (18)	16 (23)	0.48
SBP (mmHg) mean (SD)	146 (29)	144 (30)	0.61
DBP (mmHg) mean (SD)	77 (18)	80 (17)	0.23
Smoker n (%)	20 (26)	14 (20)	0.39
Ex-smoker n (%)	28 (36)	24 (34)	0.79
NYHA class III/IV n (%)	35 (45)	29 (41)	0.62
Killip class ≥IIA n (%)	22 (29)	25 (36)	0.35

eGFR = estimate glomerular filtration rate, Hb= haemoglobin g/dL, SBP=systolic blood pressure, DBP=diastolic blood pressure

I also calculated the proportions of patients with normal and abnormal pulmonary function tests and whether these patients had a clinical diagnosis of COPD (Table 8.2).

Table 8.2 Proportion of patients with HF-PSF and a diagnosis of COPD

n (%)	Abnormal PFTs (n = 27)	Normal PFTs (n = 50)
Clinical COPD (n=34)	18 (53)	16 (47)
No clinical COPD (n=43)	9 (21)	34 (79)

21% of patients with HF-PSF and no clinical diagnosis of COPD had spirometric evidence of airways obstruction. Of these 9 patients, 7 had an elevated BNP concentration. As an elevated BNP concentration is known to be a biochemical marker of LV stress, and a sensitive marker for the presence of HF, it is unlikely that these patients were misdiagnosed with HF, rather that HF and COPD may have co-existed. In the remaining two patients BNP concentration was normal. Therefore it is possible that these two patients were incorrectly diagnosed with heart failure.

Table 8.3 Proportion of patients with an elevated BNP

	Elevated BNP concentration n (%)
Clinical COPD + normal PFTs (n=16)	13 (81)
Clinical COPD + abnormal PFTs(n=18)	8 (44)
Any clinical COPD (n=34)	21 (62)
No clinical COPD + abnormal PFTs (n=9)	7 (78)
No clinical COPD + normal PFTs(n=34)	20 (59)
Any abnormal PFTs (n=27)	15 (56)

8.03.3 COPD in HF-IPSF

The HF-IPSF group consisted of patients with a clinical diagnosis of HF (n=86), preserved LV systolic function and the absence of either valvular heart disease or atrial fibrillation. Of these, 55 had PFTs performed. Of these 55, a clinical diagnosis of COPD was present in 27 patients. Table 8.4 shows the proportion of patients in each group.

Table 8.4 Proportion of patients with HF-IPSF and a diagnosis of COPD

n (%)	Abnormal PFTs (n = 18)	Normal PFTs (n = 37)
Clinical COPD (n = 27)	15 (56)	12 (44)
No clinical COPD (n = 28)	3 (11)	25 (89)

Of the 55 patients with HF-IPSF and PFTs recorded, 29 had an elevated BNP. The proportion of patients in each group with an elevated BNP concentration is shown in Table 8.4

Table 8.5 HF-IPSF: Proportion of patients with an elevated BNP

	Elevated BNP concentration n (%)
Clinical COPD + normal PFTs (n=12)	9 (75)
Clinical COPD + abnormal PFTs (n=15)	7 (47)
Any clinical COPD (n=27)	16 (59)
No clinical COPD + abnormal PFTs (n=3)	2 (67)
No clinical COPD + normal PFTs (n=25)	11 (44)
Any abnormal PFTs (n=18)	9 (50)

8.04 Discussion

It was intended that all patients with HF-PSF would have PFTs recorded. However, these could only be performed in just under half of the patients. The remainder of the patients either did not attend for PFTs as an out-patient or were not able to perform the test. A comparison of these two groups revealed that those who did not have PFTs performed were older and had higher median BNP and NT-proBNP concentrations. This highlights a major difficulty in studying this cohort of HF patients, who are very often extremely elderly. However, the higher median natriuretic peptides suggests that these patients were perhaps more unwell. Clearly, these differences suggest that the group who did have PFTs performed were not entirely representative of the HF-PSF group as a whole, However, one could argue that the group with the lowest BNP levels is the one where a misdiagnosis of HF is most likely, and by examining PFTs in this group I may in fact over- rather than underestimate the prevalence of COPD being misdiagnosed as HF.

It is now well established that COPD does not result in elevated natriuretic peptide concentrations[99;313-315] and that in clinical situations where they may be a significant overlap of symptoms and signs, natriuretic peptide levels are extremely useful for differentiating between cardiac and respiratory causes of breathlessness[99]. I have therefore examined BNP concentrations in those patients with HF-PSF and data from pulmonary function tests, in order to examine the interplay between COPD and HF and to determine whether COPD has been misdiagnosed in this cohort of patients.

The first conclusion is that the combined pathology of HF and COPD is common, this supports the recent findings of Rutten et al[316], who reviewed the literature and found that although data on the prevalence of HF in COPD and vice versa were scarce, the available data

indicated that the two conditions frequently coexisted.. In my study, approximately one-third of patients with HF-PSF or HF-IPSF had PFTs revealing COPD and half of these (in each HF group) also had an elevated BNP concentration, indicating that COPD and HF coexisted in these patients. Of these patients with spirometric evidence of COPD, one-third had no clinical diagnosis of COPD. It is therefore likely that COPD is under-diagnosed as a comorbid condition in patients with HF. Only 15% of patients with with HF-PSF had PFTs showing obstructive airways disease and a normal BNP. In the IPSF group this figure was similar (16%). This would suggest that a low proportion of patients had been incorrectly diagnosed with HF when in fact COPD was the relevant pathology.

Conversely the results highlight that HF may well be under-diagnosed in patients thought to have COPD. In both the HF-PSF and HF-IPSF groups, the majority of patients with a clinical diagnosis of COPD but normal PFTs, had an elevated BNP concentration (81% and 75% respectively). It is therefore likely that these patients have been incorrectly diagnosed with COPD, and possible that some will have been prescribed bronchodilators for breathlessness when in fact they have HF.

These results therefore highlight that as clinicians we should be more aware of the possible presence of combined pathology, or incorrect diagnosis of COPD in the HF patient. Basic spirometry should be a routine investigation for the assessment of the breathless patient, regardless of LV function.

These results also indicate that the use of BNP could appropriately direct the investigation and management of the breathless patient. A patient with signs and symptoms of heart failure and a normal BNP should have more extensive respiratory investigations. Those patients with

HF-PSF and an elevated BNP should have more cardiovascular investigations. However, spirometry should be routine, in order to exclude dual pathology, as it is likely that those patients in whom HF and COPD coexist may present complex management issues, and may perhaps benefit from joint care from both cardiology and respiratory physicians.

In summary, the goal of this analysis was to address one of the main controversies surrounding HF-PSF, namely that patients may be misdiagnosed with HF, when in fact they have other pathologies, such as COPD. In fact, these data would suggest the reverse. A low proportion of patients with either HF-PSF or HF-IPSF had both abnormal PFTs and a normal BNP, indicating misdiagnosis. On the contrary, a significant majority of patients who had been diagnosed with (and in some cases treated for) COPD, had normal PFTs but elevated BNP levels, indicating that their HF had been misdiagnosed as COPD. This finding has enormous relevance to clinical practice, and it is clear that the interplay between COPD and HF is one which requires further investigation, to ensure accurate diagnosis and treatment for these two common and important conditions.

CHAPTER NINE

MORTALITY & PROGNOSIS

9.01 Introduction

Clinical trials have shown that the case fatality related to HF is high, but has been significantly improved by the use of angiotensin-converting-enzyme (ACE) inhibitors and more recently β-blockers[317;318]. However, such studies have tended to preferentially enrol middle-aged men. Many patients with HF are elderly, and many with HF-PSF are female. The prognosis in these patients has been less well studied. This study therefore had looked at mortality in this cohort of patients.

9.02 RESULTS

9.02.01 Unadjusted case fatality from life tables

Table 9.1 shows 30 day and one, two and three-year unadjusted case fatality rates. For all individuals with HF these were 6.8%, 39.7% and 46.5%. When all HF was dichotomised to HF-RSF and HF-PSF the 30 day, one, two and three-year unadjusted case fatality was 8.7%, 32.2%, 47.2% and 57.7% respectively for HF-RSF, and 4.78%, 21.1%, 32.9% and 37% respectively for HF-PSF. The differences in the case fatality rate were statistically significant. Prognosis was poor following an admission for HF-RSF. The case fatality was almost 50% at 2 years. In the HF-PSF group, rates were lower but remained substantial at nearly 40% mortality after three years.

Table 9.1 Case fatality for HF-RSF and HF-PSF

	HF-RSF			HF-PSF			All Heart Failure		
	Case fatality %	95 % CI		Case fatality %	95% CI		Case fatality %	95% CI	
30 Day	8.7	8.68	8.77	4.73	4.7	4.8	6.76	6.73	6.79
1 year	32.2	32.14	32.3	21.02	21.02	21.2	27.03	26.98	27.08
2 year	47.9	47.78	47.9	32.84	32.8	32.9	39.71	39.66	39.77
3 year	57.7	57.61	57.8	37.02	37.02	37.2	46.49	46.43	46.55

9.02.02 Median survival

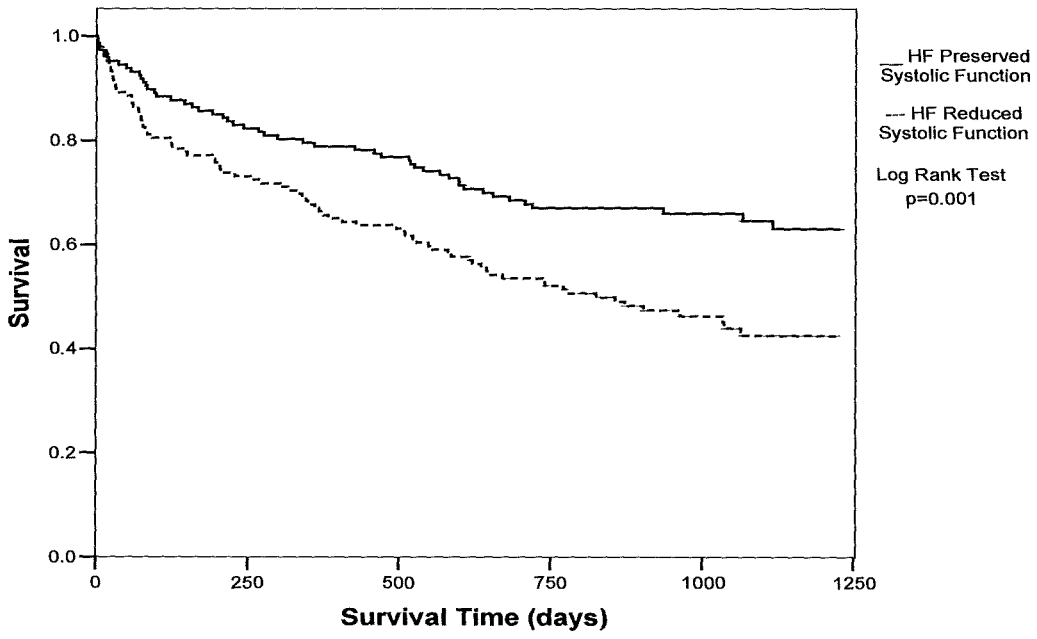
Survival time was calculated from recruitment date to date of death or censoring, which took place on 1st March 2006. Maximum follow-up was 39 months. Kaplan-Meier analysis was used to determine the median survival, which was calculated only if 50% of individuals had died at the censor date.

The median survival for all individuals with HF was greater than 1228 days (50% had not died by the censor date). The median survival for HF-RSF was 824 days (95% CI 547.27 – 1100.73) and for HF-PSF the median survival was greater than 1228 days (again, 50% had not died by the censor date).

8.02.03 Kaplan-Meier survival curves for HF-RSF and HF-PSF

A detailed description of the statistical analysis is given in Chapter 2. Unadjusted Kaplan-Meier curves for all-cause mortality demonstrated a significant difference in survival between the HF-RSF and HF-PSF groups (log rank test p = 0.001) (see Figure 9.1).

Figure 9.1 Kaplan-Meier survival curves for HF-RSF and HF-PSF



9.02.04 Multivariate analysis

Multivariate analysis was carried out using a Cox proportional hazards regression model. Variables were entered into the regression model based on the CHARM model for predictors of mortality. Not all variables from the CHARM model were available in this study[174].

The following variables were entered: smoking, age, gender (male vs. female), estimated glomerular filtration rate (eGFR), haemoglobin (Hb), heart rate (HR), atrial fibrillation (AF), diabetes mellitus (DM), hypercholesterolemia, peripheral arterial disease (PAD), cerebrovascular disease (CVD), ischaemic heart disease (IHD), chronic obstructive pulmonary disease (COPD), NYHA class, presence of bundle branch block (BBB), systolic blood pressure (SBP), diastolic blood pressure (DBP), BNP and HF group (RSF or PSF). Table 9.2 summarises the results.

Figure 9.2 Final multivariate model for all-cause mortality based on a Cox regression analysis

Variable	Hazard Ratio	95% CI	P value
Smoker	1.221	0.770 – 1.935	0.397
Age (yrs)*	1.032	1.008 – 1.057	0.009
eGFR (ml/min/m^2) *	0.985	0.972 – 0.998	0.022
Hb (g/dl)*	1.010	0.917 – 1.112	0.847
HR (beats per min)*	1.001	0.993 – 1.010	0.761
AF	1.405	0.907 – 2.177	0.128
DM	1.263	0.808 – 1.974	0.305
Hypercholesterolaemia	0.953	0.619 – 1.466	0.826
PAD	0.985	0.505 – 1.918	0.965
COPD	1.619	1.099 – 2.386	0.015
IHD	1.048	0.714 – 1.539	0.811
CVD	0.787	0.494 – 1.256	0.316
HF Group (PSF v RSF)	0.899	0.592 – 1.366	0.619
NYHA class III†	1.131	0.732 – 1.747	0.579
NYHA class IV†	2.134	1.356 – 3.359	0.001
Bundle branch block	1.874	1.247 – 2.818	0.003
SBP (mmHg)*	0.990	0.982 – 0.998	0.018
DBP (mmHg)*	1.002	0.986 – 1.017	0.846
BNP (100pg/ml)*	1.045	1.017 – 1.075	0.002
Sex (male v Female)	1.153	0.793 – 1.676	0.457

* fitted as continuous variables
† compared to class I and class II combined

After adjusting for the variables in the Cox regression model; age, eGFR, presence of COPD, NYHA class IV HF, presence of bundle branch block, SBP and BNP were found to be independent predictors of mortality. The presence of a higher eGFR and systolic blood pressure at the time of admission was associated with a better outcome in this population.

Increasing age, the presence of COPD, any bundle branch block, or higher BNP concentrations on admission were associated with a poor prognosis. In this study, for every 100 unit increase in BNP there was a 4% increase in risk of death. The presence of NHYA class IV HF was also an independent predictor of mortality in this group.

No other variables within the model independently predicted mortality after multivariate analysis. This included the distinction between reduced and preserved systolic function.

Although the Kaplan-Meier plots separate and show a significant mortality difference between the two groups, this is a univariate analysis, which does not take into account the distributions of other variables within the two groups. When these different distributions were adjusted for, by entering them into a Cox proportional hazard regression model, there was no significant difference in mortality between the two groups.

9.3 Discussion

It is now established that HF-RSF is a significant escalating public health problem in terms of mortality, morbidity and consequent economic cost. Studies such as the Euroheart Failure Survey[177] revealed that almost 50% of the 6000 patients studied had HF-PSF and consequently the medical community is beginning to appreciate that HF-PSF has similar implications in terms of mortality, morbidity and economic cost.

The 3-year unadjusted case fatality in this study confirmed findings from several recent studies (published after this study was started) that mortality in HF-RSF (58%) was worse than HF-PSF (37%). However, mortality in both groups was poor. The Helsinki Ageing Study reported four year mortality rates, 54% for HF-RSF and 43% for HF-PSF[40].

These figures are similar to the overall five-year mortality rate of 65% in the Olmsted County incidence study[19]. In this study, the age and gender-adjusted mortality rates in those with HF were higher than those without HF. However, there was no significant difference in mortality between patients with PSF and those with RSF. Data published recently after the completion of this study reported mortality rates of 65% and 68% for HF-PSF and HF-RSF respectively at five years[178].

Patients with HF-RSF in the Framingham study had an annual mortality rate of 18.9% compared with 4.1% in age and gender-matched controls over 6.2 years. Framingham patients with HF-PSF had an annual mortality rate of 8.7% compared with 3% in their controls. Hospital cohort studies show that patients with HF-PSF have better survival at all time points from admission compared with HF-RSF. However, patients with HF-PSF still have a high mortality following admission to hospital, with rates of 40-50% after four to five years of follow-up[8]. In that study median survival for all HF was greater than 3.4 years and for HF-RSF was 2.3 years. This is better than the median survival reported by McIntyre *et al* in a Scottish cohort of HF patients from 1896-1995. The median survival in this cohort was 1.5 years[319]. This indicates a small improvement in the prognosis for HF patients which may be due to the use of evidence-based medical therapy ACE-I, ARBs, aldosterone antagonists and β-blockers

Kaplan-Meier curves for HF-RSF and HF-PSF show a significant difference in mortality between the two groups. However, after multivariate analysis using a Cox proportional hazards model, classification of HF as HF-RSF or HF-PSF was not an independent predictor of survival. The difference in survival suggested by Kaplan-Meier analysis must therefore be explained by the differing distributions of variables between the two groups.

In this cohort of HF patients, independent predictors of death were: increasing age; eGFR, presence of chronic obstructive airways disease, NYHA IV HF, the presence of any bundle branch block, lower systolic blood pressure, and higher BNP concentrations. Better renal function and higher systolic blood pressure at the time of admission was correlated with improved survival. Increasing age, the presence of chronic obstructive airways disease, NYHA class IV HF, any bundle branch block and higher BNP concentrations were correlated with increased mortality. It should be noted that, this assessment of predictors of mortality is limited in that we could not adjust for ejection fraction in the multivariate analysis.

In this cohort of HF patients, after adjustment for potentially confounding variables, there was no significant difference in mortality between HF-RSF and HF-PSF. This reflects a Canadian study published recently. Bhatia *et al* reported that patients with HF-PSF had high 30-day and 1-year mortality rates that were not significantly lower than those of patients with HF-RSF with or without adjustment for clinical differences between the two groups[179]. This study showed that every 100 unit increase in BNP was associated with a 5% increase in risk of death. Kirk *et al* published data after the completion of this study demonstrating that a significantly higher NT-proBNP concentration was found in those patients who did not survive 12 months from the time of testing. In that study, NT-proBNP was found to be a strong prognostic predictor of mortality regardless of systolic function[197]. Importantly, recent data suggest that mortality may be reduced in patients in whom NT-proBNP or BNP levels fall during medical treatment for HF[320]. Previous studies have shown that BNP independently predicts morbidity and mortality in asymptomatic reduced LV systolic function and in mild to moderate HF-RSF[104;195;196]. In addition, BNP has been shown to be a strong and independent predictor of sudden cardiac death in patients with HF[107].

This study has shown that despite advances in the treatment of HF the prognosis is still poor. In addition it has provided evidence that like patients with HF-RSF, patients with HF-PSF have a similarly poor prognosis.

CHAPTER TEN

DISCUSSION

HF is recognised as a major public health problem[1;2] particularly in view of the fact that the population is ageing. In the UK the prevalence of HF is more than 100 cases per 1,000 population, in those aged 65 years and older. HF is also a significant economic burden, accounting for 2% of the UK NHS budget[3]. There has been growing interest in HF-PSF over the past decade, and epidemiological studies have suggested that 13-74% of patients with clinical HF have preserved LV systolic function[12]. There has been growing interest in HF-PSF over the past decade, and epidemiological studies have suggested that 13-74% of patients with clinical HF have preserved LV systolic function[24;26;31;32]. If approximately 40% of patients hospitalised with HF have PSF then approximately 40% of the overall cost of treating HF is due to HF-PSF. As well as representing a significant economic burden, this patient group has a poor prognosis. Reported mortality rates vary widely. The consensus from several studies however, is that mortality in patients with HF-PSF is better than those with HF-RSF but is poor compared to patients without heart failure[8;41]. As outlined in Chapter 1, there has been little evidence collected regarding clinical characteristics of patients with HF-PSF, particularly with regard to variables which may yield insights into the pathophysiology of HF-PSF. Also, outcome data for patients hospitalised with HF-PSF was scarce.

This study has examined in detail the clinical, echocardiographic and biochemical characteristics of patients admitted with heart failure on an emergency basis. The characteristics of patients with HF-PSF have been compared to those of patients with HF-RSF, with the aim of identifying important characteristics shared between the two groups and those characteristics which may be particularly common in HF-PSF. The subsequent clinical outcomes of these patients have also been documented, and the variables independently associated with an increased risk of death in this cohort have been determined through statistical analysis.

Of the total number of patients with clinical HF who agreed to enter the study, approximately half had preserved systolic function. As described in Chapter 1, prior to commencement of this study there was a wide variation in the estimated prevalence of HF-PSF, partly due to heterogeneity in sample size and patient selection. Since then, a large retrospective study has examined patients with a diagnosis of HF and an objective assessment of LVEF over a 15 year period[178] and found the prevalence of HF-PSF to be 47%, comparable to the proportion found in my study.

However, the main drawback in examining the literature as regards prevalence of HF-PSF is the lack of a single agreed definition for preserved, as distinct from reduced ejection fraction. The practice of many studies, including the recent analysis by Owan *et al*[178] has been to use a numerical ejection fraction obtained by any one of a number of methods (echocardiography, radionuclide imaging, cardiac catheterisation). Normal ranges for ejection fraction differ according to the method of measurement, meaning that it may not be valid to compare percentage ejection fractions obtained by different methods.

In my study, systolic function was determined to be either reduced or preserved from echocardiographic images by a single experienced operator, an approach which is qualitative and therefore has inherent disadvantages. However, these are minimised by use of a single technique and single operator. Given that there is no gold standard method for determination of ejection fraction in this context, or agreed cut-off for preserved ejection fraction, I think it is reasonable to compare my findings with those from the other studies cited, and conclude that HF-PSF does indeed account for around half of all cases of clinical HF.

With regard to clinical characteristics, there were some notable differences between HF-RSF and HF-PSF. The main demographic difference was that a higher proportion of patients in the HF-PSF group were female, a finding similar to those in previous studies, described in Chapter 1. This finding has also been borne out by the long-term prevalence studied published recently by Owan et al[178] and a more recent report of contemporary patients[179]. Indeed, this finding is becoming well established in the literature as a characteristic of HF-PSF[13]. This may, in part reflect the increased prevalence of coronary artery disease in men, which may well be expected to predispose them to reduced, rather than preserved systolic function heart failure. It may also be related, as discussed in Chapter 3, to an interaction between age, sex and the incidence of hypertension.

Hypertension is now recognised to be an important risk factor for the development of HF-PSF, and this is supported by the findings of my study, in which a higher proportion of patients with HF-PSF had a history of hypertension. Patterns of other important co-morbid diseases were similar to those in recent studies[178;179], with the notable exception of atrial fibrillation (AF), the prevalence of which was not significantly different between the two groups in my study, but has been found to be greater in the HF-PSF groups of both Owan *et al* and Bhatia *et al*. The reasons for this discrepancy are not clear. The proportions of patients with AF in the groups with reduced systolic function are comparable across all three studies (29%[178], 25%[179] and 30% in my study). Indeed, an increased incidence of AF in HF-PSF may be expected as AF can be both a cause and consequence of HF-PSF.

In terms of their symptoms and signs, patients in the HF-RSF group were more likely to report moderate to severe symptoms of HF (i.e. NYHA III/IV). However, severity of HF on admission, as assessed by the Killip score was at least moderate (Killip ≥IIa) in the majority

of patients in both groups. This is another area where the results from this study have improved our understanding of HF-PSF. Prior to starting this study, when there was controversy surrounding HF-PSF, it was generally perceived to be a condition which produced mild symptoms and signs. Recent evidence agrees with my own findings that this is not the case[179].

The debate surrounding HF-PSF also focused on whether symptoms and signs of heart failure in the absence of impairment of LV systolic function were merely a consequence of other comorbid pathologies. There are clearly other cardiac pathologies which can produce symptoms and signs of heart failure, for example, valvular heart disease or atrial fibrillation. Of my patients with HF-PSF, 41% had VD, AF or both. I have referred to the group without VD or AF as HF-IPSF. HF-IPSF accounted for approximately one-third of admissions with clinical HF. This definition is not one which is commonly found in the heart failure literature. However, I felt it was extremely important to make this distinction, in order to clearly define a group of patients with HF-PSF for whom there was no other clear explanation for their symptoms and signs.

Clearly the crucial question is: did all the patients in the HF-IPSF group in this study really have heart failure? They all had symptoms and signs compatible with a diagnosis of heart failure, and therefore scored positively on objective heart failure scoring systems. In addition, just over half had elevated natriuretic peptide levels, strongly indicating that heart failure was present, and certainly meeting modern definitions for the diagnosis heart failure.

Examining the findings of this study helps to clarify the roles of diagnostic tools in HF. Natriuretic peptides accurately predicted both systolic function and prognosis, but simple

echocardiographic measures failed to reliably detect diastolic dysfunction. Although echocardiography is essential for the identification of reduced systolic function and other cardiac pathology, at the current time routine echocardiography alone cannot exclude the diagnosis of HF. I would therefore propose that in a patient with suspected HF, echocardiography and natriuretic peptide testing should be employed to determine independently whether there is LV systolic dysfunction or biochemical evidence of LV compromise. These diagnostic tests should be regarded as complementary to one another, and both should be required for accurate diagnosis and classification of heart failure.

It has been suggested that, in many cases, the syndrome of HF-PSF has resulted from misdiagnosis of heart failure, when the primary pathology is quite separate. Chronic obstructive pulmonary disease (COPD) is a common condition which can produce symptoms and signs similar to or indistinguishable from those produced by heart failure. The findings from this study suggest that only a small proportion of patients with a clinical diagnosis of HF-PSF have COPD but not heart failure (on the basis of a normal BNP and PFTs diagnostic of COPD). Interestingly, in the HF-PSF group a significant proportion of patients who had a clinical diagnosis of COPD prior to admission actually had normal PFTs but an elevated BNP, indicative of the fact that their heart failure may have been previously misdiagnosed as COPD.

Clearly, COPD also exists as a comorbid condition in patients with HF, and despite the fact both are extremely common there are no studies to date that have specifically assessed the incidence of COPD in HF[316]. This study has shown, perhaps not surprisingly that the presence of COPD is an independent predictor of death in patients with HF. Not only is

COPD a serious comorbidity, but it can also limit scope for treatment with β-blockers, both of which could account for the increased mortality seen in this group of HF patients.

The relationship between HF and COPD is likely to be complex, and it is clear that COPD presents both a diagnostic and therapeutic challenge in HF management. It is possible that the use of combinations of echocardiography, BNP, pulmonary function testing and cardiac magnetic resonance imaging may provide more detailed information regarding the importance of COPD in HF and in particular, in HF-PSF.

Considering the above discussion, I would regard the first major finding of this study to be the fact that a significant proportion of acute heart failure admissions, as defined by HF scores and BNP levels, occur in the context of preserved left ventricular ejection fraction.

Having established that HF-PSF indeed exists, and accounts for a number of HF admissions, the next major finding of my study is that the prognosis associated with this condition is poor. The unadjusted Kaplan-Meier curves for HF-RSF and HF-PSF showed a significant difference in mortality between the two groups. However, after adjustment using a multivariate Cox regression analysis, there was no significant difference in survival between the two types of heart failure.

Therefore, both types of HF have a poor prognosis. If we consider case fatality, almost 50% of those with HF-RSF were dead at two years, and almost 40% of the HF-PSF group were dead after three years. Patients with HF-RSF and HF-PSF therefore have similar mortality but, unlike the former, no evidence-based treatment is available for the latter.

The only large randomised controlled trial to examine the effects of drug treatment on the prognosis of patients with HF-PSF published to date is the Candesartan in Heart failure Assessment of Reduction in Morbidity and mortality (CHARM) Programme. The CHARM-Preserved component study enrolled 3023 patients with NYHA II-IV HF and LVEF > 40% and randomised them to candesartan or placebo. After a median follow-up of 36.6 months the authors observed no difference in the primary endpoint (cardiovascular death or admission to hospital for HF) but showed a reduction in hospital admissions for HF in the group treated with candesartan[183].

Although there was no mortality benefit demonstrated in CHARM-Preserved, the result does suggest that blockade of the RAAS is of some clinical benefit in patients with HF-PSF. This study looked at renin and aldosterone measurements, in an attempt to explore possible aetiological factors in HF-PSF. Difficulties due, primarily, to the confounding effect of medications have precluded significant conclusions being drawn regarding the role of RAAS activation in this group of patients. However, the argument remains a convincing one: RAAS over-activation promotes fibrosis and hypertrophy which can lead to a reduction in ventricular compliance and abnormalities in diastolic function, producing the clinical syndrome of HF, in the absence of abnormalities in systolic function. There is therefore a plausible potential explanation for the effect of candesartan in CHARM-Preserved, and this area is one which should be a focus for future research, both in terms of focused large-scale clinical trials and of mechanistic work.

This study has detailed the clinical, echocardiographic and biochemical characteristics of patients with HF-PSF. I have shown that approximately half of the patients admitted on an emergency basis with HF had preserved systolic function. Many of these patients may have

had other causes for their symptoms and signs of HF. I have therefore characterised a group of patients who did not have VHD or AF as a possible cause for their symptoms. I propose that in this group (HF-IPSF), it is those with biochemical evidence of LV compromise that may be said to have heart failure with preserved systolic function.

Further investigation of this patient group is required in order to advance our understanding of the pathophysiology of the disease process, and to establish how best to treat these patients. For future studies, the definition of HF-PSF needs to be carefully considered. It is my feeling that a contemporary diagnosis of heart failure should include clinical signs and symptoms of heart failure, echocardiographic evidence of preserved LV systolic function and an elevated BNP or NT-proBNP concentration as biochemical evidence of LV compromise.

Newer imaging techniques such as tissue Doppler echocardiography and cardiac MRI are less influenced by the haemodynamic loading conditions, and may therefore become useful in the future as diagnostic tools. However, decisions will still need to be made regarding the appropriate criteria for establishing diastolic dysfunction.

One of the many questions that remains unanswered is that regarding the significance of underlying ischaemia. Coronary angiography is the gold standard for assessment of coronary arteries however, it is an invasive investigation with potential risks to the patient, particularly in the elderly. Cardiac MRI with gadolinium enhancement would allow for the assessment of ischaemia in a non-invasive manner. Similarly, CT coronary angiography may become a more widely utilised diagnostic tool for the assessment of coronary arterial stenosis, particularly in patients where the risk: benefit ratio of coronary angiography is unfavourable. Increased use of these non-invasive tools may therefore be a means of progressing our

knowledge regarding the underlying pathophysiology of heart failure with preserved systolic function.

Importantly, this HF cohort needs to be included in more large-scale prospective clinical trials, in order to establish a successful treatment strategy. In addition to CHARM-PRESERVED and Perindopril for Elderly People with Chronic Heart Failure (PEP-CHF), further studies of RAAS inhibition such as Irbesartan in Heart Failure with Preserved Systolic Function (I-PRESERVE), and the Trial of Aldosterone Antagonist Therapy in Adults with Preserved Ejection Fraction Congestive Heart Failure (TOPCAT) may begin to answer this question.

Further investigation of the pathophysiology and determination of the optimal treatment strategy are imperative, because, as demonstrated by this study, HF with preserved systolic function is common and carries a significant burden in terms of mortality and socio-economic cost.

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Appendix 1- Patient information sheet and consent form

THIS SHEET HAS BEEN APPROVED BY THE WEST ETHICS COMMITTEE

INFORMATION SHEET FOR PATIENTS/VOLUNTEERS IN CLINICAL RESEARCH PROJECT

Brief Title of Project

Characterisation of patients with heart failure despite preserved left ventricular systolic function: A prospective, descriptive, cohort study.

Patient's Summary (Purpose of study, nature of procedure, discomfort and possible risks in terms which the patient or volunteer can understand).

You are invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

This study is about a condition called "heart failure". Heart failure causes breathlessness, fatigue and swollen ankles and occurs when the heart does not pump normally. There are two main kinds of heart failure, one where the main muscular pump of the heart is weakened and the other where it is not. The aim of this study is to describe the nature of the second type of heart failure and its outcome. This will be done by assessing patients who present as an emergency to hospital with possible heart failure. This study may eventually allow us to develop treatments to improve outcome. We will be recruiting patients into this study for eighteen months and each patient will be followed up in the study for at least one year.

You have been chosen for this study because you presented to hospital with symptoms which could be due to heart failure. However, we know that many patients will turn out to have another explanation for their symptoms eg. a lung problem. We are hoping to recruit 700 patients over an eighteen month period into this study. It is up to you to decide whether or not to take part. If you do decide to take part you will be given the information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free at any time to withdraw without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care that you receive.

If you decide to take part in this study we will seek your permission to do 5 things:

1 To ask you a series of questions about your health and the symptoms that led to your hospital admission.

2 To examine you (focusing mainly on your heart and lungs).

3 To take an extra blood sample. We need about 20 millilitres (or about 4 teaspoonfuls). Taking this amount of blood should not be harmful. We wish to measure a number of substances that are increased in the blood if the heart is damaged or not pumping properly. Having blood taken may be uncomfortable and can leave minor bruising.

All of 1-3 should not take more than one hour

4 To collect the results of all the other routine tests you will have carried out during and after your hospital admission. Usually, these will include an ECG tracing, a chest X-ray, a heart ultrasound scan (echocardiogram), breathing tests, a treadmill exercise test and so on. We wish to collect all this information so as to have a complete picture of what might have caused your symptoms and hospital admission.

5 To follow your progress over the next year after discharge from hospital. We would like to do this in person (by telephoning you), through your hospital records and through national records (eg. the NHS system that identifies all hospital admissions). This is in order to see what happens to patients like yourself with this type of medical problem.

If you are harmed by taking part in this research project, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for a legal action but you may have to pay for it. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms are available to you.

All information which is collected about you during the course of the research will be kept strictly confidential. Any medical information from the study about you which leaves the hospital will have your name and address removed so that you cannot be recognised from it. The results from this study will be kept on a hospital computer data base and may be used in the future. The results are also likely to be published in national cardiology journals.

It should be noted that your participation in this study may not be of direct benefit to you, but could help in the development of treatment for the benefit of future patients.

If you do not wish to participate in this study, or wish to withdraw at any time after commencing the trial, your care will in no way be affected.

If you wish to take part in this study, your General Practitioner will be advised of your participation and the clinical management that you will undergo.

This proposal has been reviewed by the West Glasgow's Research and Ethics Committee. Should you require any further information then you can contact Dr Karen Hogg (page 4244) through the Western Infirmary switchboard (0141-211-2000).

WEST ETHICS COMMITTEE

FORM OF CONSENT FOR PATIENTS/VOLUNTEERS IN CLINICAL RESEARCH PROJECT

Title of Project :

Characterisation of patients with heart failure despite preserved left ventricular systolic function: A prospective, descriptive, cohort study

By signing this form you give consent to your participation in the project whose title is at the top of this page. You should have been given a complete explanation of the project to your satisfaction and have been given the opportunity to ask questions. You should have been given a copy of the patient information sheet approved by the West Ethics Committee to read and to keep. Even though you have agreed to take part in the research procedures you may withdraw this consent at any time without the need to explain why and without any prejudice to your care.

Consent:

I,.....(PRINT)

of.....

give my consent to the research procedures above, the nature, purpose and possible consequences
of which have been described to me

by.....

Patient's signature.....Date.....

Doctor's signature.....

Appendix 2: Heart Failure Scores

BOSTON CRITERIA FOR HEART FAILURE

HISTORY:

SOB* AT REST	☐	4
ORTHOPNOEA	☐	4
PND	☐	3
SOB* ON EXERTION (Level)	☐	2
SOB* ON CLIMBING	☐	1

PHYSICAL EXAMINATION:

Heart rate (91-110 bpm)	☐	1
Heart rate (>110 bpm)	☐	2
ELEVATED JVP† > 6CMS	☐	2
JVP† > 6CMS + HEPATOMEGALY / OEDEMA	☐	3
BASAL CREPS	☐	1
> BASAL CREPS	☐	2
WHEEZE	☐	3
S3 GALLOP	☐	3

CXR:

ALVEOLAR PULMONARY OEDEMA	☐	4
INTERSTIAL PULMONARY OEDEMA	☐	3
BILATERAL PLEURAL EFFUSION	☐	3
CARDIOTHORACIC RATIO > 0.5	☐	3
UPPER ZONE FLOW REDISTRIBUTION	☐	2

* shortness of breath
† jugular venous pressure

Boston Heart Failure Score:

Maximum of 4 points from each section

0-4 = No heart failure

5-7 = Possible heart failure

8-12 = Definite heart failure

NHANES SCORE

HISTORY:

SOB* when hurrying on the level or up slight hill	ف	1
SOB* when walking at ordinary pace on the level	ف	1
Do you stop for breath when walking at own pace	ف	2
Do you stop for breath after 100 yards on the level	ف	2

PHYSICAL EXAMINATION:

Heart rate 91-110	ف	1
Heart rate > 110	ف	2
Basal crepitations	ف	1
> Basal crepitations	ف	2
Raised JVP†	ف	1
Raised JVP† & oedema / hepatomegaly	ف	2

CXR:

Upper lobe diversion	ف	1
Interstitial oedema	ف	2
Alveolar fluid & pleural fluid	ف	3
Interstitial oedema & pleural fluid	ف	3

HF PRESENT IF SCORE ≥ 3

* shortness of breath
† jugular venous pressure

FRAMINGHAM CRITERIA

Framingham Criteria for Heart Failure 2 major criteria, or 1 major criteria and 2 minor criteria
Major Criteria
Paroxysmal nocturnal dyspnoea Neck vein distention Rales Radiographic cardiomegaly Acute pulmonary oedema Third heart sound Increased central venous pressure Circulation time >24secs Hepatojugular reflex Pulmonary oedema, visceral congestion, or cardiomegaly at autosy Weight loss>4.5kg in response to treatment of CHF
Minor Criteria
Bilateral ankle oedema Nocturnal cough Dyspnea on ordinary exertion Hepatomegaly Pleural effusion Decrease in vital capacity by 33% from maximal value recorded tachycardia (rate .120beats per minute)

HF = 2 major criteria or 1 major + 2 minor criteria

Appendix 3 : Case record forms

ADMISSION DATE:	**ADMITTING CONSULTANT:**				
NAME:	**MAIDEN NAME:**				
D.OB:	**HOSP No:**				
AGE:	**CHI NO:**				
SEX:	**GP DETAILS:**				
MARITAL STATUS:	**ETHNIC ORIGIN:**				
ADDRESS:	**TELEPHONE NO:**				
NEXT OF KIN:	**MOBILE NO:** **OTHER CONTACT NO:**				
OCCUPATION:	**FORMER OCCUPATION:**				
HT:	**TRANSFERRED TO WARD:**				
WT:	**DISCHARGE DATE:**				
ALCOHOL UNITS / WK:	**DATE OF DEATH:**				
SMOKING HISTORY:	**NO**	**EX + DATE**	**YES**	**NO / DAY**	**YEARS**

PATIENT HISTORY - Cardiac symptoms

	NO	YES						
SOB (Post Admission) Killip Classifcation			I	II	IIA	IIB	III	IV
SOB (Normally)			NYHA I	NYHA II		NYHA III	NYHA IV	
PND								
ORTHOPNOEA								
NOCTURAL COUGH								
COUGH								
SPUTUM			AMOUNT		COLOUR		WORSE TIME	
HAEMOPTYSIS			AMOUNT		TIMES / DAY		ADMISSTIONS	
WHEEZE								
↓ EXERCISE TOLERANCE								
ANKLE SWELLING								
CHEST PAIN								
PALPITATIONS								
GEN FATIGUE								
LEG FATIGUE								
WT LOSS								
INTERMITTENT CLAUDICATION			<200YRDS			>200YARDS		

KILLIP CLASSIFICATION: **I No Symps with normal activities, clear lungs**
II Normal activities initiate symps, but subside with rest
IIA crackles < 1/3 IIB crackles > 1/3
III Symps on minimal activity or rest / pulmonary oedema
IV Cardiogenic Shock

NYHA CLASSIFICATION: **I Normal daily activity does not initiate symps**
II Normal activity initiates symps but subside with rest
III Minimal activity initiates symps ; patient usually symp free at rest
IV Any type of activity initiates symps and symps are present at rest

PAST MEDICAL HISTORY- Cardiovascular (1)

PAST MED HX	DK	NO	YES														
Known valve disease				AS				AI				MR				MS			
				T	M	Mod	S	T	M	Mod	S	T	M	Mod	S	T	M	Mod	S
Previous valve replacement				AORTIC				DATE				MITRAL				DATE			
Myocardial infarction				VERIFIED								NON-VERIFIED							
Angina				VERIFIED ANGIO/ETT								NON-VERIFIED							
Previous CABG				DATE:															
Previous angioplasty				DATE:															
Prior heart failure				HOSPITAL DX												GP DX			
Hypertension				On Admission				Previous				Treated							
High cholesterol				On Admission				Previous				Treated							

PAST MEDICAL HISTORY- Cardiovascular (2)

PMHX	DK	NO	YES					
Previous stroke								
Previous TIA								
Previous carotid doppler				RESULT:				
Previous endarterectomy								
PVD				Clinic	Angio	Other Ix	Angioplasty	Surgery
Proven previous arrhythmia				AF	ATRIAL FLUTTER		SVT	OTHER
Cardiomyopathy				DILATED	HYPERTROPHIC		RESTRICTIVE	
Diabetes				INSULIN	NON-INSULIN		DIET	

PAST MEDICAL HISTORY- General (1)

PMHX	DK	NO	YES			
COPD				RESP CLINIC	Consultant	NO
Asthma				RESP CLINIC	Consultant	NO
Bronchiectasis				RESP CLINIC	Consultant	NO
Post TB respiratory disease				RESP CLINIC	Consultant	NO
Asbestosis				RESP CLINIC	Consultant	NO
Pleural plaques				RESP CLINIC	Consultant	NO
Pulmonary fibrosis				RESP CLINIC	Consultant	NO
Other respiratory disease				RESP CLINIC	Consultant	NO
Amyloidosis						
Sarcoidosis						
Haemochromatosis						
Rheumatoid Arthritis						
SLE						
Sjogrens						
Raynauds						
Systemic Sclerosis						
Other CT Disease						

PAST MEDICAL HISTORY- General (2)

PMHX	DK	NO	YES			
Anaemia				Investigations	Known Cause	Treated
Renal failure				Clinic	Dialysis	Transplant
Renal artery stenosis						
Thyroid disease				Hyper	Hypo	Treated
Prostatic disease				Benign	Malignant	Treated
Parkinsonism						
Multiple Sclerosis						
Motor Neurone Disease						
Muscular Dystrophy						
Osteoporosis						
Obesity				Clinic	Medication	Surgery
Anxiety						
Other						

DRUG HISTORY — Cardiovascular (1)

DRUG CLASS	DRUG NAME	NO	YES	DOSE
ANTI-PLATELET	Aspirin			
	Clopidogrel			
CARDIAC GLYCOSIDE	Digoxin			
DIURETIC	Frusemide			
	Other loop diuretic			
	Spironolactone			
	Amiloride			
	Bendrofluazide			
	Bumetanide			
	Metolazone			
	Indapamide			
	Co-amilofruse			
	Acetazolamide			
	Other Diuretic			
β-BLOCKER	Atenolol			
	Bisoprolol			
	Carvedilolol			
	Metoprolol			
	Propranolol			
	Labetalol			
	Sotalol			
	Other			
ACE INHIBITOR	Ramipril			
	Lisinopril			
	Captopril			
	Enalapril			
	Trandolopril			
	Fosinopril			
	Perindopril			
	Quinapril			

DRUG HISTORY – Cardiovascular (2)

		NO	YES	DOSE
VASODILATORS	Nitrates			
	Hydralazine			
	Minoxidil			
	GTN Spray			
	Other			
ALPHA-BLOCKERS		Prostate		Hyptertension
ARB	Losartan			
	Candesartan			
ANTI-ARRHYTHMICS				
Class I	Flecainide			
	Propafenone			
	Quinidine			
	Disopyramide			
Class II	B-Blockers			
Class III	Amiodarone			
	Sotalol			
Class IV	Ca Channel Blockers – Verapamil Diltiazem			
STATIN	Pravastatin			
	Simvastatin			
	Atorvastatin			
	Fluvastatin			
ANION-EXCHANGE RESINS				
FIBRATES				
CENTRAL ANTI-↑BP	Methyldopa			
	Moxonidine			
	Clonidine			
	Other			

DRUG HISTORY - Respiratory

DRUG CLASS	DRUG NAME	NO	YES	DOSE
INHALED B-AGONIST	Salbutamol			
	Salmeterol			
	Terbutaline			
	Bambuterol			
	Fenoterol			
	Tulobuterol			
ORAL β-AGONISTS	Salmeterol			
INHALED ANTI-MUSCARINIC	Ipratropium Bromide			
	Oxitropium Bromide			
	Other			
THEOPHYLLINE				
INHALED STEROID	Pulmicort			
	Beclomethasone			
	Becotide			
	Budesonide			
	Fluticasone			
	Serotide			
Inhaled combination Steroid/β-Agonist				
ORAL STEROIDS	Prednisolone			
	Budesonide			
LEUKOTRIENE REC ANTAGONISTS	Montelukast			
	Zafirlukast			
NEBULISERS				
HOME O_2				
ANTI-TB				

DRUG HISTORY- General (1)

DRUG CLASS	DRUG NAME	NO	YES	DOSE
INSULIN				
SULPHONYLUREAS				
METFORMIN				
PIOGLITAZONES				
ACARBOSE				
NSAIDS				
PPI				
H_2 RECEPTOR BLOCKERS				
WARFARIN				
ANTIBIOTIC				
ANALGESIA				
ANTI-EPILEPTICS				
IRON SULPHATE				
B_{12} INJECTIONS				
FOLIC ACID				
ANTI-HISTAMINE				
K^+ SUPPLEMENTS				
LAXATIVES				

DRUG HISTORY– General (2)

DRUG CLASS	DRUG NAME	NO	YES	DOSE
HRT PREPARATIONS				
HORMONE ANTAGONISTS				
ANTI-GOUT				
PANCREATIN				
ANTI-PARKINSONIAN	L-dopa			
	Madopar			
	Sinemet			
	Amantadine			
	Apomorphine			
	Bromocriptine			
	Cabergoline			
	Entacapone			
	Lisuride			
	Pergolide			
	Pramipexole			
	Ropinirole			
	Selegiline			
	Benzatropine			
	Anti-muscarinics			
NEURO-MUSCULAR	Haloperidol			
	Riluzole			
	Tetrabenazine			
ANTI-DEPRESSANTS				
BENZODIAZEPINES				
ANTI-PSYCHOTIC				
LITHIUM				
CYTOTOXICS				
IMMUNOMODULATING				
QUININE				
NASAL PREPARATIONS				
ALENDRONATE				
CALCICHEW D_3 FORTE				
ANTI-EMETIC				
OTHER				

MEDICATION DURING ADMISSION

DRUG NAME	DOSE	TIME	REASON

NEW MEDICATION STARTED ON ADMISSION

DRUG NAME	DOSE	TIME	HRS AFTER ADMISSION	REASON

MEDICATIONS STOPPED ON ADMISSION

DRUG NAME	DOSE	TIME	HRS AFTER ADMISSION	REASON

CLINICAL SIGNS (1)

CLINICAL SIGNS		ON ADMISSION	DAY 1 POST ADMISSION
RR			
HR			
BP	**Systolic**		
	Diastolic		
	Mean pulse pressure		
Weight			
BMI			

CLINICAL SIGNS (2)

CLINICAL SIGNS		ON ADMISSION			DAY 1 POST ADMISSION		
		DK	N	Y	DK	N	Y
Raised JVP							
Hepatojugular reflex							
Parasternal heave							
3rd HS							
4th HS							
Crepitations	Basal						
	Mid-Zone						
	Upper-Zone						
Leg oedema	Ankle						
	Shin						
	Knee						
	Thigh						
Sacral oedema							
Ascites							
Hepatomegaly							
Pulsatile liver							

CLINICAL SIGNS (3)

CLINICAL SIGNS		ON ADMISS			DAY 1 POST ADMISS		
		DK	N	Y	DK	N	Y
Pleural effusion clinical	R sided						
Radiological	R sided						
Clinical	L sided						
Radioligical	L sided						
	Bilateral						
Murmur	AS						
	AI						
	MR						
	MS						
	TR						
Displaced apex							
Wheeze	Inspiratory						
	Expiratory						
	General						

INVESTIGATIONS

O_2 SATS:

DATE									
TIME									
O_2 REPACEMENT									
O_2 SATS									

ABGS:

DATE									
TIME									
O_2 REPLACEMENT									
PO_2									
PCO_2									
H^+									
$HCO3^-$									

INVESTIGATIONS - ROUTINE BLOODS:

DATE									
Hb									
MCV									
WCC									
Lymph									
Neut									
Mono									
Eosino									
Plat									
Na									
K^+									
Cl^-									
HCO_3^-									
Ur									
Creat									
CK									
Trop									
Chol									
Glu									
HBA1C									
TSH									
T_4									
T_3									
Bil									
Alk P									
AST									
ALT									
GGT									
Urate									

INVESTIGATIONS

CXR:

CXR FEATURES		YES	NO
HEART FAILURE FEATURES			
Pleural Effusion	**Right**		
	Left		
	Bilateral		
Cardiomegaly			
Upper lobe diversion			
Interstitial oedema			
Alveloar oedema			
NON-HEART FAILURE FEATURES			
Hyperinflated lung fields			
Mediastinal enlargement			
Intra-thoracic mass			
Radiological old TB			
Previous pneumonectomy			
Pneumothorax			
Other			

ECG CRITERIA

*	**Sokolow + Lyon criteria:**	**S V1 + R V5 or V6 > 35mm**
	Cornell criteria:	**SV3 + R avl > 28mm (men)**
		SV3 + R avl > 20mm (female)

** **ST depression and T inversion in V5,V6**

*** **RAD (>90)**
Tall R waves in RV leads
Deep S waves in LV leads
R V1 + S V5 (V6) 10 mm

**** **ST depression and T inversion in V1-V3 (+/- aVF)**

DAY 1 POST ADMISSION ECG:

POST ADMISSION ECG	RATE						
ECG CHANGES FROM OLD ECG	NO	YES	DESCRIBE				
ECG CHANGES FROM ADMISSION	NO	YES	DESCRIBE				
ECG CHANGES	NO	YES					
Cardiac Rhythm			SR	AF	FLUTTER	VT	OTHER
AV BLOCK			1		2	3	
LBBB							
RBBB							
LVH			SL CRITERIA*		CORNELL CRITERIA*		
LVH + Strain **							
RVH***							
RVH + Strain****							
ST Elevation			INFERIOR		ANTERIOR	LATERAL	
ST Depression			INFERIOR		ANTERIOR	LATERAL	
T wave Inversion			INFERIOR		ANTERIOR	LATERAL	
Biphasic T Waves			INFERIOR		ANTERIOR	LATERAL	
Pathological Q waves			INFERIOR		ANTERIOR	LATERAL	
Prolonged QT interval							
RAD							
LAD							

INVESTIGATIONS

PFT's:

VALUE	RESULT	% Predicted
FEV_1		
FVC		
FEV_1:FVC		
VC		
TLCO		
REVERSIBILITY		
COMMENT		

Appendix 4: Electrocardiographic data collection form

POST ADMISSION ECG	**RATE**								
ECG CHANGES FROM OLD ECG	**NO**	**YES**	**DESCRIBE**						
ECG CHANGES FROM ADMISSION	**NO**	**YES**	**DESCRIBE**						
ECG CHANGES	**NO**	**YES**							
Rhythm			**SR**	**AF**	**FLUTTER**	**VT**	**OTHER**		
AV BLOCK			**1**		**2**	**3**			
LBBB									
RBBB									
LVH			**SL CRITERIA**		**CORNELL CRITERIA**				
LVH + Strain									
RVH									
RVH + Strain									
ST Elevation			**INFERIOR**		**ANTERIOR**		**LATERAL**		
ST Depression			**INFERIOR**		**ANTERIOR**		**LATERAL**		
T wave Inversion			**INFERIOR**		**ANTERIOR**		**LATERAL**		
Biphasic T Waves			**INFERIOR**		**ANTERIOR**		**LATERAL**		
Pathological Q waves			**INFERIOR**		**ANTERIOR**		**LATERAL**		
Prolonged QT interval									
RAD									
LAD									

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