

DIAGNOSIS OF SLEEP- DISORDERED BREATHING IN CHRONIC HEART FAILURE

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Declaration of Originality

I, Neil Robert Ward, hereby declare that this thesis contains the results of my own work except where otherwise acknowledged. The studies presented in this thesis were conceived and designed with the assistance of my supervisors, Professor Morrell, Professor Simonds and Professor Cowie. In addition, I acknowledge the invaluable assistance from Mr. Vitor Roldao who analysed all the polysomnography sleep studies, and Mr. Manuel de Villa for analysing the echocardiograms of study participants. I am grateful to Mr. Daniel Hughes for his assistance with the preliminary pulse oximetry analysis. Statistical support was received from Professor Kulinskaya and Dr. Bernard North of the Imperial College statistical advisory service. Information derived from the work of others and discussed in this thesis is referenced in the text and listed in the bibliography. No part of this thesis has previously been submitted in application for a higher degree. Publications in the form of abstract presentations arising from this work are listed on Page 6.

Abstract

Sleep-disordered breathing (SDB) is prevalent but underdiagnosed in chronic heart failure (CHF). The aim of this thesis was to investigate the utility of simple portable monitoring and clinical features to identify CHF patients with SDB. In addition, the influence of scoring criteria on diagnosis and classification of SDB in CHF was investigated.

In the first study, clinical characteristics in CHF patients with SDB were compared to those without SDB. No specific symptom, anthropometric characteristic or measure of heart failure severity was reliably able to identify CHF patients with SDB.

In the second study, the accuracy of heart rate variability (HRV) analysis and overnight pulse oximetry for diagnosis of SDB in CHF were investigated. The percent very low frequency increment (%VLFI) of HRV had low accuracy for diagnosis of SDB. In contrast, the >3% oxygen desaturation index measured by pulse oximetry had a high diagnostic accuracy, with sensitivity 0.97 and negative likelihood ratio 0.08 at a pre-specified cutoff of >7.5 desaturations per hour.

In the third study, the impact of hypopnoea scoring criteria on SDB diagnosis in CHF was evaluated. The prevalence of SDB changed significantly from 29% when hypopnoeas were scored with a corroborative $\geq 4\%$ oxygen desaturation, to 46% when hypopnoeas were scored with a corroborative $\geq 3\%$ oxygen desaturation or arousal from sleep ($p < 0.001$). Respiratory event scoring criteria did not influence the classification of SDB as obstructive or central sleep apnoea.

In summary, this thesis has shown that clinical features and HRV analysis can not be used to identify CHF patients with SDB. Overnight pulse oximetry has a high diagnostic accuracy and would be of greatest clinical use to rule out SDB in patients with CHF. The criteria used to score respiratory events during sleep studies can have a significant impact on the diagnosis and prevalence of SDB in CHF.

Publications Arising From This Thesis

Published Abstracts

Ward NR, Roldao V, Cowie MR, et al. Utility Of Pulse Oximetry Versus Heart Rate Variability To Screen For Sleep-Disordered Breathing In Chronic Heart Failure. Am J Respir Crit Care Med. 2011;183:A6321.

Ward NR, Cowie MR, Rosen SD, et al. Detection of sleep-disordered breathing in chronic heart failure patients: utility of heart rate variability versus pulse oximetry? Thorax. 2010;65(Suppl 4):A10-A11.

Ward NR, Roldao V, Rosen SD, et al. How Often Do Mixed Apneas Occur In Chronic Heart Failure Patients And What Is Their Impact On Diagnosis Of Sleep-Disordered Breathing? Am J Respir Crit Care Med 2010;181:A6750

Ward NR, Roldao V, Rosen SD, et al. Do Hypopnea Scoring Criteria Affect Diagnosis of Sleep Apnea in Heart Failure Patients? Am J Respir Crit Care Med 2009;179:A3626

Presented Abstracts

Ward NR, Cowie MR, Rosen SD, et al. Diagnostic Accuracy of Heart Rate Variability and Pulse Oximetry for Detection of Sleep-Disordered Breathing in Chronic Heart Failure. Barcelona Sleep and Breathing Meeting 2011.

Hughes DJ, Ward NR, Morrell MJ. A Comparison of Manual versus Automated Scoring of Overnight Pulse Oximetry in Chronic Heart Failure Patients. Undergraduate Physiological Sciences Conference, Oxford 2009.

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Table of Contents

Declaration of Originality	3
Abstract	5
Publications Arising From This Thesis	6
Published Abstracts	6
Presented Abstracts	6
Acknowledgements	7
List of Tables	15
List of Figures	19
Abbreviations	21
CHAPTER 1: INTRODUCTION.....	23
1.1. Background	25
1.2. Chronic Heart Failure	26
1.2.1. Introduction.....	26
1.2.2. Definition of Heart Failure.....	26
1.2.3. Epidemiology of Chronic Heart Failure	27
1.2.4. Diagnosis of Heart Failure	27
1.2.5. Assessment of Heart Failure	32
1.2.6. Treatment of Chronic Heart Failure.....	34
1.2.7. Prognosis of Heart Failure.....	42
1.2.8. Economic Impact of Heart Failure	42
1.3. What is Sleep-Disordered Breathing?	43
1.4. Sleep-Disordered Breathing in Chronic Heart Failure.....	43
1.4.1. Epidemiology of Sleep-Disordered Breathing in Chronic Heart Failure	43
1.4.2. Why is the Prevalence of Sleep-Disordered Breathing Increased in Chronic Heart Failure?.....	50
1.4.3. Acute Cardiovascular Consequences of Sleep-Disordered Breathing	62
1.4.4. Clinical Consequences of Sleep-Disordered Breathing in Chronic Heart Failure.....	65
1.4.5. The Impact of Sleep-Disordered Breathing on Morbidity and Mortality in Chronic Heart Failure	67
1.4.6. Treatment of Sleep-Disordered Breathing in Chronic Heart Failure	73
1.4.7. Summary for Section 1.4.....	83
1.5. Diagnosis of Sleep-Disordered Breathing in Chronic Heart Failure	84
1.5.1. Clinical Presentation of Sleep-Disordered Breathing in Chronic Heart Failure.....	84
1.5.2. Use of Screening Questionnaires for Identification of Sleep-Disordered Breathing in Chronic Heart Failure	86
1.5.3. Sleep Studies for Diagnosis of Sleep-Disordered Breathing	86

1.5.4. Evaluation of Portable Monitors for Diagnosis of Sleep-Disordered Breathing	91
1.5.5. Type 1 Sleep Studies for Diagnosis of Sleep-Disordered Breathing	95
1.5.6. Type 2 Sleep Studies for Diagnosis of Sleep-Disordered Breathing	97
1.5.7. Type 3 Sleep Studies for Diagnosis of Sleep-Disordered Breathing	99
1.5.8. Type 4 Sleep Studies for Diagnosis of Sleep-Disordered Breathing (excluding oximeters and heart rate variability monitors)	108
1.5.9. Pulse Oximetry for Diagnosis of Sleep-Disordered Breathing	114
1.5.10. Heart Rate Variability Analysis for Diagnosis of Sleep-Disordered Breathing	117
1.5.11. Type 4 Sleep Studies as a 'Rule In' or 'Rule Out' Test for Diagnosis of Sleep- Disordered Breathing	120
1.5.12. Summary of Type 4 Sleep Studies for Diagnosis of Sleep-Disordered Breathing	121
1.6. Scoring Respiratory Events for Diagnosis of Sleep-Disordered Breathing	122
1.7. Description and Structure of Thesis	125
CHAPTER 2: GENERAL METHODS	127
2.1. Regulatory Procedures	129
2.2. Participants	129
2.3. Measurements	130
2.3.1. Sleep History	130
2.3.2. Details of Medical History and Other Relevant Enquiries	131
2.3.3. Anthropometric Measures	131
2.3.4. Hospital Anxiety and Depression Scale	132
2.3.5. Subjective Measurement of Excessive Daytime Sleepiness	132
2.3.6. Objective Measurement of Excessive Daytime Sleepiness	133
2.4. Overnight Monitoring	134
2.4.1. Polysomnography	135
2.4.2. Overnight Pulse Oximetry	142
2.4.3. Measurement of Heart Rate Variability	142
2.5. Data analysis	143
2.5.1. Polysomnography	143
2.5.2. Pulse Oximetry Data Analysis	147
2.5.3. Heart Rate Variability Analysis	151
2.6. Classification and Assessment of Heart Failure Severity	161
2.6.1. Classification as Low or Normal Ejection Fraction Heart Failure	161
2.6.2. Assessment of Heart Failure Severity	161
2.6.3. New York Heart Association Classification	162
2.6.4. B-Type Natriuretic Peptide Assay	162
2.6.5. Echocardiographic Measurement of Heart Function	163
2.7. Statistical Analysis	164

CHAPTER 3: DESCRIPTION OF STUDY RECRUITMENT AND COMPARISON OF CHARACTERISTICS BETWEEN CHRONIC HEART FAILURE PATIENTS WITH AND WITHOUT SLEEP-DISORDERED BREATHING 165

3.1. Introduction	167
3.2. Methods	167
3.2.1. Statistical Analysis.....	167
3.3. Results	168
3.3.1. Recruitment of Study Participants.....	168
3.3.2. Characteristics of Chronic Heart Failure Patients	170
3.3.3. Characteristics of Chronic Heart Failure in Participants	172
3.3.4. Snoring, Witnessed Apnoeas and Daytime Sleepiness in Chronic Heart Failure Patients.....	176
3.3.5. Polysomnography Results.....	178
3.3.6. Comparison of Home and Hospital Polysomnography	180
3.3.7. Comparison of Chronic Heart Failure Patients with and without Sleep-Disordered Breathing	182
3.3.8. Impact of Sleep-Disordered Breathing on Polysomnographic Variables in Chronic Heart Failure Patients.....	186
3.4. Discussion.....	188
3.4.1. Characteristics of Study Cohort	188
3.4.2. Prevalence of Sleep-Disordered Breathing.....	189
3.4.3. Classification of Sleep-Disordered Breathing.....	190
3.4.4. Impact of Sleep-Disordered Breathing on Daytime Sleepiness and Nocturnal Sleep in Chronic Heart Failure	191
3.4.5. Home Polysomnography Studies in Chronic Heart Failure Patients	192
3.4.6. Periodic Limb Movements in Chronic Heart Failure Patients.....	193
3.4.7. Clinical Characteristics of Chronic Heart Failure Patients with Sleep-Disordered Breathing	194
3.5. Summary.....	196

CHAPTER 4: IDENTIFICATION OF SLEEP-DISORDERED BREATHING IN CHRONIC HEART FAILURE: UTILITY OF HEART RATE VARIABILITY AND OVERNIGHT PULSE OXIMETRY 197

4.1. Introduction	199
4.2. Methods	201
4.2.1. Data Analysis	203
4.2.2. Statistical Analysis.....	205
4.3. Results	207
4.3.1. Clinical Characteristics of Chronic Heart Failure Patients	208

4.3.2. Analysis of Heart Rate Variability for Diagnosis of Sleep-Disordered Breathing in Chronic Heart Failure	217
4.3.3. Overnight Pulse Oximetry for Diagnosis of Sleep-Disordered Breathing in Chronic Heart Failure.....	225
4.3.4. Pulse Rate Rise Measured from the Pulse Oximeter for Detection of Sleep-Disordered Breathing in Chronic Heart Failure	228
4.3.5. Diagnostic Accuracy of Heart Rate Variability Analysis versus Overnight Pulse Oximetry	229
4.4.1. Discussion.....	229
4.4.1. Analysis of Heart Rate Variability to Detect Sleep-Disordered Breathing in Chronic Heart Failure.....	230
4.4.2. Overnight Pulse Oximetry for Detection of Sleep-Disordered Breathing in Chronic Heart Failure.....	235
4.4.3. Alternative Portable Monitors for Identification of Sleep-Disordered Breathing in Chronic Heart Failure	238
4.4.4. Strengths of this Study	238
4.4.5. Limitations of this Study	239
4.4.6. Summary	241
CHAPTER 5: THE IMPACT OF SCORING CRITERIA ON DIAGNOSIS AND CLASSIFICATION OF SLEEP-DISORDERED BREATHING IN CHRONIC HEART FAILURE.....	243
5.1. Introduction	245
5.2. Methods	248
5.2.1. Respiratory Event Scoring.....	248
5.2.2. Statistical Analysis.....	249
5.3. Results	250
5.3.1. Hypopnoea Analysis.....	250
5.3.2. Diagnosis and Prevalence of Sleep-Disordered Breathing in Chronic Heart Failure using Different Hypopnoea Scoring Rules	251
5.3.3. Impact of Different Hypopnoea Scoring Rules on Classification of Sleep-Disordered Breathing in Chronic Heart Failure	254
5.3.4. Comparison of Patients Included and Excluded from the Hypopnoea Analysis	255
5.3.5. Mixed Apnoea Analysis	258
5.3.6. Impact of Categorisation of Mixed Apnoeas as Central or Obstructive Apnoeas ...	262
5.4. Discussion.....	265
5.4.1. Hypopnoea Analysis.....	265
5.4.2. Clinical Significance of Different Hypopnoea Scoring Criteria	267
5.4.3. Limitations of the Hypopnoea Scoring Analysis	268
5.4.4. Mixed Apnoea Analysis	270
5.4.5. Clinical Significance and Treatment of Mixed Apnoeas in Chronic Heart Failure Patients.....	272

5.4.6. Limitations of the Mixed Apnoea Analysis.....	272
5.4.7. Summary	273
CHAPTER 6: DISCUSSION.....	275
6.1. Summary of Aims.....	277
6.2. Summary of Main Findings	277
6.3. Future Directions.....	280
6.4. Conclusion	284
CHAPTER 7: REFERENCES.....	285
CHAPTER 8: APPENDIX.....	321
8.1. Monitor Validation Tables.....	323
8.2. Copy of Ethical Approval Letter.....	338
8.3. Patient Information Sheet.....	341
8.4. Study Consent Form	344
8.5. Epworth Sleepiness Scale	345
8.6. Hospital Anxiety and Depression Scale	346
8.7. Assessment of the Accuracy of a Diagnostic Test.....	349
8.7.1. Sensitivity, Specificity and Predictive Values	349
8.7.2. Likelihood Ratios	351
8.7.3. Receiver Operating Characteristic Curves.....	354
8.7.4. Difference Versus Average Plots	355

List of Tables

Table 1.1. Common Causes of Heart Failure	33
Table 1.2. Studies Reporting The Prevalence of Sleep-Disordered Breathing in Chronic Heart Failure.....	44
Table 1.3. Risk factors for the Presence of Obstructive and Central Sleep Apnoea in Chronic Heart Failure Patients	45
Table 1.4. Comparison of Studies Investigating the Relationship between Central Sleep Apnoea or Cheyne-Stokes Respiration and Mortality in Chronic Heart Failure.....	69
Table 1.5. Classification of Sleep Studies For Diagnosis of Sleep-Disordered Breathing	89
Table 1.6. Recording Parameters of Type 3 Portable Monitors.....	100
Table 1.7. Type 4 Portable Monitor Recording Parameters (excluding oximeters and heart rate variability monitors)	110
Table 1.8. Criteria Used to Score Respiratory Events for Diagnosis of Sleep-Disordered Breathing	123
Table 2.1. Sleep Scoring Criteria.....	144
Table 2.2. Comparison of the Automated and Manually Scored 4% Oxygen Desaturation Index from Overnight Pulse Oximetry	148
Table 2.3. Time Domain Parameters of Heart Rate Variability	153
Table 2.4. New York Heart Association Classification of Heart Failure	162
Table 3.1. Demographic and Anthropometric Characteristics of Participants	171
Table 3.2. Comorbidities and Spirometric Measurements in Patients	172
Table 3.3. Aetiology and Treatment of Chronic Heart Failure in Participants.....	173
Table 3.4. New York Heart Association Classification and B-Type Natriuretic Peptide Concentration in Chronic Heart Failure Patients	174
Table 3.5. Echocardiographic Measurements of Cardiac Size and Function in Chronic Heart Failure Patients.....	175
Table 3.6. Characteristics Relating to Daytime Sleepiness in Chronic Heart Failure Patients.....	177
Table 3.7. Polysomnographic Measurements of Sleep and Sleep Disturbance in all Chronic Heart Failure Patients	179

Table 3.8. Comparison of Patient Characteristics and Polysomnography Findings Between Home and Hospital Sleep Studies.....	181
Table 3.9. Comparison of Chronic Heart Failure Patients According to the Presence or Absence of Sleep-Disordered Breathing	183
Table 3.10. Comparison of Chronic Heart Failure Characteristics in Patients, According to the Presence or Absence of Sleep-Disordered Breathing.....	185
Table 3.11. Comparison of Polysomnographic Variables in Chronic Heart Failure Patients with and without Sleep-Disordered Breathing	187
Table 4.1. Anthropometric and Clinical Characteristics of all Chronic Heart Failure Patients.....	208
Table 4.2. Comparison of Anthropometric and Clinical Characteristics of Chronic Heart Failure Patients Excluded from Analysis	209
Table 4.3. Anthropometric and Clinical Characteristics in Chronic Heart Failure Patients	211
Table 4.4. Daytime Sleepiness, Polysomnographic Measurements of Sleep and Sleep- Disordered Breathing in all Chronic Heart Failure Patients	213
Table 4.5. Characteristics in Chronic Heart Failure Patients Suitable and Unsuitable for Heart Rate Variability Analysis	215
Table 4.6. Daytime Sleepiness, Polysomnographic Measurements of Sleep and Sleep- Disordered Breathing in Chronic Heart Failure Patients Suitable and Unsuitable for Heart Rate Variability Analysis	216
Table 4.7. Clinical Characteristics of Chronic Heart Failure Patients in whom the %VLFI Component of Heart Rate Variability was Measurable.....	218
Table 4.8. Daytime Sleepiness, Polysomnographic Measurements of Sleep and Sleep- Disordered Breathing in Chronic Heart Failure Patients in whom the %VLFI Component of Heart Rate Variability was Measurable.....	219
Table 4.9. Diagnostic Accuracy of %VLFI for Detection of Sleep-Disordered Breathing in Patients with Chronic Heart Failure	221
Table 4.10. Spectral and Time Domain Heart Rate Variability Parameters in Chronic Heart Failure Patients.....	224
Table 4.11. Diagnostic Accuracy of the 3% Oxygen Desaturation Index for Detection of Sleep-Disordered Breathing in Patients with Chronic Heart Failure.....	227

Table 5.1. Hypopnoea Scoring Criteria Used in Studies Reporting the Prevalence of Sleep-Disordered Breathing in Chronic Heart Failure	246
Table 5.2. Comparison of Respiratory Event Frequency and Diagnosis of Sleep-Disordered Breathing in Chronic Heart Failure Patients Using Different Hypopnoea Scoring Criteria.....	252
Table 5.3. Clinical Characteristics of Chronic Heart Failure Patients Included and Excluded from Hypopnoea Analysis.....	256
Table 5.4. Polysomnographic Measurements During Sleep in Chronic Heart Failure Patients Included and Excluded from Hypopnoea Analysis	257
Table 5.5. Clinical Characteristics of Chronic Heart Failure Patients Included in the Mixed Apnoea Analysis	259
Table 5.6. Polysomnographic Measurements During Sleep, and Classification of Sleep-Disordered Breathing in Chronic Heart Failure Patients Included in the Mixed Apnoea Analysis.....	260
Table 5.7. Frequency of Respiratory Events in Chronic Heart Failure Patients Included in the Mixed Apnoea Analysis	261
Table 5.8. Impact of Mixed Apnoea Categorisation on Respiratory Event Frequency in Chronic Heart Failure Patients	263
Table 5.9. Impact of Mixed Apnoea Categorisation on Classification of Sleep-Disordered Breathing in Chronic Heart Failure Patients.....	263
Table 5.10. The Occurrence of Mixed Apnoeas in Chronic Heart Failure Patients with Obstructive or Central Sleep Apnoea	264
Table 8.1. Results of Validation Studies of Type 3 Portable Monitors.....	323
Table 8.2. Results of Validation Studies of Type 4 Portable Monitors for Diagnosis of Sleep-Disordered Breathing (excluding oximeters and heart rate variability monitors).....	327
Table 8.3. Studies Evaluating Pulse Oximetry for the Diagnosis of Obstructive Sleep Apnoea	331
Table 8.4. Studies Evaluating Heart Rate Variability Analysis for Diagnosis of Sleep-Disordered Breathing.....	335

List of Figures

Figure 1.1. Algorithm for Diagnosis and Investigation of Heart Failure	31
Figure 1.2. An Algorithm for Treating Heart Failure.....	35
Figure 1.3. Schematic Diagram to Illustrate the Components of the Ventilatory Control System Which Contribute to Loop Gain	55
Figure 1.4. In a low loop gain system, the magnitude of the response is less than the disturbance and stability is restored.	55
Figure 2.1. Electroencephalogram recording electrode positions.....	136
Figure 2.2. Automated Versus Manual Scoring of Overnight Pulse Oximetry in Chronic Heart Failure Patients.....	149
Figure 2.3. Difference Versus Average Plot for Automated and Manually Scored >4% Oxygen Desaturation Index.....	150
Figure 2.4. Power spectrogram of heart rate variability in one participant.....	154
Figure 2.5. Heart rate increment power spectrograms in Chronic Heart Failure patients	160
Figure 3.1. Flow Diagram to Show Recruitment of Chronic Heart Failure Patients for this Thesis	169
Figure 4.1. Flow Diagram to Show Recruitment of Chronic Heart Failure Patients and Inclusion in the Heart Rate Variability Analysis	207
Figure 4.2. %Very Low Frequency Increment Receiver Operating Characteristic Curve for Diagnosis of Sleep-Disordered Breathing (AHI >15/hour) in Patients with Chronic Heart Failure.	220
Figure 4.3. %Very Low Frequency Increment ROC Curves for Diagnosis of Sleep- Disordered Breathing in Chronic Heart Failure Using Different AHI Diagnostic Thresholds.....	223
Figure 4.4. Receiver Operating Characteristic curves to show accuracy of 3% ODI for diagnosis of sleep-disordered breathing.....	226
Figure 4.5. Fagans' Nomogram	237
Figure 5.1. Difference versus Average Plot to Show Difference between Apnoea Hypopnoea Index (AHI Scored with Different Hypopnoea Rules as a Function of Mean AHI.....	253

Figure 5.2. Number of Chronic Heart Failure Patients Diagnosed with Sleep-Disordered Breathing Using Different Hypopnoea Scoring Criteria	253
Figure 5.3. Frequency of Mixed Apnoeas in Chronic Heart Failure Patients.....	262
Figure 6.1. Proposed Study Design for a Randomised Controlled Trial to Evaluate the Utility of Overnight Pulse Oximetry for the Investigation and Management of Sleep-Disordered Breathing in Chronic Heart Failure.....	281
Figure 8.1. Fagans' Nomogram	353
Figure 8.2. Receiver Operating Characteristic (ROC) Curves for Assessment of the Accuracy of a Diagnostic Test.	354
Figure 8.3. Difference versus average plot for AHI recorded by portable monitor and polysomnography	356

Abbreviations

ACE	Angiotensin converting enzyme
AHI	Apnoea hypopnoea index
ARB	Angiotensin receptor blocker
ASV	Adaptive servoventilation
AUC	Area under curve
BMI	Body mass index
BNP	B-type natriuretic peptide
CHF	Chronic heart failure
CIH	Chronic intermittent hypoxia
CO ₂	Carbon dioxide
COPD	Chronic obstructive pulmonary disease
CPAP	Continuous positive airway pressure
CRT	Cardiac resynchronisation therapy
CSA	Central sleep apnoea
CSR	Cheyne-Stokes respiration
ECG	Electrocardiogram
EEG	Electroencephalogram
EMG	Electromyogram
EOG	Electrooculogram
ESS	Epworth Sleepiness Scale
FEV ₁	Forced expiratory volume in one second
FVC	Forced vital capacity
HADS	Hospital anxiety and depression scale
HFPEF	Heart failure with preserved ejection fraction
ICD	Implantable cardioverter defibrillator

IQR	Interquartile range
LF	Low frequency
LVEF	Left ventricular ejection fraction
HF	High frequency
HRV	Heart rate variability
MSNA	Muscle sympathetic nerve activity
NPSG	Nocturnal polysomnography
NREM	Non rapid eye movement
NYHA	New York heart association classification
ODI	Oxygen desaturation index
OSA	Obstructive sleep apnoea
OSLER	Oxford sleep resistance test
PCWP	Pulmonary capillary wedge pressure
PLM	Periodic limb movement
PLMI	Periodic limb movement index
PM	Portable monitor
PRRI	Pulse rate rise index
PSG	Polysomnogram
RDI	Respiratory disturbance index
REM	Rapid eye movement
RERA	Respiratory effort related arousal
RIP	Respiratory inductance plethysmography
ROC	Receiver operating characteristic
RPG	Respiratory polygraphy sleep study
SDB	Sleep-Disordered Breathing
VLf	Very low frequency
VLFI	Very low frequency increment

CHAPTER 1: INTRODUCTION

1.1. Background

Sleep-disordered breathing (SDB) is prevalent in chronic heart failure (CHF) and it has been reported to occur in $\geq 50\%$ of patients (Javaheri, 1998b; Vazir, 2007).

Observational studies have shown the presence of SDB is independently associated with increased mortality in CHF (Lanfranchi, 1999; Wang, 2007). Treatment of SDB with positive airway pressure therapy can improve cardiac function (Sin, 2000; Kaneko, 2003). However, many CHF patients with SDB do not describe symptoms of excessive daytime sleepiness (Hastings, 2006) which are associated with the obstructive sleep apnoea hypopnoea syndrome. This can reduce clinical suspicion for SDB in CHF, and may explain why this condition is diagnosed and treated in only 2% of CHF patients (Javaheri, 2010). There is a need for research to evaluate alternative methods to improve identification and diagnosis of SDB in CHF, and this is the overall aim of this thesis.

The sections of this introduction are intended to provide a detailed background to this thesis, beginning with a description of the epidemiology, diagnosis and contemporary treatment of CHF. In the next section, the prevalence, mechanisms and consequences of SDB in CHF will be described. Potential treatments for SDB and their efficacy will be reviewed to provide a rationale for improving identification of SDB in CHF. The clinical presentation of SDB in CHF is described in the following section, and the different types of sleep study that are available for diagnosis of SDB are reviewed. The final section describes the variability in respiratory event scoring criteria that have been used in studies of SDB in CHF, as a background to the study presented in Chapter 5.

1.2. Chronic Heart Failure

1.2.1. Introduction

Heart failure is a common medical disorder estimated to affect 900,000 adults in the United Kingdom (Commission for Healthcare Audit and Inspection, 2007). It is associated with a reduction in life expectancy and impaired quality of life, but identification and treatment of heart failure can improve symptoms and prognosis. Whilst there have been significant advances in pharmacological and non pharmacological therapies for heart failure, the morbidity and mortality associated with this condition remains high. The financial expenditure related to heart failure places a substantial economic burden on healthcare and welfare systems which is projected to increase with the progressive ageing of the population. Further improvements in diagnostic pathways, disease monitoring and therapeutic strategies may help reduce the symptom burden and healthcare costs associated with heart failure.

1.2.2. Definition of Heart Failure

There is no uniform definition of heart failure. Recent United Kingdom guidelines define heart failure as “a complex clinical syndrome of symptoms and signs that suggest the efficiency of the heart as a pump is impaired” (National Institute for Clinical Excellence, 2010). In addition, objective evidence of a structural or functional abnormality of the heart is required to diagnose heart failure (Dickstein, 2008; National Institute for Clinical Excellence, 2010).

1.2.3. Epidemiology of Chronic Heart Failure

In the United Kingdom, the prevalence of heart failure in adults aged >45 years has been reported to be 2.3% (Davies, 2001). There is a similar prevalence of asymptomatic left ventricular dysfunction which is associated with an increased risk of developing the clinical syndrome of heart failure (McDonagh, 1997; Davies, 2001).

Incident heart failure is most common in elderly adults with a median age at presentation of 76 years (Cowie, 1999). The prevalence of chronic heart failure (CHF) increases markedly with age, rising from <1% in adults aged under 65 years, to 12.5% in those aged 85 years or over (Davies, 2001; Majeed, 2005). As life expectancy is increasing and the mean age of the population rises, the prevalence of CHF is expected to increase. In addition, whilst improvements in the treatment of acute coronary syndromes such as myocardial infarction have reduced mortality, this may result in an increase in the number of adults living with myocardial damage and a rise in the incidence of CHF (Ezekowitz, 2009).

Many studies of CHF prevalence have used echocardiographic evidence of low left ventricular ejection fraction to define heart failure, but the clinical syndrome of CHF may occur in adults with preserved left ventricular function. Heart failure with preserved ejection fraction (HFPEF) may be present in up to 50% of patients with CHF (Hogg, 2004), and thus the prevalence of CHF may be even higher than reported by studies which have only identified low ejection fraction heart failure.

1.2.4. Diagnosis of Heart Failure

Clinical Features of Heart Failure

The most common symptoms of heart failure include breathlessness, fatigue, exercise intolerance and fluid retention. Heart failure can also be associated with symptoms of

paroxysmal nocturnal dyspnoea, nocturia, anorexia, abdominal discomfort, confusion, memory impairment and dizziness. However, these symptoms can occur in many other medical conditions, and their specificity for diagnosing heart failure is low (National Institute for Clinical Excellence, 2010).

The clinical history may identify the presence of other medical conditions, such as hypertension, ischaemic heart disease or previous myocardial infarction, which are associated with an increased risk of developing heart failure.

Clinical examination can identify signs of heart failure. These include tachycardia, atrial fibrillation, raised jugular venous pressure, displaced apex beat, cardiac murmurs, third heart sound, lung crepitations, pleural effusion and peripheral oedema. The finding of these signs in isolation has a low predictive value for the diagnosis of heart failure, but the presence of multiple signs can increase the likelihood of this diagnosis.

Investigations Used to Diagnose Heart Failure

Diagnostic investigations may be used to confirm the presence, assess severity, and identify the aetiology of heart failure.

A 12 lead electrocardiogram (ECG) is useful to identify cardiac arrhythmias and it may show evidence of a previous myocardial infarction or left ventricular hypertrophy. Heart failure due to left ventricular systolic dysfunction is unlikely in the presence of a normal ECG (Chandrasekaran B, 2010).

A chest radiograph can detect pulmonary venous congestion, interstitial oedema and pleural effusion, whilst a posteroanterior chest X-ray can identify cardiomegaly.

Anaemia, thyroid disorders or toxicity due to excess alcohol consumption can be detected by haematological and biochemical investigations. These may also identify important comorbidities such as diabetes or renal dysfunction.

Natriuretic Peptide Assay

Measurement of serum natriuretic peptides is recommended to help rule out a diagnosis of heart failure (Chandrasekaran B, 2010; National Institute for Clinical Excellence, 2010). Whilst there is no definitive diagnostic cutoff, a plasma B-type natriuretic peptide (BNP) concentration <100 pg/ml or N-terminal pro-BNP (NT-proBNP) concentration <400 pg/ml both have a high sensitivity and low negative likelihood ratio for exclusion of heart failure (Mant, 2009). The natriuretic peptide concentration is also of prognostic significance as higher levels are independently associated with the need for subsequent heart failure hospital admission or mortality (Kubanek, 2009). It is recommended that patients with a BNP level > 400pg/ml or NT-pro BNP level > 2000 pg/ml are referred for urgent echocardiography and specialist assessment (National Institute for Clinical Excellence, 2010).

Elevated natriuretic peptide concentration may also be of value to confirm a diagnosis of heart failure in the presence of a preserved left ventricle ejection fraction on cardiac imaging (Maisel, 2003). However, concentration of natriuretic peptides can be increased by conditions other than heart failure, including tachycardia, left ventricular hypertrophy, right ventricular overload, hypoxaemia, chronic obstructive pulmonary disease, myocardial ischaemia, renal dysfunction, diabetes, age > 70 years, and infection. In addition, obesity and heart failure treatment can reduce the diagnostic sensitivity of natriuretic peptides.

Echocardiography

Echocardiography provides objective measurements of cardiac structure and function, and it is considered a mandatory investigation in heart failure management guidelines (Dickstein, 2008; National Institute for Clinical Excellence, 2010). It is commonly used to assess left ventricle systolic function by measurement of the left ventricle ejection

fraction (LVEF). The LVEF indicates the fraction of blood pumped from the left ventricle with each heart beat, and is calculated:

$$\text{LVEF} = \frac{(\text{Left ventricle end diastole volume} - \text{end systole volume})}{\text{Left ventricle end diastole volume}}$$

The LVEF is normally >45 – 50% (Dickstein, 2008). Left ventricle systolic function can also be assessed by measurement of fractional shortening, whilst the finding of regional wall motion abnormalities may indicate systolic dysfunction due to previous myocardial infarction.

The aetiology of heart failure may be identifiable by echocardiography. The finding of abnormalities in the structure and function of cardiac valves can be diagnostic.

Increased ventricular wall thickness may be present in heart failure due to longstanding hypertension, aortic stenosis, or hypertrophic cardiomyopathy.

Doppler echocardiography is used to assess left ventricle filling patterns during diastole and measurement of flow through the mitral valve, for identification of diastolic dysfunction in HFPEF.

Echocardiographic image quality may be reduced by obesity or chronic obstructive pulmonary disease, and alternative imaging techniques such as cardiac magnetic resonance imaging or radionuclide imaging may be necessary to assess cardiac structure or function in these patients.

An algorithm recommended for the diagnosis and investigation of suspected heart failure is shown in Figure 1.1.

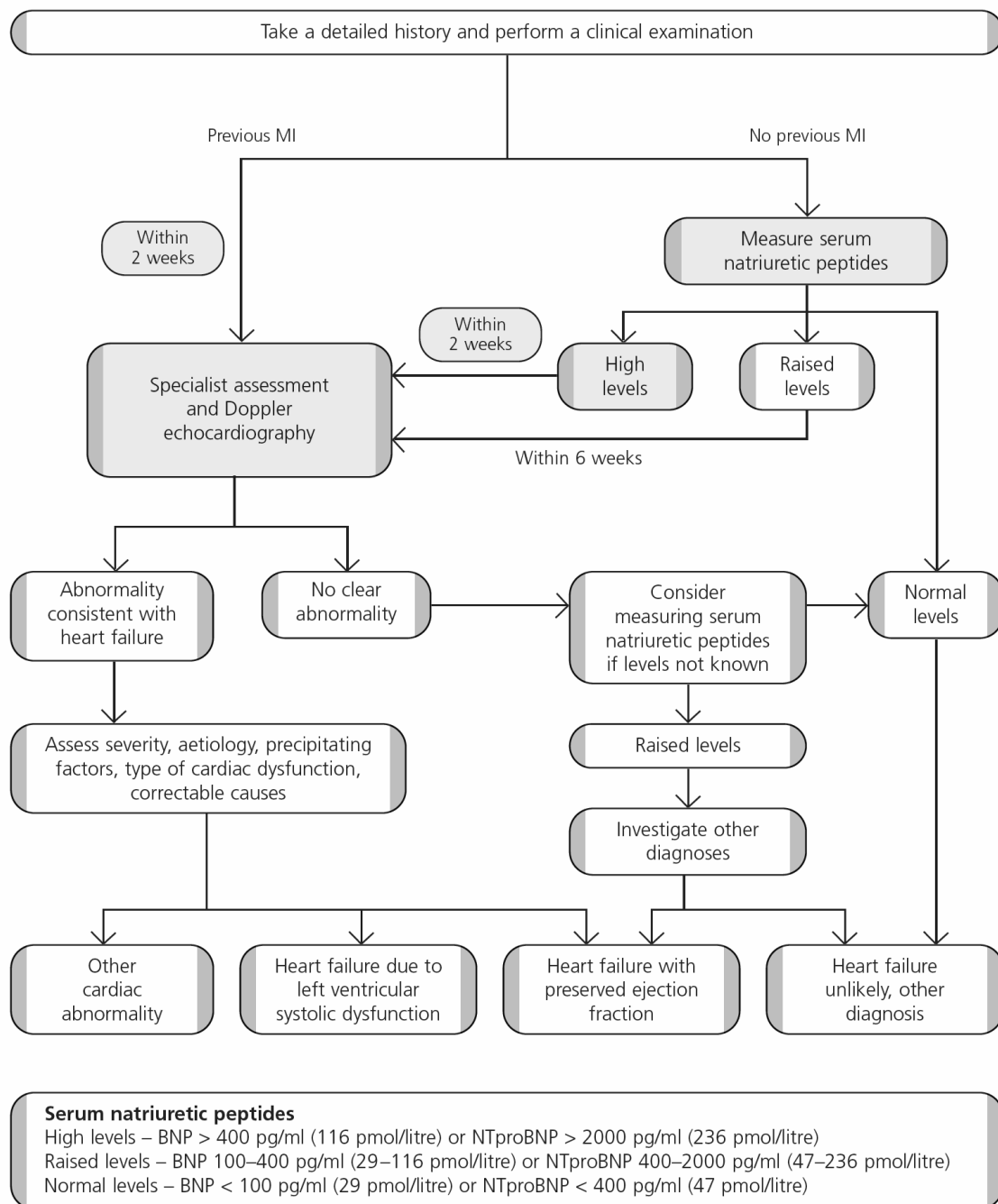


Figure 1.1. Algorithm for Diagnosis and Investigation of Heart Failure (adapted from National Institute for Clinical Excellence clinical guideline 108. Chronic heart failure: management of chronic heart failure in adults in primary and secondary care. 2011)

1.2.5. Assessment of Heart Failure

In addition to confirming the diagnosis, identification of the cause and assessment of heart failure severity are also required in order to determine the need for further investigations and appropriate therapeutic options.

Heart failure can be classified according to the underlying cause (Table 1.1). The most common cause of heart failure in the United Kingdom is ischaemic heart disease.

The duration of symptoms can be used to classify heart failure as acute, transient or chronic in nature. Acute heart failure may occur as the first manifestation of heart failure, or may occur during an acute decompensation in patients with established CHF. Transient heart failure describes symptomatic heart failure which is present for a limited time period, although long-term treatment may be required.

Heart failure has been categorised according to the presence of systolic or diastolic cardiac dysfunction. Diastolic dysfunction is seen in HFPEF, reflecting the presence of symptoms and signs of heart failure with a preserved LVEF. However, this distinction according to the LVEF may be an oversimplification, as diastolic dysfunction can occur in patients with low LVEF, whilst abnormalities of systolic function can occur in patients with HFPEF (Dickstein, 2008).

The severity of symptoms is an important aspect in the assessment of heart failure, and the New York Heart Association (NYHA) functional classification is commonly used for this purpose (see Section 2.6.3 and Table 2.4).

Identification of comorbidities is an important aspect in the assessment of heart failure. Chronic kidney disease and gout may be worsened by heart failure therapy, whilst the presence of asthma is a contraindication to the use of beta blockers. Anaemia may exacerbate heart failure symptoms. Depression is common in CHF and may be an important cause of symptoms which further impair quality of life.

Table 1.1. Common Causes of Heart Failure (adapted from Mann D. Management of Heart Failure Patients with Reduced Ejection Fraction, in Braunwalds Heart Disease: a textbook of cardiovascular medicine. Eds Libby, Bonow, Mann and Zipes. 8th ed. Saunders Elsevier, Philadelphia, USA. 2008)

Myocardial disease
Coronary artery disease - Myocardial infarction* - Myocardial ischaemia*
Chronic pressure overload - Hypertension* - Obstructive valvular disease*
Chronic volume overload - Regurgitant valvular disease - Intracardiac (left to right) shunting - Extracardiac shunting
Non ischaemic dilated cardiomyopathy - Familial/genetic disorders - Infiltrative disorders* - Toxic or drug induced damage - Metabolic disorders* - Viral or other infectious agents
Disorders of rate or rhythm - Chronic bradyarrhythmia - Chronic tachyarrhythmia
Pulmonary heart disease
Cor pulmonale
Pulmonary vascular disorders
High output state
Metabolic disorders - Thyrotoxicosis - Nutritional disorders (beriberi)
Excessive blood flow requirements - Systemic arteriovenous shunting - Chronic anaemia

* Indicates conditions that can also lead to heart failure with preserved ejection fraction

1.2.6. Treatment of Chronic Heart Failure

In addition to addressing the underlying cause of CHF, the aim of heart failure treatment is to reduce symptoms, improve quality of life, reduce hospital admissions and decrease mortality. An algorithm for the management of CHF is shown in Figure 1.2, and individual therapeutic options are discussed in detail in this section.

Lifestyle Measures and Non Pharmacological Management

Modification of lifestyle may be required to address risk factors for progressive CHF. Alcohol is a myocardial depressant and in patients with alcohol related cardiomyopathy, abstinence is associated with an improvement in left ventricular function (Guillo, 1997). Smoking cessation is recommended and weight loss may be beneficial in obese patients (Scottish Intercollegiate Guidelines Network, 2007).

Regular low intensity physical activity has been reported to increase six minute walking distance in stable CHF patients (Karapolat, 2009). Regular physical activity may also prevent worsening of exercise intolerance due to deconditioning. Current guidelines recommend an exercise based rehabilitation programme for patients with heart failure (National Institute for Clinical Excellence, 2010).

Dietary salt restriction to < 6g/day may reduce fluid retention in CHF patients, and is also recommended to reduce hypertension (Scottish Intercollegiate Guidelines Network, 2007). In CHF patients with resistant oedema or hyponatraemia, fluid restriction may be useful.

Education of patients or carers to recognise symptoms of worsening heart failure or monitoring of daily weight may help early detection of acute CHF decompensation. Home telemonitoring may reduce mortality and the incidence of unplanned heart failure related hospitalisation (Cleland, 2005; Dar, 2009).

Treating heart failure

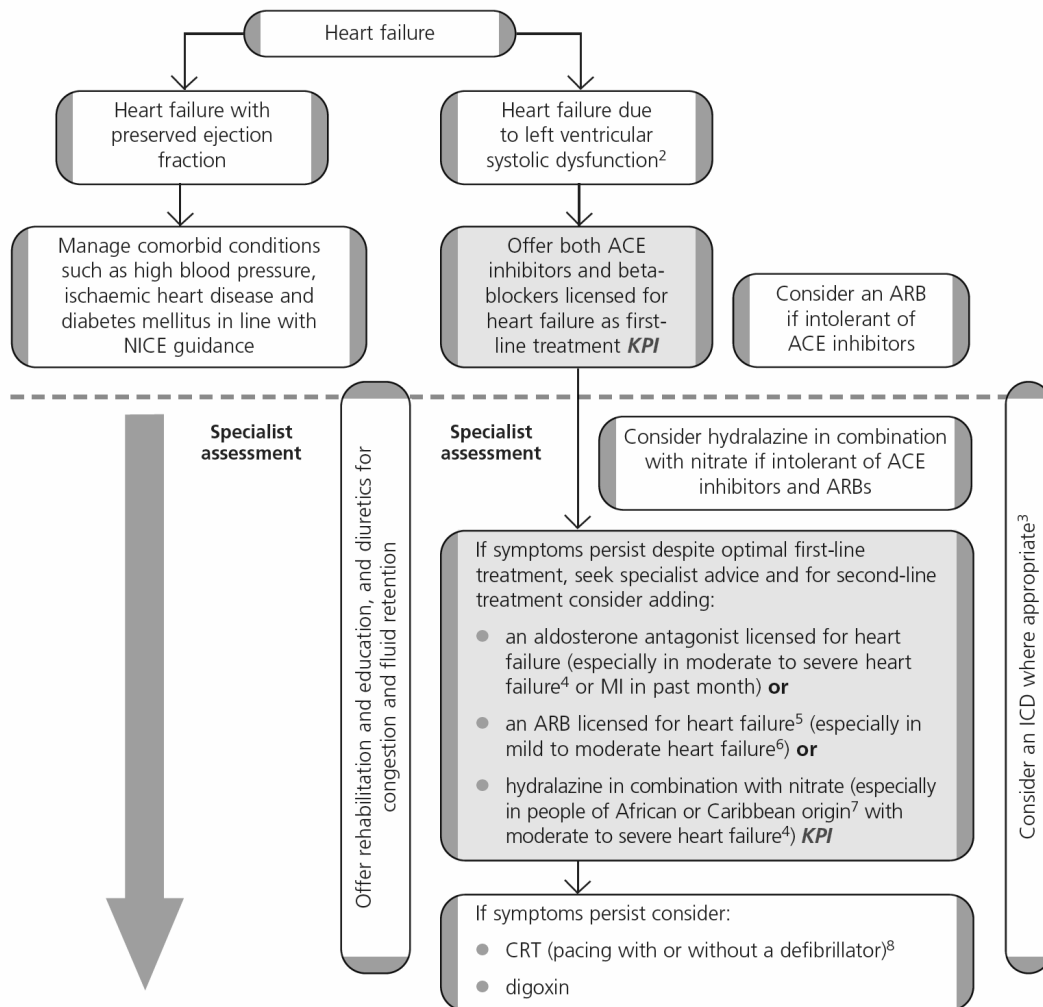


Figure 1.2. An Algorithm for Treating Heart Failure. Reproduced from National Institute for Clinical Excellence (NICE) clinical guideline 108. Chronic heart failure: management of chronic heart failure in adults in primary and secondary care (2010).

Boxes highlighted in light grey are recommended as key priorities for treatment of heart failure.

(ACE = angiotensin converting enzyme; ARB = angiotensin receptor blockers; MI = myocardial infarction; CRT = cardiac resynchronisation therapy; ICD = implantable cardioverter defibrillator)

Pharmacological Therapy for Chronic Heart Failure

Medical therapy for CHF may be used to optimise myocardial function, treat symptoms and improve survival. The different classes of pharmacological therapies used in CHF patients are described below.

Angiotensin Converting Enzyme Inhibitors

Angiotensin Converting Enzyme Inhibitors (ACEI) are effective in reducing morbidity and mortality in CHF patients with left ventricular systolic dysfunction, in patients with asymptomatic left ventricular systolic dysfunction and in patients with heart failure after a myocardial infarction. In CHF, ACEI reduce the relative risk of death by 27% (The Consensus Trial Study Group, 1987) and hospitalisation for worsening heart failure by 26% (The SOLVD Investigators, 1991). ACEI may be of greatest benefit in CHF patients with more severe left ventricular systolic dysfunction (Garg, 1995).

Current guidelines endorse the use of ACEI as first line treatment in all CHF patients with left ventricular systolic dysfunction and without contraindications to their prescription (National Institute for Clinical Excellence, 2010). However, there is a lack of evidence showing the efficacy of ACEI in HFPEF (National Institute for Clinical Excellence, 2010).

Beta Blockers

In CHF patients with left ventricular systolic dysfunction, beta blocker therapy is associated with increased cardiac function and improved quality of life. Clinical trials in mild to severely symptomatic CHF have reported that beta blocker treatment is associated with a relative risk reduction of 34% in mortality and 28 – 36% reduction in hospitalisation (Hjalmarson, 2000; Shibata, 2001; Packer, 2002).

The use of beta blockers is recommended as a first line therapy with ACEI, in symptomatic stable CHF patients with left ventricular systolic dysfunction (National Institute for Clinical Excellence, 2010). They should be cautiously introduced in patients recovering from an acute decompensation of heart failure with close monitoring in case of worsening symptoms (Scottish Intercollegiate Guidelines Network, 2007). In addition, their use is endorsed in elderly patients, and in CHF patients with comorbidities including chronic obstructive pulmonary disease and diabetes (National Institute for Clinical Excellence, 2010).

Aldosterone Antagonists

In CHF patients with a LVEF $\leq 35\%$ and severe symptoms (NYHA III or IV), the addition of spironolactone therapy has been reported to improve symptoms and reduce the risk of death and heart failure related hospital admission (Pitt, 1999). In patients with heart failure after a recent myocardial infarction, the use of eplerenone was associated with a 15% reduction in the relative risk of death (Pitt, 2003).

In the absence of contraindications such as hyperkalaemia or significant renal dysfunction, the addition of a low dose of aldosterone antagonist is recommended in CHF patients with a LVEF $\leq 35\%$ and severe symptoms despite optimal therapy with beta blocker and ACEI (Dickstein, 2008).

Angiotensin Receptor Blockers

The angiotensin receptor blockers (ARB) have been reported to reduce heart failure related hospitalisation, increase survival and improve quality of life in CHF patients with left ventricular systolic dysfunction when added to conventional medical therapy which includes treatment with an ACEI (Cohn, 2001; McMurray, 2003). ARB therapy is also

effective in reducing the risk of hospital admission or death in CHF patients with left ventricular systolic dysfunction who are intolerant of ACEI (Granger, 2003).

Guidelines currently recommend that ARB are used in CHF patients with systolic dysfunction who remain symptomatic despite optimal therapy with an ACEI and beta blocker, or as second line therapy in CHF patients who are intolerant of an ACEI (National Institute for Clinical Excellence, 2010).

Diuretic Therapy

Diuretics are used to reduce fluid retention caused by CHF, thereby improving symptoms due to peripheral or pulmonary oedema. Loop diuretics such as frusemide and bumetanide are used initially as they are more potent than thiazide diuretics. The combination of both loop and thiazide diuretics can be useful in severe CHF with resistant oedema, but this requires close monitoring of renal function.

The use of diuretic therapy in isolation can exacerbate the neurohormonal activation which occurs in association with CHF, and it is recommended that concurrent ACEI or ARB therapy is prescribed to counteract this adverse effect (Dickstein, 2008).

Other Pharmacological Therapies for Chronic Heart Failure

Prior to the introduction of ACEI, the combination of hydralazine and isosorbide dinitrate was reported to reduce mortality in symptomatic CHF patients with left ventricular systolic dysfunction (Cohn, 1986). However, this combination has since been reported to be less effective than enalapril at reducing mortality in CHF (Cohn, 1991). In African - American adults, the combination of hydralazine and isosorbide dinitrate in addition to contemporary CHF therapy has been reported to significantly reduce mortality (Taylor, 2004). In other ethnic groups, it is only recommended as an

option for adults with CHF who are intolerant of ACEI and ARB therapy (Dickstein, 2008).

In CHF patients in sinus rhythm with left ventricular systolic dysfunction, digoxin has been reported to reduce hospital admissions for worsening heart failure but has no beneficial effect on survival (The Digitalis Investigation Group, 1997; Hood, 2004). Many studies evaluating digoxin were conducted before the widespread use of beta blocker and ACEI therapy, and the prescription of digoxin for CHF patients in sinus rhythm is now recommended only when symptoms are persistent after optimal first or second line heart failure therapy (National Institute for Clinical Excellence, 2010).

Digoxin can be used to control heart rate in CHF patients with atrial fibrillation, but it has a poor efficacy at controlling ventricular rate during exercise. Current heart failure guidelines advocate the use of beta blocker therapy in preference, or in addition to digoxin in CHF with atrial fibrillation (Dickstein, 2008).

Paroxysmal atrial fibrillation frequently occurs in CHF and amiodarone may be used to chemically cardiovert this arrhythmia. Amiodarone may also reduce the frequency of DC shocks in patients with ventricular tachyarrhythmias and an implantable cardioverter defibrillator. Warfarin therapy may be appropriate to reduce the risk of systemic thromboembolism in patients with atrial fibrillation.

Pharmacological Therapy for Heart Failure with Preserved Ejection Fraction

The majority of the studies evaluating pharmacological treatment of CHF have enrolled patients with left ventricular systolic dysfunction and the effectiveness of these therapies may differ in patients with HFPEF. There is currently no robust evidence showing that any class of CHF therapy can reduce morbidity or mortality in HFPEF. Whilst clinical trials of Candesartan and Perindopril in HFPEF reported a reduction in the secondary endpoint of admission for worsening heart failure, neither medication

was associated with a reduction in the composite primary endpoint of cardiovascular death or hospitalisation (Yusuf, 2003; Cleland, 2006).

Diuretics can provide symptomatic benefit for patients with HFPEF, but it is recommended that low to medium doses are used to avoid worsening of symptoms, as these patients may be sensitive to cardiac preload (National Institute for Clinical Excellence, 2010).

Patients with HFPEF may tolerate atrial fibrillation or tachyarrhythmias poorly due to the reduction in diastolic filling time. Treatments to restore sinus rhythm or control ventricular rate may improve symptoms in this scenario.

Non Pharmacological Therapies for Treatment of Chronic Heart Failure

This category includes devices or surgical treatments to improve symptoms and mortality by increasing cardiac output.

Cardiac Resynchronisation Therapy

In CHF patients with an intraventricular conduction delay, incoordinate electrical activation of the left ventricle causes asynchronous contraction. This mechanical dyssynchrony can reduce cardiac output as the LVEF is reduced and there is reduced time in the cardiac cycle available for ventricular filling. In CHF patients with a left bundle branch block (LBBB) pattern on their ECG, the provision of cardiac resynchronisation therapy (CRT) by an atrioventricular pacing system can reduce the mechanical dyssynchrony. The use of CRT has been reported to improve NYHA functional class, exercise duration and quality of life. A meta-analysis of clinical trials of CRT has reported it is associated with a 29% reduction in all cause mortality and 38%

reduction in mortality due to progressive heart failure (Rivero-Ayerza, 2006). However, up to 30% of CHF patients may not respond to CRT therapy (Abraham, 2002).

CRT therapy is currently recommended in CHF patients with a LVEF $\leq 35\%$ and a QRS duration $> 120\text{ms}$, with moderate to severe symptoms (NYHA III or IV) despite optimal medical therapy (Dickstein, 2008).

Implantable Cardioverter Defibrillators

Implantable cardioverter defibrillator (ICD) devices reduce mortality in CHF (Moss, 1996). They are recommended for primary prevention of sudden cardiac death due to ventricular arrhythmia in CHF patients with ischaemic or non ischaemic cardiomyopathy and LVEF $\leq 35\%$, NYHA class II or III symptoms despite optimal medical therapy, and a life expectancy of > 1 year (Dickstein, 2008). ICD therapy is also used for secondary prevention in CHF patients with a LVEF $< 40\%$ who have survived an episode of ventricular fibrillation. CRT and ICD therapy can be provided in a single device (CRT – D)

Surgical Treatment for Chronic Heart Failure

Surgical options for management of CHF include repair or replacement of cardiac valves where these are the cause of heart failure. In the presence of coronary artery disease, revascularisation may be considered if angina symptoms persist despite optimal medical therapy. Cardiac transplantation may be an option for some individuals with end stage heart failure, but the opportunity for this treatment is limited by the provision of donor organs. Implantation of left ventricular assist devices may be a useful supportive measure for patients on a transplant waiting list, or in the management of patients with acute severe myocarditis (Dickstein, 2008).

1.2.7. Prognosis of Heart Failure

The prognosis of CHF is poor (Hobbs, 2007) and it accounts for 4% of all deaths in the UK (British Heart Foundation, 2008). 38% of patients do not survive more than one year after diagnosis, although thereafter the mortality rate is reduced to less than 10% per year (Cowie, 2000). Survival is adversely influenced by increasing age, the presence of comorbidities and worsening severity of CHF. Advances in pharmacological and non pharmacological therapies have improved prognosis in CHF (Jhund, 2009; Mehta, 2009) but the mortality rate six months following diagnosis of heart failure remains high at 14% (Mehta, 2009).

1.2.8. Economic Impact of Heart Failure

In England, heart failure accounts for a total of 1 million inpatient bed days, or 2% of all National Health Service (NHS) inpatient bed days (Petersen, 2002). The mean length of hospital stay is 13 days (Petersen, 2002). Healthcare costs for treatment of heart failure are estimated to cost 2% of total NHS expenditure with inpatient hospital care accounting for a substantial proportion of these costs (Stewart, 2002; Braunschweig, 2011). Hospitalisations for heart failure are projected to increase in the next 25 years due to the ageing population (Petersen, 2002).

Whilst the mortality from CHF has decreased, additional strategies are required to further reduce the morbidity, mortality and high healthcare costs associated with this disorder. Identification of concomitant conditions which impair cardiac function could provide an additional opportunity for therapeutic interventions to improve CHF. As discussed in the following sections, SDB is associated with cardiovascular morbidity and treatment can improve cardiac function in CHF. Diagnosis and treatment of SDB may be a novel therapeutic option in patients with CHF.

1.3. What is Sleep-Disordered Breathing?

There is no formal definition of sleep-disordered breathing (SDB) but in the context of CHF, it is used when it is neither convenient nor possible to distinguish between obstructive and central sleep apnoea (Javaheri, 1995). It is particularly useful in the context of CHF where both central and obstructive sleep apnoea frequently coexist in the same patient (Tkacova, 2001; Tkacova R, 2006; Vazir, 2008; Ryan, 2010). In this thesis, the term SDB encompasses central sleep apnoea (CSA), obstructive sleep apnoea (OSA), and Cheyne-Stokes respiration (CSR). Where it is necessary to distinguish between the individual forms of SDB, they will be referred to by their specific name.

1.4. Sleep-Disordered Breathing in Chronic Heart Failure

1.4.1. Epidemiology of Sleep-Disordered Breathing in Chronic Heart Failure

The occurrence of SDB in CHF has been appreciated for many centuries (Cheyne, 1818; Stokes, 1853) but it is only in the last two decades that systematic investigation has revealed the high prevalence of this disorder. In 1998 the landmark study by Javaheri et al., reported the prevalence of SDB in CHF was 51%, with the predominant form of SDB being CSA (Javaheri, 1998b). Subsequent studies have confirmed the prevalence of SDB in CHF is approximately 50% and some authors have reported that the prevalence may be even higher (Table 1.2). The most common type of SDB in CHF remains unclear; whilst many studies have reported that CSA is more prevalent than OSA, almost as many have reported the opposite (Table 1.2).

Table 1.2. Studies Reporting The Prevalence of Sleep-Disordered Breathing in Chronic Heart Failure

Author, Year	No. of Participants	Male (%)	Age (Years)	BMI (Kg/m ²)	NYHA		LVEF (%)	Type of sleep study	SDB criteria (AHI)	SDB (%)	OSA (%)	CSA (%)
					≤II (%)	≥III (%)						
Systolic Dysfunction												
Javaheri, 1998	81	100	64 (11)	27.8 (6)	70	30	25 (9)	PSG	≥15/hour	51	11	40
Sin, 1999	450	85	60 (13)	29.1 (7)	62	38	27 (16)	PSG	≥15/hour	61	29	32
Ferrier, 2005	53	77	60 (10)	27.9 (5)	75	25	34 (9)	PSG	>10/hour	68	53	15
Schulz, 2007	203	75	65 (15)	27.6 (8)	55	45	28 (14)	RPG	>10/hour	71	43	28
Oldenburg, 2007	700	80	65 (10)	26.7 (4)	ND	ND	28 (7)	RPG	>15/hour	52	19	33
Vazir, 2007	55	100	61 (12)	29.4 (5)	100	0	31 (10)	PSG	>15/hour	53	15	38
Macdonald, 2008	108	85	57 (11)	28.0 (6)	71	29	20	RPG	≥15/hour	61	30	31
Hagenah, 2008	50	88	63 (12)	26.6 (4)	ND	ND	26 (6)	PSG	>10/hour	64	20	44
Yumino, 2009	218	77	56 (13)	29.2 (5)	54	46	25 (10)	PSG	≥15/hour	47	26	21
Paulino, 2009	316	83	59 (13)	28.0 (6)	ND	ND	30 (11)	RPG	≥10/hour	81	56	25
Ferreira, 2010	103	79	66	27.2	ND	ND	ND	PSG	≥15/hour	45	ND	ND
Asymptomatic Left Ventricular Systolic Dysfunction												
Lanfranchi, 2003	47	89	59 (12)	25.9 (1)	100	0	27 (6)	RPG	≥15/hour	66	11	55
Diastolic Dysfunction												
Chan, 1997	20	35	65 (6)	28.0 (3)	ND	ND	>50%	PSG	>10/hour	55	20	35
Bitter, 2009	244	64	65 (4)	28.4 (1)	ND	ND	>55%	RPG	≥15/hour	45	23	22

NYHA = New York Heart Association class; LVEF = Left ventricle ejection fraction; PSG = Polysomnography; RPG = cardiorespiratory polygraphy

Risk Factors for Sleep-Disordered Breathing in Chronic Heart Failure

From these prevalence studies, clinical characteristics have been identified which appear to be risk factors for the presence of SDB in CHF (Table 1.3). In CHF patients, OSA is independently associated with male gender, increasing age, obesity and increased neck circumference (Sin, 1999; Yumino, 2009a; Ferreira, 2010). These risk factors are identical to those in OSA patients without CHF (Davies, 1992; Young, 2002a), suggesting that the pathogenesis of OSA may be similar regardless of the presence or absence of CHF. The occurrence of CSA in CHF is also associated with increasing age and male gender, but the presence of atrial fibrillation and daytime hypoxaemia are additional independent risk factors for this condition (Wilcox, 1998; Sin, 1999; Javaheri, 2006c; Yumino, 2009a). Differences in the pathogenesis of OSA and CSA in CHF may explain the differing risk factors for these two forms of SDB (see Section 1.3.2).

Table 1.3. Risk factors for the Presence of Obstructive and Central Sleep Apnoea in Chronic Heart Failure Patients*

	Obstructive Sleep Apnoea	Central Sleep Apnoea
	Adjusted Odds Ratio [†]	Adjusted Odds Ratio [†]
Age (per 10 yr increase)	1.52 (1.08 – 2.14)	1.48 (1.01 – 2.08)
Male gender	4.95 (1.74 – 14.07)	8.36 (2.38 - 29.38)
BMI (per 5Kg/m ² increase)	1.58 (1.08 – 2.33)	0.99 (0.62 – 1.55)
Atrial fibrillation	2.44 (0.56 – 10.55)	7.93 (1.76 – 35.65)
PCO ₂ (per 1 mmHg decrease)	1.02 (0.94 – 1.11)	1.27 (1.15 – 1.41)
Diuretic use	2.25 (0.87 – 5.82)	14.16 (2.7 – 72.48)

*Data from Yumino et al., 2009. [†] Values given with 95% confidence intervals

BMI = body mass index; PCO₂ = arterial carbon dioxide partial pressure

Association between Heart Failure Characteristics and Sleep-Disordered Breathing

There are conflicting reports regarding the association between CSA and worsening severity of CHF. Lower LVEF, higher BNP concentrations and poorer NYHA class have been reported to be associated with CSA in some studies (Javaheri, 2006c; Christ, 2007; Oldenburg, 2007b; Ferreira, 2010). However, larger studies have found these variables are not independent predictors of CSA (Sin, 1999; Yumino, 2009a).

Alternative measures of cardiac function including cardiac index and pulmonary capillary wedge pressure have shown an association between increasing severity of heart failure and CSA (Solin, 1999; Oldenburg, 2009). Whilst some authors have concluded that CSA is a feature of worsening heart failure severity (Aldabal, 2010), the direction of any causal relationship between CSA and CHF remains unclear (Naughton, 2000).

Functional classification of heart failure severity would also appear to be of little value for prediction of SDB in CHF. Vazir et al., (2007) studied mildly symptomatic male CHF patients with NYHA class II symptoms and reported SDB prevalence was 53% (Vazir, 2007). Lanfranchi et al., (2003) reported SDB prevalence was 66% in individuals with asymptomatic left ventricular systolic dysfunction (Lanfranchi, 2003). In addition, whilst CSA may be associated with more severe heart failure (as discussed above), it is important to note that CSA occurs frequently even in mildly symptomatic or asymptomatic CHF (Table 1.2) (Lanfranchi, 2003; Vazir, 2007).

The classification of CHF according to the presence of systolic or diastolic cardiac dysfunction also appears unhelpful for identifying CHF patients with SDB. Whilst the majority of studies have evaluated CHF patients with systolic dysfunction, as shown in Table 1.2, SDB also occurs in approximately 50% of CHF patients with preserved ejection fraction and evidence of diastolic dysfunction (Chan, 1997; Bitter, 2009a).

The prevalence of SDB does not appear to be influenced by the underlying aetiology of CHF. SDB has been reported to occur in 62% of patients with ischaemic cardiomyopathy (Vazir, 2007); 58% of patients with non ischaemic dilated cardiomyopathy (Usui, 2006) and 69% of patients with CHF due to valvular heart disease (Abe, 2009). Therefore, the cause of heart failure does not appear to be helpful in predicting the presence of SDB in CHF patients.

Temporal Trends in the Prevalence of Sleep-Disordered Breathing in Chronic Heart Failure

The prevalence of SDB in CHF may have fallen in parallel with the therapeutic advances in heart failure management which have occurred in recent years. However, assessment of temporal trends in the prevalence and type of SDB in CHF is complicated by methodological differences between studies. As discussed above, the prevalence of SDB, and the proportions of CSA or OSA will be influenced by differences in the clinical characteristics of the patients studied. In addition, most studies evaluating prevalence have prospectively recruited CHF patients from cardiology clinics irrespective of symptoms of SDB. However, Sin et al., (1999) evaluated CHF patients referred to a sleep clinic and the SDB prevalence of 61% in their study may have been biased by the selection of symptomatic patients (Sin, 1999).

Polysomnography or respiratory polygraphy have both been used for diagnosis of SDB, but respiratory polygraphy may systematically underestimate the AHI by a mean of 5 events/hour (Smith, 2007a) resulting in underdiagnosis of SDB. The most commonly used threshold for diagnosis of SDB in CHF is an AHI ≥ 15 /hour (Javaheri, 2007a), but the prevalence of SDB will have been increased in some studies by the use of a lower threshold of >10 /hour. Moreover, differing criteria have been used to score hypopnoea and this can significantly influence the measured AHI and prevalence of SDB (Tsai,

1999; Manser, 2001) (see also Section 5.4.1). Finally, the criteria used to distinguish obstructive from central events, particularly with regard to hypopnoeas, are not standardised and misclassification of events may account for some of the differences in prevalence of CSA and OSA.

Notwithstanding the methodological differences described above, in spite of progress in pharmacological and non pharmacological therapy for CHF, there has not been a significant reduction in the prevalence of SDB in the last decade (Table 1.2). Yumino et al. (2009) examined trends in SDB diagnosis in CHF patients seen at a single centre between 1997 and 2004. Despite increased prescription of medication of prognostic benefit including beta blockers and spironolactone, there was no change in prevalence or type of SDB over this time period (Yumino, 2009a).

Whilst it has been reported that beta blockers may reduce the propensity to CSA in patients with CHF (Tamura, 2007; Tamura, 2009), two recent studies in which beta blockers were prescribed to over 80% of participants reported that SDB prevalence remained over 50%, with predominantly CSA (Oldenburg, 2007b; MacDonald, 2008).

Comparison of Sleep-Disordered Breathing Prevalence in Chronic Heart Failure Patients and Community Dwelling Individuals

To emphasise the high prevalence of SDB in CHF, it is helpful to compare the prevalence of SDB in adults without heart failure. In community dwelling individuals, the predominant form of SDB is OSA. The prevalence of obstructive sleep apnoea syndrome (i.e. OSA and clinical symptoms of sleep apnoea such as excessive daytime sleepiness) has been reported to be between 0.3 to 5.4% of middle aged men (Stradling, 1991; Young, 1993; Udwadia, 2004) and 1.2 to 3.2% of women (Young, 1993; Bixler, 2001; Kim, 2004). As discussed above, methodological differences may account for the variations in prevalence reported by these studies. Many CHF patients

do not have symptoms of SDB (Arzt, 2006; Hastings, 2006) and it may be more relevant to consider the prevalence of asymptomatic SDB in the community. In men without symptoms of SDB, the prevalence of an AHI >15/hour has been reported to be between 5.3 to 14.2% (Young, 1993; Duran, 2001; Ip, 2001) whilst in women, the prevalence is between 1.2 to 4.7% (Young, 1993; Ip, 2004a; Kim, 2004). SDB prevalence increases with age (Young, 1993) and as the mean age of CHF patients in the community is 75 years (Dickstein, 2008), it is more informative to compare SDB prevalence in community dwelling individuals of a closer age. In men aged 60 to 70 years, SDB prevalence is between 10.8 and 24.2% (Duran, 2001; Kim, 2004) whilst in women aged 60 to 70 years, prevalence is between 9.5 to 15.9% (Duran, 2001; Kim, 2004).

Unlike OSA, CSA is exceptionally uncommon in community dwelling individuals (Young, 2002b). It is rarely seen except in the presence of cardiac or neurological disease, opiate use, or prescription of other respiratory depressant medications. However, the prevalence of CSA does increase with advancing age. One study reported that a central AHI >20/hour was observed in 5% of men aged 65 – 100 years (Bixler, 1998), although CSA remained uncommon in elderly women (Bixler, 2001). Ancoli-Israel et al., (1987) reported CSA prevalence was 10% in men and 2.5% in women aged >65 years, although a more conservative diagnostic threshold of AHI >5/hour was used in this study (Ancoli-Israel, 1987).

In summary, SDB is prevalent in CHF and occurs in approximately half of all patients, irrespective of cause or severity of heart failure. Compared to community dwelling individuals, the prevalence of SDB in CHF is increased and CSA occurs frequently.

1.4.2. Why is the Prevalence of Sleep-Disordered Breathing Increased in Chronic Heart Failure?

The Evidence That Sleep-Disordered Breathing Causes Chronic Heart Failure

The prevalence studies previously described do not determine causation. This section will review the evidence that SDB both causes, and is caused by CHF.

Obstructive Sleep Apnoea is a Cause of Chronic Heart Failure

OSA may predispose to CHF through both direct and indirect effects. The acute effects of OSA and the mechanisms by which these can directly impair cardiac function are described in Section 1.4.3.

In the longer term, OSA is known to cause hypertension and it is also associated with other cardiovascular diseases and cardiovascular risk factors which can indirectly predispose to CHF. Hypertension is the most important of these, with a 2 to 3 fold increased risk of development of CHF in hypertensive patients (Levy, 1996).

In prospective observational studies, moderate - severe OSA (AHI >15/hour) was independently associated with development of daytime hypertension (Peppard, 2000b). The most robust evidence supporting the role of OSA in causing hypertension comes from interventional studies. Randomised controlled trials have found that CPAP decreases mean 24 hour and daytime blood pressure (Pepperell, 2002; Becker, 2003; Barbe, 2010). In longitudinal observational studies OSA is an independent risk factor for development of non dipping of nocturnal blood pressure (Hla, 2008), which is recognised to cause left ventricular hypertrophy (Verdecchia, 1990). Thus, OSA may

contribute to development of CHF by causing hypertension and left ventricular hypertrophy.

OSA has also been identified as an independent risk factor for prevalent coronary artery disease in both men and women (Moore, 1996b; Moore, 1996a; Shahar, 2001), thereby increasing the risk of ischaemic cardiomyopathy. However, recent results from the Sleep Heart Health Study reported a weaker association between OSA and ischaemic heart disease, and OSA was an independent risk factor for incident coronary artery disease only in middle aged men (Gottlieb, 2010). However, the authors noted that this cohort may have been biased by a healthy survivor effect as the median age was 62 years.

OSA is associated with diabetes mellitus, an important cardiovascular risk factor. The prevalence of diabetes in OSA patients has been reported to be increased in cross sectional (West, 2006) and longitudinal observational studies (Botros, 2009; Marshall, 2009).

Prospective observational studies have also provided further evidence of a direct association between OSA and CHF. The largest of these studies is the Sleep Heart Health Study, a longitudinal observational study of over 6000 United States citizens to investigate the cardiovascular consequences of SDB (Quan, 1997). In a baseline cross sectional analysis, participants in the upper quartile for AHI (AHI >11.0/hour) had an adjusted relative risk of 2.38 for prevalent CHF, compared to participants in the lower AHI quartile (AHI <1.3/hour) (Shahar, 2001). Moreover, in a longitudinal analysis after a median follow up of 8.7 years, men with AHI >30/hour had an adjusted relative risk of 1.58 for incident CHF (Gottlieb, 2010). However, OSA was not independently associated with incident CHF in women in this study. Observational studies may be confounded by the effects of obesity, hypertension or diabetes mellitus which are independent risk factors for CHF and also common comorbidities in patients with OSA.

In the Sleep Heart Health Study, OSA remained an independent risk factor for development of CHF even after adjusting for these and other known cardiovascular risk factors.

The presence of OSA has also been reported to be associated with echocardiographic evidence of impaired cardiac function in adults without pre-existing hypertension or cardiac disease. In newly diagnosed OSA patients, there was a higher prevalence of both systolic and diastolic myocardial dysfunction, compared to healthy matched controls (Alchanatis, 2002; Arias, 2005; Shivalkar, 2006). Treatment of OSA with continuous positive airway pressure (CPAP) therapy was associated with significant improvements in cardiac structure and function (Alchanatis, 2002; Laaban, 2002; Arias, 2005; Shivalkar, 2006), although only one study has evaluated this using a methodologically rigorous randomised sham CPAP controlled trial (Arias, 2005).

The potential role of OSA in causing CHF is also supported by animal studies. In a canine model of OSA, 3 months of nocturnal intermittent airway occlusion to simulate obstructive apnoeas was associated with a significant decrease in left ventricular ejection fraction from 58 to 51% (Parker, 1999).

However, impaired cardiac function in patients with OSA is not a consistent finding, and one study has reported that echocardiographic measurements of left ventricular size and function were normal in 30 untreated OSA patients, and not significantly different from a control group of simple snorers (Hanly, 1992).

Cardiovascular risk may be increased in OSA by other mechanisms which require further elucidation. Endothelial dysfunction is recognised as an independent risk factor for cardiovascular disease (Lerman, 2005) and impaired endothelial function has been reported in OSA patients (Kohler, 2008) which can be improved by CPAP treatment (Ip, 2004b). Observational studies have shown that OSA is associated with increased

propensity to platelet activation and hypercoagulability which may be partially reversed by CPAP (Hui, 2004).

The Evidence That Chronic Heart Failure Causes Sleep-Disordered

Breathing: Pathogenesis of Sleep-Disordered Breathing

Whilst the evidence suggests that OSA may precede and cause CHF, a number of mechanisms have been identified by which CHF causes SDB. The most important of these is impairment of the normal homeostatic processes controlling breathing.

Normal Control of Breathing

The drive to breath is normally determined by metabolic requirements and non respiratory inputs. Higher central nervous system centres can temporarily override the metabolic demand to breath in response to volitional requirements, emotional changes, or activities such as eating and talking. In addition, breathing is also stimulated by a wakefulness drive to breathe that exists whilst awake (Fink, 1961).

At the onset of sleep, the wakefulness drive is withdrawn and breathing is regulated by the metabolic drive to breath, which is principally dependent on the arterial carbon dioxide (PaCO_2) concentration. If PaCO_2 falls below a critical level, termed the 'apnoeic threshold', there is cessation of drive to breath and central apnoea will result (Skatrud, 1983). At sleep onset, there is normally a reduction in tidal volume and a decrease in hypercapnic ventilatory responsiveness which contribute to a rise in PaCO_2 (Douglas, 1982; Stradling, 1985). This serves to maintain the PaCO_2 above the apnoeic threshold and in healthy individuals, during stable sleep, there is normally a difference (termed the CO_2 reserve) of 3 – 5 mmHg between eupneic PaCO_2 and the apnoeic threshold (Morrell, 1995; Meza, 1998).

In normal individuals, the PaCO₂ is tightly regulated during sleep and under stable conditions it varies by <1mmHg from its set point. Any change in PaCO₂ is detected by peripheral and central chemoreceptors which initiate a change in ventilatory drive to correct the disturbance. The magnitude and speed of the ventilatory response is dependant on three key parameters: 1) the chemoreceptor sensitivity; 2) lung-chemoreceptor feedback delay; 3) the efficiency of the lungs at correcting the disturbance. The integrated response resulting from the complex interaction between these parameters controls and determines the stability of ventilation. This integrated response can be assessed by measurement of 'loop gain', an engineering concept which describes the stability of a control system (Figure 1.3) (Khoo, 1982). In a low loop gain system, the magnitude of the response is less than the initial disturbance and stability will be restored; in a high loop gain system, the magnitude of the response is equal to or exceeds the initial disturbance, resulting in an unstable system and perpetuation or magnification of the initial disturbance (Figure 1.4) (White, 2005).

In CHF patients, changes in eupneic PaCO₂ and loop gain have been shown to have a pivotal role in causing SDB, with most evidence emphasizing the importance of these changes in causing CSA and CSR.

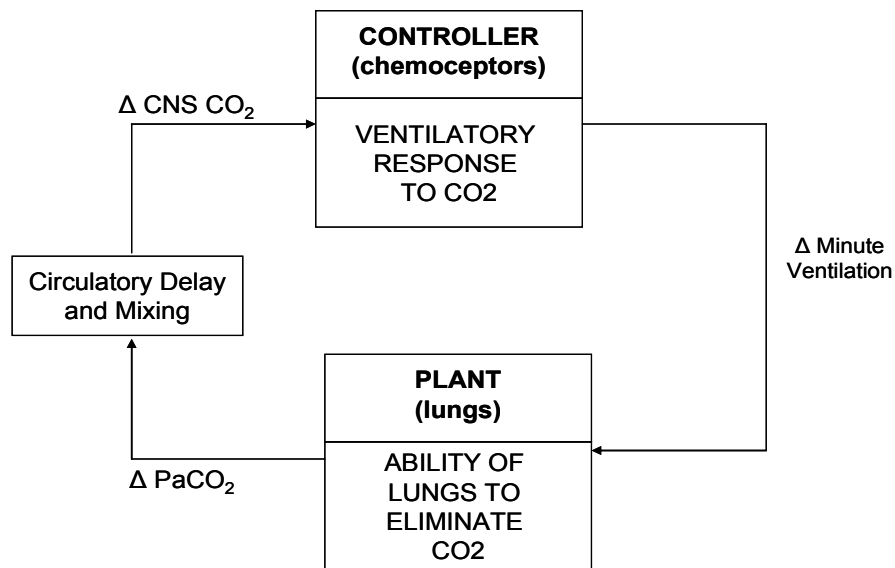


Figure 1.3. Schematic Diagram to Illustrate the Components of the Ventilatory Control System Which Contribute to Loop Gain

(PaCO₂ = Arterial carbon dioxide partial pressure, CNS = central nervous system; Δ = change in parameter)

Figure 1.4a

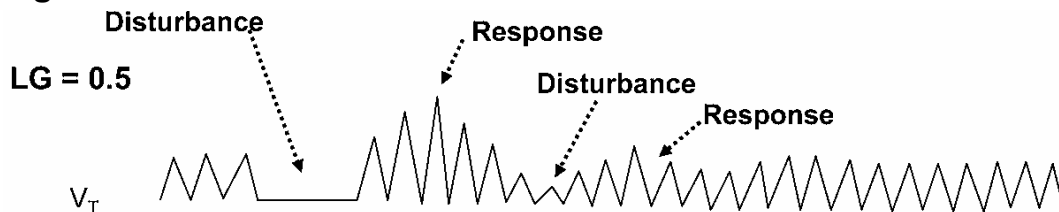


Figure 1.4b

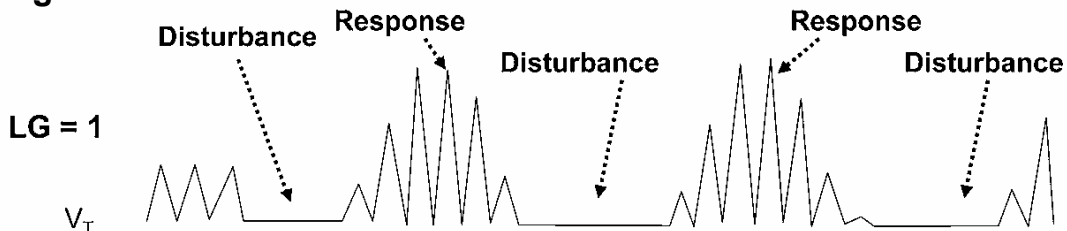


Figure 1.4. In a low loop gain system, the magnitude of the response is less than the disturbance and stability is restored (Figure 1.4a). In a high loop gain system, the magnitude of the response exceeds the disturbance and an oscillatory breathing pattern occurs (Figure 1.4b). Figure adapted from White, 2005.

(LG = Loop Gain; V_T = Tidal volume)

Mechanisms by Which Chronic Heart Failure Predisposes to Central Sleep Apnoea

CHF patients with CSA have been shown to have a lower daytime and nocturnal PaCO₂, when compared to CHF patients without SDB or with OSA (Hanly, 1993; Javaheri, 1998a). In addition, failure of the sleep induced increase in PaCO₂ and a reduced CO₂ reserve has been observed in these patients (Xie, 2002). When these occur in combination, there is a greater propensity to the PaCO₂ falling below the apnoeic threshold causing central apnoea. In contrast, measures which raise the PaCO₂ during sleep, including low levels of inhaled CO₂, can prevent occurrence of central apnoeas (Lorenzi-Filho, 1999; Szollosi, 2004).

The mechanisms leading to reduction in eupneic PaCO₂ in CHF include both chronic hyperventilation and increased chemoreceptor sensitivity. CHF induced chronic hyperventilation is thought to be driven by pulmonary vagal afferent activity caused by pulmonary congestion and interstitial fluid (Yu, 1998). Pulmonary capillary wedge pressure (PCWP) reflects pulmonary venous congestion and pulmonary interstitial fluid, and it has been reported to be higher in CHF patients with CSA compared to those with OSA or no SDB (Solin, 1999). PCWP is also correlated with resting PaCO₂ and severity of CSA (Solin, 1999; Oldenburg, 2009), and reduction of PCWP is associated with a rise in PaCO₂ and improvement in CSA (Lorenzi-Filho, 2002; Abe, 2009). However, whilst PCWP may be a useful predictor of CSA in research studies, it is not a practical measure for clinical purposes.

Increased hypercapnic chemoreceptor sensitivity is also important in causing the hypocapnia observed in CHF patients with CSA. The hypercapnic ventilatory response is higher in CHF patients with CSA, than in CHF patients with OSA or without SDB (Javaheri, 1999a). Increased central sympathetic activity in association with CHF has

been reported to be a possible mechanism underlying this enhanced chemosensitivity (Yamada, 2004), although this requires further evaluation.

Mechanisms by Which Chronic Heart Failure Predisposes to Cheyne-Stokes Respiration

The oscillatory breathing pattern seen with CSR is characteristic of an unstable ventilatory control system. CHF patients have been shown to have derangements in all three parameters which control ventilation and predispose to CSR.

Chemosensitivity is an important determinant of the magnitude of a ventilatory response; an excessive response to hypercapnia (or hypoxia) can result in ventilatory overshoot and the ensuing hypocapnia can cause central apnoea. Increased hypercapnic chemosensitivity has been described in patients with CSA and CSR and is an important contributor to the increased loop gain seen in these patients (Wilcox, 1998; Javaheri, 1999a). Autoregulation of cerebral blood flow is also important in stabilising ventilatory control by minimising changes in CO₂ and hydrogen ion at the central chemoreceptors, thereby reducing fluctuations in ventilatory drive. Impaired cerebrovascular reactivity has been observed in CHF patients with CSA, but not in CHF patients without SDB and this may be important in contributing to ventilatory overshoot in CHF (Xie, 2005).

Prolongation of lung – chemoreceptor feedback reduces the effectiveness of chemoreceptor control by providing outdated information about the prevailing PaCO₂ (Guyton, 1956). Animal studies suggest that supraphysiological increases in circulation time are needed to initiate CSR (Guyton, 1956) and the presence of a circulatory delay may be of greatest importance when it occurs in combination with other perturbations in the ventilatory control system. The contribution of feedback delay to overshoot of the ventilatory response and perpetuation of ventilatory instability in CHF is supported by

reports that the length of the apnoea - hyperpnoea cycle in CSR is correlated ($r = 0.75$) with the circulation time (Naughton, 1993; Wedewardt, 2010).

A further contributing factor to ventilatory instability relates to lung function and lung volumes. If changes in ventilation cause rapid changes in blood gas tensions, this can predispose to overshoot of the homeostatic set point and initiate oscillations in ventilatory drive. The lung and body tissue stores of oxygen and carbon dioxide are important to dampen the oscillations in PaO_2 and PaCO_2 that occur with changes in ventilation. Reduction in lung volumes due to pleural effusion or cardiomegaly may predispose to more rapid changes in blood gas concentrations. Impaired pulmonary diffusing capacity has been reported to be independently associated with CSA in CHF patients, emphasising the importance of lung function in contributing to ventilatory stability (Szollosi, 2008).

Whilst the above changes establish a susceptibility to CSA or CSR in CHF patients, it is apparent from clinical observation that many CHF patients will have periods of stable breathing interspersed with periods of SDB. This can be explained by the importance of sleep state changes in precipitating SDB and in modifying ventilatory stability. In many cases, SDB is precipitated by a transitory arousal from sleep. This is associated with reversal of the tidal volume and chemosensitivity changes that occurred at sleep onset resulting in an increase in ventilation and decrease in PaCO_2 towards wakefulness levels. On resumption of sleep, particularly in CHF patients with reduced CO_2 reserve, PaCO_2 may now be below the apnoeic threshold and central apnoea follows. The rise in PaCO_2 during central apnoea stimulates the chemoreceptors to restart respiration, but the high loop gain ventilatory control system then perpetuates the initial ventilatory disturbance, causing oscillations in ventilatory drive and the classical periodic breathing or Cheyne-Stokes respiratory pattern (Naughton, 1998). The hyperpnoeas occurring during CSR cause further arousals which also serve to perpetuate this cycle. The role

of arousals in triggering CSA and CSR has led some authors to suggest that they may have an central role in the pathogenesis of CSA in CHF (Ruttanaumpawan, 2009).

Ventilatory stability is also modified by sleep stage. It has been observed that CSA is more common in non rapid eye movement (NREM) sleep and is reduced or ceases completely in rapid eye movement (REM) sleep (Hanly, 1989b). During REM sleep, ventilatory drive is less dependent on PaCO₂ with greater input from non metabolic excitatory drive which has been attributed to dreaming or increased sympathetic activity during this stage of sleep. In addition reduction in CO₂ chemosensitivity (Douglas, 1982) and an increase in CO₂ reserve (Xi, 1993) also reduce the susceptibility to CSA and CSR during REM sleep. A reduction in frequency of SDB has also been observed from stage 1 NREM to stage 4 NREM (Hanly, 1989b; Ratnavadivel, 2009) and this may be caused by a decrease in hypercapnic chemosensitivity (Douglas, 1982) and arousal frequency (Bonnet, 1978) from light to deep NREM sleep.

Ventilatory Control Instability and Obstructive Sleep Apnoea

Whilst there is a large body of evidence supporting a role for OSA in causing CHF, recent observations suggest that CHF may also cause, or worsen pre-existing OSA. The ventilatory instability which underlies CSA or CSR in CHF may also predispose to OSA.

Sleep apnoea is traditionally dichotomised into OSA or CSA according to whether the airway remains open or closes during apnoea. However, CSA and OSA frequently co-exist in one night and it has become evident that this classification may be less than straightforward. Airway closure has been observed to occur in CSA (Badr, 1995), and in CHF patients with CSA or CSR at the nadir of ventilatory drive during apnoea (Alex, 1986; Onal, 1986). Moreover, the observation of periodic breathing in patients with

OSA (Ryan, 2005) suggests that the abnormalities in ventilatory drive which cause CSA or CSR may also contribute to upper airway obstruction. The mechanism underlying the increased propensity for upper airway narrowing or closure during periods of reduced central ventilatory drive is thought to be a relatively greater reduction in upper airway dilator muscle activity compared to chest wall inspiratory muscle activity (Hudgel, 1987).

The association between impaired ventilatory control and OSA is supported by reports of higher loop gain in patients with severe OSA, compared to those with mild OSA (Younes, 2001). The role of ventilatory instability in causing OSA may be of greatest importance in patients with an anatomic susceptibility to upper airway collapse. In non CHF patients with OSA and an anatomic predisposition to upper airway closure (as measured by pharyngeal closing pressure), there was a linear relationship between AHI and loop gain (Wellman, 2004).

In CHF, there is a significant correlation ($r = 0.67$) between lung to ear circulation time (a surrogate measure of lung to chemoreceptor delay) and hyperpnoea duration in OSA or periodic breathing (Ryan, 2005). This may be an important factor contributing to the ventilatory instability in CHF patients with OSA. The importance of lung – chemoreceptor feedback delay in causing OSA is supported by the observation that in 13 CHF patients who received cardiac resynchronisation therapy, a reduction in obstructive apnoeas was closely correlated ($r = 0.89$) with the decrease in circulation time (Stanchina, 2007).

However, the prolonged circulation time in CHF patients with OSA may be a consequence, rather than the cause of OSA. The haemodynamic effects of repeated obstructive apnoeas may impair left ventricular function over the course of the night resulting in a lengthening of lung to chemoreceptor time (Bradley, 2003). This raises the interesting question of whether prolongation of circulation time caused by OSA may

promote ventilatory instability and predispose to CSA, which may explain the observation that some CHF patients have OSA in the first half of the night, followed by CSA in the second half of the night (Tkacova, 2001).

Other Mechanisms by Which Chronic Heart Failure may Predispose to Sleep-Disordered Breathing

Recent interest has focused on the role of overnight shift in intravascular and extracellular fluid in causing upper airway narrowing and increased propensity to collapse. Upper airway cross sectional area has been observed to increase when central venous pressure was reduced (Shepard, 1996). This led to the hypothesis that increased venous return to the chest during negative intrathoracic pressure may have an important role in maintaining upper airway patency during inspiration.

Recent studies have also suggested that overnight fluid shift from the legs to the upper body may be an important cause of OSA. In healthy men, application of antigravity trousers to the legs caused reduction in leg fluid volume with increased neck circumference, decreased upper airway cross sectional area and increased pharyngeal resistance (Chiu, 2006; Shiota, 2007). In non obese men, the overnight change in leg fluid volume was strongly correlated ($r = -0.77$) with the AHI (Redolfi, 2009).

Therefore, the propensity to OSA may be increased by conditions which predispose to fluid retention and dependent oedema, such as CHF. In patients with diastolic heart failure, intensive diuretic therapy was associated with a reduction in the severity of OSA and an increase in the upper airway diameter suggesting that upper airway oedema may have been contributing to SDB (Bucca, 2007). In CHF patients, the overnight reduction in leg volume was inversely correlated with both change in neck circumference ($r = -0.78$) and AHI ($r = -0.88$) (Yumino, 2010). This study also observed that treatment with CPAP attenuated the overnight increase in neck circumference

despite similar change in overnight leg volume. These findings led the authors to propose that CPAP not only treats OSA through its actions as a pneumatic splint for the upper airway, but also acts to prevent overnight redistribution of fluid to the neck by raising intrathoracic pressure (Yumino, 2010). Further randomized controlled studies are needed to evaluate this novel proposed mechanism of action.

In addition, the overnight redistribution of dependent fluid has also been reported to be important in the pathogenesis of CSA in CHF. The change in overnight leg volume is larger in patients with CSA than in patients with OSA, suggesting greater fluid shifts in CSA (Yumino, 2010). The overnight change in leg volume in patients with CSA was correlated with nocturnal transcutaneous CO₂ ($r = 0.57$), and it was hypothesised that the redistribution of higher volumes of dependent fluid caused increased left atrial pressure and PCWP, which contributed to ventilatory instability (Yumino, 2010).

1.4.3. Acute Cardiovascular Consequences of Sleep-Disordered Breathing

Sleep is normally associated with a reduction in sympathetic nervous activity and a relative dominance of cardiac parasympathetic activity (Somers, 1993). Heart rate and blood pressure both decrease during NREM sleep, although increases in heart rate and blood pressure occur in REM sleep (Khatri, 1967).

The cycle of apnoeas and hypopnoeas occurring in SDB cause considerable autonomic and haemodynamic perturbations. The repeated interruption to ventilation, arousals from sleep and surges in negative intrathoracic pressure associated with SDB have both immediate and long term consequences for cardiovascular function. Much of the research which has elucidated the mechanisms by which SDB adversely affects the cardiovascular system has been performed in animals, healthy humans and patients

with OSA. In many of these studies, alteration in autonomic nervous system activity favouring sympathetic overactivity and parasympathetic withdrawal has been identified as particularly important in mediating many of the adverse consequences of SDB.

Interruption of ventilation during apnoea or hypopnoea causes hypoxia, hypercapnia and respiratory acidosis. Whilst hypoxia can cause a vagally mediated bradycardia (the diving reflex) (Zwillich, 1982), it is also an important cause of increased sympathetic nervous system activity seen in OSA (Cutler, 2004). Hypercapnia and hypoxia act synergistically to elicit a greater increase in muscle sympathetic nerve activity (MSNA) than either stimulus alone (Somers, 1989).

Chronic intermittent hypoxia (CIH) has been reported to increase carotid body chemosensitivity (Narkiewicz, 1999) and this is thought to be an important mechanism underlying the increased MSNA during wakefulness and sleep in patients with OSA (Somers, 1995). Augmentation of sympathetic activity by tonic peripheral chemoreceptor activity in OSA is also suggested by the observation that awake OSA patients breathing 100% oxygen at rest had a significant reduction in MSNA, whilst there was no change MSNA in healthy controls (Narkiewicz, 1998b). Recent studies in which CIH was experimentally induced for 28 days in young healthy human volunteers have also reported increased MSNA in association with increased daytime diastolic blood pressure (Tamisier, 2009; Gilmartin, 2010). Thus, CIH appears to have a key role in mediating increased sympathetic nervous activity in SDB.

Hypoxia during apnoea has also been implicated in causing both electrocardiographic and symptomatic myocardial ischaemia during OSA (Franklin, 1995; Moore, 2000), although this may only occur in the setting of pre-existing coronary artery disease (Chen, 1998). In addition, CIH has also been implicated in the increased production of reactive oxygen species and systemic inflammation that has been observed in OSA patients (Dyugovskaya, 2002; Ryan, 2008).

Spontaneous arousal from sleep has been observed to cause increase in heart rate and blood pressure, independently of the respiratory changes that occur with transition from sleep to wakefulness (Trinder, 2001; Goff, 2008). Both spontaneous and induced arousals from sleep are associated with an increase in sympathetic nervous activity and a reduction in vagal activity (Horner, 1995; Morgan, 1996). Combined hypoxia and sleep arousal may elicit a synergistic increase in sympathetic nervous activity (Morgan, 1998), although the cardiovascular response to arousal is not increased by concomitant hypoxia and hypercapnia (O'Driscoll, 2004). Sleep fragmentation has been shown to be a risk factor for higher levels of awake systolic blood pressure, independently of confounding variables (Morrell, 2000). Thus, increased sympathetic nervous system activity caused by CIH is augmented by the effects of arousal from sleep.

The mechanical effects of inspiratory efforts against an occluded upper airway generate pronounced negative intrathoracic pressure which adversely effects cardiac function (Tolle, 1983; Bradley, 2001a). Negative intrathoracic pressure increases the ventricular transmural pressure and cardiac afterload (Chen, 1998), whilst also reducing left ventricular preload (Tolle, 1983; Shiomi, 1991). These haemodynamic changes result in a reduction in left ventricular stroke volume and cardiac output during apnoea, which can be exacerbated by bradycardia (Garpestad, 1995).

Negative intrathoracic pressure also increases transmural wall pressure in the intrathoracic major arteries, which combined with reduction in cardiac output, can lead to a fall in blood pressure during apnoea. Reflex baroreceptor activation by decrease in blood pressure leads to an increase in peripheral and cardiac sympathetic activity, with the aim of increasing heart rate and peripheral vasoconstriction, to restore blood pressure. At termination of apnoea, blood pressure can increase rapidly due to the increased total peripheral vascular resistance caused by vasoconstriction (Garpestad, 1995). Whilst resumption of cardiac filling and increase in heart rate occur with the

resumption of respiration, cardiac output may remain reduced for some time after the end of the apnoea due to the increased afterload caused by the high peripheral vascular resistance (Garpestad, 1992).

The changes described above have been observed in studies of obstructive apnoeas, but significant haemodynamic changes have also been observed in central apnoeas (Chen, 1997). It has been postulated that greater sympathetically mediated peripheral vascular resistance, or loss of sympatho-inhibitory modulation by pulmonary stretch receptor afferents (Goso, 2001) are important factors in causing haemodynamic changes in cardiac output during central apnoea. In animal studies, increase in LV afterload occurred with both obstructive and central apnoea, but reduction in stroke volume and cardiac output was greatest during central apnoea (Tarasiuk, 1994; Chen, 1997). However, these findings were not replicated in a recent observational study of stroke volume changes during CSA and OSA in patients with CHF (Yumino D, 2009).

1.4.4. Clinical Consequences of Sleep-Disordered Breathing in Chronic Heart Failure

This section will review the evidence that SDB adversely affects quality of life, morbidity and survival in patients with CHF.

Daytime Symptoms and Sleep Quality in Chronic Heart Failure patients with Sleep-Disordered Breathing

It has been consistently shown that in patients with CHF, SDB is rarely accompanied by subjective daytime sleepiness. The Epworth sleepiness scale (Johns, 1991) is the recommended screening tool to assess subjective daytime sleepiness in patients being investigated for OSA (Scottish Intercollegiate Guidelines Network, 2003). However,

Epworth sleepiness scale scores are frequently normal in CHF patients, and do not differ in CHF patients with SDB compared to those without SDB (Arzt, 2006; Hastings, 2006; Rao, 2006; Johansson, 2010). This finding is of great importance for the diagnosis of SDB in patients with CHF, as questioning about subjective daytime sleepiness is a commonly used clinical screening tool and absence of subjective sleepiness may lower clinical suspicion of SDB. Moreover, the presence or absence of subjective daytime sleepiness is frequently used to help decide whether therapy for SDB is necessary and therefore, other markers of SDB severity may be needed to determine the need for treatment in CHF.

Whilst SDB in CHF does not give rise to subjective daytime sleepiness or self reported poor sleep quality (Redeker, 2010b), it is associated with poorer performance on objective measures of daytime sleepiness. When assessed by maintenance of wakefulness test or multiple sleep latency test, CHF patients with SDB had shorter sleep latency, than those without SDB (Hanly, 1995; Hastings, 2006). Additionally objective measurement of sleep quality has shown that SDB in CHF is associated with greater duration of time in bed, increased sleep fragmentation, reduced sleep efficiency and decreased daytime activity compared to CHF patients without SDB (Hastings, 2006).

It is unclear why SDB does not cause subjective daytime sleepiness in CHF patients, despite reduced sleep quality. There is no difference in nap duration or nap frequency between CHF patients with and without SDB, suggesting that CHF patients with SDB are not using naps as a strategy to reduce daytime sleepiness (Hastings, 2006). It has been suggested that increased neurohumoral activation, particularly sympathetic nervous system activation occurring in CHF, may be important in stimulating alertness to overcome the detrimental effects of the sleep disturbance (Lambert, 1995).

There have been conflicting reports on the effect of SDB on quality of life in patients with CHF. SDB has been reported to be independently associated with impaired quality of life in some studies (Skobel, 2005; Carmona-Bernal, 2008; Mills, 2009), whilst others have found that it is not (Rao, 2006; Johansson, 2010; Midgren, 2010; Redeker, 2010b). Severe SDB was independently associated with poorer self reported physical functioning (Redeker, 2008) and this concurs with observations that CHF patients with SDB are less physically active than patients without SDB (Hastings, 2006).

The importance of the effects of SDB on sleep quality in CHF are reinforced by a recent statement from the American Heart Association, highlighting the potential role of sleep disturbance in contributing to impairment in self care (Riegel, 2009).

1.4.5. The Impact of Sleep-Disordered Breathing on Morbidity and Mortality in Chronic Heart Failure

Sleep-Disordered Breathing and Hypertension in Chronic Heart Failure

OSA is recognised as an independent risk factor for hypertension in the general population, and is also associated with hypertension in CHF. The presence of OSA (AHI >10/hour) in CHF patients is independently associated with a significantly higher daytime blood pressure, with an adjusted odds ratio of 2.89 for systolic hypertension (BP >140mmHg) (Sin, 2003). In patients with dilated cardiomyopathy, OSA was associated with a significantly higher prevalence of left ventricular hypertrophy, independent of blood pressure and other confounding variables, suggesting that OSA may exert effects on left ventricular remodelling independent of hypertension (Usui, 2006).

Sleep-Disordered Breathing and Arrhythmias in Chronic Heart Failure

SDB in CHF is associated with an increased risk of arrhythmias. In CHF patients with severe CSA, there was a significantly greater prevalence of non sustained ventricular tachycardia, and a trend to greater ventricular ectopy, compared to CHF patients without SDB (Lanfranchi, 2003). A significant reduction in ventricular ectopy was seen in CHF patients with SDB who responded to CPAP treatment, whilst there was no change in frequency of ventricular ectopic beats in patients in whom CPAP did not suppress SDB (Javaheri, 2000). Atrial fibrillation is of prognostic importance in CHF (Middlekauff, 1991; Pocock, 2006) and SDB may predispose to this arrhythmia. In adults without CHF, OSA is associated with an increased prevalence of atrial fibrillation (Gami, 2004) with a higher risk of recurrence of atrial fibrillation after cardioversion (Kanagala, 2003). In CHF patients, the presence of CSA is independently associated with a greater prevalence of atrial fibrillation (Javaheri, 2006c).

Central Sleep Apnoea and Mortality in Chronic Heart Failure

Studies which have evaluated the impact of CSA and CSR on mortality in CHF have reported conflicting results (Table 1.4). Whilst some have reported that CSA or CSR is an independent predictor of mortality (Hanly, 1996b; Lanfranchi, 1999; Corra, 2006; Javaheri, 2007b), others have found that it is not independently associated with mortality after accounting for severity of heart failure and age (Andreas, 1996b; Roebuck, 2004; Luo, 2009). In a longitudinal study of 353 randomly selected elderly men who were screened for SDB during an inpatient hospital stay and then followed up for a mean of 5.7 years, CSA was independently associated with mortality in patients with a diagnosis of CHF (Ancoli-Israel, 2003).

Table 1.4. Comparison of Studies Investigating the Relationship between Central Sleep Apnoea or Cheyne-Stokes Respiration and Mortality in Chronic Heart Failure

Author, Year	No. Patients	Entry criteria	Follow Up (mths)	Male (%)	Mean Age (yrs)	Mean LVEF (%)	Ischaemic HF (%)	Beta Blocker (%)	CSA or CSR diagnostic criteria	Independent risk for increased mortality?
Andreas, 1996	36	LVEF <40%	32 $\pm$ 15	86	54 $\pm$ 12	20 $\pm$ 8	11	ND	CSR>20% TST	No
Hanly, 1996	16	LVEF <35% NYHA 3-4	45	100	64 $\pm$ 7	23 $\pm$ 6	100	0	Any CSR	Yes
Lanfranchi, 1999	62	LVEF $\leq$ 35% NYHA 2-3	28 $\pm$ 13	88	57 $\pm$ 9	23 $\pm$ 6	53	ND	No cutoff*	Yes
Roebuck, 2004	78	NYHA 2	52	83	53 $\pm$ 9	20 $\pm$ 7	53	14	AHI >5/hour	No
Corra, 2006	133	LVEF <40%	39 $\pm$ 20	94	58 $\pm$ 10	23 $\pm$ 7	64	71	No cutoff*	Yes
Javaheri, 2007	88	LVEF <45%	51	100	65 $\pm$ 10	24 $\pm$ 9	75	10	AHI >5/hour	Yes
Luo, 2009	128	LVEF <45% NYHA 2-4	35	82	56	35	52	89	AHI >5/hour	No

* AHI used as a continuous variable in multivariate logistic stepwise regression analysis model.

LVEF = Left ventricular ejection fraction; CSA = Central sleep apnoea, CSR = Cheyne-Stokes respiration; NYHA = New York heart association class; ND = No data provided; TST = Total sleep time; AHI = Apnoea hypopnoea index. Values shown are mean $\pm$ SD

Comparison between studies evaluating the impact of CSA and CSR on mortality is complicated by differences in the baseline characteristics of the patients enrolled in each study and different criteria for diagnosis of SDB (Table 1.4). In addition, increased prescription of medical therapy of prognostic benefit (e.g. beta blockers) may also have influenced any association between CHF mortality and CSA or CSR reported in these studies.

If CSA is associated with increased mortality in CHF, treatment of CSA may be associated with improved survival. This hypothesis was the rationale behind the Canadian continuous positive airway pressure for patients with central sleep apnea and heart failure (CANPAP) trial, which aimed to study the impact of CSA on mortality in CHF (Bradley, 2001b). This randomised controlled trial ultimately found no survival benefit when CPAP was used to treat CSA (Bradley, 2005).

However, there are a number of significant methodological considerations which may influence the interpretation of the results of the CANPAP study. The premature closure of the study meant that it was underpowered to detect a significant difference in survival. In addition, CSA was not effectively treated in approximately half of the patients allocated to CPAP and the prognosis of CHF improved in all CHF patients over the course of the study, attributed to increased prescription of beta blockers and spironolactone. Post hoc analyses of the CANPAP data have suggested that in CHF patients in whom CSA was adequately treated, survival was significantly improved with a transplant free survival hazard ratio of 0.37 (95% C.I. 0.14 to 0.97) (Arzt, 2007). It is expected that the impact of CSA on survival in CHF will be addressed by further randomised controlled treatment studies which are currently underway (Bradley, 2010; Teschler, 2010).

Whilst the relationship between nocturnal CSR and mortality in CHF requires further clarification, the presence of daytime CSR or exertional periodic breathing has

consistently been shown to be associated with reduced survival (Corra, 2006; Brack, 2007; La Rovere, 2007; Poletti, 2008). The presence of daytime periodic breathing is associated with worsening CHF severity, but correction for NYHA, BNP or LVEF in these studies did not explain the association with mortality. While some authors have suggested that screening for daytime periodic breathing may be of prognostic use (La Rovere, 2007), a significant number of CHF patients with nocturnal CSR would remain undiagnosed by this method (Brack, 2007). Moreover, the combination of nocturnal CSR and daytime periodic breathing was of greater prognostic significance than the occurrence of either breathing disorder in isolation, suggesting that both daytime and nocturnal screening is necessary for complete risk assessment (Corra, 2006).

Obstructive Sleep Apnoea and Mortality in Chronic Heart Failure

There are conflicting reports on the impact of OSA on mortality in CHF. Two longitudinal observational studies with a median follow up interval of 35 and 52 months found that OSA was not associated with excess mortality in CHF patients (Roebuck, 2004; Luo, 2009). In contrast, two other non randomised studies have reported that OSA is independently associated with shorter survival in CHF. Mortality was significantly higher in CHF patients with moderate to severe OSA (AHI >15/hour) compared to those with mild OSA (AHI <15/hour) or no OSA (Wang, 2007). Survival in 14 CHF patients in whom OSA was treated with CPAP was significantly longer than in CHF patients with untreated OSA (Wang, 2007). In 88 CHF patients with moderate to severe OSA (AHI >15/hour), survival was significantly longer in patients adherent to CPAP therapy, compared to those in whom OSA was untreated (hazard ratio 2.03) or in patients who were not adherent to CPAP (hazard ratio 4.02) (Kasai, 2008). Moreover, the impact of OSA may depend on the underlying cause of CHF and it has

recently reported that OSA is independently associated with mortality in patients with ischaemic cardiomyopathy, but not in CHF due to other causes (Yumino, 2009b).

The non randomised allocation of treatment in studies evaluating the impact of CPAP therapy on mortality in CHF means that the possibility of residual confounding or selection bias must be considered when interpreting these results. For instance, it has been shown that adherence to medical therapy, even if this is a placebo, is associated with lower mortality which may be due to overall healthy behaviour (Simpson, 2006). The evidence for an association between CPAP adherence and compliance with pharmacological therapies is conflicting. One study has reported that CPAP non adherence is not associated with non adherence to other prescribed medications (Villar, 2009), but a subsequent study has suggested that non adherence to CPAP therapy is associated with lower adherence to prescribed lipid lowering medications (Platt, 2010)

In the general population, both moderate OSA (AHI >15/hour) and severe OSA (AHI >30/hour) have been reported to be an independent risk factor for mortality (Marshall, 2008; Young, 2008). Untreated severe OSA, was associated with a 5 fold increased risk of cardiovascular mortality, independent of age, sex, BMI, and other potential confounders (Young, 2008). Divergence in survival occurred after 5 years in the Busselton Health study (Marshall, 2008), and after 10 years of follow up in the Wisconsin Health Cohort Study (Young, 2008), suggesting that prolonged periods of observation or intervention may be needed to detect the adverse effects of OSA. In addition, whilst the presence or absence of subjective daytime sleepiness has been reported to influence the pathological effects of OSA in some studies (Barbe, 2001), it is noteworthy that the association of both moderate and severe OSA with mortality was seen even in the in the absence of subjective sleepiness (Marshall, 2008; Young, 2008). This would suggest that asymptomatic OSA in CHF may be of prognostic importance.

1.4.6. Treatment of Sleep-Disordered Breathing in Chronic Heart

Failure

Lifestyle Modification

The initial treatment of SDB should aim to address any contributory lifestyle factors.

The most important modifiable risk factor for OSA in adults without CHF is obesity (Young, 2002b). Reduction in body weight is associated with a decrease in AHI (Peppard, 2000a) and weight loss is an effective treatment for mild OSA (Foster, 2009; Johansson, 2009; Tuomilehto, 2009; Tuomilehto, 2010). However, the association between body mass index and OSA is weaker in CHF patients (Arzt, 2006), whilst body mass index was not predictive of CSA in CHF patients (Javaheri, 1998b; Yumino, 2009a). Thus, weight loss may be of greatest benefit in overweight CHF patients with OSA. Other lifestyle factors include avoidance of alcohol and sedative drugs which may predispose to upper airway instability through their muscle relaxant effects.

Optimisation of Chronic Heart Failure Therapy

Optimisation of heart failure treatment is an important approach to treatment of SDB and the contemporary treatment of CHF is discussed in Section 1.2.5. In non randomised uncontrolled studies, captopril and carvedilol have been shown to reduce CSA when added to CHF therapy (Walsh, 1995; Tamura, 2009).

Improvement in SDB after treatment of acute decompensated CHF was observed in one study (Dark, 1987), but a second study with incomplete follow up found no change in SDB after a mean of 24 days (Padeletti, 2009).

Cardiac resynchronisation therapy has been found to reduce the AHI in CHF patients, with greatest reduction in CSA (Gabor, 2005; Oldenburg, 2007a). Implantation of a left ventricular assist device in severe CHF has been reported to improve or abolish CSA (Vazir, 2010). Cardiac transplantation has also been reported to reduce the severity of CSA, although interestingly, 30% of patients developed OSA during follow up after transplant (Mansfield, 2003).

Therefore, optimisation of cardiac therapy to improve cardiac function appears to be of most benefit to reduce CSA, but it may be associated with little or no improvement in OSA. Whilst one study has reported that diuretic therapy can reduce OSA in CHF, this has only been investigated in patients with diastolic heart failure and it is thought that their mechanism of action is related to reduced airway oedema, rather than improvement in cardiac function (Bucca, 2007). It should be noted that many of the studies evaluating optimisation of medical therapy only showed an improvement in AHI and not complete abolition of SDB, suggesting that other therapeutic approaches, particularly for OSA, are still be required.

Continuous Positive Airway Pressure Therapy for Treatment of Obstructive Sleep Apnoea in Chronic Heart Failure

In adults without CHF, the optimum treatment for controlling OSA is continuous positive airway pressure (CPAP) therapy (Balk, 2011). In CHF patients with SDB, CPAP is effective at preventing upper airway obstruction, normalising the AHI and improving overnight oxygenation (Malone, 1991). In addition, CPAP may be associated with improvement in cardiac function (Baratz, 1992). In a non randomised uncontrolled study of 8 obese men with dilated cardiomyopathy and OSA, 4 weeks of CPAP therapy was associated with an increase in LVEF from 37 to 49%, with reversal of these improvements after stopping CPAP for 1 week (Malone, 1991). In further non

randomised (Ferrier, 2008; Johnson, 2008) and randomised controlled trials (Kaneko, 2003; Mansfield, 2004) of CHF patients with OSA, CPAP therapy was associated with increases in LVEF from 4.7 to 8.3%.

However, some studies have found that CPAP does not benefit LVEF. In a study in which CPAP was compared to bilevel positive airway pressure (PAP) for treatment of OSA in CHF, LVEF increased in the bilevel PAP group but there was no significant change in the CPAP group (Khayat, 2008). Autotitrating PAP therapy for OSA in CHF was not associated with a significant change in LVEF, although adherence in this study was low, and OSA may not have been adequately suppressed (Smith, 2007b).

CPAP is thought to exert beneficial effects on cardiac function by preventing intermittent hypoxia and cardiac afterload changes caused by OSA, which result in increased sympathetic nervous system activity (see Section 1.4.3). In CHF patients with OSA, daytime MSNA, systolic blood pressure and heart rate were significantly reduced by CPAP therapy (Usui, 2005). CPAP has also been proven to decrease left ventricular afterload, nocturnal blood pressure and overnight heart rate in CHF patients (Tkacova, 1998).

There may be a subset of CHF patients in whom CPAP is of greatest benefit; one study has reported that improvements in cardiac function with CPAP therapy for OSA were most marked in patients with a baseline LVEF >30% (Egea, 2008). Concern has also been raised that CPAP may be detrimental in some CHF patients (Baratz, 1992; Davies, 1993; Becker, 1995). Increase in intrathoracic pressure during CPAP therapy may impair cardiac filling causing a reduction in preload and a decrease in cardiac output. Studies evaluating the effects of CPAP therapy on cardiac function in CHF patients, have reported a reduction in stroke volume following acute use of CPAP, but that stroke volume recovered and LVEF significantly increased from baseline with chronic use of CPAP (Yoshinaga, 2007; Johnson, 2008). It is unclear if the impact of

CPAP on preload is the same for all CHF patients, particularly those with diastolic impairment where preload may be of greatest importance to maintain cardiac output.

In summary, there have been a number of short term studies which have shown that CPAP therapy for OSA in CHF can produce physiological benefits including reduction in nocturnal blood pressure, heart rate, sympathetic nervous system activity, and improvement in cardiac function. Whilst improvement in LVEF is a prognostic indicator (Cintron, 1993) and may be of use as a surrogate marker for clinical benefit, there is a need for adequately powered long term studies to evaluate the impact of OSA treatment on clinically relevant outcomes in CHF, including hospital admissions and mortality.

Perhaps reflecting the lack of evidence of long term benefit, there are currently no guidelines on treatment of OSA in CHF. In the general population, it is recommended that CPAP treatment should be offered to all adults with moderate to severe symptomatic OSA (National Institute for Health and Clinical Excellence, 2008). It therefore seems appropriate that stable CHF patients with symptomatic moderate to severe OSA should be offered a trial of CPAP therapy for symptom control (rather than prognostic benefit) with close monitoring to ensure no deterioration in their cardiac status. However, as discussed in Section 1.4.4, most CHF patients with SDB are not symptomatic, and the optimal treatment of OSA in these patients remains uncertain and an area for future research.

Treatment of Central Sleep Apnoea in Chronic Heart Failure

The optimum treatment for CSA in CHF is controversial. Different therapeutic options may be broadly classified according to whether they are targeted at stimulating ventilation, stabilising ventilatory control or assisting ventilation.

Respiratory Stimulants

Respiratory stimulants including theophylline (Javaheri, 1996) and acetazolamide (Javaheri, 2006a) can reduce CSA but their use is limited by potential side effects including risk of ventricular arrhythmias and metabolic acidosis respectively.

Measures to increase PaCO₂

Measures to increase PaCO₂ will increase the respiratory rate and may also stabilise ventilation by increasing CO₂ reserve. Inhaled CO₂ (Steens, 1994) and added deadspace (Khayat, 2003) have both been shown to eliminate CSA. However, these treatments may not reduce the sympathetic nervous system activation associated with SDB. It has been reported that arousal frequency was unchanged when CSA was controlled with inhaled CO₂, (Szollosi, 2004) whilst plasma catecholamine concentration increased following a night of inhaled CO₂ treatment (Andreas, 1998b).

Nocturnal Oxygen Therapy

Nocturnal oxygen therapy can stabilise ventilatory control and is effective at reducing CSA and CSR. The mechanisms by which oxygen therapy reduces ventilatory instability include a decrease in tidal volume with an increase in resting PaCO₂ and CO₂ reserve (Andreas, 1999), and by decreasing the hypercapnic ventilatory response (Andreas, 1998a). In addition, oxygen therapy is associated with a reduced

susceptibility to apnoea by prevention of hypoxia (Xie, 2006) and a decrease in PaO₂ swings during ventilatory fluctuations, due to increased body tissue stores of oxygen. The increase in lung and body oxygen stores during oxygen therapy results in a significant reduction in overnight hypoxia which may also stabilise ventilation.

In both randomised and non randomised controlled studies, nocturnal oxygen therapy has been shown to significantly decrease CSA and reduce overnight hypoxia (Hanly, 1989a; Andreas, 1996a; Staniforth, 1998b; Javaheri, 1999b). In those CHF patients in whom CSA was not completely abolished, oxygen desaturation during apnoeas and hypopnoeas was markedly reduced or prevented by nocturnal oxygen therapy (Javaheri, 1999b). Treatment of CSA with nocturnal oxygen resulted in improved sleep quality and heart failure symptoms in some (Hanly, 1989a; Andreas, 1996a) but not all studies (Staniforth, 1998b). Treatment with nocturnal oxygen therapy may be as efficacious as CPAP for treatment of CSR in CHF; when each therapy was used in random order on successive nights, there was no significant difference in the reduction in AHI achieved with either oxygen or CPAP (Krachman, 1999).

Reduction in overnight hypoxia by nocturnal oxygen has also been reported to be associated with reduction in sympathetic nervous system activity in CHF patients with CSA. In awake patients, a small decrease in MSNA was seen during voluntary central apnoea preceded by 20 minutes of supplemental nasal oxygen, compared to central apnoeas preceded by room air (Andreas, 2003). In addition, a decrease in urine noradrenaline (but not plasma catecholamines) has been reported after 4 weeks of nocturnal oxygen treatment in CHF patients with CSR (Staniforth, 1998b).

Cardiac function has also been observed to improve after 12 weeks of nocturnal oxygen therapy, with mean increase in LVEF of 5.5% (Sasayama, 2006), which was maintained when oxygen treatment was continued over 1 year (Sasayama, 2009).

It has been observed that nocturnal oxygen therapy does not suppress CSA in all CHF patients. Responders to oxygen therapy have been reported to have a significantly higher daytime PaCO₂ than non responders (39±5 mmHg versus 36±4mmHg) suggesting that baseline PaCO₂ may be important in predicting response to nocturnal oxygen therapy (Javaheri, 1999b).

Continuous Positive Airway Pressure Therapy for Treatment of Central Sleep Apnoea

Whilst CSA is primarily caused by ventilatory instability rather than upper airway collapse, CPAP has been shown to reduce or abolish central apnoeas in some CHF patients (Naughton, 1995a; Naughton, 1995b; Kohnlein, 2002). Suggested mechanisms by which CPAP may acutely prevent central apnoea include stabilisation of the upper airway; increase in functional residual capacity and improvement in PaO₂ (Krachman, 2003); a rise in PaCO₂ due to reduction in pulmonary capillary wedge pressure or increased deadspace associated CPAP (Naughton, 1994); or reduction in cardiac afterload with improvement in cardiac output and circulation time (Naughton, 1995b; Bradley, 2005; Ryan, 2010). In addition, CPAP may also exert more chronic effects to treat CSA. In CHF patients in whom CSA was unsuppressed at the initiation of CPAP, persistence with therapy was associated with a significant reduction in AHI and resolution of CSA in some patients after 12 weeks (Arzt, 2009). The mechanisms underlying the slower beneficial effect of CPAP for CSA are thought to include improvement in cardiac function, and reduction in hypercapnic ventilatory responsiveness with stabilisation of ventilatory control (Arzt, 2005).

In addition, CPAP therapy for CSA or CSR in CHF has been reported to reduce sympathetic activity, which may be of prognostic importance (Naughton, 1995a).

CPAP has been found to have a positive effect in CHF patients with CSA and CSR, by inducing reverse cardiac remodelling. In a randomised controlled study of 29 CHF patients with CSR, significant improvement in LVEF (+7.7%) was seen with CPAP treatment (Naughton, 1995b). In a study of 66 CHF patients in which 37 had no SDB and CSA occurred in 29, CPAP was randomly allocated irrespective of the presence or absence of CSA. After treatment for 3 months, there was no overall improvement in LVEF in either therapeutic group, but when stratified by the presence or absence of CSA, LVEF was significantly increased in CSA patients who used CPAP (Sin, 2000). In addition, mortality at 2.2 years was significantly reduced in CSA patients who were allocated CPAP (Sin, 2000). Improvement in LVEF in CHF patients with CSA was also seen after 3 months of CPAP use in the CANPAP randomised controlled trial, but this was not associated with a reduction in hospitalisation or death after a mean follow up of 2 years (Bradley, 2005). Although the CANPAP study did not show a mortality benefit with treatment of CSA, 43% of the patients allocated to CPAP therapy had persistent CSA (AHI >15/hour) despite treatment. In a post hoc analysis of the subgroup of CHF patients in whom CSA was adequately suppressed (AHI <15/hour) by CPAP, survival was significantly improved (Arzt, 2007). This has led some authors to suggest that CPAP therapy remains an appropriate treatment for CSA in CHF (Bradley, 2006).

Whilst CPAP treatment of CSA can reduce the AHI and improve cardiac function, it may have little impact on the impaired sleep quality associated with this form of SDB. It has been reported that despite suppression of CSA in CHF with CPAP, arousal frequency was unchanged, meaning that morbidity associated with sleep fragmentation is not addressed by this therapy (Ruttanaumpawan, 2009).

Investigation of the impact of CPAP treatment may be confounded by poor adherence. In OSA, it is recommended that CPAP is used for a minimum of 4 hours per night for symptomatic benefit (Weaver, 2007). Most long term studies of CPAP therapy for treatment of CSA in CHF have reported that nightly use is less than 4 hours (Bradley,

2006). In addition, investigation may be confounded by a heterogeneous response to CPAP. As noted above, Arzt et al, reported that 43% of CHF patients had incomplete suppression of CSA (Arzt, 2007) with CPAP, whilst Javaheri observed that 57% of CHF with CSA did not respond to CPAP (Javaheri, 2000). At present, it is not clear how to predict which CHF patients with CSA will respond to CPAP. Whilst CPAP titration has been suggested to ensure effective treatment of CSA, even those in whom AHI is not suppressed during titration may have a further clinically significant reduction in AHI after 12 weeks of continued CPAP use (Bradley, 2006; Javaheri, 2006b; Arzt, 2009).

In summary, many small studies have shown physiological benefits with CPAP therapy for CSA in CHF, and the post hoc analysis of the CANPAP data suggests it may prolong survival. However, there is no robust evidence that CPAP reduces mortality in CHF patients with CSA, and its use for treatment of CSA in CHF remains contentious (Bradley, 2006; Javaheri, 2006b). This has stimulated the investigation of other forms of assisted ventilation for treatment of CSA in CHF.

Other Forms of Positive Airway Pressure Therapy for Treatment of Central Sleep Apnoea

Bilevel PAP therapy has been reported to control CSA in a randomised controlled study of 21 CHF patients, with significant improvements in LVEF after use for 3 months (Kohnlein, 2002; Noda, 2007). However, concerns have been raised about the potential for worsening of CSA with bilevel PAP due to over ventilation, reduction in PaCO₂ and worsening ventilatory instability (Johnson, 2005). This concern has resulted in a shift towards the use of alternative forms of PAP which are able to adapt the ventilatory support to suit the patient's requirements. Much of the recent research has focussed on the use of adaptive servo ventilation for treatment of CSA or CSR in CHF.

Adaptive servo ventilation (ASV) provides variable inspiratory support, which is inversely related to the patients own effort. Ventilatory support is increased during hypopnoea and decreased during hyperpnoea, whilst back up breaths are initiated during central apnoea. The aim of this mode of ventilatory support is to overcome the oscillations in ventilation caused by fluctuations in respiratory drive, thereby reducing ventilatory instability. In addition, the variable ventilatory support offered by ASV is not associated with over ventilation and reduction in PaCO₂ (Szollosi, 2006a).

In randomised controlled trials, ASV treatment for CSA and CSR in CHF has been shown to be effective at suppressing AHI and improving overnight oxygenation (Pepperell, 2003). It is superior to both CPAP (Teschler, 2001; Philippe, 2006; Arzt, 2008) and bilevel PAP (Fietze, 2008) at controlling CSA. ASV also results in improved sleep quality compared to CPAP (Teschler, 2001) and reduction in objective daytime sleepiness (Pepperell, 2003). Observational and randomised controlled trials have reported that ASV therapy for CSA or CSR in CHF is associated with improvements in symptoms (Philippe, 2006), exercise capacity (Oldenburg, 2008), reduction in BNP concentration (Oldenburg, 2008), urine norepinephrine (Kasai, 2010) and increase in LVEF (Philippe, 2006; Oldenburg, 2008; Kasai, 2010). ASV has also been reported to be of benefit in CHF patients with preserved ejection fraction, with improvements in parameters of diastolic cardiac function (Bitter, 2009b).

It is helpful to note that many of these improvements in heart function with ASV therapy have been observed in patients on contemporary medical therapy including widespread use of beta blockers. Many of the early CPAP studies were performed before beta blockers were part of recommended therapy and it is interesting that in more recent studies in which ASV has been compared to CPAP, control patients on CPAP have experienced no change in LVEF (Philippe, 2006) or far smaller increases (+1.9%) (Kasai, 2010) than observed in earlier studies; in all cases ASV resulted in significantly greater increase in LVEF than CPAP. Moreover, patient adherence to ASV is

significantly better than that seen with CPAP (Philippe, 2006; Kasai T, 2008) further suggesting that ASV may be the treatment of choice for CSA in CHF. However, it is salutatory to recall that similar physiological improvements were noted with CPAP and the long term prognostic benefit associated with ASV remains to be evaluated. This will be addressed by two large ongoing randomised controlled trials in which over 2000 patients will be enrolled (Bradley, 2010; Teschler, 2010).

1.4.7. Summary for Section 1.4.

SDB is prevalent in CHF irrespective of the cause or severity of heart failure. CSA may occur more commonly as heart failure severity increases. Most CHF patients with SDB do not complain of symptoms of excessive daytime sleepiness and this may reduce clinical suspicion for SDB in CHF. In CHF patients in whom the cardiovascular system is already impaired, the occurrence of repeated apnoeas and hypopnoeas during sleep may impose an additional burden. Data from some observational studies has reported that SDB is associated with increased morbidity and reduced survival in CHF.

Treatment aimed at optimising cardiac function may improve CSA. However, CPAP therapy is likely to be of greatest benefit in CHF patients with symptomatic OSA. Whilst CPAP therapy for OSA is associated with short term physiological improvements, the long term benefit of CPAP therapy for asymptomatic OSA requires further research. CPAP therapy may alleviate CSA in some CHF patients and can increase LVEF. However, not all CHF patients with CSA respond to CPAP and there is no robust evidence that it is associated with improved clinical outcomes. ASV appears to be a promising PAP therapy which may be superior to CPAP for controlling CSA with greater adherence by patients.

1.5. Diagnosis of Sleep-Disordered Breathing in Chronic Heart Failure

1.5.1. Clinical Presentation of Sleep-Disordered Breathing in Chronic Heart Failure

Investigation for SDB is usually triggered following complaint about symptoms such as excessive daytime sleepiness, snoring, choking episodes at night or witnessed apnoeas. Many clinical staff will be experienced in assessing the pretest probability of OSA based on the presence or absence of these symptoms in association with pertinent findings from a physical examination. However, in patients with CHF, SDB may not be accompanied by these symptoms or they may be mistakenly attributed to their heart failure syndrome (Arzt, 2006; Hastings, 2006; Rao, 2006; Johansson, 2010).

CHF patients with SDB often have no evidence of excessive daytime sleepiness when assessed with the Epworth sleepiness scale (ESS) and subjective daytime sleepiness does not differ between CHF patients with and without SDB (Hastings, 2006). Daytime sleepiness is not influenced by the type of SDB, with no significant difference in ESS in CHF patients with OSA or CSA (Sin, 1999; Vazir, 2007).

Snoring is a common symptom which may indicate the presence of OSA in the general population. However, habitual snoring may be a poor discriminator for the presence or absence of SDB in CHF as it reported to occur in 44% of patients with SDB, compared to 50% without SDB (Javaheri, 1998b). Moreover, habitual snoring was reported by only 28% of CHF patients with CSA, suggesting that snoring is particularly insensitive for identification of CSA in CHF (Javaheri, 1998b). In addition, symptoms of SDB such as nocturnal choking or waking feeling breathless may be misdiagnosed as paroxysmal nocturnal dyspnoea as a consequence of CHF.

Self reported sleeping difficulties may also be insensitive for the detection of SDB in CHF. Many CHF patients are elderly, and increasing age is associated with an increased prevalence of subjective and objective sleep disturbance independent of any comorbidities (Unruh, 2008; Johansson, 2010). In addition, difficulty sleeping is a frequent symptom in CHF even in the absence of SDB (Redeker, 2010a). In CHF patients who do complain of daytime tiredness or fatigue, these symptoms may be attributed to their heart failure syndrome or to medical therapy such as beta blockers.

In the absence of a clear syndrome of clinical features attributable to SDB in CHF, diagnostic criteria for SDB in CHF are likely to be influenced by diagnostic or inclusion criteria used in research studies. Multicentre randomised controlled trials of treatment of SDB in CHF will help establish a benchmark for the severity of disease at which treatment may be beneficial (Bradley, 2005; Bradley, 2010; Teschler, 2010). It is notable that all these studies have used the same diagnostic criterion of an AHI >15/hour, irrespective of the presence or absence of symptoms related to SDB. Thus, diagnosis and treatment of SDB in CHF may be based solely on a metric of disease severity such as the AHI. This is in marked contrast to the diagnosis and treatment of obstructive sleep apnoea hypopnoea syndrome in adults without CHF, where symptoms are often of greater importance than the AHI (or other metric of OSA severity) in determining the need for treatment (Scottish Intercollegiate Guidelines Network, 2003; National Institute for Health and Clinical Excellence, 2008).

However, this does not mean that the presence or absence of symptoms is of no consequence in the diagnosis of SDB in CHF. They are still important in assessing any clinical response to treatment of SDB, whilst some (McArdle, 1999) but not all (Kohler, 2010) studies have suggested symptoms may be important predictors of adherence to PAP therapy in patients with OSA.

1.5.2. Use of Screening Questionnaires for Identification of Sleep-Disordered Breathing in Chronic Heart Failure

A number of questionnaires assessing symptoms, with or without anthropometric measures, have been proposed as screening tools for identification of OSA in the general population (Viner, 1991; Flemons, 1994; Deegan, 1996; Netzer, 1999; Chung, 2008). Whilst these questionnaires have high sensitivity and may be useful to exclude OSA, their low specificity (from 28 to 53%) restricts their utility to rule in OSA.

Moreover, these questionnaires have not been validated in CHF patients. It is likely that their diagnostic performance would differ significantly in this population in view of the different clinical presentation and the high prevalence of CSA. One study has evaluated a questionnaire for detection of SDB in CHF based on a combination of symptoms (nocturia, fatigue, daytime sleepiness, snoring, nocturnal sweating, witnessed apnoeas and nap) but this had a poor diagnostic accuracy (Bitter, 2011).

Therefore, a sleep study is currently required to diagnose or confidently exclude SDB in CHF.

1.5.3. Sleep Studies for Diagnosis of Sleep-Disordered Breathing

This section will review the evidence relating to the use of different types of sleep study for diagnosis of SDB. The majority of studies which have evaluated the technology used to diagnose SDB have been performed in cohorts of adults with suspected OSA, and only a small number of studies have been conducted in patients with CHF. Where there is evidence pertinent to the use of sleep studies in CHF, this will be highlighted.

Introduction

There is no anatomic or physiologic “gold standard” investigation for the diagnosis of SDB. The most comprehensive sleep study available is attended, in laboratory, nocturnal polysomnography (PSG), and this is considered the reference standard for diagnosis of SDB (Kushida, 2005). Respiratory signals recorded during PSG allow identification of the type of SDB (e.g. obstructive or central sleep apnoea), which is important both for diagnostic reasons and to determine the optimum treatment in CHF patients (Javaheri, 2007a).

A quantitative measurement of SDB severity is provided by PSG and the most frequently used indices are the number of apnoeas and hypopnoeas occurring per hour of sleep, or apnoea hypopnoea index (AHI). An alternative metric, the respiratory disturbance index (RDI) is calculated from the number of apnoeas, hypopnoeas and respiratory effort related arousals (RERA) per hour of sleep. In the absence of SDB, PSG can also provide diagnostic information to indicate the presence of other sleep related disorders which may account for any presenting symptoms.

Unfortunately, PSG is both time consuming and resource intensive to perform and interpret. Within most countries and particularly the United Kingdom, there are limited facilities for this service resulting in delays in diagnosis (Flemons, 2004; Masa Jimenez, 2007). This has stimulated the development of a number of alternative monitoring devices of varying complexity, for use in the diagnosis and management of SDB. These monitors have collectively been termed portable monitors (PM) in recognition that their compact size and digital recording technology allow ambulatory studies which can be performed outside of the sleep laboratory setting.

A review by the American Sleep Disorders Association (ASDA - now renamed the American Academy of sleep Medicine (AASM)) in 1994, classified sleep studies into 4

types according to the number and nature of the bioparameters evaluated (Table 1.5) (American Sleep Disorders Association Report, 1994).

A Type 1 sleep study requires attended, in laboratory polysomnography and is considered the reference standard for diagnosis of SDB. The monitors used in the remaining 3 types of sleep study are recognised as PM devices. Type 2 monitors record the same 7 bioparameters as type 1 sleep studies, but may be used in an unattended hospital setting, or in the patient's home. Type 3 monitors record a minimum of 4 channels including 2 for respiratory effort signals, one for ECG or heart rate and one for oxygen saturation. Type 4 monitors have 1 or 2 channels recording cardiopulmonary bioparameters.

Since the 1994 classification, a number of monitors have been developed which measure bioparameter signals not included in the original ASDA classification such as peripheral arterial tone and actigraphy. These novel monitors could not be classified using the ASDA system as they did not fulfil the criteria for either type 3 or 4 monitors. Subsequent technology reviews of PM devices have amended the original classification of sleep monitors so that type 4 monitors are now defined as those recording one or two cardiopulmonary bioparameter signals, or those recording more than two channels but not fulfilling criteria for a type 3 PM (Flemons, 2003).

Table 1.5. Classification of Sleep Studies For Diagnosis of Sleep-Disordered Breathing (modified from Ferber et al. 1994)

	Type 1 Standard Polysomnography	Type 2 Comprehensive Portable Polysomnography	Type 3 Modified Portable Sleep Apnoea Testing	Type 4 Continuous single or dual bioparameter recording
Measuring Parameters	Minimum of 7 including EEG, EOG, chin EMG, ECG, airflow, respiratory effort and oxygen saturation	Minimum of 7 including EEG, EOG, chin EMG, ECG or heart rate, airflow, respiratory effort and oxygen saturation	Minimum of 4 including ventilation (at least 2 channels of respiratory movement, or respiratory movement and airflow), heart rate (or ECG) and oxygen saturation	Minimum of one
Body position	Documented or objectively measured	May be objectively measured	May be objectively measured	Not measured
Leg movement	EMG or motion sensor desirable but optional	EMG or motion sensor desirable but optional	May be recorded	Not recorded
Personnel	In constant attendance	Not in attendance	Not in attendance	Not in attendance
Interventions	Possible	Not possible	Not possible	Not possible

EEG = Electroencephalography; EOG = Electrooculography; EMG = Electromyography; ECG = Electrocardiography

Overview of Advantages and Disadvantages of Portable Monitoring Devices

The use of PM devices has a number of limitations in comparison to NPSG. As the number of channels recorded by each monitor decreases there is a reduction in the diagnostic information it can provide, potentially leading to inconclusive results and the need for a further sleep study with more sophisticated monitoring.

Most type 3 and type 4 PM devices do not provide objective measurement of sleep duration and these monitors use 'total recording time' or 'time in bed' as the denominator for calculation of the AHI or RDI. This can lead to a systematic bias in the assessment of SDB severity by PM devices. In patients experiencing prolonged difficulty sleeping during the recording period, the lack of an accurate measurement of sleep time may lead to a significant underestimation of the AHI, potentially resulting in a false negative result.

A limitation of particular relevance to diagnosis of SDB in CHF is that many type 3 and 4 PM devices are unable to distinguish central from obstructive apnoeas. Measurement of oronasal airflow with thorax and abdominal respiratory movements are suggested as the minimum requirement for this purpose (Iber, 2007). In addition, many type 4 PM devices measure surrogate biomarkers related to the consequences of SDB (e.g. heart rate variability or peripheral artery tonometry) rather than direct measurements of breathing, and this may reduce the accuracy of these monitors.

Finally, PM devices are associated with a higher study failure rate than attended PSG (Lloberes, 2001). Use outside of a hospital setting, in many cases with the patient attaching or starting the recording device, and the lack of a technician to replace detached sensors or correct other technical problems will inevitably result in more frequent failures, requiring the sleep study to be repeated.

Against these disadvantages must be balanced the potential advantages. These principally relate to reduced financial expenditure with lower capital cost of PM devices compared to PSG, potential for reduced hospital bed days and reduction in staff time required for set up, overnight attendance and analysis (Chervin, 1999). Whilst not formally evaluated, PM devices are less cumbersome than PSG and patients may find them less intrusive to sleep. The option of a home sleep study may also be preferred by many patients.

Thus, although sleep studies using PM devices may have a number of disadvantages, so long as their limitations are borne in mind and the result interpreted in the context of the clinical scenario, they could significantly improve access to diagnosis of SDB. The potential advantages have stimulated much research to develop and evaluate the accuracy of PM devices and this will be reviewed in the following sections.

1.5.4. Evaluation of Portable Monitors for Diagnosis of Sleep-Disordered Breathing

Three different approaches have been used to evaluate the diagnostic accuracy of PM devices. One approach is to assess agreement between a numerical variable (typically the AHI) measured by a PM device and reference standard. In this situation, agreement may be quantified by statistical correlation (e.g. Pearson correlation coefficient), or by calculation of mean difference and limits of agreement with difference versus average plots (also known as Bland Altman plots). This approach can be helpful to identify a systematic bias in the AHI measured by the PM device (see also Appendix 8.7.4).

A second approach is to evaluate agreement by clinical categories of SDB. Categories are usually defined according to AHI thresholds and the most common categories are

SDB present or SDB absent. Agreement between clinical category diagnosed by PM device and reference standard may be evaluated with a 2 x 2 table to determine sensitivity, specificity, and positive and negative predictive values. The sensitivity and specificity can also be used to calculate the positive and negative likelihood ratios which indicate how much the PM test result changes the certainty of a diagnosis (see Appendix 8.7.2). A clinically useful PM to screen for SDB would need to have sufficiently high positive (>10) or low negative likelihood ratios (<0.1) that it provides a clinically meaningful change in the post test probability of the disorder (Jaeschke, 1994).

When SDB is categorised into more than two categories (e.g. none, mild, moderate, or severe according to AHI thresholds), Cohen's kappa coefficient has been used to assess agreement.

A PM that has a high concordance with PSG in classifying patients into clinically meaningful categories of SDB is likely to have a high diagnostic utility. This approach to evaluation may of greater clinical value than assessing agreement between a numerical variable such as the AHI (or RDI) recorded by the PM and PSG, as a number of methodological considerations (discussed below) will influence this metric.

In recognition that type 1 sleep studies are not a true gold standard for SDB diagnosis or for assessing diagnostic accuracy of PM devices (Trikalinos, 2007), recent research has adopted a third approach to evaluate PM devices. Instead of comparing the result from a PM device to a reference standard, this approach evaluates clinically important outcomes when PM devices are used as part of a diagnostic pathway (Kuna, 2011a). This approach is more relevant to medical practice as it evaluates the outcomes from clinical management pathways which include the use of a PM. Whilst it may take many years to determine if use of PM devices for SDB diagnosis is associated with a difference in morbidity or mortality, clinically important outcomes such as adherence to

treatment, change in symptoms and cost effectiveness have been assessed in shorter term studies (Mulgrew, 2007; Berry, 2008; Antic, 2009; Skomro, 2009; Kuna, 2011b).

Methodological Limitations in Evaluation of Portable Monitors for Diagnosis of Sleep-Disordered Breathing

The inability to score sleep inherent with type 3 and 4 sleep studies requires a different denominator for calculation of the AHI (or RDI). Instead of 'total sleep time' which is measurable by PSG, the PM must use 'time in bed' or 'total recording time'. Therefore, the denominator used by a PM is likely to be higher than PSG, particularly in people who sleep poorly during their sleep study, and this will result in a systematic bias to a lower AHI recorded by these monitors. Differences in scoring criteria between PSG and PM, particularly the ability to score hypopnoea when associated with an EEG arousal (see Section 5.1) may result in the detection of a greater number of respiratory events with PSG. Finally different airflow sensors used for PSG and PM may influence the AHI measured by each device. It is recommended that both nasal pressure monitoring and thermistor are used to measure oronasal airflow during PSG (Iber, 2007). However, many PM devices use only one airflow sensor with the potential to overestimate the number of hypopnoeas if nasal pressure monitoring is used in isolation, or underdiagnose hypopnoeas if a thermistor is used alone (see Section 2.3.1).

The reference standard for diagnosis of SDB used for comparison of PM devices is invariably a type 1 sleep study. Ideally, the type 1 sleep study should be performed synchronously with the PM sleep study, in order to allow the most objective evaluation of diagnostic accuracy. However, many studies have compared the results of PM devices and type 1 sleep studies performed on different nights, raising the possibility that diagnostic accuracy may be confounded by night to night variability in SDB (Le Bon, 2000; Bittencourt, 2001; Vazir, 2008). False positives and false negatives found in

these studies may simply reflect normal nightly variation in AHI rather than shortcomings in the technology of the PM device. Night to night variation in SDB may also be influenced by the environment (e.g. home or hospital setting) in which the sleep study is performed (Portier, 2000; Yin, 2006; Smith, 2007a) and this may be a further source of bias when results from home PM sleep studies are compared to type 1 sleep studies.

Most research with PM devices has evaluated their performance in selected populations of patients and it may be inappropriate to extrapolate results to other groups of patients. The majority of studies have evaluated PM devices for diagnosis of OSA in adults referred for investigation of suspected sleep apnoea. Inevitably, such individuals have a high pretest probability for OSA and the results of monitor validation studies in these populations may not be applicable when SDB is less prevalent. Only a small number of studies have looked at the accuracy of type 3 or 4 PM devices to screen for SDB in the general population where pretest probability will be lower (Ballester, 2000; Zou, 2006).

The majority of validation studies have excluded individuals with comorbid pulmonary or cardiac disease, and it remains unclear how accurate PM devices will be in these individuals who may develop nocturnal hypoxaemia unrelated to OSA. It is important that PM devices intended for detection of SDB in CHF are evaluated specifically for this purpose, in view of the increased prevalence of central sleep apnoea and Cheyne-Stokes respiration in this population.

In the following sections, I will look at each type of sleep study according to the ASDA classification, with a more detailed discussion of individual PM devices and the evidence to support their use in differing clinical situations.

1.5.5. Type 1 Sleep Studies for Diagnosis of Sleep-Disordered Breathing

The ASDA classification defined type 1 sleep studies as attended in laboratory polysomnography, recording a minimum of 7 bioparameters, including electroencephalogram (EEG), electrooculogram (EOG), submental electromyogram (EMG), electrocardiogram (ECG), oronasal airflow, respiratory effort and oxygen saturation (these parameters are discussed in detail in Section 2.3.1) . Body position must be recorded for type 1 sleep studies, either by the recording device or the attending technician, and it is optional but desirable to record anterior tibialis EMG. Additional bioparameters may be recorded according to the clinical indication or during research studies. These may include visual and audio recording of the patient during sleep, snoring, carbon dioxide monitoring (by end tidal or transcutaneous measurement), oesophageal pressure and flow or pressure signal from a positive airway pressure mask.

The minimum duration of overnight recording has not been systematically studied. A review of portable monitoring in 1994 advised that overnight polysomnography should be recorded for a minimum of 6 hours. Long recordings will reduce the likelihood of a false negative result by allowing observation of all sleep stages and sleeping positions, but in many OSA patients, sleep apnoea is evident with the first few hours of sleep. This has lead to the use of split night sleep studies, where diagnosis and initiation of treatment can be accomplished during a single night of polysomnography (Patel, 2007). In order to have sufficient time to both diagnose and achieve an adequate CPAP titration, the Centers for Medicare and Medicaid Services (CMS) in the United States currently accept that 2 hours of continuous sleep is adequate for the diagnosis of obstructive sleep apnoea (CMS, 2010) .

Outcome Measurements from Type 1 Sleep Studies

Polysomnography provides information on sleep architecture, including total sleep duration, sleep latency and sleep efficiency. Sleep architecture can be characterised by measurement of the duration of each sleep stage and frequency of arousals. The main outcome measure recorded from the respiratory channels is the AHI, but important information is also recorded about the frequency of oxygen desaturations and nocturnal hypoxaemia. These measurements will be discussed in detail in Section 2.3.1.

Additional respiratory outcomes include the frequency of arousals in association with oronasal airflow limitation or crescendo snoring, also known as respiratory effort related arousals (RERA) which may occur in the upper airway resistance syndrome (Guilleminault, 1993).

Measurement of nocturnal leg movements may indicate the presence of periodic limb movement syndrome.

Indications for Type 1 Sleep Studies

Type 1 polysomnography is considered the reference standard for diagnosis or exclusion of sleep related breathing disorders (Kushida, 2005). It is recommended to be used to ensure adequate treatment of SDB during titration of positive airway pressure therapy. It is also recommended in the diagnosis of narcolepsy, and periodic limb movement syndrome. Level 1 polysomnography with additional EEG derivations and video recording can also be used in the diagnosis of parasomnias and nocturnal epilepsy (Kushida, 2005).

Disadvantages of Type 1 Sleep Studies

Type 1 polysomnography is currently accepted as the reference standard for diagnosis of SDB but it can not be considered a true gold standard as false negative studies can occur (Le Bon, 2000; Bittencourt, 2001; Hutter, 2004). One study in which polysomnography was repeated on 2 consecutive nights showed that up to 25% of participants who had a negative sleep study on the first night were subsequently diagnosed with sleep apnoea after the second night (Le Bon, 2000). However, such a marked change in diagnosis has not been seen in other studies; no significant first night effect was reported in the subset of the Sleep Heart Health study who underwent repeat unattended polysomnography (type 2 sleep study) (Quan, 2002).

Whilst night to night variability in AHI may be unavoidable, it is plausible that type 1 sleep studies may contribute to this process. Inadequate length or quality of sleep in the inpatient setting, increased sleep in the supine position and change in usual habits (such as abstinence from alcohol on the night of the sleep study) may all result in an atypical night of sleep during polysomnography. In patients with mild SDB in whom the effects of night to night variability may be of greatest diagnostic consequence (Le Bon, 2000), the use of PM devices to perform sleep studies on consecutive nights may improve diagnostic accuracy (Rofail, 2010a).

1.5.6. Type 2 Sleep Studies for Diagnosis of Sleep-Disordered Breathing

The 1994 ASDA classification described type 2 sleep monitors as comprehensive portable polysomnography, recording a minimum of 7 channels. The principle difference from type 1 sleep monitoring is that the recording is unattended, and may be performed outside of the sleep laboratory. ECG recording may be replaced by pulse

rate recording and body position may not be objectively measured. Otherwise, the signals recorded are the same as those acquired by polysomnography during type 1 sleep studies, meaning that identical information should be provided about sleep and respiratory measurements.

Type 2 sleep studies were used in the Sleep Heart Health Study, the largest epidemiological study of SDB to date, in which almost 7000 community dwelling participants were screened for SDB in their own home (Quan, 1997). In a subset of the SHHS, 64 participants had an additional type 1 sleep study for validation of the home recording technique. There was no significant difference found in the median respiratory disturbance index (RDI) measured by either method (Iber, 2004).

Four other studies have compared type 2 monitors with the reference standard in participants with a high pretest probability of OSA (Orr, 1994; Mykityn, 1999; Portier, 2000; Gagnadoux, 2002). Very high sensitivity (81-100%) and specificity (93-100%) were found in three studies reporting these outcomes (Orr, 1994; Mykityn, 1999; Portier, 2000). Whilst two studies reported the 95% limits of agreement in AHI between type 1 and 2 sleep studies were as high as + 30/hour, this may have been an unavoidable consequence of the recordings being performed on different nights and in different environments (Portier, 2000; Gabor, 2005). In patients who underwent type 1 and 2 sleep studies on the same night, there was excellent agreement (Spearman correlation coefficient = 0.93) in the measurement of SDB and other sleep variables (Orr, 1994).

Limitations of Type 2 Sleep Studies

The major drawback with type 2 sleep studies is the higher rate of signal loss and study failure due to their use in an unattended setting. Poor quality recordings result in the exclusion of 5 to 20% of type 2 sleep studies, and a 4 fold higher failure rate compared

to type 1 sleep studies (Portier, 2000). In the SHHS, 91% of participants had an acceptable quality recording at first attempt, 4% required a second recording to obtain an acceptable quality study, and 5% had two or more unsuccessful recordings (Kapur, 2000).

Indications for Type 2 Sleep Studies

Based on the available evidence, a recent guideline from the AASM has recommended that type 2 monitors can be used for the diagnosis of OSA in patients with a high pretest probability, and without comorbid conditions including severe pulmonary disease, neuromuscular disease or congestive heart failure (Collop, 2007).

1.5.7. Type 3 Sleep Studies for Diagnosis of Sleep-Disordered Breathing

The ASDA classification defines type 3 sleep studies as those using a PM capable of recording a minimum of 4 channels, including ventilation or airflow (at least 2 channels of respiratory movement, or respiratory movement and airflow), heart rate or electrocardiogram and oxygen saturation signals. However, many type 3 portable monitors have additional recording channels, most commonly used to record snoring or body position signals. Table 1.6 shows the type 3 PM devices which have been developed and evaluated for diagnosis of SDB, and the signals recorded by each monitor. Whilst many of these PM devices have been discontinued following mergers between competing healthcare companies, details of the monitors are included in the table to illustrate the different parameters which may be monitored by type 3 PM devices.

Table 1.6. Recording Parameters of Type 3 Portable Monitors

PORTABLE MONITORING SYSTEM (manufacturer)	RECORDING PARAMETERS								
	Snore	Airflow	Thorax Effort	Abdomen Effort	Pulse Oximetry	ECG or HR	Body Position	Leg Movement	Other
APNOESCREEN II (Erich Jaeger GMBH & CoKg, Germany)	-	+ (TR)	+	+	+	-	+	-	Actigraphy
BITMED NGP 140 (Meditel Ingeniería Médica, Spain)	+	+ (TR)	+	+	+	HR	+	+	
EDENTRACE II* (Edentech, USA)	+	+ (TR)	+	-	+	HR	+	-	
EMBLETTA (Embla, USA)	-	+ (NP)	+	+	+	HR	+	Optional	
MERLIN* (Healthdyne Technologies, USA)	+	+ (TR)	+	+	+	HR	+	-	
MICRO-DIGITRAPPER-S* (Synectics Medical, Sweden)	+	+ (TR)	+	+	+	HR	+	-	
NIGHTWATCH* (Healthdyne Technologies, USA)	-	+ (TR)	+	+	+	-	+	+	Eye + body movement

* = No Longer Available; ECG = Electrocardiogram; HR = Heart rate; TR = Thermistor; NP = Nasal pressure measurement; + = signal recorded; - = signal not recorded

Table 1.6 (continued). Recording Parameters of Type 3 Portable Monitors

PORTABLE MONITORING SYSTEM (manufacturer)	RECORDING PARAMETERS								
	Snore	Airflow	Thorax Effort	Abdomen Effort	Pulse Oximetry	ECG or HR	Body Position	Leg Movement	Other
NOVASOM QSG (Sleep Solutions Inc, USA)	+	+ (sound)	+	-	+	HR	-	-	Voice alert if sensors dislodge
POLYG* (CNS Inc, USA)	-	+ (TR)	+	+	+	ECG	+	-	
POLY-MESAM* (MAP Germany)	+	+ (NP)	+	+	+	ECG	+	-	
SIBEL HOME 300 (Sibel S.A, Spain)	+	+ (TR)	+ (IMP)	-	+	HR	+	-	
SNAP (SNAP Laboratories International, USA)	+	+ (NP)	+	-	+	HR	Optional	Optional	
STARDUST II (Respironics Inc, USA)	+	+ (NP)	-	+	+	HR	+	-	

* = No Longer Available; ECG = Electrocardiogram; HR = Heart rate; TR = Thermistor; NP = Nasal pressure measurement; IMP = impedance; + = signal recorded; - = signal not recorded * = No Longer Available; HR = Heart rate; TR = Thermistor; NC = Nasal pressure measurement

Validation of Type 3 Portable Monitors

Validation studies of type 3 PM devices have invariably used type 1 sleep studies as the reference standard. Many of these studies have assessed the portable monitors in a laboratory setting, with the type 1 sleep study performed on a different night. The authors of these studies acknowledge the potential problems with this method of validation with different sleep patterns in the home and hospital environment (Hutter, 2004) and change in SDB severity from night to night.

Whilst type 3 PM devices may be used for home sleep studies, only a limited number have been evaluated to assess their performance outside of the sleep laboratory (White, 1995; Ancoli-Israel, 1997; Whittle, 1997; Dingli, 2003; Reichert, 2003; Quintana-Gallego, 2004; Yin, 2006). In addition, whilst type 3 sleep studies are defined as unattended studies, at least one type 3 PM device was developed with the aim of improving the quality of home studies by real time telemonitoring of signals (White, 1995). The technician had to telephone 53% of patients to correct poor signals and such contacts may also have intruded on sleep (White, 1995).

The overwhelming majority of participants included in type 3 PM device validation studies were recruited from sleep clinics or sleep laboratories. Most of these participants were male, with an elevated body mass index. Such a population will have an increased prevalence of OSA and a higher pretest probability of the disease. As the predictive value of a test is dependent on the prevalence (see Appendix 8.7.1), the results of these studies should only be applied to similar populations of patients. Only a limited number of studies have looked at the performance of level 3 sleep monitors in other circumstances, for instance screening the general population (Ballester, 2000) or to screen CHF patients for SDB (Quintana-Gallego, 2004; Smith, 2007a).

Diagnostic Accuracy of Type 3 Portable Monitors

Individual validation studies have shown considerable variation in the accuracy of type 3 PM devices to diagnose SDB. This variation may be due to true differences in the performance of each monitor, but also reflects differences in the prevalence of SDB across different studies, the setting in which the monitor is used, differences in scoring (both in definitions of respiratory events and whether automated or manual scoring is employed) and the AHI cutoff value. The results of studies to evaluate the diagnostic accuracy of type 3 PM devices are presented in Appendix Table 8.1.

Use of Type 3 Sleep Studies

Many healthcare systems have embraced the use of home portable monitoring to overcome shortages in the availability of type 1 sleep studies (Douglas, 2003). However, some professional bodies have been reluctant to endorse type 3 sleep studies citing a lack of evidence of their effectiveness (Chesson, 2003). Systematic reviews and meta analyses of studies of type 3 PM devices are difficult to perform due to the differing methodology and outcome measures but have now been completed (Flemons, 2003; Ghegan, 2006; Trikalinos, 2007).

Practice parameters issued jointly by the American Academy of Sleep Medicine, the American Thoracic Society, and the American College of Chest Physicians in 2003 initially recommended type 3 PM devices should only be used in an attended hospital setting (Chesson, 2003). A more recent meta-analysis (Ghegan, 2006) and American health care technology assessment have been more supportive towards the use of home monitoring, concluding that unattended type 3 sleep studies used in the sleep laboratory may have high positive likelihood ratios and low negative likelihood ratios for diagnosis of OSAHS (Trikalinos, 2007). In 2007, the American Academy of Sleep Medicine updated their guidelines for the use of unattended portable monitors for the

diagnosis of OSA. These recommended type 3 PM devices may be used as an alternative to type 1 sleep studies, both in the sleep laboratory and home setting, but only in patients assessed as having a high pretest probability of moderate to severe OSA (Collop, 2007). The guidelines caution that there is insufficient evidence to support the use of type 3 sleep studies for diagnosis of OSA in patients with comorbid conditions (including moderate to severe pulmonary disease, congestive heart failure and neuromuscular disease) or for general screening of asymptomatic populations.

Whilst some manufacturers include optional recording channels for EMG or EOG recording e.g. Embletta X20, (Embla, Broomfield USA), the use of type 3 PM devices for evaluation of periodic limb movement syndrome or other causes of excessive daytime somnolence has not been systematically studied.

Type 3 Sleep Studies for Diagnosis of Sleep-Disordered Breathing in Chronic Heart Failure

Two studies have evaluated the performance of type 3 sleep studies for the diagnosis of SDB in patients with CHF (Quintana-Gallego, 2004; Smith, 2007a). Quintana-Gallego et al., (2004) found a sensitivity of 68% and specificity of 95% for diagnosis of SDB (AHI >15/hour) using the Apnoescreen II portable monitor in a home setting (Quintana-Gallego, 2004).

Smith et al., (2007) used the Embletta portable monitor to perform type 3 sleep studies in 20 CHF patients (Smith, 2007a). There was a reasonable correlation between AHI measured by home Embletta and type 1 sleep study ($r = 0.54$), but a high number of false negative results occurred with a negative predictive value of 57% and positive predictive value of 83%. When the Embletta was evaluated in the sleep laboratory, whilst sensitivity or predictive values are not reported, there was a very good correlation ($r=0.94$) with the AHI recorded by synchronous type 1 sleep study (Smith,

2007a). Thus, whilst home type 3 sleep studies may appear to have a high false negative rate for diagnosis of SDB in CHF, some apparent false negative results may be due to night to night variability in SDB severity and difference in sleeping patterns in the home setting, rather than an inherent shortcoming in the technology of the type 3 PM devices.

Automated Versus Manual Scoring of Type 3 Sleep Studies

Manual scoring of the signals recorded by type 3 PM devices is superior to automated analysis (Zucconi, 1996; Calleja, 2002; Dingli, 2003). Large differences in measured outcomes can occur when the two different scoring methods are used. Moderate agreement was reported ($\text{Kappa} = 0.54$) between manually scored Embletta recordings and type 1 sleep study, but agreement was poor ($\text{Kappa} = 0.10$) when automated scoring was used for analysis (Dingli, 2003). Manual scoring was also superior to automated scoring with the Merlin portable sleep monitor (Calleja, 2002) and MicroDigitrapper-S portable monitor (Zucconi, 1996).

Advantages of Type 3 Sleep Studies

The reduction in sensors and recording equipment means that type 3 PM devices are less cumbersome than type 1 sleep studies. This may help overcome the first night effect that may occur with type 1 sleep studies (Le Bon, 2000). 29 patients who used the Edentec 4700 type 3 sleep monitor for home sleep studies on two occasions showed no evidence of first night effect (Redline, 1991). Type 1 sleep studies may promote sleeping in a supine position which will worsen positional OSA, and the percentage of time spent in the supine position was lower during type 3 sleep studies than type 1 sleep studies (Yin, 2006; Smith, 2007a). Significantly increased time spent

in bed has also been reported with home type 3 sleep studies, suggesting that the hospital environment and timetable may contribute to sleep disruption in type 1 sleep studies (Yin, 2006; Smith, 2007a).

Home monitoring with type 3 sleep monitors can reduce the time to diagnosis of OSA (Whittle, 1997). Type 3 sleep studies are a cost effective alternative to polysomnography with lower monitor purchase price, lower costs for each sleep study and reduced requirement for sleep laboratory space in comparison to type 1 sleep studies (Whittle, 1997; Golpe, 2002; Alonso Alvarez, 2008; Masa, 2011; Pietzsch, 2011). Cost savings are still seen after accounting for failed or inconclusive studies that need to be repeated or require an additional type 1 sleep study (Golpe, 2002; Alonso Alvarez, 2008). Technician time for set up of the sleep study is reduced, with time savings of 25 to 50 minutes when using the type 3 portable monitor, in comparison to type 1 sleep studies (Man, 1995; Calleja, 2002). Further cost savings can be made as overnight technician attendance is not required and time taken to analyse and score the portable monitor recording is shorter than that required for type 1 sleep studies (Dingli, 2003).

Disadvantages of type 3 sleep studies

A number of studies have shown that type 3 sleep studies may underestimate the AHI compared to type 1 sleep studies (Zucconi, 1996; Verse, 2000; Calleja, 2002). This systematic difference has been attributed to the use of 'time in bed' rather than 'total sleep time' as the denominator for the portable monitor AHI. Most studies have found that the systematic difference between AHI measurements is small when OSA is absent or mild (AHI <15/hour) but large differences between the two measurements can occur at higher values of the AHI (Ballester, 2000; Candela, 2005).

The principal disadvantage of type 3 PM devices is the greater rate of sensor loss or study failure compared to type 1 sleep studies. Reported rates of study failure range from 0 to 18% (Whittle, 1997; Alonso Alvarez, 2008). Success rate is influenced by the skill of the person attaching the sensors, with no failures reported when a technician attached the level 3 PM (either in the hospital or patient's home), but a failure rate of 10% when the sensors were attached by the patient (Parra, 1997).

Another potential drawback is the dilemma of a negative or inconclusive type 3 sleep study in a patient in whom there is a high clinical suspicion of SDB. In order to exclude a false negative result or diagnose other sleep related conditions, an additional type 1 sleep study may be required. An alternative approach may be to offer an empirical trial of CPAP if the type 3 sleep study is negative but there is a high pretest probability of OSA (Senn, 2006). Type 3 sleep studies can also be difficult to interpret in patients who report that they had little sleep on the night of the study. Without measurement of sleep duration or sleep stage, it may be impossible to exclude a false negative result due to insufficient sleep or no REM sleep on the night of the sleep study.

In many countries, type 1 sleep studies are used for OSA diagnosis and initiation of treatment in a split night protocol (Kushida, 2006). Split night protocols can not be performed with type 3 sleep studies and cost savings associated with home sleep studies will be reduced if an additional type 1 sleep study is required for CPAP titration. However, automatically titrating CPAP has been shown to be a safe and effective option for initiation of OSA treatment in many patients (Masa, 2004; Cross, 2006), suggesting that diagnosis and treatment of OSA can be accomplished without type 1 sleep studies.

Summary of Type 3 Sleep Studies

In summary, many type 3 PM devices have an acceptably high specificity and sensitivity for diagnosis of moderate to severe OSA when they are used in patients with a high pretest probability of disease and the signals are scored manually. They offer the option of a cheaper, less cumbersome investigation which can be performed in the patient's home. Whilst there is a higher rate of study failure with type 3 PM devices and false negative results can occur, in preselected patients they provide a convenient alternative to type 1 sleep studies for diagnosis of OSA.

1.5.8. Type 4 Sleep Studies for Diagnosis of Sleep-Disordered Breathing (excluding oximeters and heart rate variability monitors)

Type 4 sleep studies are defined as those using a PM recording one or two channels of cardiopulmonary signals, or those using a PM device capable of recording more than 2 channels but not fulfilling criteria for type 3 sleep studies (Flemons, 2003). In this chapter, I will review the evidence relating to oximeters and heart rate variability monitors in separate sections.

Type 4 Portable Monitors (except oximeters and heart rate variability monitors)

This category includes a diverse range of PM devices with some recording up to 6 channels of data. Table 1.7 lists the bioparameters recorded by type 4 PM devices for which validation studies have been published. It should be noted that development of these monitors is an ongoing process and currently marketed versions may include additional or alternative recording channels to the model of monitor used in the

validation study. For example, the Apnoea Risk Evaluation System (ARES, Advanced Brain Monitoring; California, USA) PM device evaluated by Westbrook et al (2005) recorded snoring, oxygen saturation, pulse rate, head position and movement (Westbrook, 2005). The current version of this device (ARES 5-Series Unicorder) includes additional recording channels to measure airflow (by nasal cannulae), and forehead venous pressure as a surrogate measure of respiratory effort.

A number of type 4 PM devices record novel bioparameters which are not measured in the traditional PSG montage. These include photoplethysmography to assess peripheral arterial tone (WatchPAT 100, Itamar Medical Ltd, Israel), actigraphy (WatchPAT 100; Apnoescreen I, Jaeger, Germany; Reggie, Camtech, Norway) and pulse transit time (Visi-3, Stowood Scientific Instruments, Oxford, UK). Peripheral arterial tone provides an indirect measurement of sympathetic nervous system activity (Grote, 2001) and when combined with measurement of changes in heart rate, it can be used as a surrogate marker of the occurrence of autonomic arousals (Pillar, 2002). Arousals or periods of wakefulness may also be associated with movement and this can be detected by actigraphy. Exclusion of epochs containing sustained movements can provide a more accurate estimate of total sleep time (Cole, 1992; Sadeh, 1994). Pulse transit time is inversely proportional to blood pressure and has been shown to provide an indirect measurement of respiratory effort for distinguishing between central and obstructive respiratory events, and for detection of autonomic arousals (Pitson, 1994; Argod, 1998; Smith, 1999).

Table 1.7. Type 4 Portable Monitor Recording Parameters (excluding oximeters and heart rate variability monitors)

PORTABLE MONITOR SYSTEM	RECORDING PARAMETERS						OUTCOME MEASURE
	Snore	Airflow	Oximetry	Heart Rate	Sleep Position	Other	
Airflow and oximetry signals only	-	+ (NP)	+	-	+		RDI
ApneaLink	-	+ (NP)	-	-	-		AHI/TIB
ApnoeScreen	-	+ (TR)	+	+	+	Wrist actimetry	RDI, ODI and % time Sao2<90%
ARES	+	-	+	+	-	Head position and movement	ARES RDI
Autoset	-	+ (NP)	-	-	-		AI, AHI and respiratory irregularity index
MESAM IV	+	-	+	+	+		HRV index, ODI and snoring index
OxiFlow	-	+ (TR)	+	-	-		RDI /TRT
Reggie	-	+ (TR)	+	-	+	Actimetry, naso-pharyngeal or oesophageal pressure	AHI/TIB
SleepStrip	-	+ (TR)	-	-	-		SleepStrip score
Somnocheck	+	+ (TR)	+	+	+		AHI (per duration of measurement)
WatchPAT 100	-	-	+	+	-	PAT, Actigraphy	PAT AHI/RDI/ ODI

NP = Nasal pressure; TR = Thermistor; RDI = Respiratory disturbance index; AHI = Apnoea hypopnoea index; TIB = Time in bed; HRV = Heart rate variability; ODI = Oxygen desaturation index; AI = Apnoea index; TRT = Total recording time; PAT = Peripheral arterial tone

Evaluation of Type 4 Sleep Studies (excluding oximeters and heart rate variability monitors)

Validation studies of type 4 PM have almost all used type 1 sleep studies as the reference standard. The sample size in each study has tended to be small and only 4 studies have enrolled more than 100 participants (Esnaola, 1996; Shochat, 2002; Bar, 2003; Westbrook, 2005). With the exception of 4 studies (Bar, 2003; Westbrook, 2005; Zou, 2006; Erman, 2007), all validation studies have evaluated the PM device exclusively in participants referred to sleep clinics, in whom the pretest probability of OSA would be higher than the general population. The WatchPAT 100 (Itamar Medical Ltd, Israel) was evaluated in a sample of hypertensive people recruited from the Skaraborg Sleep Study (Zou, 2006), whilst the ApneaLink (Resmed, USA) was used in a sample of patients recruited from a diabetes clinic (Erman, 2007). A small number of studies have included a minority of healthy volunteers in the population studied (Bar, 2003; Ayappa, 2004; Westbrook, 2005).

The majority of studies have also evaluated the type 4 portable monitor in the sleep laboratory setting with synchronous type 1 sleep study, rather than in the home setting where many are marketed for use. One study evaluated the performance of the WatchPAT 100, using synchronous home type 2 sleep studies as the reference standard (Zou, 2006). Other studies have evaluated the type 4 PM devices in the home setting but with type 1 sleep studies performed on a different night (Golpe, 2002; Pittman, 2004; Westbrook, 2005; Pang, 2006), and the problems previously described with night to night variability in SDB and differences between sleep in the home and hospital environment may have confounded the results of these studies.

The results of studies to evaluate the diagnostic accuracy of type 4 PM devices are presented in the Appendix, Table 8.2.

The wide range of correlation coefficients, sensitivity and specificity reported by studies of the diagnostic accuracy of type 4 PM devices may be explained by the diverse range of bioparameters recorded by the different devices, and the differing study methodologies. A number of type 4 PM have shown acceptable sensitivity and specificity for diagnosis of OSA when evaluated in a sleep laboratory setting, but some type 4 PM have shown poor diagnostic accuracy compared to type 1 sleep studies for diagnosis of OSA (Table 8.2).

Meta analyses and technology assessments have acknowledged that some type 4 PM perform better than others, but as a whole there is felt to be insufficient evidence to recommend type 4 sleep studies for home diagnosis of OSA (Chesson, 2003; Flemons, 2003; Trikalinos, 2007).

Type 4 Portable Monitors (excluding oximeters and heart rate variability monitors) for Diagnosis of Sleep-Disordered Breathing in Chronic Heart Failure

The Apnealink (Resmed, UK) is the only monitor in this category which has been evaluated for detection of SDB in CHF. This type 4 PM measures airflow via a nasal cannula connected to a pressure transducer, with automated analysis of this signal to score respiratory events. In 41 CHF patients, the Apnealink had a sensitivity of 87% and specificity of 95% for detection of Cheyne-Stokes respiration, with positive and negative likelihood ratios of 17 and 0.14 respectively, (Weinreich, 2009).

Advantages of Type 4 Portable Monitors (excluding oximeters and heart rate variability monitors)

As fewer channels are recorded by portable monitors, technician time required to

attach the monitor to the patients is reduced (Baltzan, 2000). Some type 4 PM such as the ARES Unicorder and SleepStrip (SLP Ltd, Israel) do not require any technician contact with the patient and can be posted to the patients' home with written instructions for use (Shochat, 2002; Westbrook, 2005). The reduced number of parameters recorded by type 4 PM means that manual scoring of the portable monitor record requires less training and technician time than that needed for PSG analysis (Esnaola, 1996; Baltzan, 2000). Type 4 sleep studies have been shown to have a lower cost, even after accounting for the proportion of inconclusive or failed studies which would require a repeat PM study or subsequent type 1 sleep study (Esnaola, 1996; Golpe, 2002).

Disadvantages of Type 4 Portable Monitors (excluding oximeters and heart rate variability monitors)

The disadvantages of type 3 PM discussed above are also relevant to type 4 sleep studies. In addition, the failure rate of type 4 sleep studies is higher than that seen with type 1 sleep studies and may be higher than that seen with type 3 sleep studies. Whilst some studies reported no failures (Rees, 1998), others found one quarter of studies were unsuccessful (Shochat, 2002). The failure rate of type 4 PM is influenced by the operator, and was almost twice as high when patients attached the Apnoescreen portable monitor in their own home, compared to hook up by a technician (Golpe, 2002).

Some type 4 PM (e.g. SleepStrip) rely exclusively on automated scoring of signals with no option for manual review of recorded data. The ability to verify automated scoring is a desirable feature, as manual scoring of type 4 PM has been shown to provide greater diagnostic agreement with type 1 sleep studies (Baltzan, 2000; Ficker, 2001).

One type 4 PM (WatchPAT) measures peripheral arterial tone (PAT) as a surrogate marker of EEG arousals, and respiratory events can be scored after detection of an arousal on the (PAT) signal if there is a corroborative increase in heart rate (Pittman, 2004). However, arousals may also occur in response to external stimuli or with periodic limb movements and the analysis algorithm used in this PM is unable to distinguish between different types of arousal. This could lead to a falsely positive elevated RDI with this device if it is used in other sleep related disorders associated with frequent arousals.

1.5.9. Pulse Oximetry for Diagnosis of Sleep-Disordered Breathing

Pulse oximeters provide a simple and readily available tool to record nocturnal oxygen saturation for diagnosis of SDB. Evaluation of their utility for the diagnosis of OSA is complicated by technical differences between oximeters, or differences in the sampling frequencies and recording algorithms used in the recording software (Farre, 1998a; Wiltshire, 2001; Zafar, 2005). Comparison of validation studies is also hampered by the variety of different outcome measures which have been used, including cumulative time below a threshold oxygen saturation (typically 90%), the frequency of desaturations below a specified threshold (typically 4%) or a measure of the variability of the oxygen saturation over the entire study, known as the delta (Δ) index. In addition to these quantitative analyses, visual analysis of the overnight oximeter trace has also been used to provide a qualitative analysis (Douglas, 1992; Series, 1993). The technical aspects relating to oximetry and calculation of outcome measures are discussed in more detail in Section 2.3.1 and 2.4.2.

Appendix Table 8.3 lists recent published studies using nocturnal oximetry for diagnosis of OSA, with the outcome measure used and sensitivity and specificity results.

To date, almost all studies have evaluated oximetry in individuals with a high pretest probability of OSA. Even in this selected population, it can be seen from Table 8.3 that a wide range of sensitivity (32-100%) and specificity (27-100%) has been reported. The diagnostic accuracy may be particularly influenced by the characteristics of the patient in whom it is used. False positive oximetry results are more likely to occur in adults with impaired lung function and lower baseline oxygen saturation (Chiner, 1999). False negative results can occur in young adults in whom overnight oxygen saturations are highest (Gries, 1996), or in lean individuals who may have lesser desaturation during SDB (Scottish Intercollegiate Guidelines Network, 2003). These limitations need to be borne in mind when interpreting the results.

Whilst it has been suggested that oximetry should only be used as a preliminary investigation or risk stratification tool prior to a more sophisticated sleep study (Olson, 1999; Gurubhagavatula, 2001), oximetry has been found to be safe and effective when used as the only confirmatory test before commencing treatment for OSA (Mulgrew, 2007; Antic, 2009). Moreover, it has also been reported that diagnosis of OSA by type 1 sleep study is no better than diagnosis by overnight pulse oximetry in helping clinicians to predict the outcome of CPAP therapy (Whitelaw, 2005).

Pulse Oximetry for Diagnosis of Sleep-Disordered Breathing in Chronic Heart Failure

Two studies have evaluated the utility of oximetry to screen for SDB in CHF patients with low ejection fraction heart failure; both measured the mean number of oxygen desaturations per hour, reported as the oxygen desaturation index (ODI). In 50 CHF patients screened with overnight pulse oximetry, an ODI >10/hour had a sensitivity of 85% and specificity of 93% for detection of SDB (AHI>15/hour) (Series, 2005).

However, this study used an oxygen desaturation criteria of >2% to calculate the ODI

which is not a commonly used measure in the United Kingdom. Staniforth et al., (1998) evaluated the diagnostic accuracy of the >4% ODI measured by overnight pulse oximetry in 41 CHF patients. At a cutoff of >15/hr, the >4% ODI was reported to have a sensitivity of 87% with specificity of 81% for detection of CSR (Staniforth, 1998a).

Oximetry is unable to reliably distinguish between OSA and CSA. Whilst visual inspection of oximetry traces has a sensitivity of 100% for detection of CSA/CSR, specificity was only 17% (Series, 2005). Thus, even if SDB is detected by oximetry, a subsequent more sophisticated sleep study will be required to determine the proportion of central and obstructive events.

Advantages of Pulse Oximetry for Diagnosis of Sleep-Disordered

Breathing

Oximetry can be used as a simple, safe and readily accessible tool for initial screening in patients in whom there is a high probability of OSA. When used as the first investigation for diagnosis of OSA, it can reduce the number of patients subsequently requiring a type 1 sleep study (Chiner, 1999). The use of oximetry as the initial diagnostic test is cheaper than performing type 1 sleep studies on all patients, even after accounting for those oximetry studies where more sophisticated sleep studies are subsequently required (Epstein, 1998). Scoring of oximetry traces, particularly visual inspection can be performed rapidly.

Disadvantages of Pulse Oximetry for Diagnosis of Sleep-Disordered

Breathing

In keeping with the low specificity found in many studies, guidelines emphasise that a normal oximetry trace may not reliably exclude SDB and should be followed by a more

detailed sleep study when there is a high clinical suspicion of OSA (Scottish Intercollegiate Guidelines Network, 2003). In addition, as discussed above, false negative results may occur most frequently in young or lean adults. False negative oximetry results will also occur in the upper airways resistance syndrome which is not associated with oxygen desaturation (Yamashiro, 1995).

1.5.10. Heart Rate Variability Analysis for Diagnosis of Sleep-Disordered Breathing

Characteristic oscillations in heart rate can accompany inspiration and expiration due to change in efferent cardiac vagal and sympathetic nerve activity occurring during the respiratory cycle. This cardiorespiratory coupling is most commonly seen in the form of respiratory sinus arrhythmia in young or athletic individuals. Marked sinus arrhythmia has been reported in patients with severe OSA (Tilkian, 1977) and it has been suggested that the cyclical heart rate pattern associated with obstructive apnoeas may be a useful screening tool for OSA (Guilleminault, 1984).

A number of different analysis techniques have been used in studies evaluating the diagnostic accuracy of heart rate variability (HRV) analysis for diagnosis of SDB (see Appendix Table 8.4). The different techniques used for HRV analysis are discussed in detail in Section 2.4.3.

Of the different methods available for analysis of heart rate variability, frequency domain analysis (also known as spectral analysis) has consistently been shown to be the most useful technique for diagnosis of OSA. The power in the very low frequency (VLF) band of the spectral density is elevated in OSA patients, and was reduced following treatment of SDB with dental devices (Shiomi, 1996). Analysis of HRV by measurement of the heart rate increment (rather than the R – R interval) may have

greater accuracy for diagnosis of SDB, particularly when VLF power is expressed as the proportion of the total power in the heart rate increment spectral density plot, or percent very low frequency increment (%VLFI) (Roche, 2002). The sensitivity of %VLFI for diagnosis of OSA (AHI >10/hour) has been reported to be 78 to 87% (Roche, 2002; Roche, 2004), and sensitivity increased to 91 % at an AHI cutoff for SDB of >15/hour (Roche, 2007). A significant reduction of %VLFI has been observed after 3 months of CPAP treatment, further suggesting that there is a causal relationship between OSA and %VLFI (Roche, 2002). However, a high false positive rate has also been reported in some studies using %VLFI to diagnose OSA, with the specificity ranging from 30 to 70% (Roche, 2007).

Alternative HRV analysis methods such as wavelet analysis may also be of value for detection of SDB, with high accuracy reported for diagnosis of OSA (Roche, 2003).

Despite positive reports of the utility of HRV analysis for diagnosis of OSA, there appears to have been limited uptake of this technique by sleep clinics. This may be due to concerns about diagnostic accuracy, and unfamiliarity of respiratory and sleep physicians with HRV analysis. One approach to address these shortcomings has been to combine analysis of HRV with measurement of an additional respiratory parameter. Heneghan et al., (2008) reported a sensitivity of 92%, negative predictive value of 88% and negative likelihood ratio of 0.08 for exclusion of OSA, using a proprietary algorithm which measured both respiratory effort (derived from the ECG signal) and HRV (Heneghan, 2008). Combined analysis of HRV and oximetry has a superior diagnostic accuracy compared to measurement of either parameter in isolation (Zamarron, 2003). An index combining oximetry and HRV was reported to have an optimum sensitivity of 70% and specificity of 96% for diagnosis of OSA (Raymond, 2003).

Measurement of oximetry with HRV may help discriminate between a rise in heart rate following an autonomic arousal associated with SDB and heart rate rises due to other

reasons; the presence of arousals without accompanying oxygen desaturation may indicate other causes of sleep fragmentation unrelated to OSA (Raymond, 2003; Krishnaswamy, 2010).

The Use of Heart Rate Variability Analysis for Diagnosis of Sleep-Disordered Breathing in Patients with Chronic Heart Failure

Characteristic changes in HRV have also been reported in CHF patients with SDB. Time domain and frequency domain measures of HRV were uniquely different in 10 minute recordings during episodes of CSA and OSA (Szollosi, 2007). Both VLF power and %VLFI have been found to be increased in CHF patients with CSR (Tateishi, 2002; Tateishi, 2003) with corresponding reductions when apnoea frequency was reduced by oxygen therapy (Tateishi, 2002).

There have been conflicting reports about the utility of HRV to detect SDB in CHF. Vazir et al., (2007) measured heart rate variability (HRV) by frequency domain analysis in 60 patients with CHF, and found that a %VLFI $\geq 2.23\%$ had a sensitivity of 85% and specificity of 65% for detection of sleep disordered breathing (AHI > 20 events/hr) (Vazir, 2006). In their study 27 of the 60 patients were excluded from HRV analysis due to arrhythmia or cardiac pacing, which may limit the applicability of this technique. More recently, Damy et al (2009) measured HRV in 84 CHF patients and found that the %VLFI was a poor predictor for the presence or absence of SDB (AHI > 15/hour), with positive and negative predictive values of only 35% and 54% respectively (Damy, 2009). However, this study used respiratory polygraphy as the reference standard for SDB diagnosis, raising the possibility that inaccuracies in measurement of AHI may have occurred. In addition, HRV may also be influenced by other conditions which disturb sleep, such as periodic limb movements (Sforza, 2007) and these would not have been detected by polygraphy.

1.5.11. Type 4 Sleep Studies as a 'Rule In' or 'Rule Out' Test for Diagnosis of Sleep-Disordered Breathing

Detection of SDB in CHF patients using type 4 PM devices may require a different approach to that used for diagnosis of OSA in the general population. Most research and guidelines emphasise that PM devices appear to be most useful as a rule in test to diagnose OSA in patients in whom there is already a high pretest probability based on clinical suspicion (Collop, 2007). As a rule in test, the diagnostic threshold for a type 4 PM may be selected to minimise the likelihood of a false positive test result. Whilst the threshold which reduces false positive results may increase the number of false negative results, this may be of less consequence in OSA as the high clinical suspicion will prompt further more detailed sleep studies even if the initial type 4 study is negative.

When used to screen for SDB in CHF, type 4 devices may be of greatest value as a rule out test (Vazir, 2006). In CHF, it may be desirable to select the threshold for a screening test which minimises false negatives, as there may be no other symptoms or signs to alert the clinician to the presence of SDB. Whilst a threshold which minimises false negatives is likely to increase the number of false positive results, this may be of less clinical consequence in CHF as any positive result with a type 4 PM is likely to need to be followed up with a more detailed sleep study to classify SDB as CSA or OSA. Thus, whilst a false positive type 4 sleep study in a CHF patient may create added demand on sleep study resources, it is unlikely to lead to instigation of inappropriate treatment which may be of no benefit or harmful (Davies, 1993; Bradley, 2005). When type 4 PM devices are used to screen for SDB in CHF, it may be safer to choose an optimal cutoff value for a positive or negative result that minimises the number of false negatives, at the expense of a higher number of false positives.

1.5.12. Summary of Type 4 Sleep Studies for Diagnosis of Sleep-Disordered Breathing

In summary, there is a diverse range of type 4 PM devices, some of which include bioparameters to provide a surrogate measure of SDB, rather than directly measuring respiration. Some monitors have a high specificity to rule in OSA in patients with a high pretest probability, but false positives can occur, particularly with type 4 PM devices which rely on measurement of autonomic arousals. Whilst type 4 sleep studies for diagnosis of OSA are not endorsed by the AASM (Collop, 2007), type 4 PM are used in many sleep centres around the world. When used in patients with a high pretest probability of OSA, they may be a useful tool to reduce diagnostic delay (Ahmed, 2007). However, negative results from type 4 sleep studies should be interpreted cautiously. The clinician should be aware of the limitations of the particular type 4 PM device being used and the result must be interpreted in the context of the patient's clinical presentation.

1.6. Scoring Respiratory Events for Diagnosis of Sleep-Disordered Breathing

The hallmark of sleep apnoea is the repetitive occurrence of apnoeas during sleep. However, less marked reductions in breathing in the form of hypopnoeas can also cause symptoms of the obstructive sleep apnoea syndrome (Gould, 1988) and contribute to morbidity associated with SDB (Punjabi, 2008). More subtle reductions in breathing which do not fulfil the criteria for hypopnoea but are associated with sleep disruption can also occur (Guilleminault, 1993), and these may be scored in the presence of RERA (Iber, 2007).

Whilst the frequency of respiratory events during sleep is the most commonly used metric to diagnose SDB, there is considerable variation in the criteria used to define these events. Use of different definitions can have a significant impact on the measured AHI, influencing diagnosis and severity of OSA (Redline, 2000). Even within the field of research into SDB in CHF, there have been a number of differing definitions used to score respiratory events (Table 1.8). The greatest controversy relates to the scoring of hypopnoeas (Moser, 1994), and this area will be reviewed in detail in Chapter 5.

Therefore, in addition to the potential technological influences of the different types of PM used to diagnose SDB, the criteria used to score respiratory events must also be borne in mind when interpreting the result from any sleep study. The impact of respiratory event scoring criteria on diagnosis and classification of SDB in CHF is investigated in the studies described in Chapter 5.

Table 1.8. Criteria Used to Score Respiratory Events for Diagnosis of Sleep-Disordered Breathing

	Toronto Group 1-3	SERVE-HF*	Cincinnati Group 4-6	Gottingen Germany 7,8	Brompton Hospital, London	AASM Sleep Scoring Manual 2007 ⁹
APNOEA	Absence of tidal volume excursion ≥ 10 s	>90% reduction in peak amplitude of nasal cannula and oral thermistor signal lasting >10s	Cessation of inspiratory airflow lasting 10 seconds or longer	Absence of oronasal airflow for >10s	Cessation of airflow >10s	Drop in thermal sensor excursion by $\geq 90\%$ for ≥ 10 s and > 90% of event duration meets amplitude criteria for apnea
Obstructive apnoea	Apnoea with out-of-phase rib cage and abdominal motion, or airflow limitation present	Apnoea with ≥ 3 consecutive obstructed breaths	Apnoea in the presence of rib cage and abdominal excursions	Apnoea with continued respiratory efforts during the breathing pauses	Apnoea with continued paradoxical chest and abdominal movement >10s	Apnoea with continued or increased inspiratory effort throughout the entire period of absent airflow
Central Apnoea	Apnoea without thoracoabdominal movements	Apnea with absent thoracoabdominal excursions.	Apnoea in the absence of rib cage and abdominal excursions	Apnoea not fulfilling criteria for obstructive	Apnoea with complete cessation of chest and abdominal movements	Apnoea with absent inspiratory effort throughout the entire period of absent airflow
Mixed apnoea	A central apnoea terminated by at least 3 obstructed inspiratory efforts (with a progressive rise in oesophageal pressure swings)	No criteria	No criteria	No criteria	Apnoea with cessation of abdomen & chest movement in first half of the apnoea (first 5 secs) followed by paradoxical movement in the latter half	Apnoea with absent inspiratory effort in the initial portion of the apnoea followed by resumption of inspiratory effort in the second portion of the event
HYPOPNOEA	$\geq 50\%$ reduction in tidal volume from baseline for ≥ 10 seconds	$\geq 30\%$ reduction in airflow and a $\geq 3\%$ desaturation for more than 10s OR $\geq 50\%$ reduction in airflow for >10s	Reduction of airflow (or thoracoabdominal excursions) lasting ≥ 10 seconds associated with $\geq 4\%$ decrease in oxyhaemoglobin saturation and/or an arousal.	Fall in oronasal airflow over 50% of baseline for >10 s	Reduction in airflow >50% for ≥ 10 s in association with a $\geq 4\%$ oxygen desaturation or EEG arousal	Drop in nasal pressure signal excursion $\geq 30\%$ for >10s and $\geq 4\%$ oxygen desaturation OR Drop in nasal pressure signal by $\geq 50\%$ for >10s with $\geq 3\%$ oxygen desaturation or associated EEG arousal

*SERVE-HF = randomised controlled trial of adaptive servoventilation for treatment of predominantly central sleep apnoea in chronic heart failure

Table 1.8. (continued) Criteria Used to Score Respiratory Events for Diagnosis of Sleep-Disordered Breathing

	Toronto Group 1-3	SERVE-HF	Cincinnati Group 4-6	Gottingen Germany 7,8	Brompton Hospital, London 9,10	AASM Sleep Scoring Manual 2007 11
Obstructive hypopnoea	Hypopnoea with out-of-phase motion of the rib cage and abdomen, or airflow limitation present	Obstructive vs central hypopnoeas determined by presence/absence of inspiratory flow limitation and/or paradoxical abdominal/thoracic movements on RIP	Hypopnoea with thoracoabdominal excursions out of phase or airflow decreased out of proportion to thoracoabdominal excursions	Hypopnoea with persistent and/or increasing effort and snoring during event with inspiratory flow limitation on nasal pressure signal	Continued but paradoxical chest and abdominal excursion	No Criteria but states classification should not be performed without quantitative assessment of ventilatory effort (Poes, calibrated RIP, diaphragm/intercostal EMG)
Central hypopnoea	Hypopnoea without airflow limitation, (as detected with measurement of nasal pressure)	See above	Hypopnoea with thoracoabdominal excursions in phase and changes in excursions proportional to changes in airflow.	Hypopnoeas not fulfilling criteria for obstructive	Hypopnoea with reduced chest and abdominal excursion	See above
CHEYNE-STOKES RESPIRATION	Crescendo-decrescendo pattern of hyperpnoea alternating with central apnoeas or hypopnoeas at a rate >10/hr of sleep	≥ 3 episodes of continuous cycles of waxing and waning tidal volumes with periods of hyperventilation separated by central apnoeas or hypopnoeas		At least three regular cycles of increasing and decreasing airflow with increasing and decreasing thoracic and abdominal efforts		≥ 3 consecutive cycles of cyclical crescendo and decrescendo change in breathing amplitude and ≥5 central apnoeas and hypopnoeas/hr OR duration of cyclical breathing ≥ 10 mins
Criteria for Central Sleep Apnoea diagnosis	AHI ≥15/hr, with >50% events determined to be central	AHI > 15/h with ≥50% central events and central AHI ≥10/h	AHI>15/hr with >50% central apnoeas	AHI>10/hr with >50% central apnoeas	AHI≥15/h and >50% apnoeas/hypopnoeas central (or mixed)	

1. Bradley, 2005; 2. Takasaki, 1989; 3. Naughton, 1993; 4. Javaheri, 1995; 5. Javaheri, 1998b; 6. Javaheri, 2006c; 7. Andreas, 1998b; 8. Schulz, 2007; 9. Vazir, 2007; 10. Hastings, 2010; 11. Iber, 2007

1.7. Description and Structure of Thesis

The primary aim of this thesis is to evaluate the diagnostic accuracy of two simple portable monitors for the detection of SDB in CHF. This thesis will also investigate other aspects relating to the diagnosis of SDB in CHF, including the characteristics of CHF patients with and without SDB, and the impact of differing respiratory event scoring criteria on the diagnosis of SDB in CHF.

To provide a background to this thesis, the Introduction has reviewed the epidemiology and consequences of SDB in CHF. The difficulty in detecting SDB in patients with CHF due to lack of clinical symptoms has been highlighted, and the evidence relating to the use of different types of sleep study for diagnosis of SDB has been reviewed. The general methods used for all the studies in this thesis will be described in Chapter 2. Additional background to the individual studies will be presented in each chapter, with further details of study protocols, data analysis and statistical analyses where necessary.

Chapter 3 will describe the recruitment of a cohort of CHF patients who underwent investigation for SDB. The characteristics of patients with SDB will be compared to those without SDB, to evaluate if there are any clinical features which may be of use to discriminate between the presence or absence of SDB in CHF.

The results of the study to investigate the diagnostic accuracy of heart rate variability analysis and overnight pulse oximetry are presented in Chapter 4. In Chapter 5, the impact of different hypopnoea scoring criteria on the diagnosis and severity of SDB in CHF will be examined, and the relevance of mixed apnoeas to classification of SDB as OSA or CSA will also be investigated.

In Chapter 6, the results of the studies presented in this thesis will be discussed, with some suggestions as to how the results, and areas of uncertainty identified during this research could be developed in the future.

CHAPTER 2: GENERAL METHODS

2.1. Regulatory Procedures

This study received ethical approval from the Brompton, Harefield and NHLI research ethics committee (COREC 07/Q0404/32). It was registered with the Research and Development departments of the Royal Brompton and Harefield NHS Trust (project reference: 2007LF001B) and Ealing Hospital NHS Trust (project reference: 08/198). All participants gave written informed consent before participation and research was conducted in accordance with Good Clinical Practice guidelines. Copies of the ethical approval letter, patient information sheet and consent form are included in Appendix Sections 8.2, 8.3 and 8.4.

2.2. Participants

Patients with a diagnosis of chronic heart failure (CHF) were recruited between November 2007 and May 2010, from specialist heart failure clinics at the Royal Brompton Hospital and a general cardiology clinic at Ealing Hospital, London. Enrolment of patients from Ealing Hospital was planned to ensure the study population was not wholly comprised of patients recruited from a tertiary care centre who may not be representative of the typical CHF patient. Inclusion criteria were chosen with the aim of recruiting a heterogeneous cohort of CHF patients with both low and preserved ejection fraction heart failure, and a range of disease severity. Participants were aged 18 to 90 years, had a diagnosis of CHF in accordance with European Society of Cardiology guidelines (Swedberg, 2005) and were clinically stable (defined as no hospitalisation, change in symptoms or cardiac medication for at least 4 weeks). Exclusion criteria were the presence of other conditions likely to inhibit sleep or the use of continuous positive airway pressure (CPAP) therapy for sleep-disordered breathing (SDB). Unlike many studies of SDB in CHF, the presence of comorbid pulmonary and

neurological diseases were not specified as exclusion criteria to ensure the results would be applicable to real world CHF patients.

Study Environment

In order to reduce travelling and facilitate recruitment, all participants were offered the choice of having the sleep study and other research investigations performed in their own home or in the research sleep department of the Royal Brompton Hospital, London. Most participants (73%) opted to complete the research in their home. Participants who chose to have polysomnography performed in hospital cited concerns about the use of the monitoring equipment at home, or lived outside of London and requested to stay overnight to coincide with prearranged outpatient clinic appointments.

2.3. Measurements

2.3.1. Sleep History

All participants underwent a structured interview conducted by the same researcher on the evening of their sleep study. Sleep opportunity was assessed by enquiry about sleeping habits and, where appropriate, shift work. Direct questions were used to assess causes of sleep disturbance including insomnia symptoms, snoring, frequency of nocturia, nocturnal breathlessness, choking or gasping, leg movements and a history of witnessed apnoeas. Sleep quality was assessed by subjective rating, the frequency of nocturnal awakenings, and by self report of feeling refreshed upon waking in the morning. Daytime symptoms related to poor sleep were elicited by questions about the occurrence of daytime tiredness, frequency and duration of naps; subjective daytime sleepiness was formally assessed with the Epworth Sleepiness Scale (Johns, 1991).

2.3.2. Details of Medical History and Other Relevant Enquiries

Details of each participant's medical history were collected, with direct questions to record the presence of diabetes, hypertension, atrial fibrillation, pacemaker implant and chronic obstructive pulmonary disease or asthma. A record was made of all prescribed and over the counter medications. Caffeine intake was assessed by questions about daily intake of tea, coffee and other caffeine containing drinks.

2.3.3. Anthropometric Measures

Neck circumference was measured on the evening before the sleep study. With the participant in a seated position, an inelastic dressmaker's tape measure was used to measure neck circumference at the level of the cricothyroid cartilage.

Waist circumference was measured at the horizontal level of the iliac crest, with the participant stood upright and the abdomen exposed (NHLBI Obesity Education Initiative, 2000). Hip circumference was then measured at the horizontal plane of the greater trochanter. Neck, waist and hip circumferences were measured to the nearest 0.5cm

Height and weight were measured on the morning after the sleep study. The participant stood upright next to a vertical surface, without footwear, and height was measured to the nearest 0.5cm with a retractable steel tape measure (Draper, Hampshire, UK).

Weight was measured with the participant dressed in their nightclothes, using a pair of portable scales (Salter, Tonbridge, UK) and recorded to the nearest 0.2 kg.

Spirometry was measured with a Vitalograph 2120 (Vitalograph, Maids Moreton, UK).

With the participant in a seated position, a relaxed vital capacity manoeuvre was performed initially, followed by a minimum of 3 forced vital capacity (FVC) manoeuvres.

Spirometry was considered satisfactory if there was <150ml difference between the two

largest values of forced vital capacity (Miller, 2005). Forced expiratory volume in 1 second (FEV1) and FVC were determined from the spirometry traces with the highest value of these variables.

2.3.4. Hospital Anxiety and Depression Scale

The hospital anxiety and depression scale (HADS) is a brief self administered questionnaire to screen for the presence of anxiety and/or depression. It comprises 7 statements about symptoms of anxiety (HADS-A) alternating with 7 statements about symptoms of depression (HADS-D) (Zigmond, 1983). The participant is asked to choose one of 4 options describing how closely each statement applies to them and each response is scored from 0 to 3 (see Appendix 8.6). The HADS is often reported with separate scores for the anxiety and depression subscales of the questionnaire, with a maximum score of 21 in each domain. Optimal sensitivity and specificity for identification of anxiety disorder or depression has been reported with a cutoff score of ≥ 8 in each respective subscale (Zigmond, 1983). A score of ≥ 11 in either subscale represents a high probability for the presence of the respective condition (Bjelland, 2002). The HADS has been validated to screen for anxiety and depression in both hospital outpatients and primary care patients (Wilkinson, 1988). It is particularly useful in patients with chronic health conditions as it is reported to be unaffected by comorbid physical illness (Zigmond, 1983).

2.3.5. Subjective Measurement of Excessive Daytime Sleepiness

Subjective daytime sleepiness was formally assessed by the Epworth Sleepiness Scale (ESS) (Johns, 1991). This is a self administered questionnaire which asks about the recent likelihood of falling asleep during the day during 8 different situations (see

Appendix 8.5). The patient is asked to rate their chance of dozing off or falling asleep as 'no chance', 'slight chance', 'moderate chance' or 'high chance', corresponding to a score from 0 to 3. The sum of all responses is the Epworth score and provides an indication of the level of daytime sleepiness, with the lowest possible score of 0, and the highest possible score being 24. A score of >10 has been reported to indicate excessive daytime sleepiness (Johns, 1993; Johns, 1997), whilst a score of ≥ 16 is indicative of a high level of daytime sleepiness (Johns, 1991).

2.3.6. Objective Measurement of Excessive Daytime Sleepiness

Daytime sleepiness was objectively assessed with the Oxford Sleep Resistance (OSLER) test (Stowood Scientific Instruments, Oxford, UK). This version of the maintenance of wakefulness test uses a behavioural response, rather than electroencephalographic monitoring, to verify the participant is awake (Bennett, 1997). The OSLER test comprises a control unit with a light emitting diode (LED) which is illuminated for 1 second every 3 seconds, and a hand held switch unit with a proximity sensor which the participant uses to acknowledge they have seen the LED flash, thereby indicating they are still awake. The test duration is 40 minutes, but it is prematurely terminated if the participant fails to acknowledge 7 consecutive illuminations of the LED. A cutoff of 7 missed illuminations corresponds to a duration of 21 seconds, which is approximately equivalent to an epoch of sleep defined by electroencephalography (Rechtschaffen, 1968). Test duration is recorded by the control unit and this provides a measurement of sleep latency. In patients with OSA, mean sleep latency is significantly shorter than control patients (10.5 minutes versus 39.8 minutes respectively) (Bennett, 1997).

In the original description by Bennet et al., (1997), the OSLER test was repeated at 2 hour intervals on 4 occasions during one day (Bennett, 1997). It has subsequently

been reported that 3 OSLER tests at 2 hour intervals had equivalent diagnostic value to 4 tests (Priest, 2001). Further analysis of OSLER error profiles has reported that a single session at 0900 has similar sensitivity to a 3 session protocol, for detection of excessive daytime sleepiness (Mazza, 2002).

In this thesis, participants were asked to complete a single OSLER test for objective measurement of daytime sleepiness. All OSLER tests were performed in the same setting as the sleep study. Participants who had their sleep study in the hospital performed the OSLER test reclining on a bed in the room in which the sleep study was performed. In those participants who were studied at home, the test was performed in the bedroom or in a quiet living room with curtains closed and a comfortable chair that the participant reported they could fall asleep in. OSLER tests were performed in the morning immediately after removal of sleep study equipment in the majority of participants but a minority of tests were performed on the evening before the sleep study to accommodate those who had commitments early the next morning (see Section 3.3.4. for comparison of the results of OSLER tests performed in the evening and morning). The test duration and number of missed illuminations was recorded for each participant.

2.4. Overnight Monitoring

Unattended nocturnal polysomnography was performed in all participants. Additional recordings of overnight oxygen saturation and electrocardiogram were performed with synchronous finger pulse oximetry and ambulatory electrocardiography.

2.4.1. Polysomnography

Polysomnography was performed in all participants with the SOMNOscreen system (SOMNOmedics GmbH, Germany). Data was recorded on an integral compact flash card which was downloaded and stored on a personal computer the morning after each sleep study.

Measurements for Monitoring and Staging of Sleep

The identification of sleep onset and determination of sleep stage is based on characteristic changes in the electroencephalogram (EEG), electrooculogram (EOG) and surface electromyogram (EMG) (Rechtschaffen, 1968).

The EEG was monitored by recording of brain electrical activity detected at the surface of the scalp with 10mm gold cup electrodes (Grass technologies, Rhode Island, USA) sited according to the International ten twenty EEG electrode system (Klem, 1999).

This system uses the nasion and inion as reference points, with EEG electrodes placed at increments of 10 or 20% along transverse and sagittal lines linking these landmarks (Figure 2.1A). The sleep EEG was recorded with electrodes placed in the C3 and C4 positions, with a common reference electrode in the Cz position (see Figure 2.1B).

Prior to application of recording electrodes, the correct positions were identified and marked with a chinagraph pencil. A mild abrasive paste (Nuprep, Weaver and Company, Colorado, USA) was used to abrade the scalp surface, followed by cleaning with an alcohol soaked swab. This step removed a superficial layer of the epidermis and oily secretions to assist electrode adhesion and to reduce the impedance between the electrode and scalp. Each gold cup electrode was filled with conducting paste (Ten20 conductive paste, Weaver and Company, Colorado, USA) and secured to the scalp with a thin layer of adhesive (Collodion, SLE Ltd., South Croydon, UK) around the perimeter of the electrode. Reference electrodes were placed over left and right mastoid processes (A1 and A2 respectively; Figure 2.1B) and a ground electrode was

placed on the centre of the forehead. The skin was prepared as previously described, but disposable self adhesive electrodes (Neuroline, Ambu Ltd., Cambridgeshire, UK) were used at these sites.

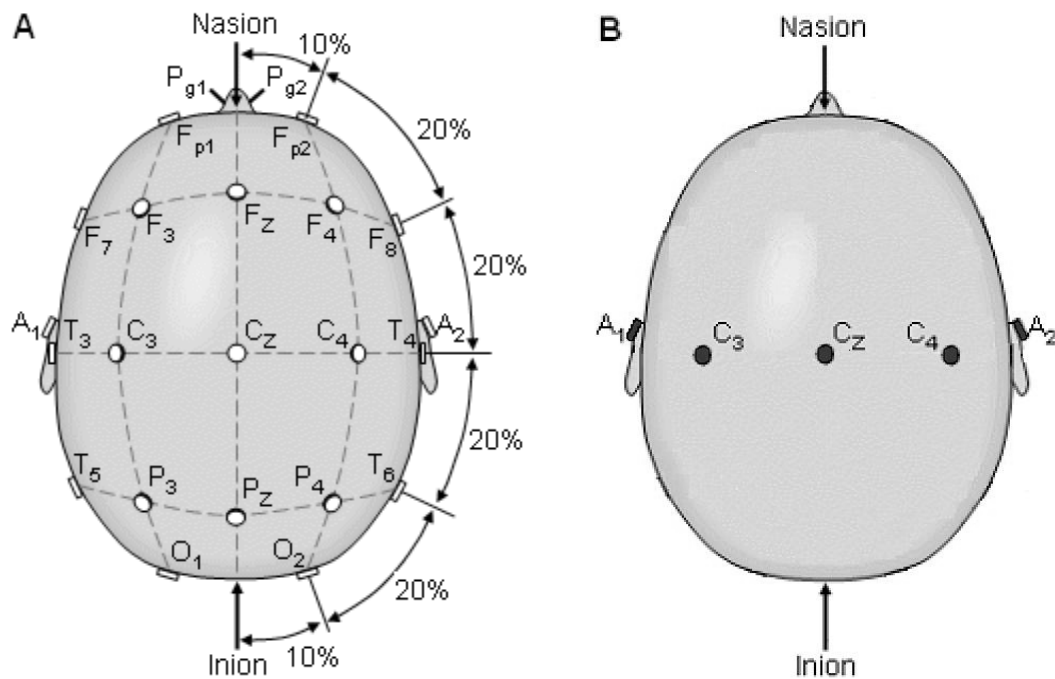


Figure 2.1. (A) Top of head view showing recording electrode positions for full electroencephalography (EEG), using the international ten twenty system. (B) Top of head view showing recording electrode positions for sleep EEG in the current study. (Figures adapted from Malmivo & Plonsey. Bioelectromagnetism: Principles and Applications of Bioelectric and Biomagnetic Fields. New York: Oxford University Press; 1995)

The EOG was recorded with self adhesive electrodes placed 1 cm lateral and superior to the right outer canthus, and 1 cm lateral and inferior to the left outer canthus. Both EOG electrodes were referenced to the A1 mastoid electrode. Asymmetric placement of the EOG electrodes permits conjugate vertical eye movements to be distinguished from electrode artefact or high voltage EEG activity. Conjugate vertical eye movements

produce opposing deflections in the right and left EOG signals, whilst artefact or EEG activity will cause in phase deflections in both EOG signals.

The EMG was recorded from surface electrodes placed in the submental area. After skin preparation, self adhesive electrodes were placed 2 cm posterior to the inferior edge of the mandible, and 2 cm to either side of the midline.

After application of all electrodes, an impedance test was performed to ensure all electrodes had a low resistance for optimal detection of brain electrical activity. An impedance of <10,000 Ohms was considered acceptable, and where this was exceeded, further conducting paste was added to gold cup electrodes, or the electrode was replaced until impedance was satisfactory.

The EEG and EOG signals were digitally sampled at a rate of 128 Hz, whilst the EMG signals were sampled at a rate of 256 Hz (Iber, 2007). The signals were processed by differential amplifiers to generate a conventional EEG montage (C3/A2; C4/A1, Right EOG/A1 and Left EOG/A1) for sleep scoring (Rechtschaffen, 1968). Conventional filter settings (High pass filter: 0.2 Hz; Low pass filter: 35 Hz) were applied to the differential amplifier output to remove signals outside of the frequencies of interest.

Respiratory Measurements During Polysomnography

Respiration was assessed by measurement of airflow, thoracic and abdominal movements, and oxygen saturation of haemoglobin.

Nasal airflow was quantified by measurement of nasal pressure. Pressure changes in the anterior nares were transmitted by a nasal cannula (Adult nasal pressure cannula, Embla, Colorado, USA) to a differential pressure transducer, referenced to atmospheric pressure. The differential pressure transducer contains a thin membrane which is deflected when a pressure difference exists between the two ports of the transducer.

The voltage output of the transducer is proportional to the deflection of the membrane and can be used to measure the pressure difference between the ports.

The measurement of nasal airflow by monitoring of nasal pressure relies on the Bernouilli principle, which states that an increase in the velocity of a gas is associated with a simultaneous decrease in the pressure exerted by the gas. Monitoring of nasal pressure provides a semi-quantitative measure of the velocity of air passing through the nostrils, due to both non laminar flow of air through the nose, and a non linear relationship between pressure and velocity. The Bernouilli equation states that the velocity of a gas is proportional to the square root of the gas pressure. Therefore, the nasal pressure signal is equivalent to the square of the airflow; for example, when nasal airflow decreases to 70% of baseline, the nasal pressure will decrease to 49%. This non linearity can result in nasal pressure overestimating apnoeas compared to other airflow sensors (Redline, 2007) as the amplitude of the nasal pressure signal will fall below <10% (a commonly used criteria to score apnoea) when nasal airflow decreases to $\leq 30\%$. It has been suggested that square root transformation of the nasal pressure signal may increase diagnostic accuracy (Farre, 2001) but, in practice, this is not performed as it is not associated with a significant improvement in detection of apnoeas or hypopnoeas (Heitman, 2002)

The waveform of the nasal pressure airflow signal can also provide useful information about the occurrence of flow limited events which do not fulfil the requirements to be scored as apnoeas and hypopnoeas (Hosselet, 1998; Hernandez, 2001). In this thesis, the presence of flattening of the nasal airflow signal was used to indicate increased upper airway resistance, and to assist in distinguishing obstructive from central hypopnoeas (see Chapter 5).

Respiratory effort was assessed by measurement of thorax and abdomen movements. For the first 48 polysomnography studies, respiratory movements were measured with

pneumatic effort belts and differential pressure transducers. However, movement or kinking of the pneumatic tube caused intermittent signal failure in some early studies. Whilst this was improved by careful taping of the pneumatic tubing, following introduction of respiratory inductance plethysmography (RIP) transducers for use with the SOMNOscreen, this equipment was adopted for measurement of respiratory effort. The thorax effort belt was placed around the upper chest and secured with two strips of elasticated adhesive tape (Mefix, Molnlycke Healthcare, Goteborg, Sweden) to prevent displacement during the night. The abdominal belt was placed around the abdomen at the level of the midpoint between the lower ribs and iliac crest, and secured in position with the adhesive tape.

The principle underlying RIP is the measurement of changes in current caused by an alteration in cross sectional area enclosed by a wire (Watson, 1988). A thin zigzagging wire is sewn into the RIP belt (Sleepsense, SLP Inc., Illinois, USA) and an alternating current passed through this wire to create a magnetic field. Changes in the cross sectional area enclosed by this wire cause changes in this magnetic field which induce a change in the frequency of the current. This change in frequency can be measured and converted into a voltage which is linearly related to the change in cross sectional area. When calibrated, RIP can be used to provide measurements of tidal volume and airflow. However, if the RIP belts become displaced after calibration, this measurement is no longer accurate (Whyte, 1991). In this thesis, uncalibrated RIP was used to provide a semi-quantitative measure of thorax and abdominal movement.

Haemoglobin oxygen saturation during polysomnography was measured by finger pulse oximetry. A finger clip oximeter probe (Nonin 8000 Softsensor, Nonin, Minnesota, USA) was initially used but sensor displacement and intermittent loss of oxygen saturation signal occurred in a small number of studies. To overcome this issue, from participant number 92, a flexible finger oximeter probe (Nonin 8000J FlexSensor) was

used which was secured for the night with an adhesive dressing (Nonin 8000JFW Fingerwrap). The oximeter accuracy was $\pm 2\%$.

Oximetry provides a measure of the average oxygen saturation of haemoglobin. It relies on the principle that the light absorption characteristics of haemoglobin are altered by the binding of oxygen. The oximeter probe contains two LEDs emitting light at red (660nm) and infrared (910nm) wavelengths, and a photodetector to measure transmitted light. When the oximeter probe is applied to a fingertip or earlobe, a constant proportion of emitted light will be absorbed by the soft tissues. The absorption of light by blood constituents can be determined from changes in the quantity of transmitted light occurring during fluctuations in arterial volume with each cardiac cycle. The ratio of red and infrared light absorbed during these pulsatile fluctuations is used to calculate the oxygen saturation of haemoglobin.

The data acquisition and processing characteristics of the oximeter can influence the oxygen saturation recorded. Higher sampling rates provide a greater temporal resolution of changes in oxygen saturation, but may be increasingly susceptible to the effects of artefact. One strategy to reduce the impact of artefact is the presentation of the average oxygen saturation over a pre-specified time interval or number of heart beats. However, if the averaging interval is set too long, this may result in small fluctuations in oxygen saturation being missed, or in underestimation of the nadir of oxygen desaturations (Farre, 1998a). In addition, the frequency with which oxygen saturation values are stored is also important in determining the resolution of the oximeter (Wiltshire, 2001).

The SOMNOscreen algorithm sampled oxygen saturation with each heart beat and used an averaging time of 4 heart beats. The measured oxygen saturation signal was updated after every heart beat.

Additional Measurements Recorded During Polysomnography

A single channel electrocardiogram (ECG) recording was performed, with ECG electrodes (Blue sensor, Ambu Ltd., Cambridgeshire, UK) placed below the right sternoclavicular joint and in the left axilla (modified lead II position). The ECG was sampled at 256 Hz.

Body position was recorded by means of an inbuilt sensor in the SOMNOscreen which can discriminate between prone, supine, left, right and upright positions.

Anterior tibialis EMG was recorded to allow measurement of limb movements. After skin preparation, two ECG electrodes were placed 3 cm apart at the junction of the upper third and lower two thirds of each anterior tibialis muscle. The limb movement sensor was attached to these electrodes and covered with a surgical bandage (Cobaan, 3M Healthcare, Berkshire, UK) to minimise the risk of accidental disconnection during the night.

Snoring was recorded with a microphone placed on the left side of the neck, lateral to the upper trachea.

After attaching all recording equipment to the participant, correct placement and function of sensors, impedance testing and calibration were checked with the signals temporarily displayed on a laptop computer. For participants undergoing home PSG, the device was programmed to automatically start and stop according to their usual bedtime. PSG studies performed in hospital were set up later in the evening and the recording was manually started by the researcher.

All participants were asked to record the time that they turned out the light after going to bed, and to record the time that they got out of bed the next morning. They were also asked to note any symptoms, and the time that they occurred. Participants undergoing

home sleep studies were provided with a telephone number to contact in the event of any problems.

2.4.2. Overnight Pulse Oximetry

In addition to oximetry performed as part of the polysomnography, all participants underwent synchronous measurement of overnight oxygen saturation with a second oximeter (Minolta Pulsox 3i, Konica Minolta, Osaka, Japan). This wrist worn oximeter was used with a flexible finger probe (Konica Minolta Probe LM-5C), which was applied to a finger adjacent to the PSG oximeter.

The recording characteristics of the Pulsox 3i include an accuracy of $\pm 2\%$, an averaging time of 5 seconds, with a measurement value stored every 5 seconds. The oximeter was manually started by the researcher after attachment of all monitoring equipment. On the morning after the study, oximetry data was downloaded and stored on a personal computer using dedicated software (Download 2001, Stowood Scientific Instruments, Oxford, UK).

2.4.3. Measurement of Heart Rate Variability

Ambulatory electrocardiography was performed synchronously with the PSG and oximetry recording, to allow subsequent measurement of heart rate variability. An Holter monitor (VistaPlus, Novacor, France) was used to record a two channel ECG, at a sampling rate of 200Hz. Recording electrodes (Blue sensor, Ambu Ltd., Cambridgeshire, UK) were placed bilaterally below the sternoclavicular joints and over the 5th intercostal space in the anterior axillary line, with a fifth electrode located over the 4th intercostal space to the right of the sternal margin. Ambulatory ECG recording was started manually after all monitoring equipment had been attached to the

participant. Data was recorded to a compact flash card which was downloaded and stored on a personal computer using proprietary software (Holtersoft, Novacor, France) the morning after each study.

2.5. Data analysis

2.5.1. Polysomnography

All polysomnography sleep studies were scored by the same experienced polysomnographer (Mr. Vitor Roldao) who was blinded to the participant identity and results of the oximetry and heart rate variability.

Scoring of Wakefulness and Sleep

The Rechtschaffen and Kales criteria were used to distinguish wakefulness from sleep (Rechtschaffen, 1968). Characteristic changes in the frequency and amplitude of the EEG signal, the occurrence of fast or slow eye movements on the EOG channel, and the amplitude of the EMG signal were used to differentiate wakefulness from sleep and to determine the stage of sleep (Table 2.1).

Arousals from sleep were scored when there was an abrupt shift in EEG frequency for ≥ 3 seconds, providing there were at least 10 seconds of preceding stable sleep. (Iber, 2007). Arousals from REM sleep were only scored when an increase in EEG frequency was associated with an increase in submental EMG lasting >1 second. Arousals were classified as respiratory event related or periodic limb movement related depending on their temporal relationship to these events. In the absence of a clear precipitating cause, arousals were classified as spontaneous.

Table 2.1. Sleep Scoring Criteria. Adapted from (Rechtschaffen, 1968)

	EEG	EOG	EMG
Stage Wake	Low voltage, mixed frequency EEG. Alpha activity (8-13Hz) may be seen (most prominent with eyes closed).	REMs and eye blinks present	Usually relatively high amplitude
Stage 1	Low voltage, mixed frequency EEG with prominence of theta rhythm (4-7Hz activity). Vertex sharp waves. No K complexes or sleep spindles	Slow eye movements, no REMs	EMG usually less than relaxed wake
Stage 2	Background relatively low voltage, mixed frequency. Sleep spindles (12-14Hz waveforms, >0.5secs) and K complexes	Occasional SEMs usually earlier in stage	Tonic activity, usually lower than stage 1
Stage 3	Delta waves (<2Hz, >75 μ V amplitude) occurring in 20-50% of an epoch. Sleep spindles may or may not be present	No eye movements	Tonic, low level
Stage 4	>50% delta waves. Sleep spindles may or may not be present	No eye movements	Tonic, low level
Stage REM	Relatively low voltage, mixed frequency. Saw tooth waves may be seen. No K complexes or sleep spindles	Episodic REMs	Lowest levels seen. Occasional bursts of phasic activity

EEG = Electroencephalogram; EOG = Electrooculogram; EMG = Electromyogram; REM = Rapid eye movement, SEM = Slow eye movement

Polysomnography Respiratory Event Scoring Criteria

Apnoea was scored when there was a $\geq 90\%$ decrease in the amplitude of the nasal airflow signal lasting ≥ 10 seconds and not thought to be due to mouth breathing.

Obstructive apnoeas were scored in the presence of ongoing respiratory effort, indicated by continued or out of phase thorax and abdominal movements. Central apnoea was scored when cessation of nasal airflow was unaccompanied by thoracic or abdominal movement. Mixed apnoea was scored when respiratory effort was absent during the initial portion of the apnoea, but 3 or more obstructed breaths occurred before resumption of airflow.

Hypopnoeas were defined as a $\geq 50\%$ (but $< 90\%$) decrease in amplitude of the nasal airflow signal in association with a $\geq 3\%$ oxygen desaturation or an EEG defined arousal from sleep. The definition of hypopnoea is inconsistent (Moser, 1994) and the criteria used to score these events can significantly influence the measured AHI and diagnosis of OSA (Tsai, 1999; Manser, 2001; Rueland, 2009). The impact of using different scoring criteria to define hypopnoea in patients with CHF is evaluated in Chapter 5.

Hypopnoeas were also categorised as central or obstructive in origin. If there was evidence of airflow obstruction during the event, indicated by the presence of snoring, flattening of the nasal pressure signal or out of phase deflections on the thorax and abdomen RIP signals, an obstructive hypopnoea was scored. In the absence of all of these findings, a central hypopnoea was scored. The gold standard for distinguishing central and obstructive respiratory events is oesophageal manometry (AASM Task Force Report, 1999) measurement but this is rarely used in clinical sleep studies and was impractical for home studies. Thus, the above criteria were selected as an alternative method of distinguishing obstructive and central events and have been used

in a number of other studies of SDB in CHF (Takasaki, 1989; Bradley, 2005; Schulz R, 2007).

The apnoea hypopnoea index (AHI) was the principal metric used for diagnosis of SDB in this thesis, and was calculated as the mean number of apnoeas and hypopnoeas per hour of sleep. SDB was defined as AHI ≥ 15 /hour (Javaheri, 1998b).

Cheyne-Stokes Respiration (CSR) was scored in the presence of ≥ 3 consecutive cycles of crescendo - decrescendo change in breathing amplitude with ≥ 5 central apnoeas/hypopnoeas per hour, or if cyclical breathing persisted for ≥ 10 minutes. CSR was quantified by the number of episodes, and the percentage of total sleep time during which it occurred (Iber, 2007).

The severity of overnight hypoxaemia was quantified by measurement of the cumulative time (minutes) and the percentage of total sleep time during which oxygen saturation was $< 90\%$.

Periodic Limb Movement Scoring

Limb movements were identified from phasic bursts of activity in the anterior tibialis EMG. Periodic limb movements (PLM) were scored in the presence of ≥ 4 consecutive limb movements separated by > 5 seconds, but < 90 seconds (Iber, 2007). As limb movements may be precipitated by respiratory events, any increase in anterior tibialis EMG activity that occurred within 0.5 seconds of a respiratory event was not scored as a limb movement. The PLM index was calculated as the mean number of PLMs per hour of sleep. Arousals were classified as PLM related when they occurred within 0.5 seconds of the start or finish of a limb movement.

2.5.2. Pulse Oximetry Data Analysis

Oximetry data recorded by the Pulsox 3i was analysed with an automated scoring program (Download 2001, Stowood Scientific Instruments, Oxford, UK). Only data recorded during the time in bed interval, determined from the participant diary, was entered into the analysis. The primary outcome measured from this data was the $\geq 3\%$ ODI, calculated as the mean number of $\geq 3\%$ oxygen desaturations per hour in bed. The mean number of $\geq 4\%$ oxygen desaturations per hour, the cumulative time and percentage of time with oxygen saturation $< 90\%$, were also recorded.

Validation of Automated Analysis of Oximetry Data

Automated scoring of the ODI was validated against the manually scored ODI in a random subset of studies. The sample size for this analysis was chosen to be adequately powered to find a minimum clinically important difference in ODI of $> 5.0/\text{hour}$, assuming a standard deviation in ODI measurements of 8.3, as has previously been reported in CHF patients (Staniforth, 1998a). Using these values, a sample size of 43 participants was determined to have power $(1 - \beta)$ of 0.8 at significance level (α) of 0.05, to find a difference in ODI $\geq 5/\text{hour}$ between the two scoring methods. A random number generator was used to select 43 participants to undergo automated and manual scoring of their oximetry data. Mean 4% ODI scored by the automated software was significantly higher than manually scored 4% ODI ($p < 0.01$ by Students paired T-test; Table 2.2) but this statistical difference was not considered to be of clinical significance.

Table 2.2. Comparison of the Automated and Manually Scored 4% Oxygen Desaturation Index from Overnight Pulse Oximetry in 43 Chronic Heart Failure Patients

	Manual Scoring	Automated scoring	Mean Difference
Mean (SD) 4% ODI	12.0 (14.4)	13.6 (14.7)	1.6 (0.8)*

*p=<0.01

The 4% ODI scored by automated analysis was highly correlated with the manually scored ODI, with a Pearson correlation coefficient of 0.99 (Figure 2.2). There was a bias towards higher ODI values with automated scoring compared to manual scoring, with a mean difference of 1.6/hour (95% confidence interval 1.4 to 1.9/hour) and limits of agreement of 0.01 to 3.1/hour (Figure 2.3).

Thus, automated scoring of the 4% ODI from oximetry recordings has an excellent correlation with manual scoring. The small bias towards higher ODI values was not considered to be of clinical importance. Moreover, automated scoring was completed in less time than manual scoring, with a median (interquartile range) reduction in analysis time of 9.0 (7.0 to 12.0) minutes.

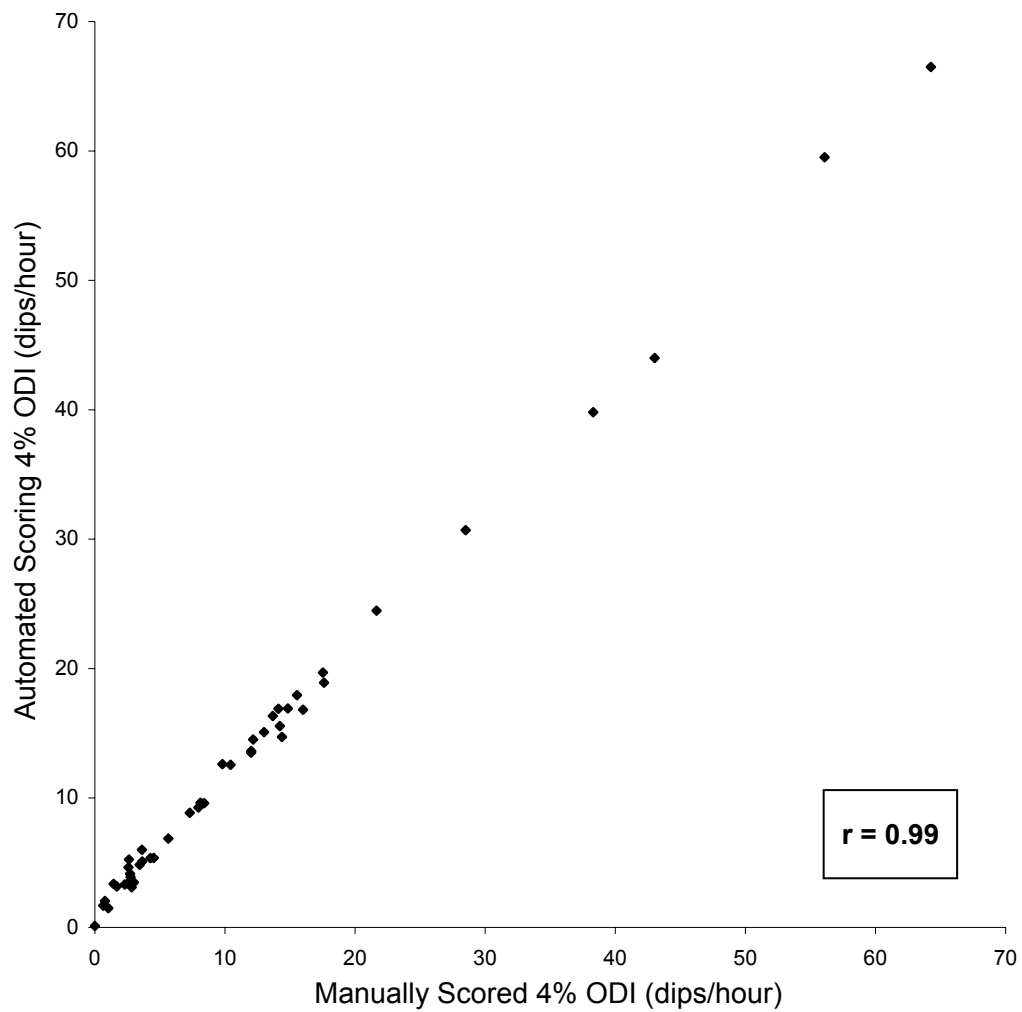


Figure 2.2. Automated versus manual scoring of overnight pulse oximetry in Chronic Heart Failure patients showing a correlation of 0.99 between the 4% ODI scored by the two methods.

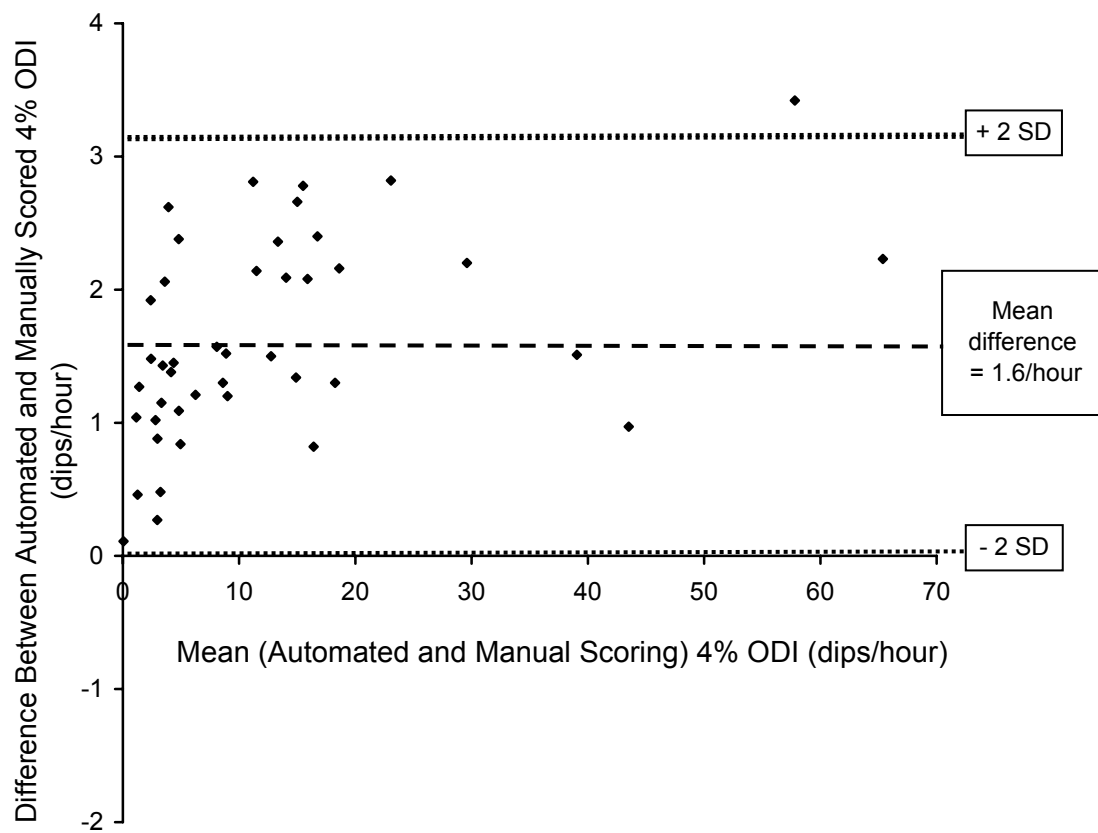


Figure 2.3. Difference versus average Plot for Automated and Manually Scored $\geq 4\%$ Oxygen Desaturation Index

2.5.3. Heart Rate Variability Analysis

Introduction

Heart rate is controlled by the balance between vagal parasympathetic and sympathetic cardiac nerve activity. In the absence of both parasympathetic or sympathetic innervation, as seen with denervation following cardiac transplant, the intrinsic rate of depolarisation of the sinoatrial node results in a resting heart rate of 100 to 120 beats per minute (Beck, 1969). Under normal resting conditions, parasympathetic activity predominates and variations in heart rate are largely mediated through alterations in vagal activity. During exercise, heart rate is predominantly regulated by sympathetic efferent activity, with reflex inhibition of vagal activity. Analysis of HRV is a non invasive technique which can be used to provide beat by beat information on the autonomic processes modulating heart rate, under normal and abnormal physiological conditions.

Heart Rate Variability Measurement

HRV analysis is most commonly performed using the series of RR intervals measured from an ECG. Computerised analysis of the ECG signal is used to identify landmarks or fiducial points in the QRS complex and the peak of the R wave is typically used for this. The RR interval can then be precisely measured as the time between two adjacent fiducial points. Temporal resolution of the RR interval measurement is dependent on the rate at which the ECG is digitally sampled and current guidelines recommend an optimum sampling frequency of 250 – 500 Hz (Task Force of the European Society of Cardiology, 1996).

The quality of HRV analysis is critically dependent on the integrity of the RR interval data. Computerised analysis can identify spurious fiducial points in the presence of low

voltage QRS, tall T waves or artefact, leading to inaccurate RR intervals. Manual editing and correction of automatically detected fiducial points is therefore recommended to ensure validity of the RR interval data (Task Force of the European Society of Cardiology, 1996). The edited interbeat intervals are also known as the normal – normal or NN intervals to highlight that only normal sinus beats are included in the HRV analysis. In long term (24 hour) recordings where manual editing is too time consuming to be practical for use in the clinical setting, alternative strategies such as analysis algorithms using RR interval template matching or interpolation are used to optimise the accuracy of fiducial point identification.

The duration of the ECG recording is of great importance when measuring HRV. As recording duration increases, HRV will increase and it is therefore essential to standardise the recording length for comparisons within and between subjects. Certain HRV parameters reflect autonomic mechanisms regulating heart rate over minutes to hours, and the ECG recording must therefore be of sufficient duration to be able to capture the physiological process under investigation (Task Force of the European Society of Cardiology, 1996). However, too much ECG data can be prohibitively time consuming to manually edit, or can lead to technical problems when performing frequency domain analysis of HRV (see Frequency Domain Methods).

Analysis Methods for Measurement of Heart Rate Variability: Time Domain Methods

Time domain measurement of HRV relies on statistical measures of dispersion to describe the variance of the RR time intervals. Increased variance of RR intervals is seen as HRV increases. The derivations of time domain parameters of HRV measured in this thesis (see Chapter 4) are shown in Table 2.3.

Table 2.3. Time Domain Parameters of Heart Rate Variability

HRV parameter	Derivation
SDNN	Standard deviation of all NN intervals
SDANN	Standard deviation of the averages of NN intervals in all 5 minute segments of the entire recording
SDNN index	Mean of the standard deviations of all NN intervals for all 5 min segments of the entire recording
RMSSD	The square root of the mean of the squares of differences between adjacent NN intervals
NN50 count	Number of pairs of adjacent NN intervals differing by more than 50 ms in the entire recording
pNN50	NN50 count divided by the total number of all NN intervals

Analysis Methods for Measurement of Heart Rate Variability: Frequency

Domain Methods

Frequency domain analysis (also known as spectral analysis) of HRV is used to identify the frequency of oscillations in the series of RR interval measurements. This is commonly accomplished by applying a discrete Fourier transform to the RR time series data to transform it into a frequency series. The frequency content of this series can be expressed as a power spectral density function (Figure 2.4) which provides information about the distribution of HRV as a function of frequency.

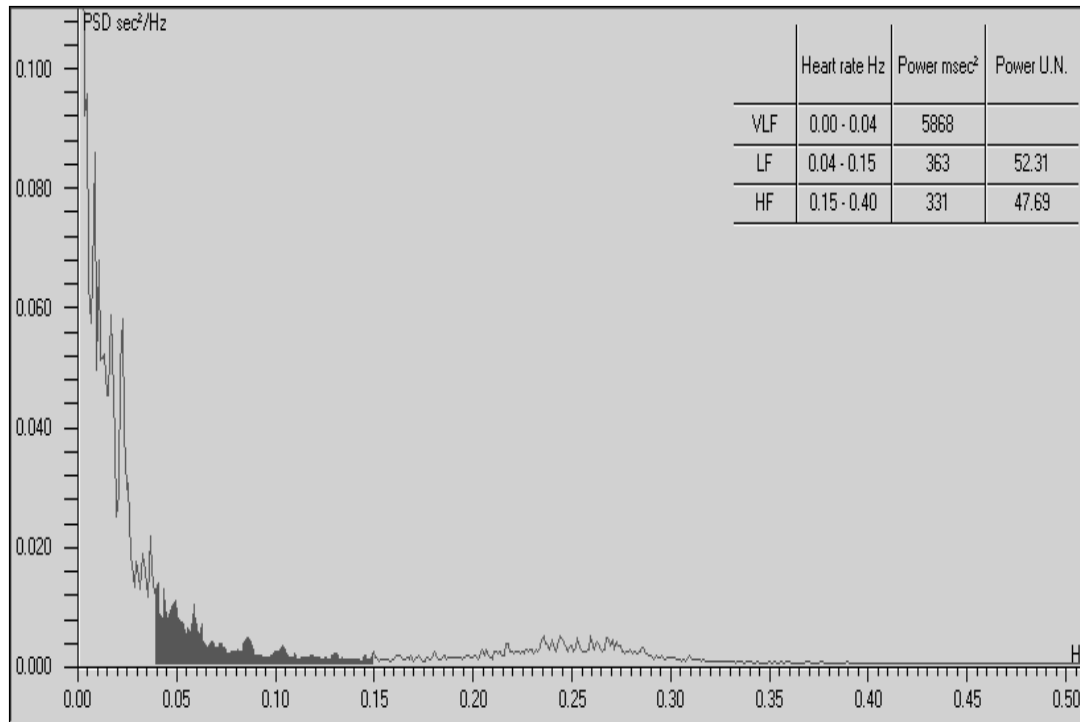


Figure 2.4. Power spectrogram of heart rate variability (HRV) in one participant, showing the frequency content within the heart rate signal recorded over 6 hours. The area beneath the line is used to calculate power of the different spectral components of HRV. (VLF = Very low frequency, LF = Low frequency, HF = High frequency)

Measurement of spectral power within a specified frequency band can be used to quantify frequency (or spectral) components of HRV. Three main frequency components are distinguished in short term recordings: Very Low Frequency (VLF) below 0.04Hz; Low Frequency (LF) 0.04 – 0.15Hz; High Frequency (HF) 0.15 – 0.4Hz. In long term recordings (24 hours), an Ultra Low Frequency (ULF) band <0.003Hz is recognised, and the frequency range for the VLF spectral component is 0.003 – 0.04Hz. As different physiological processes can cause oscillations in heart rate at characteristic frequencies, spectral analysis of HRV can be used to provide quantitative and qualitative information about these processes.

Frequency domain analysis of HRV is most effective when the frequency of heart rate oscillations is stable, also referred to as stationarity of the data series. In this situation, changes in power within frequency bands, or a shift in the peak frequency of the signal can be used to provide quantitative and qualitative information about the autonomic processes modulating heart rate. However, when there are multiple competing processes affecting heart rate, changes in the frequency distribution of HRV become more difficult to interpret or unreliable. Therefore, when HRV is used to investigate physiological mechanisms controlling heart rate, it is helpful for studies to be conducted in a controlled environment where conflicting influences can be minimised.

In addition, whilst the shortest possible recording will reduce the likelihood of non stationarity of data, the recording must remain of sufficient duration to observe the frequency of interest. Current guidelines recommend a recording duration of 10 times the wavelength of the lower limit of the spectral component being investigated (Task Force of the European Society of Cardiology, 1996). A minimum recording duration of 1 minute is recommended to assess the HF component of HRV, and approximately 2 minute recording duration when assessing the LF component. Therefore, for assessment of HRV due to respiratory sinus arrhythmia, a recording duration of approximately one minute would be sufficient, whilst assessment of HRV associated with Cheyne-Stokes respiration (with a cycle time of 60 seconds) would require a minimum recording duration of 10 minutes.

Physiological Correlates of Heart Rate Variability Parameters

The physiological processes underlying the different components of HRV have been evaluated by observation of the effects of physiological or pharmacological manipulation of the autonomic system.

High Frequency Component of Heart Rate Variability

The HF component of HRV has been determined to reflect cardiac parasympathetic activity, which is principally regulated by respiratory gating of vagal efferent activity during inspiration and expiration (Task Force of the European Society of Cardiology, 1996). Thus, the peak frequency in the HF band of HRV is determined by the frequency of respiration, and a change in respiratory rate can induce a shift in the distribution of power in this band.

Low Frequency Component of Heart Rate Variability

Interpretation of the LF component of HRV is less straightforward. Within this band are physiologic oscillations at a frequency of 0.1Hz which are thought to be associated with baroreceptor reflexes (deBoer, 1987). LF power has been observed to both increase (Montano, 1994) and decrease in situations associated with sympathetic excitation (Malliani, 1991). This paradox may be due to reduction in power of all spectral components which occurs at higher heart rates. In order to overcome this issue, it has been suggested that the power in each spectral component of HRV is expressed as a proportion of the total spectral power and reported in normalised units (n.u.) (Task Force of the European Society of Cardiology, 1996). However the interpretation of LF remains controversial with some authors suggesting it is a marker of cardiac sympathetic modulation (Montano, 1994), whilst others have reported it is influenced by both sympathetic and parasympathetic modulations (Akselrod, 1981).

Very Low Frequency Component of Heart Rate Variability

Physiological correlates of the VLF spectral component are also incompletely understood, but have been shown to be influenced by sleep apnoea (Shiomi, 1996),

Cheyne-Stokes respiration (Tateishi, 2003) and other slow biological rhythms including thermoregulation and neurohumoral changes (Taylor, 1998).

Time Domain Parameters of Heart Rate Variability

The pNN50 and RMSSD time domain parameters of HRV reflect short term changes in heart rate analogous to the HF spectral component of HRV. Thus, pNN50 and RMSSD reflect cardiac parasympathetic activity (Malik, 2004). SDNN measured from long term recordings reflects overall HRV which is dependent on the relative balance between cardiac parasympathetic and sympathetic activity; reduction in HRV due to increased cardiac sympathetic activity is associated with a decrease in SDNN, and this has been reported to be an adverse prognostic indicator in individuals with cardiac disease (Kleiger, 1987).

Certain time domain measures of HRV are strongly correlated with frequency domain measures, and may prove simpler to measure. The measures of short term variability, pNN50 and RMSSD had very strong ($r > 0.85$) correlations with HF power (Task Force of the European Society of Cardiology, 1996). SDNN, a measure of heart period variance, is a surrogate for total power when measured from the whole recording, whilst measurement of the SDNN index is strongly correlated with VLF power (Task Force of the European Society of Cardiology, 1996).

Heart Rate Variability Analysis for Diagnosis of Sleep-Disordered Breathing

The mechanism by which measurement of HRV can be used to identify sleep-disordered breathing relies on the entrainment of heart rate by respiratory rhythms (Guilleminault, 1984). The most common manifestation of cardiorespiratory coupling is

sinus arrhythmia, where the RR interval increases during expiration and decreases during inspiration. This gives rise to a characteristic oscillation in heart rate occurring at the same frequency as respiration. As quiet respiration has a frequency of 12 – 14 breaths per minute, HRV due to respiratory sinus arrhythmia has a frequency of 0.2 to 0.23 Hz, and contributes much of the power in the high frequency band of HRV.

Entrainment of heart rate also occurs with obstructive apnoeas (Guilleminault, 1984) and Cheyne-Stokes respiration (Leung, 2003) due to the associated changes in autonomic activity with these events. HRV induced by SDB has a lower frequency due to the prolonged duration of the apnoea/hyperpnoea cycle compared to normal breathing. Cheyne-Stokes respiration due to CHF typically has a cycle length of 60 seconds, giving rise to HRV at a frequency of 0.017Hz, thus increasing power within the very low frequency band. Moreover, if heart rate is entrained by any form of SDB in which the mean apnoea/hyperpnoea cycle length is ≥ 25 seconds, power in the very low frequency (<0.04 Hz) band of HRV will also be increased.

Analysis of Ambulatory ECG and Measurement of Heart Rate Variability

Anonymised ambulatory ECG recordings were scored in random order to ensure blinding to the identity of the participant and the result of the polysomnography. All participants with a paced cardiac rhythm for $>10\%$ of all QRS complexes, atrial fibrillation or $>10\%$ ectopic beats were excluded from HRV analysis.

Analysis of HRV was performed twice, using two different time intervals. The initial analysis was performed on a 6 hour recording from 0000 to 0600, as has been reported in previous studies using HRV to detect SDB (Vazir, 2006; Roche, 2007; Damy, 2009). A second analysis was performed on the time in bed interval, determined from the participant diary, to see if this would improve diagnostic accuracy.

An initial automated analysis of the ECG was performed with dedicated software (Holtersoft, Novacor, France). As the accuracy of HRV analysis is dependent on correct identification of RR intervals between normal QRS complexes, manual verification of automated scoring was performed in all participants with correction of misidentified ectopic beats and artefacts. Time spent on manual editing was limited to 20 minutes to ensure that the use of HRV analysis for diagnosis of SDB would not be too time consuming to be of value in the clinical setting.

After completion of manual editing, time domain and frequency domain parameters of HRV were measured. In addition to analysis of HRV by measurement of the RR interval, the power spectral density of the heart rate increment (defined as the backward difference between RR intervals of consecutive cardiac cycles) was also determined for measurement of the percent very low frequency increment (%VLFI); this component of HRV represents the very low frequency power (0.01 – 0.05Hz) of the heart rate increment power spectrum expressed as the percentage of total power (0.01 – 0.5Hz). (Figure 2.5). The %VLFI has been reported to have a greater diagnostic accuracy than other measures of HRV for detection of OSA ; at an optimum %VLFI cutoff of $\geq 2.4\%$, sensitivity for OSA was 86.5% with specificity of 52% (Roche F, 2002).

Figure 2.5A

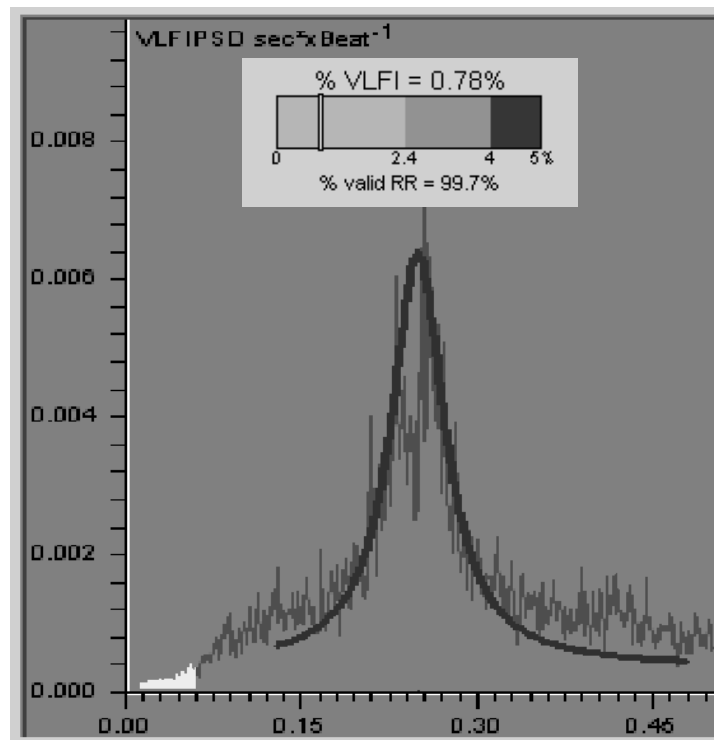


Figure 2.5B

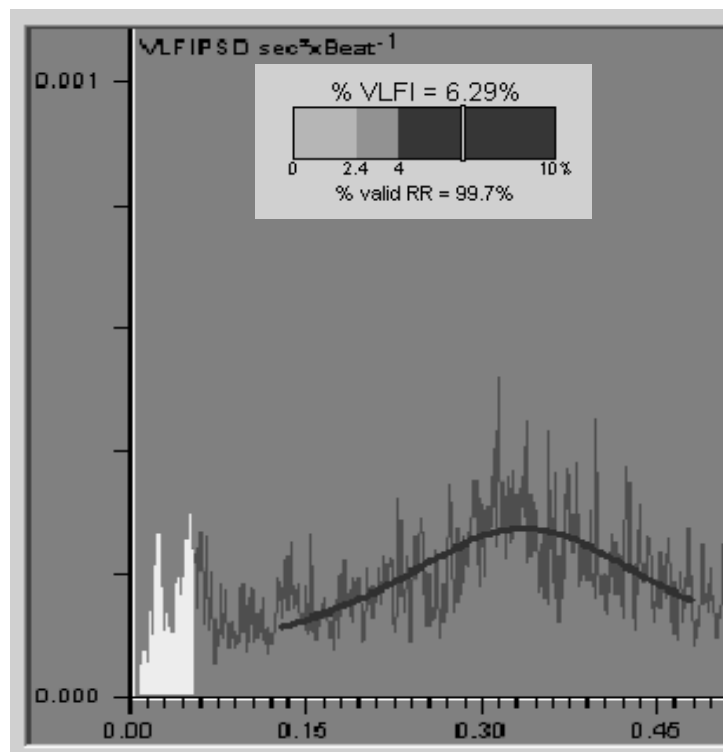


Figure 2.5. Heart rate increment power spectrograms in CHF patients. The very low frequency increment (VLFI) power is highlighted in white. In Figure A, the VLFI comprises a small proportion of the total heart rate increment spectral power and %VLFI is 0.78%. In Figure B, the VLFI comprises a greater proportion of the total heart rate increment power and %VLFI is 6.29%

2.6. Classification and Assessment of Heart Failure Severity

2.6.1. Classification as Low or Normal Ejection Fraction Heart

Failure

Participants were classified as having CHF due to systolic dysfunction (low ejection fraction), or heart failure with preserved ejection fraction (HFPEF). Classification was based on clinical and echocardiographic features at the time of initial diagnosis of CHF, in order to avoid misclassifying those participants in whom their left ventricle ejection fraction had improved to normal values following treatment.

2.6.2. Assessment of Heart Failure Severity

Severity of heart failure can be assessed in a number of ways, including subjective measures based on symptoms, or objective measurement of functional capacity or cardiac function. Both subjective and objective measures can provide important prognostic information, and are helpful to assess response to heart failure treatment.

Symptom based questionnaires and scores are relatively quick to apply and non invasive but they can have poor reproducibility (Raphael, 2007). Echocardiographic, magnetic resonance or radionuclide imaging can be used to objectively measure cardiac function, but these measurements may correlate poorly with symptoms or functional capacity (Witte, 2004). Moreover, commonly used measures of cardiac function such as the ejection fraction may be poorly reproducible when measured by different imaging methods (Bellenger, 2000) or prone to interobserver variability (Otterstad, 1997). In addition, measurement of left ventricular ejection fraction is not helpful for assessment of heart failure severity in patients with HFPEF. Therefore, in

the absence of a clear gold standard to assess heart failure severity, a combination of subjective and objective measures was used in this thesis.

2.6.3. New York Heart Association Classification

The New York Heart Association (NYHA) classification is based upon symptoms and exercise capacity reported by the patient (Table 2.4) (The Criteria Committee of the New York Heart Association, 1994). It is a commonly used measure to assess functional capacity in CHF and the NYHA class has been shown to be a prognostic indicator (Bettencourt, 2000).

Table 2.4. New York Heart Association Classification of Heart Failure

Class I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnoea.
Class II	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnoea.
Class III	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity results in fatigue, palpitation, or dyspnoea.
Class IV	Unable to carry on any physical activity without discomfort. Symptoms at rest. If any physical activity is undertaken, discomfort is increased.

2.6.4. B-Type Natriuretic Peptide Assay

B-type natriuretic peptide (BNP) is a cardiac neurohormone secreted by the ventricles in response to volume expansion and pressure overload. Its biological actions include vasodilatation, natriuresis and diuresis. These effects are mediated through increase in

glomerular filtration, reduction in renin release and suppression of sympathetic vascular tone, resulting in reduction in blood pressure, cardiac preload and afterload. BNP measurement is of diagnostic (Cowie, 1997; McDonagh, 1998) and prognostic value in CHF (McDonagh, 2001), with elevated concentrations in both systolic and diastolic heart failure (Krishnaswamy, 2001). BNP concentrations correlate well with heart failure severity measured by exercise capacity and echocardiographic measurement (Clerico, 1998; Kruger, 2002; Sakurai, 2003; Williams, 2004) and can be used to assess response to treatment (Stanek, 2001).

BNP was assayed by a two-site immunoenzymatic assay (Triage BNP, Biosite Inc, California, USA) by the biochemistry department of the Royal Brompton Hospital. A blood sample for BNP assay was collected from each participant on the morning after their sleep study, using a 3.5ml container with EDTA preservative (EDTA Vacutainer, Becton, Dickinson and Company, New Jersey, USA). After collection, the sample was centrifuged at 3000 rpm for 10 minutes at room temperature, to separate plasma from other blood constituents. Aliquots of 1.0 ml plasma were stored in cryogenic vials (Cryotube 1.0ml, Nunc, Thermo Fisher Scientific, Denmark) at -80 degrees centigrade, until assayed for BNP.

2.6.5. Echocardiographic Measurement of Heart Function

Transthoracic echocardiography is part of the routine clinical assessment of patients with CHF and is used to assess cardiac anatomy and function (National Institute for Clinical Excellence, 2003). Two dimensional cardiac images are generated by the reflection of ultrasound waves from the different cardiac structures and this can be used to measure cardiac chamber size and function. Systolic function is commonly determined by measurement of left ventricular ejection fraction, which has important prognostic implications (Curtis, 2003). However, CHF may occur in the presence of a

normal ejection fraction, particularly in females or in older patients (Owan, 2006). Doppler echocardiography can provide further information about cardiac function by determining quantity and direction of blood flow across the cardiac valves, for diagnosis of diastolic or valvular dysfunction.

The echocardiography measurements required for this study were obtained by re-analysis of echocardiograms performed as part of participants routine clinical care. All echocardiograms were analysed by an experienced echocardiography technician, Mr. Manuel de Villa, who was unaware of the SDB status of each participant.

Measurements of left ventricular function included systolic and diastolic dimensions, and ejection fraction. Where possible, Simpsons biplane method was used to assess global left ventricular ejection fraction. In participants in whom echocardiography images were not of sufficient quality, LVEF was calculated using the left ventricle end systolic and diastolic measurements, although this method is less accurate in the presence of regional wall motion abnormalities. Left atrial diameter and area were measured, and diastolic function was quantified by measurement of the E and A velocities of blood flow across the mitral valve with calculation of the E/A ratio. Right ventricular size was assessed by measurement of maximal RV inlet diameter at end diastole, whilst right ventricle function was evaluated by measurement of tricuspid annular plane systolic excursion (TAPSE).

2.7. Statistical Analysis

Statistical analysis was performed with a commercial computer program (SPSS V.16.0, IBM, Illinois, USA). Full details of the statistical methods used will be provided in each chapter. A description of the statistical methods used to assess the accuracy of a diagnostic test is provided in Appendix 8.7.

**CHAPTER 3: DESCRIPTION OF STUDY
RECRUITMENT AND COMPARISON OF
CHARACTERISTICS BETWEEN CHRONIC HEART
FAILURE PATIENTS WITH AND WITHOUT SLEEP-
DISORDERED BREATHING**

3.1. Introduction

Sleep-disordered breathing (SDB) is prevalent in chronic heart failure (CHF) but many patients do not describe typical symptoms associated with sleep apnoea (see Section 1.5.1). To date, only a limited number of clinical and anthropometric characteristics have been identified which are associated with the occurrence of SDB in CHF (see Table 1.3). However, treatment for CHF has evolved and the prevalence of obesity has increased since many of these studies were published (Javaheri, 1998b; Sin, 1999). This thesis has recruited a cohort of CHF patients who are optimally treated with contemporary medical and device therapy, and this data will be used to re-evaluate the clinical features associated with SDB in CHF.

In this chapter, I will describe the recruitment of CHF patients for this thesis. All patients underwent investigation to determine the presence or absence of SDB, and I will compare the demographic, anthropometric and clinical characteristics between patients with and without SDB. In addition, I will also evaluate the impact of SDB on measures of daytime sleepiness and polysomnographic measurements of sleep in CHF patients.

3.2. Methods

The methods required for the measurements described in this chapter have previously been described in the General Methods (Chapter 2).

3.2.1. Statistical Analysis

The primary aim of this thesis was to investigate the diagnostic accuracy of heart rate variability analysis to identify SDB in CHF. The required sample size was therefore calculated to be adequately powered to test the hypotheses described in Section 4.1,

and the calculation is described in detail in Section 4.2.2. In brief, an a priori sample size of 180 CHF patients was calculated to be powered ($1-\beta = 80\%$) to detect a one sided difference of $>10\%$ between the sensitivity/specificity of heart rate variability analysis and polysomnography, at a significance level (α) of 0.05.

As the data was not normally distributed, results are presented as median and interquartile range (IQR). Mann-Whitney or Kruskal-Wallis tests were used to compare continuous variables between groups. Categorical variables were compared using Fishers exact test or a chi-square test. The diagnostic accuracy of continuous biomarkers was assessed by measurement of the area under the curve (AUC) of the receiver operating characteristic (ROC) curve. The relationship between binary variables and SDB was quantified using odds ratios, and 95% confidence intervals for these ratios are presented.

3.3. Results

3.3.1. Recruitment of Study Participants

Potential participants were recruited from cardiology outpatient clinics at the Royal Brompton Hospital and Ealing Hospital between November 2007 and April 2010. The medical notes of 1182 unique patients (median age 69.4 years (59.8 to 76.6); 39% female) were reviewed to assess eligibility for recruitment (Figure 3.1). 722 (61%) of these patients did not have a diagnosis of CHF. In the remaining 460 (39%) patients with CHF (median age 70.3 years (61.5 to 76.9); 28% female), 71 patients did not fulfil criteria for recruitment due to recent change in cardiac failure therapy, treatment for obstructive sleep apnoea, ineligibility due to age, or inability to comprehend study information (Figure 3.1).

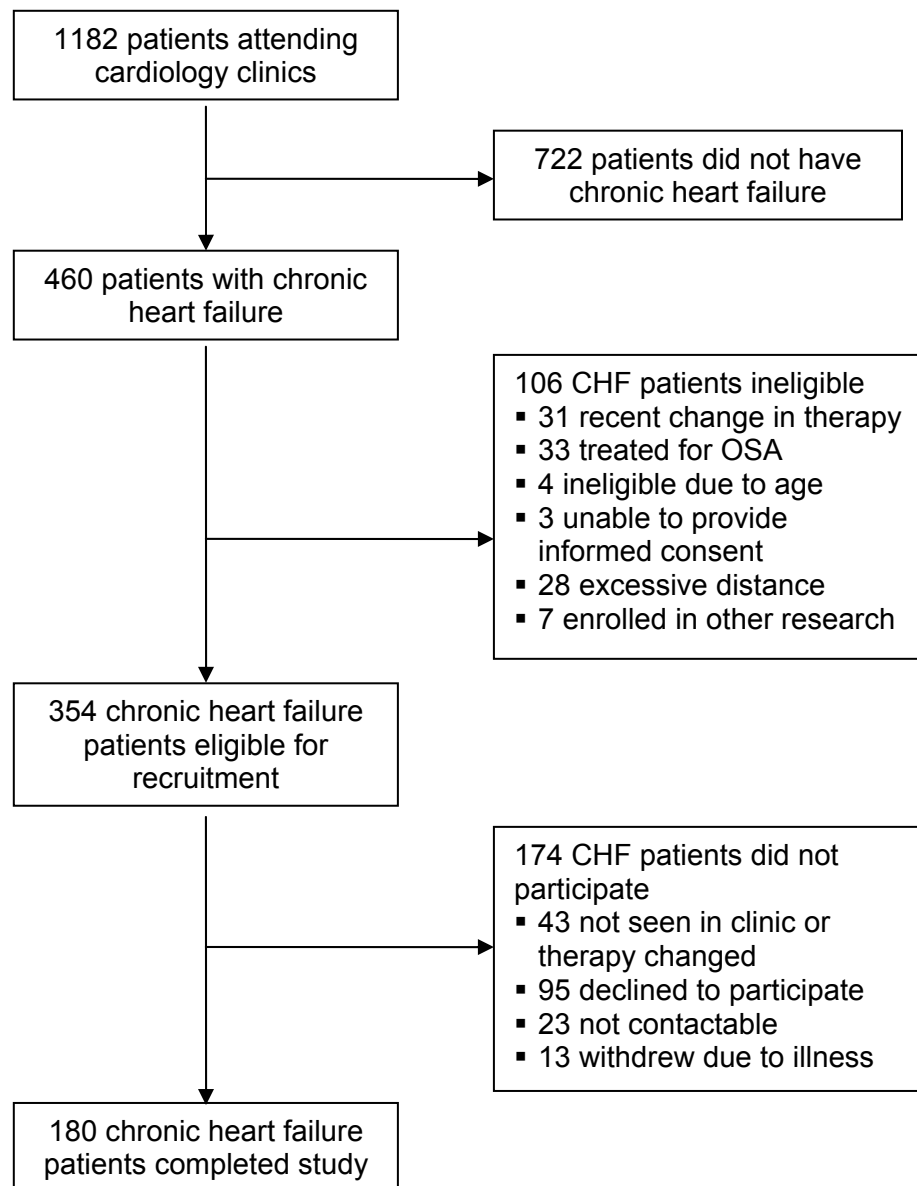


Figure 3.1. Flow Diagram to Show Recruitment of Chronic Heart Failure Patients for this Thesis

An additional 35 patients were not suitable for recruitment due to excessive travelling time required to perform a home sleep study, or prior enrolment in other research studies. Therefore, 354 patients (median age 70.7 years (62.1 to 77.4); 27% female) were identified who were eligible to participate. Of these, 43 (12%) patients were not offered a study information sheet because they left the clinic before the research fellow could meet them, or a change in their medication during the clinic consultation meant they were no longer eligible for recruitment. The remaining 311 patients received information about the study but 95 (27%) declined to participate, 23 (6%) could not be contacted again. 13 (3%) patients who agreed to participate became unwell and withdrew before their sleep study was performed. In total, 180 (51%) patients eligible for recruitment consented to participate.

3.3.2. Characteristics of Chronic Heart Failure Patients

180 CHF patients completed the study, of whom 154 (86%) were male. The median age of all patients was 69.6 (58.9 to 76.6) years with no significant difference in age between male and female participants (Table 3.1). Men had a significantly larger neck circumference and smaller hip circumference than women. The majority of participants were classified as overweight or obese, with a median BMI of 29.1 (25.4 to 32.7) kg/m². There was a trend to higher BMI in women (31.1 kg/m²) than men (29.0 kg/m²), although this did not reach statistical significance ($p = 0.11$). The proportion of 'never smokers' was significantly higher in female participants.

Comorbidities were common in study participants (Table 3.2). 46 (26%) CHF patients reported a diagnosis of diabetes mellitus and 94 (52%) reported a diagnosis of hypertension (Table 3.2). Ischaemic heart disease was reported by 92 (51%) patients, and was present in a significantly greater proportion of men than women. COPD or

asthma was reported by 37 (24%) patients. When measured by spirometry, 54 (35%) had evidence of airflow obstruction with an FEV1/FVC ratio of <70%.

Table 3.1. Demographic and Anthropometric Characteristics of Participants

		All Patients (n=180)	Male Patients (n=154)	Female Patients (n=26)	p value*
Age (years)		69.6 (58.9 – 76.6)	70.2 (59.4 – 77.0)	63.1 (53.7 – 76.5)	0.30
BMI (kg/m²)		29.1 (25.4 – 32.7)	29.0 (25.2 – 32.6)	31.1 (26.0 – 36.9)	0.11
White ethnicity (n, %)[†]		140 (78%)	122 (79%)	18 (69%)	0.31
Neck size (cm)		40.0 (38 – 43)	41.0 (39 – 43)	37.0 (35 – 39)	<0.001
Waist size (cm)		105.0 (96 – 114)	105.0 (96 – 114)	107.0 (94 – 120)	0.75
Hip size (cm)		102.0 (97 – 109)	101.0 (97 – 108)	107.0 (101 – 120)	0.006
Waist:Hip ratio		1.02 (0.98 – 1.06)	1.03 (0.99 – 1.06)	0.99 (0.90 – 1.02)	<0.001
Smoking history (n, %)	Never	72 (40)	53 (34)	19 (73)	0.001
	Ex	85 (47)	79 (51)	6 (23)	
	Current	23 (13)	22 (14)	1 (4)	
Smoking (pack years)		25.5 (10 – 48)	25.0 (9.5 – 48)	30.0 (25 – 65)	0.44

Values shown are median (interquartile range), or where indicated, number (percent) of patients (n, %)

*p values are given for the difference between male and female participants

[†] Other ethnicities included Asian Indian (11%), Black African (4%), Asian Pakistani (2%) and other (4%)

Table 3.2. Comorbidities and Spirometric Measurements[†] in Patients

	All Patients (n=180)	Male Patients (n=154)	Female Patients (n=26)	p value*
Diabetes Mellitus (n, %)	46 (26%)	40 (26%)	6 (23%)	0.75
Hypertension (n, %)	94 (52%)	83 (54%)	11 (42%)	0.27
Ischaemic Heart Disease (n, %)	92 (51%)	84 (55%)	8 (31%)	0.03
COPD/Asthma (n, %)	37 (24%)	31 (20%)	6 (23%)	0.73
FEV1 (%predicted)	68 (59 – 83)	68 (57 – 82)	61 (48 – 88)	0.64
FVC (%predicted)	73 (62 – 88)	73 (62 – 87)	73 (55 – 105)	0.85
FEV1/FVC ratio	74 (65 – 79)	74 (65 – 79)	76 (63 – 81)	0.63

COPD = chronic obstructive pulmonary disease, FEV1 = Forced expiratory volume in 1 second, FVC = Forced vital capacity

Values shown are median (interquartile range), or number (percent) of patients (n, %)

[†] Spirometric measurements were available for 153 patients

*p values are given for the difference between male and female participants

3.3.3. Characteristics of Chronic Heart Failure in Participants

The most common causes of CHF were ischaemic cardiomyopathy and dilated cardiomyopathy, occurring in 140 (78%) participants (Table 3.3). Valvular heart disease and heart failure with preserved ejection fraction were present in 20 (11%) and 11 (6%) of patients. Cardiac arrhythmias were prevalent with atrial fibrillation in 55 (31%)

patients. A permanent cardiac pacemaker had been implanted in 51 (28%) patients, 32 (18%) of whom had devices inserted to provide cardiac resynchronization therapy.

Angiotensin converting enzyme inhibitor or angiotensin receptor blocker therapy was prescribed to 162 (90%) of patients, with beta blockers and loop diuretic therapy also commonly prescribed (Table 3.3).

Table 3.3. Aetiology and Treatment of Chronic Heart Failure in Participants (n = 180)

Characteristic	Number of patients (%)
Ischaemic cardiomyopathy	81 (45%)
Dilated cardiomyopathy	59 (33%)
Heart failure due to valvular disease	20 (11%)
Heart failure with preserved ejection fraction	11 (6%)
Other cause of heart failure*	9 (5%)
Atrial Fibrillation	55 (31%)
Cardiac Pacemaker	51 (28%)
Cardiac Resynchronisation Therapy	32 (18%)
ACE inhibitor/ARB	162 (90%)
Beta Blocker	130 (72%)
Loop diuretic	123 (68%)
Aldosterone antagonist	76 (42%)
Digoxin	30 (17%)
Amiodarone	27 (15%)

*includes hypertrophic cardiomyopathy, hypertension and atrial fibrillation

ACE = angiotensin converting enzyme; ARB = angiotensin receptor blocker

The majority of participants were in New York Heart Association (NYHA) functional class II (Table 3.4). B-type natriuretic peptide (BNP) assay was performed in 178 (99%) participants with median BNP concentration 125 pg/ml, but there was a wide range of BNP values from 3 to 1512 pg/ml. The group median and mean BNP both increased as NYHA classification worsened (Table 3.4).

Table 3.4. New York Heart Association Classification and B-Type Natriuretic Peptide Concentration in Chronic Heart Failure Patients

New York Heart Association class	Number of Participants	B-Type Natriuretic Peptide (pg/ml)			
		Median	Interquartile range	Mean	Standard deviation
I	24	64	24 – 125	119	145
II	113*	128	69 – 246	204	238
II	41	166	61 – 382	261	279
IV	2	310	-	310	350
All	180	125	55 – 247	207	241

*BNP assay results were not available for 2 participants in NYHA class II

Echocardiograms were available for analysis in 156 (87%) participants. In the remaining 24 participants, echocardiograms could not be re analysed due to technical problems caused by software incompatibility, or because the echocardiogram had been performed at their local hospital before referral to the Brompton Hospital. In addition, it was not possible to complete all required echocardiographic measurements in some participants due to insufficient stored images or poor image quality, whilst the presence of atrial fibrillation prevented measurement of mitral A wave velocity and calculation of E/A ratio in 38 (21%) participants.

Data summarizing the median and interquartile range for all echocardiographic measurements obtained, and the number of participants in whom each echocardiographic parameter could be measured are presented in Table 3.5. The median left ventricle ejection fraction (LVEF) was 41% (29 to 58%). When the 11 participants with a diagnosis of heart failure with preserved ejection fraction were excluded, median LVEF decreased to 38% (27 to 50%).

Table 3.5. Echocardiographic Measurements of Cardiac Size and Function in Chronic Heart Failure Patients

Echocardiographic Parameter	Value	Number of patients in whom the parameter was measurable
Left ventricle ejection fraction (%)	41 (29 – 58)	156
Left ventricle end diastole volume (ml)	139 (100 – 191)	153
Left ventricle end systole volume (ml)	79 (47 – 130)	153
Mitral E wave velocity (m/s)	0.8 (0.6 – 1.1)	147
Mitral A wave velocity (m/s)	0.7 (0.5 – 0.9)	92
E/A ratio	1.0 (0.6 – 1.6)	92
Left atrial diameter (cm)	4.7 (4.2 – 5.3)	155
Left atrial area (cm²)	26 (21 – 32)	146
Isovolumic time (s/min)	11 (8 – 15)	126
Right ventricle inlet diameter (cm)	4.0 (3.7 – 4.6)	138
Right ventricle long axis systolic amplitude (cm)	1.5 (1.2 – 1.8)	86
Tricuspid regurgitation peak velocity (m/s)	2.6 (2.4 – 3.0)	87
Right ventricle systolic pressure (mmHg)	30 (25 – 40)	77

Values shown are median (interquartile range)

Whilst the study population included a heterogeneous population of CHF patients, over half of all participants had evidence of left ventricle dilatation with median left ventricle end systolic volume of 79 (47 – 130) ml, and left atrial enlargement was also prevalent, with median left atrial area of 26 (21 – 32) cm² (Table 3.5).

3.3.4. Snoring, Witnessed Apnoeas and Daytime Sleepiness in Chronic Heart Failure Patients

Snoring was reported frequently, with 116 (64%) patients describing snoring at least once per week (Table 3.6). There was no gender difference in the proportion of participants reporting snoring. 34 (19%) patients reported never snoring, whilst 30 (17%) were unaware if they snored (usually due to living alone). In contrast, only 33 (18%) patients reported witnessed apnoeas during sleep. Afternoon naps on at least one day per week were reported by 126 (70%) patients, with 81 (45%) reporting naps on 4 or more days each week.

The median daily caffeine intake was the equivalent of 3 cups per day. Most patients had a Hospital Anxiety Depression Scale score in the normal range (median score 11).

The majority of patients had no evidence of evidence of excessive daytime sleepiness, with median Epworth sleepiness scale (ESS) score of 7 (4 to 10), and no significant difference between men and women (Table 3.6). The majority of participants had no evidence of objective daytime sleepiness, with a median OSLER test duration of 40 (27.5 to 40) minutes; 53 (29%) patients fell asleep during the single OSLER test. There was no significant difference in OSLER test duration in CHF patients who performed the test during the evening (n = 27; median duration 40 minutes) and those who performed the test in the morning (median duration 40 minutes; p = 0.71).

Table 3.6. Characteristics Relating to Daytime Sleepiness in Chronic Heart Failure Patients

		All Patients (n=180)	Male Patients (n=154)	Female Patients (n=26)	P value*
Snoring (n, %)	Never	34 (19%)	30 (19%)	4 (15%)	0.51
	<4 days/week	63 (35%)	55 (36%)	8 (31%)	
	≥4 days/week	53 (29%)	46 (30%)	7 (27%)	
	Unknown	30 (17%)	23 (15%)	7 (27%)	
Witnessed Apnoeas (n, %)	None	112 (62%)	95 (62%)	17 (65%)	0.60
	Yes	33 (18%)	30 (19%)	3 (12%)	
	Unknown	35 (19%)	29 (19%)	6 (23%)	
Afternoon naps (n, %)	Never	54 (30%)	44 (29%)	10 (38%)	0.40
	<4 days/week	45 (25%)	41 (27%)	4 (15%)	
	≥4 days/week	81 (45%)	69 (45%)	12 (46%)	
HADS – A		6 (3 – 10)	6 (3 – 9)	9 (4 – 11)	0.11
HADS – D		5 (3 – 8)	5 (3 – 8)	5 (4 – 9)	0.57
HADS – Total		11 (6 – 17)	11 (6 – 16)	14 (9 – 19)	0.22
Caffeine intake (cups/day)		3 (2 – 5)	3 (2 – 5)	2.8 (1 – 5.3)	0.26
Epworth Score		7 (4 – 10)	7 (5 – 10)	7 (3 – 11)	0.24
OSLER (minutes)		40 (27.5–40)	40 (30 – 40)	40 (17 – 40)	0.75

Values shown are median (interquartile range) or where indicated, number (percent) of patients (n,%).

HADS – A = Hospital anxiety and depression score (anxiety score); HADS – D = Hospital anxiety and depression score (depression score); OSLER = Oxford sleep resistance test

*p values are given for the difference between male and female patients

3.3.5. Polysomnography Results

182 polysomnograms were performed in 180 CHF patients. Two participants required repeat polysomnography due to technical failure on the first study. The median total sleep time in all patients was 348 (279 to 399) minutes, with a sleep latency of 23 (14 to 38) minutes, sleep efficiency of 72% (59 to 80%) and arousal index of 19.2 (13.5 to 26.7)/hour (Table 3.7). Sleep architecture was abnormal with predominantly light sleep (stage 1 = 28% (17 to 44%) and stage 2 = 38% (26 to 48%) of total sleep time). Deep sleep occurred for 11% (6 to 18%) of sleep. REM sleep was preserved with a median duration of 19% (14 to 24%) of total sleep time

Sleep-disordered breathing events occurred frequently with a median apnoea hypopnoea index of 13.4/hour (7.2 to 25.8/hour; Table 3.7). The majority of events were hypopnoeas with a median hypopnoea index of 9.2/hour (5.2 to 16.7/hour). 80 (44%) CHF patients fulfilled the criteria for diagnosis of SDB, with an AHI ≥ 15.0 /hour. SDB occurred in similar proportions of male (45%) and female (43%) CHF patients. Obstructive sleep apnoea (OSA) was the predominant form of SDB in 55 patients (86% male), whilst the remaining 25 patients (88% male) had predominantly central sleep apnoea (CSA). A more detailed description of the type and frequency of respiratory events is given in Section 5.3.2 and Table 5.7.

The median 4% oxygen desaturation index (measured from the polysomnogram oximeter) was 8.2 dips/hour, with normal mean overnight oxygen saturation in most patients (Table 3.7). Whilst the median duration of sleep time with oxygen saturation $<90\%$ was 3.3%, in a small number of studies the oximeter probe became displaced on the finger causing periods of artefactual low oxygen saturation readings which may have contributed to the overnight hypoxia seen in some patients.

Table 3.7. Polysomnographic Measurements of Sleep and Sleep Disturbance in all Chronic Heart Failure Patients

Parameter	Value
Total sleep time (mins)	348 (279 – 399)
Sleep latency (mins)	23 (14 – 38)
Sleep efficiency (%)	72 (59 – 80)
Stage 1 sleep (% TST)	28 (17 – 44)
Stage 2 sleep (% TST)	38 (26 – 48)
Deep sleep (% TST)	11 (6 - 18)
REM sleep (%TST)	19 (14-24)
Supine position (% of sleep time)	23 (7 – 50)
Arousal index (/hour)	19.2 (13.5 – 26.7)
Apnoea hypopnoea index (/hour)*	13.4 (7.2 – 25.8)
Apnoea index (/hour)	1.9 (0.3 – 7.2)
Hypopnoea index (/hour)	9.2 (5.2 – 16.7)
4% Oxygen desaturation index (/hour)[†]	8.2 (3.6 – 19.5)
Duration SpO2 <90% (% of sleep time)	3.3 (0.5 – 21.0)
Mean nocturnal SpO2 (%)	93 (91 – 94)
Nadir SpO2 (%)	84 (80 – 88)
Periodic limb movement index (/hour)	13.3 (2.6 – 42.9)
PLM with arousal index (/hour)	1.1 (0.1 – 5.1)
Nocturia (episodes/night)	1 (1 – 2)

*AHI calculated with hypopnoeas defined as a $\geq 50\%$ reduction in nasal airflow for ≥ 10 seconds associated with a 3% oxygen desaturation or arousal from sleep.

[†]Oxygen desaturation index measured from PSG oximeter

TST = total sleep time; REM = rapid eye movement; SpO2 = oxygen saturation;

PLM = periodic limb movement

Values are median (interquartile range)

Cheyne-Stokes respiration occurred infrequently and was observed in 37 (21%) patients with a median duration of 36 (13 to 100) minutes or 13% of sleep time.

Periodic limb movements (PLM) occurred frequently, with a median index of 13.3/hour (Table 3.7). Only a small proportion of PLM were associated with arousals from sleep and the median periodic limb movement with arousal index was 1.1/hour. 117 (65%) patients had a periodic limb movement index (PLMI) of >5.0/hour, whilst in 86 (48%) patients the PLMI was >15.0/hour.

3.3.6. Comparison of Home and Hospital Polysomnography

132 (73%) patients opted to have the sleep study performed in their own home.

Participants who had home polysomnography were significantly older (median age 71.5 years) than those who were studied in hospital (median age 64.4 years; $p = 0.02$), but there were no significant differences in gender, BMI, Epworth score or severity of heart failure between patients studied in their home and in hospital (Table 3.8).

Home study patients had a significantly increased total sleep time (357 minutes versus 313 minutes; $p = 0.01$) and time in bed (510 minutes versus 480 minutes; $p = 0.007$) compared to patients studied in hospital, but sleep efficiency was similar between the two study environments. Sleep architecture was similar in both environments with no significant differences in proportion of light, deep or REM sleep.

There was no significant difference in sleeping position, arousal index, PLM, SDB or overnight hypoxaemia between patients undergoing polysomnography in their home or the hospital (Table 3.8). The diagnosis of SDB did not differ significantly according to the site of the sleep study, with 58 (44%) of home patients and 22 (46%) of hospital patients having an AHI >15.0/hour ($p = 0.87$).

Table 3.8. Comparison of Patient Characteristics and Polysomnography Findings Between Home and Hospital Sleep Studies

Parameter	Home (n = 132)	Hospital (n = 48)	p value*
Age (years)	71.5 (59.6 – 77.1)	64.4 (56.9 – 73.8)	0.02
Male (n, %)	110 (83)	44 (92%)	0.23
BMI (Kgm ⁻²)	28.7 (25.1 – 32.7)	30.1 (26.3 – 33.8)	0.26
Epworth Score	7 (4 – 10)	7 (4 – 11)	0.95
OSLER duration (minutes)	40 (24.3 – 40)	40(33 – 40)	0.29
NYHA class (I/II/III/IV)	17/88/25/2	7/25/16/0	0.16
Left Ventricle EF (%)	41 (31 – 55)	42 (28 – 59)	0.89
BNP (pg/ml)	126 (62 – 255)	109 (32 -230)	0.45
Time in bed (mins)	510 (463 – 553)	480 (412 – 540)	0.007
Total sleep time (mins)	357 (287 – 413)	313 (247 -372)	0.01
Sleep latency (mins)	24 (14 – 39)	23 (14 – 38)	0.73
Sleep efficiency (%)	72 (59 – 81)	72 (55 – 80)	0.41
Stage 1 sleep (% TST)	30 (19 – 46)	25 (15 – 41)	0.17
Stage 2 sleep (%TST)	37 (26 – 47)	40 (22 – 54)	0.31
Deep sleep (%TST)	10 (6 – 18)	11 (6 – 18)	0.99
REM sleep (%TST)	19 (14 – 24)	17 (13 – 25)	0.44
Supine position (%TST)	20 (7 – 48)	26 (7 – 58)	0.43
Arousal index (events/hour)	19.0 (13.4 – 26.4)	19.4 (13.7 – 28.6)	0.92
PLM index (/hour)	15.7 (2.8 – 42.9)	10.4 (2.1 – 43.5)	0.38
PLM with arousal index (/hour)	1.2 (0.1 – 6.8)	1.1 (0.1 – 3.4)	0.56
AHI (/hour)	13.5 (7.7 – 22.5)	13.2 (5.3 – 31.1)	0.97
4% oxygen desaturation index (/hour)	8.1 (3.6 – 18.9)	8.7 (3.8 – 25.3)	0.60
Duration SpO2 <90% (% sleep time)	3.3 (0.4 – 19.8)	3.5 (0.7 – 24.7)	0.56
Mean nocturnal SpO2 (%)	93 (91 – 94)	92.5 (90 – 94)	0.76
Nadir SpO2 (%)	84 (80 – 88)	83 (79 – 87)	0.52
Nocturia (episodes/night) [†]	1.5 (1 – 3)	1 (0 – 2)	0.01

*p values are given for the difference between home and hospital participants

[†]Episodes of nocturia on night of sleep study.

EF = ejection fraction. See previous Tables for definition of abbreviations.

Values are median (interquartile range) or where indicated, number (%) of participants.

Home study patients had significantly more episodes of nocturia on the night of the sleep study than those who were studied in the hospital (Table 3.8). However, there was no significant difference in the usual frequency of nocturia reported on other nights, with a median of 1.5 episodes per night in both home and hospital patients.

3.3.7. Comparison of Chronic Heart Failure Patients with and without Sleep-Disordered Breathing

SDB was present in 80 (44%) of CHF patients and was associated with significant differences in body habitus. BMI, neck, hip and waist circumference were all higher in patients with SDB compared to those without (Table 3.9). There were no significant differences in age or gender between patients according to the presence or absence of SDB. Whilst BMI was significantly higher in patients with OSA (32.0 (28.9 to 36.3) kg/m²) than CSA (29.7 (25.8 to 33.0) kg/m²; $p = 0.04$), neck circumference did not differ significantly between these patients (OSA = 41.5 (39.5 to 43) cm, CSA = 42 (39.5 to 44) cm; $p = 0.66$).

COPD or asthma was self reported significantly less often by CHF patients with SDB ($p = 0.002$; Table 3.9), although there were no significant differences in spirometric measures of airflow obstruction in patients with and without SDB. There were no other significant differences in comorbidities between the two groups.

Subjective sleepiness did not differ between patients with and without SDB. Median ESS score was 7 in both groups and 43 (24%) CHF patients had an ESS score >10. SDB was present in only 22 (51%) of CHF patients with ESS score >10, 7 of whom had CSA. The ESS score had a low diagnostic accuracy for the detection of SDB, with an AUC of 0.53 (95% confidence interval 0.44 to 0.62). In addition, CHF patients with SDB had no evidence of objective daytime sleepiness when measured with the OSLER test.

Table 3.9. Comparison of Chronic Heart Failure Patients According to the Presence or Absence of Sleep-Disordered Breathing

Parameter		SDB present (n = 80)	No SDB (n = 100)	p value*
Age (years)		67.1 (57.7 – 75.0)	71.7 (59.4 – 77.1)	0.11
Male (n, %)		69 (86%)	85 (85%)	0.84
BMI (Kg/m ²)		31.0 (27.9 – 35.4)	27.4 (24.4 – 31.5)	<0.001
Neck Circumference (cm)		42.0 (39.5 – 43.0)	39.0 (37.0 – 41.0)	<0.001
Waist circumference (cm)		109 (101 – 117)	100 (94 – 109)	<0.001
Hip circumference (cm)		105 (100 – 112)	100 (95 – 106)	<0.001
Waist/Hip ratio		1.03 (0.99 – 1.07)	1.01 (0.97 – 1.05)	0.07
Diabetes Mellitus (n, %)		23 (29%)	23 (23%)	0.40
Hypertension (n, %)		43 (54%)	51 (51%)	0.77
Ischaemic heart disease (n, %)		37 (46%)	55 (55%)	0.29
COPD/Asthma (n, %)		8 (10%)	29 (29%)	0.002
FEV1 (% predicted)		69 (58 – 83)	68 (48 – 84)	0.49
FVC (% predicted)		75 (63 – 85)	72 (59 – 89)	0.84
FEV1/FVC ratio		75 (67 – 79)	73 (64 – 79)	0.14
Epworth Score		7 (5 – 11)	7 (4 – 11)	0.49
OSLER (mins)		40.0 (24.5 – 40.0)	40.0 (31.0 – 40.0)	0.22
Snoring (n, %)	Never	13 (16%)	21 (21%)	0.004
	<4 days/wk	29 (36%)	34 (34%)	
	>4 days/wk	32 (40%) [#]	21 (21%) [#]	
	Unknown	6 (8%)	24 (24%)	
Witnessed apnoeas (n, %)	None	43 (54%)	69 (69%)	0.001
	Yes	24 (30%) [†]	9 (9%) [†]	
	Unknown	13 (16%)	22 (22%)	
Afternoon nap (n, %)	Never	25 (31%)	29 (29%)	0.21
	<4 days/wk	40 (50%)	41 (41%)	
	>4 days/wk	15 (19%)	30 (30%)	
Caffeine intake (cups/day)		3 (1.6 – 5.0)	3 (2 – 4.5)	0.84

*p values are given for the difference between participants with and without SDB

[#] p = 0.008 for difference between participants with SDB and without SDB

[†] p <0.0001 for difference between participants with SDB and without SDB

See Table 3.1 and 3.2 for definition of abbreviations

Values are median (interquartile range) or where indicated, number (%) of participants

Patients with SDB were significantly more likely to report snoring on >4 days/week. The odds ratio for SDB in patients who snored >4 days/week was 2.5 (95% C.I. 1.3 to 4.8). There were no significant differences in the numbers of 'never snorers' or 'snorers <4 days/week' in patients with or without SDB (Table 3.9). The presence of reported snoring >4 days/week had a higher odds ratio for the presence of OSA (2.9 (95% CI 1.4 to 6.0)) than CSA (1.8 (95% CI 0.7 to 4.7)).

Witnessed apnoeas were reported more often by patients with SDB, and the odds ratio for SDB in patients with witnessed apnoeas was 4.3 (95% C.I. 1.9 to 10.0). However, there were a number of SDB patients false negative for witnessed apnoeas, and sensitivity for this symptom was 30% (95% CI. 21 to 41%), although specificity was 91% (95% CI 84 to 95%). There were no significant differences in the frequency of daily naps or caffeine intake irrespective of the presence or absence of SDB.

A significantly greater number of CHF patients with SDB were prescribed beta blocker therapy, with the highest rate of prescription in patients with CSA (88%) compared to patients with OSA (80%) or no SDB (64%; $p = 0.007$). There were no other significant differences in medical therapy between patients with and without SDB. (Table 3.10). The number of participants with atrial fibrillation did not differ according to the presence or absence of SDB ($p = 0.42$), but when evaluated according to the type of SDB, atrial fibrillation was present in a significantly higher proportion of CHF patients with CSA (52%) compared to OSA (25%; $p = 0.024$) and no SDB (28%; $p = 0.032$). The odds ratio for CSA in patients with atrial fibrillation was 2.8 (95% C.I. 1.1 to 6.8). Whilst higher numbers of participants with SDB had received cardiac resynchronization therapy, this difference did not reach statistical significance (Table 3.10).

Table 3.10. Comparison of Chronic Heart Failure Characteristics in Patients, According to the Presence or Absence of Sleep-Disordered Breathing

Parameter	SDB present (n = 80)	No SDB (n = 100)	p value*
Atrial fibrillation (n, %)	27 (34%)	28 (28%)	0.42
Cardiac pacemaker (n, %)	25 (31%)	26 (26%)	0.51
Cardiac resynchronization therapy (n, %)	19 (24%)	13 (13%)	0.08
Beta blocker (n, %)	66 (83%)	64 (64%)	0.007
ACE inhibitor/ARB (n, %)	72 (90%)	90 (90%)	1.0
Loop diuretic therapy (n,%)	55 (69%)	68 (68%)	1.0
Aldosterone antagonist (n, %)	31 (39%)	45 (45%)	0.50
Amiodarone (n, %)	11 (14%)	16 (16%)	0.83
Digoxin (n,%)	15 (19%)	15 (15%)	0.55
NYHA class (I/II/III/IV)	12/47/19/2	12/66/22/0	0.36
BNP (pg/ml)	111 (42 – 313)	130 (74 – 208)	0.73
Left ventricle ejection fraction (%)	42 (29 – 58)	40 (29 – 58)	0.92
Left ventricle end diastole volume (ml)	150 (103 – 200)	129 (96 – 179)	0.12
Left ventricle end systole volume (ml)	90 (47 – 136)	75 (45 -123)	0.36
Left atrial diameter (cm)	4.9 (4.2 – 5.5)	4.6 (4.1 – 5.2)	0.16
Left atrial area (cm²)	28 (22 – 34)	25 (21 – 30)	0.08

Values are median (interquartile range) or number (percent) of patients (n, %)

*p values are given for the difference between participants with and without SDB

See Tables 3.3 and 3.4 for definition of abbreviations

There were no significant differences in NYHA classification, LVEF or BNP concentration between CHF patients with and without SDB (Table 3.10). In CHF patients with CSA, LVEF (34% (19 to 52%)) and BNP concentration (239 (62 to 542) pg/ml) were not significantly different from CHF patients without SDB. However, CHF patients with OSA had significantly higher LVEF (45% (32 to 52); $p = 0.048$) and lower BNP concentration (100 (31 to 204) pg/ml; $p = 0.035$) than patients with CSA. When compared to CHF patients without SDB, the LVEF and BNP was not significantly different in CHF patients with OSA.

BNP concentration had a low diagnostic accuracy as a marker of SDB when assessed by ROC curve with an AUC of 0.49 (95% C.I. 0.40 to 0.57). Echocardiographic measurements of cardiac size and function did not differ significantly between participants with and without SDB (Table 3.10). The left ventricle ejection fraction also had a poor diagnostic accuracy to indicate the presence of SDB, with an AUC of 0.50 (95% C.I. 0.40 to 0.59). After excluding patients with OSA, the diagnostic accuracy of BNP and LVEF for CSA in CHF remained poor (AUC = 0.65 and 0.38 respectively).

3.3.8. Impact of Sleep-Disordered Breathing on Polysomnographic Variables in Chronic Heart Failure Patients

SDB occurred in 80 (44%) of CHF patients in this study. Total sleep time, sleep latency and sleep efficiency were not significantly different between patients with and without SDB (Table 3.11). Patients with SDB had a significantly longer duration of stage 1 sleep compared to those without SDB ($p = 0.015$), but there were no other differences in sleep architecture. SDB was associated with greater sleep disruption, with a significant increase in the arousal index compared to patients without SDB.

Table 3.11. Comparison of Polysomnographic Variables in Chronic Heart Failure Patients with and without Sleep-Disordered Breathing

Parameter	SDB present (n = 80)	No SDB (n = 100)	P value*
Total sleep time (mins)	348 (290 – 403)	346 (266 – 400)	0.56
Sleep latency (mins)	22 (13 – 33)	27 (14 – 42)	0.11
Sleep efficiency (% TST)	74 (59 – 81)	69 (60 – 80)	0.30
Stage 1 sleep (% TST)	32 (21 – 47)	25 (14 – 42)	0.015
Stage 2 sleep (% TST)	37 (21 – 46)	39 (27 – 52)	0.16
Deep sleep (% TST)	10 (6 – 17)	11 (6 – 18)	0.72
Rapid eye movement sleep (% TST)	17 (13 – 24)	19 (14 – 25)	0.42
Supine position (%TST)	24 (6 – 60)	22 (8 – 47)	0.97
Arousal index (events/hour)	23.6 (18.6 – 36.2)	16.2 (12.3 – 21.7)	<0.001
PLM index (/hour)	11.4 (2.9 – 47.1)	15.3 (2.0 – 39.8)	0.80
PLM with arousal index (/hour)	1.1 (0 – 5.8)	1.2 (0.1 – 5.1)	0.99
Apnoea hypopnoea index (/hour)	27.5 (19.4 – 41.3)	7.7 (4.2 – 11.0)	-
4% ODI (/hour)	21.3 (13.3 – 32.1)	4.1 (1.7 – 6.7)	<0.001
Cheyne-Stokes respiration (%TST)	0 (0 – 6.1)	0 (0 – 0)	<0.001
Duration SpO2 <90% (%TST)	8.5 (1.8 – 24.8)	1.1 (0.1 – 19.1)	<0.001
Mean nocturnal SpO2 (%)	92 (91 – 94)	93 (90 -95)	0.19
Nadir SpO2 (%)	81 (76 – 84)	87 (83 – 89)	<0.001
Nocturia (episodes/night)	1 (0 – 2)	1 (1 – 2.5)	0.38

*p values are given for the difference between participants with and without SDB

See previous Tables for definition of abbreviations

Values are median (interquartile range)

In addition, SDB was associated with increased duration of Cheyne-Stokes respiration, increased frequency of oxygen desaturations, lower nadir oxygen saturation and a longer duration of the night with oxygen saturation <90% (Table 3.11). However, there was no increase in the frequency of nocturia in association with SDB.

3.4. Discussion

This study has recruited the pre-specified sample size of 180 CHF patients who were assessed for symptoms of sleep-disordered breathing followed by objective measurement of sleep and sleep disturbance using polysomnography.

The cohort was comprised predominantly of ageing male CHF patients with mild symptomatic heart failure (NYHA functional class II), most of whom were classified as overweight or obese using body mass index criteria (World Health Organisation, 2000). SDB was diagnosed in 80 (44%) CHF patients and OSA occurred more frequently than CSA.

3.4.1. Characteristics of Study Cohort

The predominance of male participants in this cohort is similar to that observed in previous studies investigating the prevalence (Javaheri, 2006c; Oldenburg, 2007b; Vazir, 2007; MacDonald, 2008; Paulino, 2009; Yumino, 2009a) and treatment of SDB in CHF (Bradley, 2005). Whilst CHF occurs more commonly in working age men than women due to coronary heart disease, in elderly patients, the prevalence of heart failure is similar in both genders (Majeed, 2005). In the current study, 28% of CHF patients eligible for recruitment were female but they comprised 14% of the final cohort. These observations suggest that female patients are under-represented in studies of

SDB in CHF. The finding in the current study that SDB occurred in similar proportions of male and female patients means it is important to try and address this imbalance in future studies.

CHF patients recruited for this thesis are older with a higher BMI than have been enrolled in other studies evaluating the prevalence of SDB. As shown in Table 1.2, the mean age of CHF participants previously studied has tended to be younger (mean age 55.6 to 66 years) with lower BMI (mean 25.9 to 29.4 kg/m²) than the cohort enrolled in the current study. For comparison, the mean [SD] age of participants in this study was 66.9 [13.0] years, and mean BMI 30.0 [6.1] kg/m².

The cohort of patients recruited for this thesis had a diverse range of causes and severity of CHF. Previous studies of SDB in CHF have often exclusively enrolled patients with low ejection fraction heart failure (Javaheri, 2006c; Oldenburg, 2007b; Vazir, 2007). However, SDB has been reported to be prevalent in asymptomatic CHF (Lanfranchi, 2003), mild symptomatic CHF (Vazir, 2007), and heart failure with preserved ejection fraction (Bitter, 2009a). In keeping with these reports, whilst the current study has enrolled a heterogeneous cohort of CHF patients, the prevalence of SDB remained high.

3.4.2. Prevalence of Sleep-Disordered Breathing

Systematic investigation of the occurrence of SDB has suggested a wide range in the prevalence of this disorder in CHF, with some studies reporting the prevalence of SDB in CHF to be as high as 71% (Paulino, 2009) or 81% (Schulz, 2007), whilst one study observed a prevalence of only 24% (Rao, 2006). Many authors have reported the prevalence to be in excess of 50% (see Table 1.2), but four previous studies have found the prevalence of SDB in CHF to be from 45 to 49%, (Javaheri, 2006c; Bitter,

2009a; Yumino, 2009a; Ferreira, 2010) which is very similar to the prevalence of SDB in the current study. Moreover, Vazir et al., (2007) have previously studied CHF patients from the Royal Brompton hospital and reported a similar SDB prevalence of 53% in men with mild symptomatic heart failure due to left ventricular systolic dysfunction (Vazir, 2007). This would suggest that a representative cohort of CHF patients has been recruited for this thesis. The large differences in the prevalence of SDB observed in individual studies are likely to be explained by variation in the type of sleep study and criteria used to diagnose SDB, or the characteristics of the enrolled participants, as discussed in Section 1.4.1.

3.4.3. Classification of Sleep-Disordered Breathing

In this study, the majority of participants with SDB were categorised as having OSA. CSA was diagnosed in 25 participants. Whilst there has been considerable variability in the proportions of CHF patients categorised as having OSA or CSA in prevalence studies (see Table 1.2), the prevalence of CSA in the current study is lower than previously reported. This may be due to the enrolment of a large number of CHF patients who were overweight or obese in this study. Excess body weight is strongly associated with OSA (Peppard, 2000a; Young, 2002b) and this may have resulted in a predisposition to this type of SDB in our cohort of CHF patients.

The prevalence of CSA observed in this study may also reflect the relatively small number of CHF patients enrolled with moderate or severe symptomatic heart failure, with 23% in NYHA class III and 1% in NYHA class IV. Increasing severity of heart failure, measured by NYHA, left ventricle ejection fraction, or BNP has been associated with increasing prevalence of CSA (Javaheri, 2006c; Christ, 2007; Oldenburg, 2007b; Bitter, 2009a; Ferreira, 2010) although this has not been confirmed in all studies (Sin, 1999; Yumino, 2009a). In addition, cardiac resynchronization therapy has been

reported to improve or resolve CSA (Sinha, 2004; Oldenburg, 2007a; Kara, 2008) and the use of these devices in 32 (18%) patients may have influenced the prevalence of CSA.

3.4.4. Impact of Sleep-Disordered Breathing on Daytime Sleepiness and Nocturnal Sleep in Chronic Heart Failure

The presence of SDB in CHF patients was rarely associated with excessive daytime sleepiness, when assessed by the Epworth score and OSLEP test. When compared to patients without SDB, there was no significant difference in Epworth score, OSLEP duration, frequency of daytime naps or sleep latency in patients in whom SDB occurred. Previous studies that have enrolled patients with low ejection fraction heart failure have reported that CHF patients with SDB do not describe excessive daytime sleepiness and that Epworth scores in CHF patients do not differ between those with or without SDB (Arzt, 2006; Hastings, 2006; Rao, 2006; Johansson, 2010). The absence of sleepiness in association with SDB in CHF contrasts with the excessive daytime somnolence reported with the obstructive sleep apnoea hypopnoea syndrome. It has been hypothesised that the central nervous system excitation associated with the heart failure syndrome (Lambert, 1995) is protective against excessive daytime sleepiness with SDB in CHF.

Alternatively, the reported lack of sleepiness in CHF with SDB may reflect an inability of the ESS to identify this symptom complex in elderly CHF patients. The ESS was originally described for measurement of sleepiness in young and middle aged adults (Johns, 1991; Johns, 1993) and it may be insensitive to daytime sleepiness in elderly individuals. In addition, the ESS has been reported to be poorly correlated with the AHI in adults investigated for OSA (Weaver, 2004). In the context of possible limitations of

the ESS, it is notable that whilst SDB in CHF is not associated with subjective sleepiness, it has been reported to be associated with an increase in objectively measured daytime sleepiness and a reduction in daytime physical activity and functioning compared to CHF patients without SDB (Hastings, 2006; Redeker, 2010b).

Whilst SDB did not affect daytime sleepiness in this study, it was associated with evidence of greater sleep disruption. The proportion of stage 1 light sleep and arousal index were both significantly increased in patients with SDB compared to those without. However, total sleep duration and sleep efficiency did not differ in patients according to the presence or absence of SDB. These findings are consistent with previous studies which have also reported significantly increased stage 1 sleep, but no significant alteration to total sleep time in CHF patients with SDB (Javaheri, 2006c; Vazir, 2007).

3.4.5. Home Polysomnography Studies in Chronic Heart Failure

Patients

Home sleep studies were chosen by 132 (73%) participants. Technical failure occurred in 2 participants, although in each case home polysomnography was successfully repeated at a second visit. Home polysomnography was associated with an average of 30 minutes extra time in bed and 44 minutes additional total sleep time, which was significantly longer than polysomnography performed in hospital. However, sleep architecture, arousal index, AHI, ODI or PLM index did not significantly differ between home and hospital studies, suggesting that intrinsic sleep disorders were unaffected by the environment in which the sleep study was performed.

Home unattended polysomnography has been used to diagnose SDB in over 6000 community dwelling individuals participating in the epidemiological Sleep Heart Health Study (Redline, 1998). The findings of the current study suggest that home

polysomnography appears to be an acceptable and technically reliable method of recording sleep and sleep disturbance in CHF patients. Moreover, it may allow a more representative nights sleep than in hospital polysomnography, with extra time in bed and increased total sleep time.

3.4.6. Periodic Limb Movements in Chronic Heart Failure Patients

An unanticipated finding from polysomnography was the high frequency of periodic limb movements during sleep in CHF patients. A PLMI of >5.0/hour was observed in 117 (65%) patients, whilst in 86 (48%) of participants the PLMI was >15.0/hour.

However, few of these periodic limb movements were associated with electroencephalographic arousals from sleep and the median PLM with arousal index was 1.1/hour.

A high prevalence of periodic limb movement syndrome (PLMS) occurring in 20 to 52% of CHF patients has previously been reported (Hanly, 1996a; Javaheri, 2006c; Skomro, 2009). Whilst the cause for the increased prevalence of PLMS in CHF is uncertain, other authors have noted that only a small number of arousals were caused by the leg movements (Javaheri, 2006c).

Furthermore, PLMS (PLMI >5/hour) may occur in up to 45% of community dwelling people of 65 years or older (Ancoli-Israel, 1991). In the current study, 109 (61%) participants were >65 years, and this may have influenced the observed prevalence of PLMS. In addition, periodic limb movements may occur in association with iron deficiency (Stefansson, 2007) or as an unwanted consequence of commonly prescribed medications including antidepressant therapy (Hornyak, 2006), which may also be important influences in CHF. However, PLMs have been reported to be

associated with cardiovascular morbidity (Ali, 1991; Koo, 2011) and in view of their high prevalence in CHF, this warrants further investigation in the future.

3.4.7. Clinical Characteristics of Chronic Heart Failure Patients with Sleep-Disordered Breathing

There were few clinical characteristics which differed significantly between patients with and without SDB. BMI, neck, waist and hip circumference were all significantly higher in participants with SDB compared to those without. As may be expected, CHF patients with OSA had the highest BMI and a significantly increased neck size compared to CHF patients without SDB. Neck circumference is strongly associated with OSA (Stradling, 1991; Davies, 1992), but neck circumference was also significantly higher in CHF patients with CSA.

CHF patients with SDB were significantly less likely to report COPD or asthma than participants without SDB. Whilst there was no significant difference in spirometric measures of airflow obstruction, this finding may require further evaluation in prospective studies.

Traditional symptoms associated with OSA such as regular snoring and witnessed apnoeas were significantly more common in CHF patients with SDB, but the diagnostic utility of these features was limited. In CHF patients who complained of snoring on 4 or more nights per week, the odds ratio was highest for the presence of OSA. The odds ratio for SDB in patients who reported witnessed apnoeas was greater at 4.3, but the sensitivity for this symptom was low. The commonly used ESS score had an AUC of 0.53, indicating that it is unable to discriminate between the presence and absence of SDB in CHF.

In this study, the presence of atrial fibrillation was associated with an odds ratio of 2.8 for the occurrence of CSA. The odds ratio for CSA in CHF patients with atrial fibrillation has previously been reported to be 7.93 (95% C.I. 1.76 – 35.65) (Yumino, 2009a). However, the study by Yumino et al., recruited CHF patients between 1997 and 2004, and the use of cardiac resynchronisation therapy in patients with moderate – severe heart failure will have increased since this date. The use of cardiac resynchronisation therapy in 18% of CHF patients in the current study may have influenced the relationship between atrial fibrillation and CSA, resulting in the lower odds ratio we have found.

In this study, there were no differences in severity of heart failure in the whole group of CHF patients with SDB, compared to those without SDB. However, the difference in LVEF and BNP concentration between CHF patients according to the type of SDB would suggest that CSA is associated with more severe heart failure than OSA. Sin et al., (1999) also observed that the LVEF was higher in CHF patients with OSA than patients with CSA or without SDB (Sin, 1999). The greater use of beta blocker therapy in CHF patients with CSA may also suggest more severe heart failure in these patients, and the only patients in this study with NYHA class IV symptoms both had CSA. As discussed above, the association of CSA with worsening severity of CHF has been noted in some, but not all studies. Our findings would suggest that there may be important differences in heart failure severity between CHF patients with CSA and OSA which may be implicated in the pathogenesis of the different types of SDB, and influence the aims or indications for treatment of SDB in CHF.

BNP and left ventricle ejection fraction are commonly used biomarkers for assessment of severity of CHF but these had a poor diagnostic accuracy for SDB. Whilst the inclusion of patients with HFPEF may have influenced the diagnostic accuracy of LVEF, studies which have exclusively enrolled CHF patients with low ejection fraction heart failure have also reported that LVEF is not associated with SDB (Sin, 1999;

Yumino, 2009a). BNP concentration has previously been reported to be increased in CHF patients with CSA (Carmona-Bernal, 2005; Christ, 2007; Poletti, 2008). The low number of CHF patients with CSA in our cohort is likely to have reduced our power to detect a significant difference in BNP concentration according to the presence or absence of CSA.

3.5. Summary

In this contemporary cohort, there were few symptoms which differed between CHF patients with and without SDB. Whilst snoring more than 4 days/week, and witnessed apnoeas occurred more commonly in patients with SDB, they had a low odds ratio or poor sensitivity/specificity for diagnostic use. The ESS and biomarkers of heart failure severity were not helpful for detection of SDB in CHF. Therefore, in the absence of clinical features which can be used to reliably differentiate CHF patients with SDB from those without, a simple screening test would be of great value to help identify the presence of SDB.

**CHAPTER 4: IDENTIFICATION OF SLEEP-
DISORDERED BREATHING IN CHRONIC HEART
FAILURE: UTILITY OF HEART RATE VARIABILITY
AND OVERNIGHT PULSE OXIMETRY**

4.1. Introduction

Sleep-disordered breathing (SDB) is highly prevalent in chronic heart failure (CHF), occurring in approximately half of all patients (Javaheri, 2006c; Oldenburg, 2007b; Vazir, 2007; Yumino, 2009a). It can adversely affect quality of life and is independently associated with increased morbidity and mortality (Hastings, 2006; Javaheri, 2007b; Wang, 2007). Treatment of SDB in CHF has been associated with improvement in cardiac function (Naughton, 1995b; Kaneko, 2003; Mansfield, 2004; Bradley, 2005) and may prolong survival (Arzt, 2007; Wang, 2007; Jilek, 2011). However, only a minority of patients receive testing for SDB and this important comorbidity is under diagnosed in CHF (Javaheri, 2010).

One of the difficulties with identifying SDB in CHF is that many affected patients do not complain of symptoms which would alert their healthcare provider to its presence. As discussed in section 1.5.1, CHF patients with SDB are unlikely to complain of excessive daytime sleepiness (Arzt, 2006; Hastings, 2006), whilst snoring occurs infrequently in CHF patients with predominantly central sleep apnoea (Javaheri, 1998b). Questionnaires which are commonly used to screen for the obstructive sleep apnoea hypopnoea syndrome, such as the Epworth sleepiness scale (Johns, 1991) may be unable to predict the presence or absence of SDB in patients with CHF (Arzt, 2006). Furthermore, CHF is associated with shorter sleep duration and reduced sleep efficiency independent of SDB (Arzt, 2006), and symptoms such as self reported poor sleep quality occur commonly in CHF patients (Redeker, 2008; Johansson, 2010).

As the presence or absence of clinical symptoms is often unhelpful, a sleep study may be required to rule in or rule out SDB in CHF. Polysomnography is recommended as the reference standard for diagnosis of SDB in CHF (Kushida, 2005) but there is limited access to this investigation which can result in diagnostic delays (Flemons, 2004; Masa Jimenez, 2007). A simple screening test may be useful as part of a phased testing

approach to identification of SDB in CHF, although such a test must have a high diagnostic accuracy to produce a clinically meaningful change in the post-test probability of disease.

Overnight measurement of a single respiratory or cardiac parameter may be suitable for this purpose, as this can be conveniently and economically performed with single channel portable monitors (see Section 1.5.8 and 1.5.9). To date, analysis of heart rate variability (Vazir, 2006), overnight pulse oximetry (Series, 2005) or nasal airflow measurement (Weinreich, 2009) have been reported to have acceptable diagnostic accuracy to screen for SDB in CHF. However, these studies have evaluated the portable monitors in small series of patients with low ejection fraction heart failure, and adequately powered studies are required to address the utility of these screening tests for diagnosis of SDB in unselected CHF patients.

Analysis of heart rate variability (HRV) appears to be particularly convenient to screen for SDB in CHF as many patients already undergo ambulatory ECG monitoring during their cardiological assessment. Our department has previously reported that measurement of the very low frequency increment (%VLFI) parameter of HRV has a sensitivity of 85% and negative predictive value of 87% to rule out SDB in patients with CHF due to systolic dysfunction (Vazir, 2006). However, HRV could not be analysed in 45% of CHF patients due to cardiac arrhythmias or paced cardiac rhythm. Therefore, alternative screening strategies are required for those CHF patients who are unsuitable for HRV analysis.

The aim of this study is to evaluate the diagnostic utility of spectral analysis of heart rate variability and overnight oximetry to screen for SDB in patients with CHF. Whilst previous studies of portable monitoring in CHF have enrolled only patients with systolic myocardial dysfunction (Series, 2005; Vazir, 2006), this study has included CHF patients with heart failure and preserved ejection fraction (HFPEF) in keeping with a real world population of CHF patients. The following hypotheses were tested:

1. Spectral analysis of HRV can be used in a general cardiology clinic setting to rule out SDB in patients with CHF.
2. Overnight pulse oximetry can be used in a general cardiology clinic setting to rule out SDB in CHF patients with atrial fibrillation, paced cardiac rhythm, ectopics or artefacts on ambulatory ECG monitoring.
3. HRV analysis has a higher accuracy compared to overnight pulse oximetry for the diagnosis of SDB in patients with CHF.

4.2. Methods

Patients with a diagnosis of CHF were recruited from cardiology clinics at the Royal Brompton and Ealing Hospitals in London, between November 2007 and May 2010. Enrolment criteria included a diagnosis of CHF in accordance with guidelines from the European Society of Cardiology (Swedberg, 2005), clinically stable condition for more than 4 weeks and age 18 – 90 years. Exclusion criteria were the presence of diseases likely to inhibit sleep or current treatment for SDB. Patients eligible for enrolment were invited to participate irrespective of clinical suspicion of SDB. This study received ethical approval from the Brompton, Harefield and NHLI research ethics committee (COREC 07/Q0404/32) and participants gave written informed consent before participation.

The methods required for the measurements described in this chapter have previously been described in the General Methods (Chapter 2). In brief, all patients were offered the choice to have the overnight monitoring performed in their own home or in the research sleep department of the Royal Brompton Hospital. A structured clinical interview was conducted on the evening of the sleep study, to enquire about normal sleeping habits and sleep related symptoms. Anthropometric characteristics including

height, weight, and circumference of neck, waist and hip were measured. Spirometry was performed with the patient in a seated position, using a handheld spirometer (Vitalograph 2120, Maids Moreton, UK). Subjective daytime sleepiness was quantified with the Epworth sleepiness scale (ESS) (Johns, 1991) and the Hospital Anxiety and Depression score (Zigmond, 1983) was used to screen for mood disorders.

The presence of SDB was determined by nocturnal polysomnography.

Electroencephalography (EEG), electrooculography and submental electromyogram (EMG) were recorded for analysis of sleep. Measurement of thoracoabdominal movements, nasal pressure and oxygen saturation were performed to assess respiration. The polysomnography oximeter updated oxygen saturation with each heart beat and used an averaging time of 4 heart beats. Snoring was detected with a tracheal microphone and bilateral anterior tibialis EMG was monitored for identification of leg movements. Data was recorded with an ambulatory polysomnography system (SOMNOscreen, SOMNOmedics GmbH, Germany) which also detected body position. All patients were asked to keep a diary to record the time that they turned out the light after going to bed, and the time that they got out of bed in the morning.

Ambulatory electrocardiography was recorded synchronously with polysomnography by a two channel Holter recorder (VistaPlus, Novacor, Paris, France) for analysis of heart rate variability. A wrist worn oximeter (Pulsox 3i, Konica Minolta, Osaka, Japan) was also worn for synchronous recording of overnight oxygen saturation. The recording characteristics of the Pulsox 3i include an averaging time of 5 seconds, with a measurement value stored every 5 seconds.

Daytime sleepiness was objectively measured with the OSLER test (Bennett, 1997), which was performed on the morning after the sleep study in the majority of patients.

Severity of heart failure was assessed subjectively by the New York Heart Association classification (The Criteria Committee of the New York Heart Association, 1994).

Cardiac function was objectively assessed by venous blood assay of B-type natriuretic peptide (Triage BNP, Biosite Inc, California, USA) and by analysis of echocardiograms performed as part of each patients routine clinical care.

4.2.1. Data Analysis

All polysomnography sleep studies were analysed by the same experienced polysomnographer who was blinded to the patients identity, and the results of the oximetry and HRV analysis. Wakefulness, sleep stage and arousals were scored according to standard criteria (Rechtschaffen, 1968; Iber, 2007). Recommended definitions were used for analysis of respiratory events (Iber, 2007). Apnoea was scored when nasal airflow was reduced to $<10\%$ of baseline for ≥ 10 seconds. Obstructive apnoeas were scored when the thoracoabdominal effort signals showed continuing respiratory excursions, whilst central apnoea was scored when respiratory efforts were absent. Hypopnoea was scored when nasal airflow reduced by $\geq 50\%$ of baseline, with an associated oxygen desaturation of $\geq 3\%$ and/or an EEG arousal from sleep. Obstructive hypopnoea was scored in the presence of snoring, flattening of the nasal pressure airflow signal or out of phase thorax and abdominal effort signals. Central hypopnoea was scored when all these features were absent. The mean number of apnoea and hypopnoeas per hour of sleep was expressed as the apnoea hypopnoea index (AHI). SDB was defined as an AHI ≥ 15 events/hour and was further classified as obstructive sleep apnoea (OSA) or central sleep apnoea (CSA) according to the predominant type of respiratory event.

Ambulatory ECG recordings were anonymised prior to analysis with a commercial software program (Holtersoft, Novacor, Rueil-Malmaison, France). CHF patients with paced cardiac rhythm for $>10\%$ of all QRS complexes, atrial fibrillation or $>10\%$ of ectopic beats were excluded from HRV analysis. Manual verification of automated

scoring was performed to ensure all QRS complexes had been identified and to permit correction of misidentified ectopic beats or artefact. Manual editing was limited to 20 minutes to ensure the technique would not be too cumbersome for clinical use. Heart rate variability was analysed during the period from midnight to 0600, as previously described (Roche, 2004; Vazir, 2006). In addition to measurement of recommended time domain and spectral components of HRV (Task Force of the European Society of Cardiology, 1996), the spectral density of the heart rate increment was also measured. The ratio of the power in the very low frequency (VLF) band (0.01 to 0.05 Hz) to the total power of the heart rate increment spectral density function (0.01 – 0.5Hz) is expressed as the percent very low frequency increment (%VLFI) (Roche, 2002). The %VLFI has been reported to be the optimum HRV parameter for detection of SDB (Roche, 2002) and this was pre-specified as the primary outcome of the HRV analysis. A %VLFI diagnostic cutoff of $\geq 2.23\%$ has been reported to have high sensitivity for detection of SDB in CHF (Vazir, 2006) and the same cutoff was selected a priori for use in this study.

In order to improve the diagnostic accuracy of the %VLFI, simultaneous identification of a high frequency (HF) peak in the heart rate increment spectral density is recommended (Poupard, 2010). The HF peak corresponds to the respiratory influence on HRV. Absence of a HF peak below 0.4Hz may indicate autonomic dysfunction which increases the risk of a false negative result when %VLFI is used to screen for OSA (Poupard, 2010). Therefore, CHF patients in whom a HF peak below 0.4Hz was not identifiable in the heart rate increment spectral density function were excluded from the HRV analysis, even if HRV was otherwise measurable.

Overnight oxygen saturation recorded from the wrist worn oximeter was analysed for the 'time in bed' interval with an automated scoring program (Download 2001, Stowood Scientific, Oxford, UK). The number of $\geq 3\%$ oxygen desaturations per hour was expressed as the 3% oxygen desaturation index (ODI). An a priori ODI cutoff of >7.5

dips/hour was chosen to determine the presence of SDB. The diagnostic accuracy of the 3%ODI was assessed in all CHF patients, and in accordance with the hypotheses being tested, the diagnostic accuracy was evaluated separately in the subgroup of CHF patients in whom HRV could not be analysed, and in the subgroup of patients in whom HRV could be measured. The diagnostic accuracy of the $\geq 4\%$ ODI was also determined.

In CHF patients suitable for HRV analysis, the pulse signal recorded during the overnight pulse oximetry was also analysed to determine the frequency of pulse rate rises. An average heart rate rise of 10 beats per minute (bpm) has been reported to occur following arousal from sleep (Pitson, 1994), whilst a pulse rate rise of ≥ 6 has also been reported to be correlated ($r = 0.68$) with breathing related EEG arousals (Adachi, 2003). Therefore, the current study measured the mean number of pulse rate rises of ≥ 6 bpm and ≥ 10 bpm per hour, to determine the association of these metrics with sleep fragmentation and SDB in CHF.

All echocardiograms were analysed by the same experienced echocardiographer who was unaware of the results of the other investigations. Cardiac function was characterised by measurement of cardiac chamber size, left ventricular ejection fraction and Doppler indices of mitral inflow.

4.2.2. Statistical Analysis

The sample size calculation for this study was performed with the support of Professor Kulinskaya of the Imperial College Statistical Advisory Service. The sample size was calculated to be adequately powered ($1-\beta = 80\%$) to detect a one sided difference of $>10\%$ between the sensitivity/specificity of HRV and polysomnography, at a significance level (α) of 0.05. As there is no true gold standard for diagnosis of SDB, polysomnography was considered the reference standard and the method of Lui and

Cumberland was used to determine the number of patients required (Lui, 2001). The %VLFI component of HRV has previously been reported to have a sensitivity of 85% and specificity of 65% to detect SDB in CHF (Vazir, 2006). Using these values, it was calculated that 110 true positives were required to detect a >10% difference in sensitivity between polysomnography and %VLFI, whilst 180 true negatives were required to detect a >10% difference in specificity.

The diagnostic accuracy of the %VLFI component of HRV and oximetry was compared by measurement of the area under the curve (AUC) of the receiver operating characteristic (ROC) curves for each test. The AUC for the %VLFI has been reported to be 0.82 (Vazir, 2006). A sample size of 154 patients was calculated to be adequately powered ($1-\beta = 80\%$) at a significance level of 0.05, to detect a one sided difference of $\geq 10\%$ in the AUC for oximetry, with a correlation of 0.3 to 0.6 between the two results (Hanley, 1983).

Results are presented as median with interquartile range (IQR) as the majority of the measured parameters were not normally distributed. Mean (SD) values are given for selected variables to allow comparison with other studies. Mann-Whitney or Kruskal-Wallis tests were used to compare continuous variables between two or more groups. Categorical variables were compared using Fisher's exact test or a chi-square test. Correlations between continuous variables were assessed with Spearman's rank correlation coefficient

Sensitivity, specificity, predictive values and likelihood ratios were determined for the %VLFI component of HRV and oximetry at the a priori thresholds. The diagnostic accuracy of the %VLFI component of HRV and oximetry, independent of any threshold for either test, were assessed by measurement of the AUC of the ROC curve (Baker, 2003). Statistical analyses were performed using a commercial software program (SPSS V.16.0, IBM Inc, Chicago, USA).

4.3. Results

354 CHF patients were identified who were eligible for recruitment (Figure 4.1). 43 patients left the clinic before meeting the research fellow, 95 declined to participate, 23 could not be contacted after receiving the patient information sheet and 13 agreed to participate but could not be studied due to deterioration in their clinical condition. 180 patients completed the study, of whom 132 (73%) chose to have the overnight monitoring performed in their own home. Following analysis of polysomnography data, 7 patients (3 of whom were studied in their home) were excluded from further analysis due to insufficient sleep (total sleep time <200 minutes).

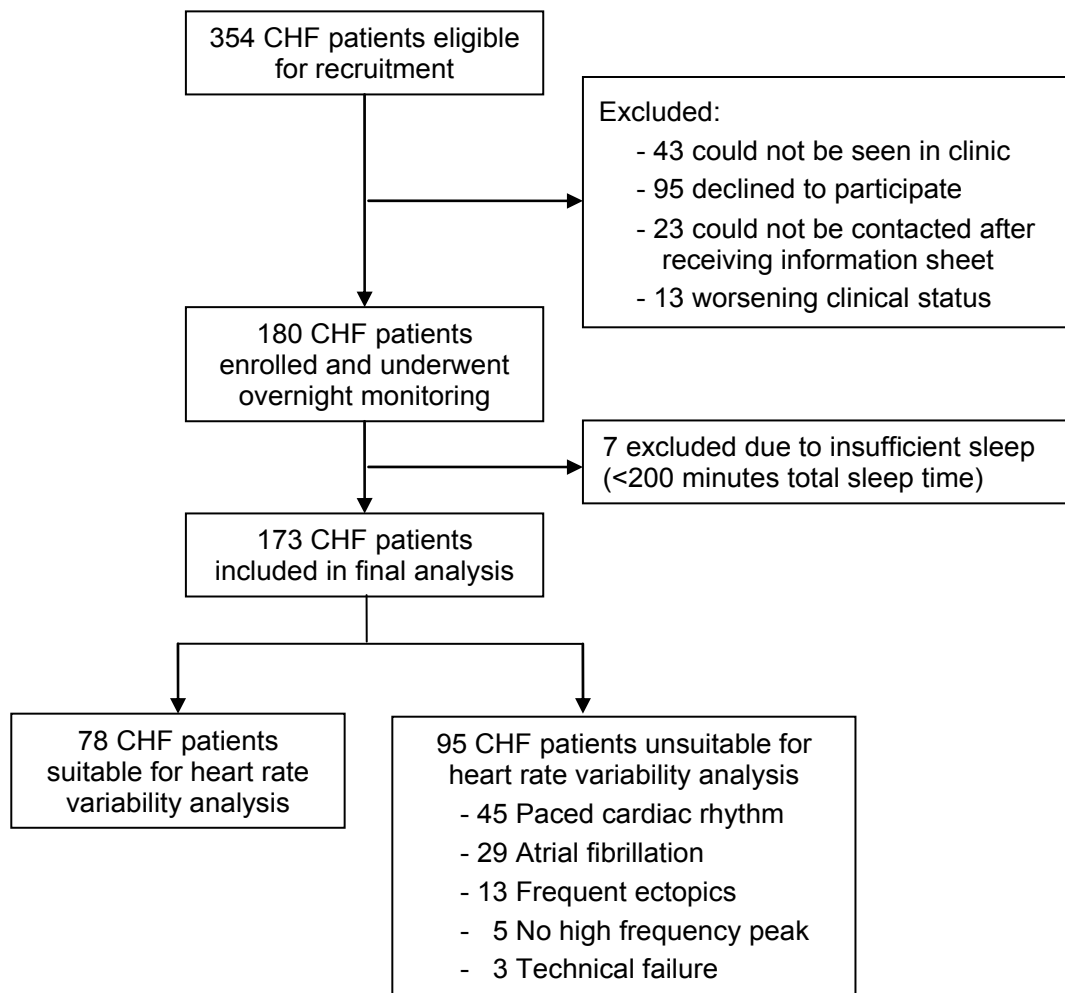


Figure 4.1. Flow Diagram to Show Recruitment of Chronic Heart Failure Patients and Inclusion in the Heart Rate Variability Analysis

4.3.1. Clinical Characteristics of Chronic Heart Failure Patients

173 CHF patients were included in the analysis with median (IQR) age 69.8 (58.8 to 76.8) years (mean $\pm$ SD age = 66.9 $\pm$ 13.2 years), 86% were male and the majority were overweight (Table 4.1). The most frequent cause of CHF was ischaemic cardiomyopathy, and 134 (77%) patients had New York Heart Association (NYHA) class I or II symptoms. Medication prescribed for CHF included beta blockers in 126 (73%) patients and angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARB) in 157 (91%). Common comorbidities included, atrial fibrillation (31%), diabetes (25%) and self reported COPD or asthma (20%).

Table 4.1. Anthropometric and Clinical Characteristics of all Chronic Heart Failure Patients (n = 173)

Clinical Characteristic	Value
Age (years)	69.8 (58.8 – 76.8)
Male (n,%)	148 (86)
BMI (kg/m ²)	29.1 (25.4 – 32.7)
Neck size (cm)	40.0 (38.0 – 43.0)
Waist/Hip ratio	1.02 (0.98 – 1.06)
Diabetes (n,%)	44 (25)
COPD/Asthma (n,%)	34 (20)
Ischaemic cardiomyopathy (n,%)	89 (51)
Beta blocker (n,%)	126 (73)
ACEI/ARB (n,%)	157 (91)
Atrial fibrillation (n,%)	53 (31)
Cardiac pacing (n,%)	49 (28)
NYHA (I/II/III/IV)	24/110/37/2
BNP (pg/ml)	118 (55 – 239)
Left Ventricle ejection fraction (%)	40 (28 – 58)

Values shown are median (IQR), or number (percent) of patients (n, %).

BMI = body mass index; ACEI/ARB = angiotensin converting enzyme inhibitor or angiotensin receptor blocker; COPD = chronic obstructive pulmonary disease; NYHA = New York heart association classification, BNP = B-type natriuretic peptide

There were no significant differences in demographic or anthropometric characteristics between CHF patients included and excluded from analysis (Table 4.2). However, the 7 excluded patients had a trend toward a higher ESS score and their sleep latency during the OSLER test was significantly shorter (22.2 minutes; $p = 0.03$), in keeping with the reduced total sleep time measured on the sleep study.

Table 4.2. Comparison of Anthropometric and Clinical Characteristics of Chronic Heart Failure Patients Excluded from Analysis

	CHF Patients Included (n = 173)	CHF Patients Excluded (n = 7)	p value
Age (years)	69.8 (58.8 – 76.8)	67.1 (60.2 – 75.1)	0.76
Male (n,%)	148 (85.5)	7 (100)	1.0
BMI (kg/m²)	29.1 (25.4 – 32.7)	28.4 (24.3 – 33.9)	0.48
Neck circumference (cm)	40.0 (38.0 – 43.0)	39.5 (37.0 – 41.5)	0.21
Waist/Hip ratio	1.02 (0.98 – 1.06)	1.05 (0.99 – 1.10)	0.77
Diabetes (n, %)	44 (25)	2 (29)	1.0
Hypertension (n, %)	92 (53)	2 (29)	0.19
Ischaemic cardiomyopathy (n, %)	89 (51)	3 (43)	0.72
COPD/Asthma (n, %)	34 (20)	3 (43)	0.15
Atrial fibrillation (n, %)	53 (31)	2 (29)	0.64
Cardiac pacing (n, %)	49 (28)	2 (29)	0.64
Beta blocker (n, %)	126 (73)	4 (57)	0.40
ACE/ARB (n, %)	157 (91)	5 (71)	0.15
Epworth Score	7 (4 – 10)	10 (6 – 16)	0.12
OSLER duration (mins)	40.0 (32.1 – 40.0)	22.2 (12.4 – 40.0)	0.03
NYHA (I/II/III/IV)	24/110/37/2	0/3/4/0	0.15
BNP (pg/ml)	118 (55 – 239)	225 (128 – 498)	0.16
Left Ventricle EF (%)	40 (28 – 58)	49 (45 – 62)	0.08

Values shown are median (IQR), or number (percent) of patients (n, %).

EF = ejection fraction; See Table 4.1 for definition of additional abbreviations

SDB was present in 77 (45%) CHF patients, with median AHI 27.0 (19.2 to 40.6) events/hour (mean $\pm$ SD AHI = 32.4 ± 18.2 events/hour). Obstructive sleep apnoea was the predominant form of SDB, occurring in 53 (31%) patients. Body mass index, neck circumference and waist to hip ratio were significantly higher in CHF patients with OSA compared to those without SDB (all $p < 0.005$) (Table 4.3). In addition, CHF patients with central sleep apnoea (CSA) had a significantly greater neck circumference ($p < 0.005$) than CHF patients without SDB.

Self reported COPD or asthma (20%) was present in 20% of all CHF patients but was significantly more common in patients without SDB ($p < 0.007$; Table 4.3). Spirometry was performed in 146 patients and in contrast to self reported obstructive airways disease, there was no significant difference in objectively measured FEV1 or FVC between the three groups of CHF patients. However, the FEV1/FVC ratio was significantly higher in CHF patients with OSA, compared to CHF patients without SDB and CHF patients with CSA.

Whilst the NYHA class showed no significant difference in severity of heart failure between CHF patients with and without SDB, the median BNP was significantly higher in CHF patients with CSA, compared to those with OSA or with no SDB. Median left ventricle ejection fraction (LVEF) was 34% in CHF patients with CSA, but this was not statistically different from patients with OSA (43%) or no SDB (40%).

Table 4.3. Anthropometric and Clinical Characteristics in Chronic Heart Failure Patients (n = 173)

	No SDB (n = 96)	OSA (n = 53)	CSA (n = 24)	p value[§]
Age (years)	71.9 (59.4 – 77.6)	66.4 (55.4 – 74.8)	69.0 (60.2 – 77.2)	0.14
Male (n,%)	81 (84)	46 (87)	21 (88)	0.88
BMI (kg/m²)	27.4 (24.7 – 31.6)*	32 (28.8 – 36.4)* [†]	29.4 (25.6 – 31.5) [†]	<0.001
Neck size (cm)	39.0 (37.0 – 41.0)* [#]	41.8 (39.5 – 43.0)*	42.0 (39.3 – 43.8) [#]	<0.001
Waist/Hip ratio	1.01(0.97 – 1.05)*	1.05(1.01 – 1.08)* [†]	1.01 (0.97 – 1.03) [†]	0.003
Diabetes (n,%)	22 (23)	17 (32)	5 (21)	0.40
COPD/Asthma (n,%)	27 (28)*	4 (8)*	3 (13)	0.007
FEV1 (% predicted)	68 (50 – 83)	71 (59 – 85)	64 (57 – 77)	0.46
FVC (% predicted)	73 (61 – 89)	78 (63 – 88)	72 (61 – 81)	0.79
FEV1/FVC	73 (63 – 78) [‡]	77 (68 – 82) ^{‡†}	72 (65 – 76) [†]	0.048
Ischaemic cardiomyopathy (n,%)	54 (56)	23 (43)	12 (50)	0.32
Beta blocker (n,%)	62 (65) ^{‡#}	43 (81) [‡]	21 (88) [#]	0.02
ACEI/ARB (n,%)	87 (91)	46 (87)	24 (100)	0.18
Atrial fibrillation (n,%)	27 (28) [#]	14 (27)	12 (50) [#]	0.09
Cardiac pacing (n,%)	24 (26)	15 (30)	10 (42)	0.27
NYHA (I/II/III/IV)	12/64/20/0	9/30/14/0	3/16/3/2	0.37
B-Type Natriuretic Peptide (pg/ml)	128 (69 – 201) [#]	100 (31 – 228) [†]	265 (63 – 546) ^{#†}	0.033
Left ventricle ejection fraction (%)	40 (28 – 58)	43 (32 – 58)	34 (19 – 52)	0.11

[§]p value for comparison between CHF patients without SDB ('No SDB'), CHF patients with OSA and CHF patients with CSA, by Kruskal Wallis test;

*p<0.005 for comparison between CHF patients without SDB ('No SDB') and patients with OSA; [†]p<0.05 for comparison between CHF patients with OSA and patients with CSA; [#]p<0.05 for comparison between CHF patients with CSA and patients without SDB ('No SDB'); [‡]p<0.05 for comparison between CHF patients without SDB ('No SDB') and patients with OSA

Values shown are median (IQR), or number (percent) of patients (n, %). SDB = sleep-disordered breathing; OSA = obstructive sleep apnoea; CSA = central sleep apnoea; FEV1 = Forced expiratory volume in 1 second; FVC = Forced vital capacity; See Table 4.1 for additional abbreviations

The median ESS score in CHF patients with SDB was 7 and did not differ significantly from patients without SDB (median ESS 7; $p = 0.45$) (Table 4.4). Most patients completed the full 40 minutes of the OSLER test and there was no difference in test duration according to the presence or absence of SDB.

Total sleep time and sleep efficiency were similar in patients with and without SDB, but sleep architecture differed with a significantly greater proportion of stage 1 light sleep and higher arousal index in patients with OSA and CSA. CHF patients with SDB also experienced greater overnight hypoxia, with a significantly longer time with oxygen saturation $<90\%$ during sleep.

Table 4.4. Daytime Sleepiness, Polysomnographic Measurements of Sleep and Sleep-Disordered Breathing in all Chronic Heart Failure Patients (n = 173)

	No SDB (n = 96)	OSA (n = 53)	CSA (n = 24)	p value[§]
Epworth Sleepiness Scale score	7 (4 – 10)	7 (5 – 10)	7 (4 – 10)	0.68
OSLER duration	40.0 (38.5 – 40.0)	40.0 (32.5 – 40.0)	40.0 (21.1– 40.0)	0.27
Total Sleep Time (mins)	355 (284 – 401)	357 (290 – 411)	337 (300 – 404)	0.75
Sleep efficiency (%)	69 (61 – 80)	75 (59 – 81)	72 (64 – 81)	0.53
Stage 1 sleep (% TST)	25 (14 – 42) [‡]	33 (19 - 48) [‡]	31 (24 – 47)	0.06
Stage 2 sleep (% TST)	39 (27 - 52)	39 (19 - 47)	36 (25 - 43)	0.31
Deep sleep (% TST)	11 (6 – 18)	9 (6 – 17)	12 (8 – 20)	0.39
REM sleep (% TST)	19 (15 – 25)	17 (13 – 24)	17 (13 – 24)	0.96
Arousal Index (events/hour)	16.2 (12.5 – 21.8) ^{* #}	24.9 (19.0 – 39.4) [*]	19.7 (16.2 – 26.3) [#]	<0.001
AHI (events/hour)	7.6 (4.1 – 11.0)	27 (18.4 – 39.8)	27.4 (20.5 – 44.0)	
Apnoea Index (events/hour)	0.4 (0.1 – 2.6)	7.0 (3.0 – 15.9)	7.7 (0.9 – 17.9)	
Hypopnoea Index (events/hour)	5.9 (3.3 – 8.2)	17.1 (13.1 – 15.9)	18.1 (13.7 – 24.7)	
Time SpO2 <90% (% TST)	1.1 (0.1 – 19.8)	4.9 (1.7 – 22.7)	14.3 (2.4 – 26.3)	<0.001
PLM Index (events/hour)	14.3 (2.0 – 33.1)	12.5 (2.7 – 52.5)	8.7 (2.6 – 29.3)	0.80

[§]p value for comparison between CHF patients without SDB ('No SDB'), CHF patients with OSA and CHF patients with CSA, by Kruskal Wallis test;

[‡]p<0.05 for difference between CHF patients without SDB ('No SDB') and patients with OSA; ^{*}p<0.005 for difference between CHF patients without SDB ('No SDB') and patients with OSA; [#]p<0.05 for difference between CHF patients with CSA and patients without SDB ('No SDB')

Values shown are median (IQR). OSLER = Oxford sleep resistance test, TST = total sleep time; REM = rapid eye movement; SpO2 = finger pulse oxygen saturation. PLM = periodic limb movement. See Table 4.3 for other abbreviations

The %VLFI component of HRV was measurable in 83 (48%) of CHF patients. In 5 of these patients, a simultaneous HF peak could not be identified in the heart rate increment spectral density function and these results were excluded from further analysis. In the remaining CHF patients, paced cardiac rhythm (n = 45), atrial fibrillation (n = 29), >10% ectopic beats (n = 13) and technical failure (n = 3) prevented measurement of HRV (Figure 4.1). CHF patients in whom %VLFI was measurable were significantly younger (median age 66.2 years) than patients in whom %VLFI could not be measured (median age 72.2 years; p 0.006) (Table 4.5). BNP was significantly higher in CHF patients unsuitable for measurement of %VLFI suggesting more severe heart failure in this group, although there was no significant difference in the LVEF or NYHA class between the two groups.

Daytime sleepiness, assessed by the ESS and OSLER duration did not differ in CHF patients suitable and unsuitable for HRV analysis (Table 4.6). In addition, there were no significant differences in sleep duration, sleep architecture, apnoea hypopnoea index or duration of overnight hypoxia between these two groups. However, the periodic limb movement index (PLMI) in CHF patients in whom HRV was not measurable was 19.1/hour, which was significantly higher than that recorded in CHF patients suitable for HRV analysis (6.2/hour; p = 0.01).

Table 4.5. Characteristics in Chronic Heart Failure Patients Suitable and Unsuitable for Heart Rate Variability Analysis

	Patients with %VLFI measurement (n = 78)	Patients without %VLFI measurement (n = 95)	p value
Age (years)	66.2 (53.7 – 74.8)	72.2 (60.7 – 77.1)	0.006
Male (n,%)	67 (86)	81(85)	1.0
BMI (kg/m²)	30.1 (26.8 – 32.9)	28.5 (25.0 – 32.6)	0.10
Neck circumference (cm)	40.5 (38.3 – 42.3)	40.0 (37.5 – 43.0)	0.87
Waist/Hip ratio	1.02 (0.98 – 1.06)	1.02 (0.97 – 1.06)	0.67
Diabetes (n,%)	22 (28)	22 (23)	0.49
COPD/Asthma (n,%)	18 (23)	16 (17)	0.34
Ischaemic cardiomyopathy (n,%)	43 (55)	46 (48)	0.45
Beta blocker (n,%)	55 (71)	71 (75)	0.61
ACEI/ARB (n,%)	69 (89)	88 (93)	0.43
Atrial fibrillation (n,%)	0	53 (56)	
Cardiac pacing (n,%)	4 (5)	45 (47)	
NYHA (I/II/III/IV)	13/49/16/0	11/61/21/2	0.47
BNP (pg/ml)	69 (29 – 157)	170 (100 – 320)	<0.001
Left Ventricle ejection fraction (%)	40 (28 – 58)	43 (32 – 58)	0.76

Values shown are median (IQR), or number (percent) of patients (n,%).

%VLFI = percent very low frequency increment; See Table 4.1 for definition of additional abbreviations.

Table 4.6. Daytime Sleepiness, Polysomnographic Measurements of Sleep and Sleep-Disordered Breathing in Chronic Heart Failure Patients Suitable and Unsuitable for Heart Rate Variability Analysis

	Patients with %VLFI measurement (n = 78)	Patients without %VLFI measurement (n = 95)	p value
Epworth Scale Score	7 (4 – 10)	7 (4 – 10)	0.60
OSLER duration	40.0 (39.3 – 40.0)	40.0 (22.2 – 40.0)	0.28
Total Sleep Time (mins)	353 (284 – 405)	349 (291 – 400)	0.82
Sleep efficiency (%)	73 (60 – 81)	72 (62 – 80)	0.66
Stage 1 sleep (% TST)	26 (14 – 42)	31 (19 – 47)	0.14
Stage 2 sleep (% TST)	39 (27 – 48)	38 (25 – 50)	0.37
Deep sleep (% TST)	12 (7 – 20)	9 (6 – 15)	0.10
REM sleep (% TST)	19 (14 – 25)	18 (14 – 24)	0.51
Arousal Index (events/hour)	19.5 (13.5 – 27.2)	18.5 (13.5 – 26.4)	0.49
AHI (events/hour)	13.6 (6.4 – 25.8)	12.8 (7.2 – 24.1)	0.84
Apnoea Index (events/hour)	1.4 (0.2 – 8.3)	2.3 (0.3 – 6.8)	0.96
Hypopnoea Index (events/hour)	9.4 (3.9 – 17.3)	8.9 (5.6 – 15.0)	0.70
Time SaO₂ <90% (% TST)	1.8 (0.2 – 19.5)	4.8 (0.8 – 22.1)	0.30
3% ODI (dips/hour)	14.8 (7.7 – 24.9)	13.8 (8.3 – 23.6)	0.99
PLM Index (events/hour)	6.2 (1.5 – 23.9)	19.1 (4.0 – 49.1)	0.01

Values shown are median (IQR).

%VLFI = percent very low frequency increment; PLM = periodic limb movement; See Table 4.4 for definition of additional abbreviations

4.3.2. Analysis of Heart Rate Variability for Diagnosis of Sleep-Disordered Breathing in Chronic Heart Failure

In the 78 (45%) CHF patients in whom %VLFI was measured, SDB was present in 36 (46%) individuals with median AHI 26.9 (18.0 to 41.2) events/hour (mean AHI = 33.7 $\pm$ 21.6 events/hour). The predominant form of SDB was OSA, occurring in 31 patients with median AHI 28.0 (17.7 to 41.6) events/hour. Clinical characteristics of CHF patients in whom %VLFI could be measured are shown in Table 4.7. Patients with OSA were significantly more obese than those with no SDB ($p = 0.001$) or CSA ($p = 0.03$), and had significantly higher neck circumference ($p < 0.001$) and waist to hip ratio ($p = 0.02$) than those without SDB.

There was no significant difference in total sleep time, sleep efficiency or sleep architecture according to the presence or absence of SDB in CHF patients in whom HRV was measurable (Table 4.8). The occurrence of OSA was associated with a significantly higher arousal index (22.4/hour) than patients without SDB (17.1/hour, $p = 0.001$). Oxygen saturation (SaO₂) was $<90\%$ for a significantly higher proportion of the time asleep in CHF patients with OSA (4.7%) compared to no SDB (0.4%; $p < 0.005$). Whilst the median time with SaO₂ $<90\%$ was 8.3% of sleep time in patients with CSA, this value was not statistically different from patients with OSA or without SDB.

Table 4.7. Clinical Characteristics of Chronic Heart Failure Patients in whom the %VLFI Component of Heart Rate Variability was Measurable (n = 78)

	No SDB (n = 42)	OSA (n = 31)	CSA (n = 5)	p value[§]
Age (years)	65.6 (53.2 – 75.5)	63.9 (53.1 – 71.5)	73.6 (66.2 – 80.8)	0.18
Male (n,%)	35 (83)	27 (87)	5 (100)	0.58
BMI (kg/m²)	27.8 (25.0 – 32.5)*	32.1 (29.6 – 35.3)* [†]	27.7 (25.9 – 30.9) [†]	0.001
Neck size (cm)	39.0 (37.5– 40.7)*	42.0 (40.1 – 43.1)*	41.0 (39.5 – 42.8)	0.001
Waist/Hip ratio	1.01(0.96 – 1.05) [‡]	1.04(1.01 – 1.09) [‡]	0.97 (0.93 – 1.05)	0.03
Diabetes (n,%)	10 (24)	11 (36)	1 (20)	0.50
COPD/Asthma (n,%)	13 (31)	3 (10)	2 (40)	0.07
Ischaemic cardiomyopathy (n,%)	26 (62)	14 (45)	3 (60)	0.36
Beta blocker (n,%)	25 (60)	26 (84)	4 (80)	0.07
ACEI/ARB (n,%)	3 (91)	26 (84)	5 (100)	0.48
NYHA (I/II/III/IV)	4/29/9/0	7/17/7/0	2/3/0/0	0.26
BNP (pg/ml)	80 (35 – 162)	42 (24 – 125)	48 (31 – 557)	0.48
Left Ventricle EF (%)	41 (28 – 57)	50 (32 – 63)	39 (22 – 51)	0.47

[§]p value for comparison between CHF patients without SDB ('No SDB'), CHF patients with OSA and CHF patients with CSA, by Kruskal Wallis test

* p<0.005 for difference between CHF patients without SDB ('No SDB') and patients with OSA; [‡] p<0.05 for difference between CHF patients without SDB ('No SDB') and patients with OSA; [†] p<0.05 for difference between CHF patients with OSA and patients with CSA

Values shown are median (IQR), or number (percent) of patients (n,%). See Tables 4.1 and 4.3 for definition of abbreviations

Table 4.8. Daytime Sleepiness, Polysomnographic Measurements of Sleep and Sleep-Disordered Breathing in Chronic Heart Failure Patients in whom the %VLFI Component of Heart Rate Variability was Measurable

	No SDB (n = 42)	OSA (n = 31)	CSA (n = 5)	P value[§]
Epworth Sleepiness Scale score	7 (4 – 10)	7 (5 – 13)	7 (6.5 – 11)	0.57
OSLER duration	40.0 (40.0 – 40.0)	40.0 (38.1 – 40.0)	34.5 (1.3– 40.0)	0.09
Total Sleep Time (mins)	346 (265 – 401)	357 (320 – 415)	354 (285 – 426)	0.58
Sleep efficiency (%)	70 (59 – 82)	75 (59 – 81)	74 (60 – 89)	0.72
Arousal Index (events/hour)	17.1 (12.9 – 22.8)*	22.4 (1.7 – 35.5)*	19.4 (17.0 – 27.2)	0.004
Stage 1 sleep (% TST)	22 (12 – 35)	30 (19 – 44)	36 (22 – 62)	0.08
Stage 2 sleep (% TST)	42 (28 – 54)	39 (29 – 47)	17 (12 – 41)	0.14
Deep sleep (% TST)	13 (8 – 20)	10 (6 – 20)	12 (5 – 25)	0.40
REM sleep (% TST)	19 (15 – 26)	17 (12 – 24)	22 (15 – 25)	0.40
AHI (events/hour)	7.5 (3.2 – 11.1)	28.0 (17.7 – 41.6)	22.0 (18.1 – 27.8)	
Apnoea Index (events/hour)	0.3 (0.1 – 2.2)	7.3 (1.4 – 16.6)	5.8 (1.4 – 20.1)	
Hypopnoea Index (events/hour)	4.2 (2.1 – 7.7)	19.7 (14.4 – 25.8)	13.7 (7.7 – 18.0)	
Time SaO₂ <90% (% TST)	0.4 (0 – 19.5)*	4.7 (1.7 - 35.5)*	8.3 (1.7 – 16.7)	0.01
%VLFI (%)	2.46 (1.45 – 4.41)	2.35 (1.39 – 5.41)	0.78 (0.58 – 4.18)	0.39
3% ODI (events/hour)	8.8 (5.0 – 12.4)* [#]	25.4 (19.5 – 39.0)*	17.9 (15.5 – 26.2) [#]	<0.001
PLM Index (events/hour)	6.5 (1.2 – 23.5)	4.9 (1.5 – 33.8)	8.5 (1.1 – 83.7)	0.95

[§]p value for comparison between CHF patients without SDB ('No SDB'), CHF patients with OSA and CHF patients with CSA, by Kruskal Wallis test;

*p<0.005 for difference between CHF patients with OSA and patients without SDB ('No SDB'); [#]p<0.005 for difference between CHF patients with CSA and patients without SDB ('No SDB').

Values shown are median (IQR). See Table 4.1 and 4.4 for definition of abbreviations

The %VLFI was not correlated with the AHI (Spearman's $\rho = 0.005$) and there was no significant difference in %VLFI according to the presence or absence of SDB.

Median %VLFI was 2.46% (1.45 to 4.41) in CHF patients without SDB, 2.35% (1.39 to 5.41) in CHF patients with OSA and 0.78% (0.58 to 4.18) in CHF patients with CSA ($p = 0.39$; Table 4.8).

The %VLFI had an AUC of 0.50 (95% confidence interval 0.37 to 0.63, $p=0.99$) for diagnosis of SDB (Figure 4.2). At the a priori threshold of $\geq 2.23\%$, %VLFI had a poor diagnostic accuracy for detection of SDB in CHF, with a sensitivity of 58%, specificity of 48%, positive likelihood ratio of 1.11 and negative likelihood ratio of 0.88 (Table 4.9)

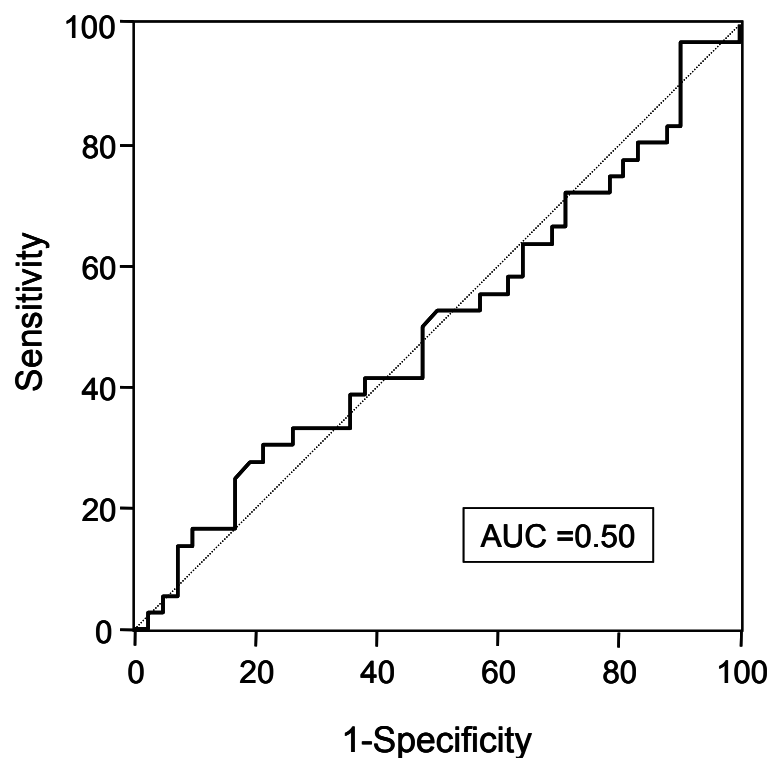


Figure 4.2. %Very Low Frequency Increment Receiver Operating Characteristic Curve for Diagnosis of Sleep-Disordered Breathing (AHI >15/hour) in Patients with Chronic Heart Failure.

Table 4.9. Diagnostic Accuracy of %VLFI for Detection of Sleep-Disordered Breathing in Patients with Chronic Heart Failure (n = 78)

% VLFI parameter	%VLFI threshold	AHI threshold for SDB diagnosis (events/hour)	Sensitivity (95% C.I.)	Specificity (95% C.I.)	Positive Predictive Value (95% C.I.)	Negative Predictive Value (95% C.I.)	Positive Likelihood ratio (95% C.I.)	Negative Likelihood ratio (95% C.I.)	Area under ROC curve (95% C.I.)
%VLFI ₀₋₆	≥2.23	5	59 (47 – 71)	59 (35 – 82)	84 (73 – 95)	29 (14 – 44)	1.43 (0.78 – 2.63)	0.70 (0.42 – 1.15)	0.55 (0.39 – 0.71)
		15	58 (42 – 74)	48 (33 – 63)	49 (34 – 64)	57 (41 – 74)	1.11 (0.75 – 1.66)	0.88 (0.53 – 1.44)	0.50 (0.37 – 0.63)
		20	56 (37 – 75)	45 (32 – 59)	33 (19 – 47)	69 (53 – 84)	1.02 (0.67 – 1.57)	0.97 (0.57 – 1.65)	0.49 (0.34 – 0.63)
		30	63 (39 – 86)	47 (34 – 59)	23 (11 – 36)	83 (70 – 95)	1.17 (0.75 – 1.83)	0.80 (0.40 -1.59)	0.54 (0.37 – 0.70)
	≥2.4	15	47 (31 – 64)	50 (35 – 65)	45 (29 – 61)	53 (37 – 68)	0.94 (0.60 – 1.49)	1.06 (0.69 – 1.63)	0.50 (0.37 – 0.63)
%VLFI _{diary}	≥2.23	15	56 (39 – 72)	43 (28 – 58)	45 (31 – 60)	53 (36 – 70)	0.97 (0.66 – 1.44)	1.04 (0.63 – 1.72)	0.48 (0.35 – 0.61)

%VLFI₀₋₆ = %VLFI measured between midnight and 0600; %VLFI_{diary} = %VLFI measured using diary sleep time; AHI = apnoea hypopnoea index; 95% C.I. = 95% confidence interval; ROC curve = receiver operating characteristic curve

A %VLFI threshold of 2.4% has been reported to be the optimal cutoff value for detection of OSA in patients without CHF. Using this threshold for detection of SDB in CHF patients, diagnostic accuracy worsened, with sensitivity 47%, specificity 50%, positive likelihood ratio of 0.94 and negative likelihood ratio of 1.06 (table 4.9).

The diagnostic accuracy of %VLFI was assessed using different AHI thresholds of >5, >20 and >30 events/hour for diagnosis of SDB. Whilst there was an improvement in sensitivity and negative predictive value at an AHI threshold of ≥ 30 events/hour, likelihood ratios were not improved and the area beneath the ROC curve was not significantly improved (Table 4.9, Figure 4.3a - c).

Diagnostic accuracy of the %VLFI calculated using the sleep diary times (%VLFI_{diary}) was also assessed. There was no significant improvement in sensitivity (56%), specificity (43%) or area beneath the %VLFI_{diary} ROC curve (AUC = 0.48) using this method (Table 4.9, Figure 4.3d)

Spectral and time domain components of HRV were also quantified in the 78 CHF patients with measurement of %VLFI (Table 4.10). There was a significant increase in absolute low frequency (LF) power in CHF patients with OSA compared to CHF patients without SDB or with CSA, although this difference was not seen when LF power was expressed in normalised units (nu). The percentage of adjacent NN intervals which differ by >50 milliseconds (pNN50) and the square root of the mean of the squares of differences between adjacent NN intervals (RMSSD) time domain measurements also differed significantly between CHF patients without SDB and those with OSA. These HRV parameters showed improved diagnostic accuracy compared to %VLFI with AUC (95% confidence interval) of 0.69 (0.57 to 0.80) for absolute LF power, 0.71 (0.60 to 0.83) for pNN50, and 0.70 (0.58 to 0.81) for RMSSD.

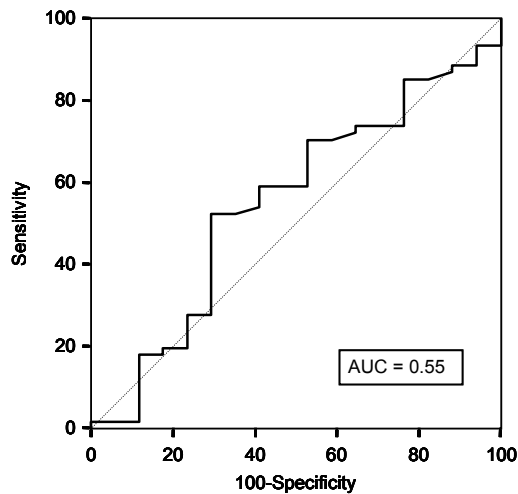


Figure 4.3a

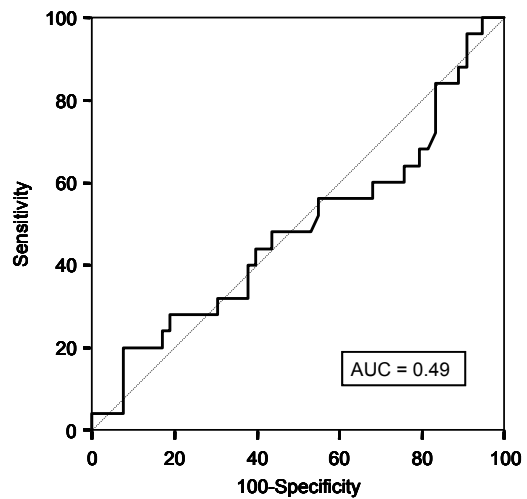


Figure 4.3b

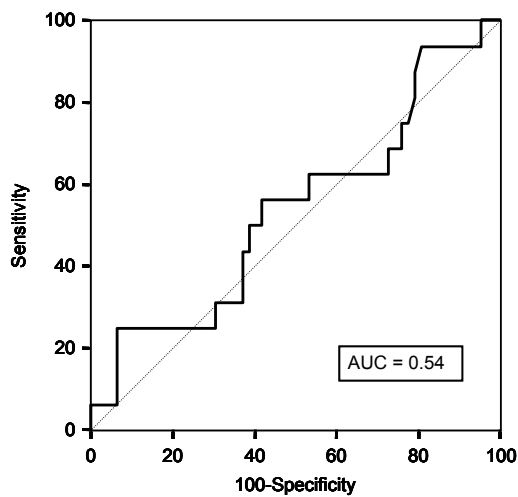


Figure 4.3c

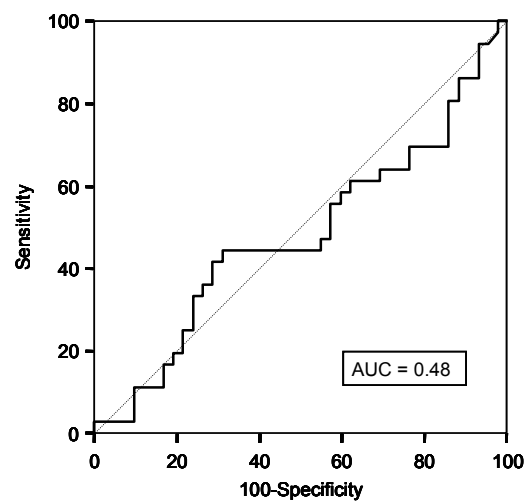


Figure 4.3d

Figure 4.3. %VLFI ROC curves for diagnosis of Sleep-Disordered Breathing in Chronic Heart Failure using different AHI diagnostic thresholds of ≥ 5 /hour (figure 4.3a), ≥ 20 /hour (Figure 4.3b) ≥ 30 /hour (Figure 4.3c).

Figure 4.3d shows the %VLFI_{diary} ROC curve.

(The dashed line indicates the line of identity which would be expected if results occurred by pure chance. AUC = area under the curve)

Table 4.10. Spectral and Time Domain Heart Rate Variability Parameters in Chronic Heart Failure Patients

	No SDB (n = 41)	OSA (n = 31)	CSA (n = 5)	p value[§]
VLF power (absolute)	3526 (2162 – 7513)	4150 (2835 – 6624)	4960 (3050 – 8012)	0.73
LF power (absolute)	299 (161 – 629)*	515 (391 – 1366)*	380 (89 – 3860)	0.009
LF power (nu)	68.4 (55.8 – 77.8)	70.7 (57.8 – 82.7)	66.0 (49.0 – 84.5)	0.77
HF power (absolute)	116 (51.8 – 215)	281 (123 – 468)	123 (46 – 1965)	0.30
HF power (nu)	31.6 (22.2 – 44.2)	29.3 (17.3 – 42.2)	34.1 (15.5 – 51.0)	0.77
LF/HF ratio	2.16 (1.27 – 3.51)	2.41 (1.26 – 4.78)	1.94 (1.20 – 6.50)	0.82
SDNN	68 (55 – 99)	78 (67 – 97)	89 (55 – 118)	0.40
SDANN	50 (37 – 72)	47 (39 – 66)	51 (34 – 77)	0.92
SDNNI	35 (27 – 42)	41 (36 – 55)	41 (30 – 54)	0.10
pNN50 (%)	2.12 (0.92 – 7.49)*	8.81 (3.32 – 18.58)*	12.68 (3.04 – 20.44)	0.006
RMSSD	24 (20 – 36)*	35 (27 – 57)*	36 (22 – 110)	0.01
Mean NN	921 (819 – 1061)	948 (860 – 1036)	944 (862 – 1008)	0.86

[§]p value for comparison between CHF patients without SDB ('No SDB'), CHF patients with OSA and CHF patients with CSA, by Kruskal Wallis test;

*p<0.005 for difference between CHF patients with OSA and patients without SDB ('No SDB')

VLF = Very low frequency; LF = Low frequency; HF = High frequency; nu = normalised units; SDNN = standard deviation of NN intervals; SDANN = standard deviation of average NN interval during all 5 minute epochs throughout recording; SDNNI = mean of the standard deviations of NN intervals during all 5 minute epochs throughout recording; pNN50 = proportion of adjacent NN intervals which differ by >50 milliseconds; RMSSD = the square root of the mean of the squares of differences between adjacent NN intervals; NN = normal to normal interbeat interval

Values shown are median (IQR). See Table 4.3 for definition of additional abbreviations

4.3.3. Overnight Pulse Oximetry for Diagnosis of Sleep-Disordered Breathing in Chronic Heart Failure

The 3% ODI was determined from the Pulsox-3i oximeter recording in 171 CHF patients. Technical failure prevented measurement in 2 patients. Median 3% ODI in all CHF patients was 14.2 (8.2 to 24.2) dips/hour. The median 3% ODI was significantly higher in CHF patients with OSA (25.4 dips/hour) and CSA (17.9 dips/hour) compared to CHF patients without SDB (8.8 dips/hour, $p < 0.001$) (Table 4.8).

In all 171 CHF patients in whom overnight oximetry was measured, the area under the 3% ODI ROC curve was 0.92 (95% C.I. 0.88 to 0.96), indicating a high diagnostic accuracy (Figure 4.4a). Two false negative results would have occurred using the pre-specified 3% ODI threshold of >7.5 dips/hour to diagnose SDB. At this threshold, the 3% ODI had sensitivity of 97% and negative likelihood ratio of 0.08 (Table 4.11).

However, there were 65 false positive results with overnight oximetry, and the 3% ODI had specificity of 32% with positive likelihood ratio of 1.43 for diagnosis of SDB in CHF.

In CHF patients in whom %VLFI was not measurable, the 3% ODI could be determined in 94 (99%) patients and had a high accuracy for diagnosis of SDB, with an area under the ROC curve of 0.92 (95% C.I. 0.86 to 0.98; Figure 4.4b). At the threshold of >7.5 dips/hour, the 3% ODI had sensitivity of 98%, specificity of 24%, positive likelihood ratio of 1.28 and negative likelihood ratio of 0.10 for diagnosis of SDB in this group of CHF patients (Table 4.11).

In CHF patients included in the HRV analysis, the 3% ODI could be measured in 77 (99%) patients. Diagnostic accuracy of the 3% ODI was similarly high in this group, with area under the 3% ROC curve of 0.91 (95% C.I. 0.85 to 0.98). At the >7.5 dips/hour cutoff, sensitivity was 97% and specificity 41% with negative likelihood ratio of 0.07 for diagnosis of SDB (Table 4.11, Figure 4.4c).

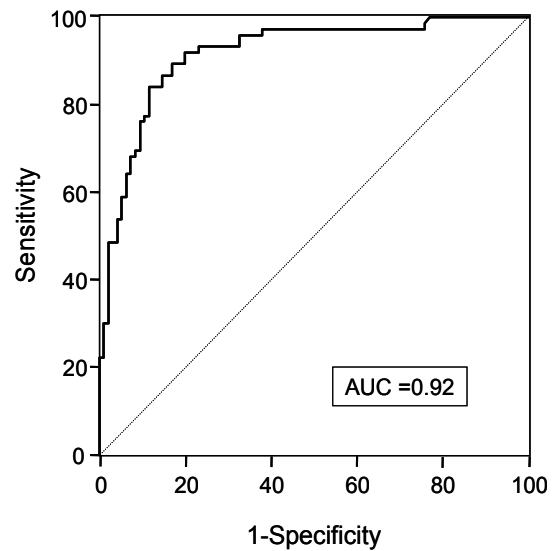


Figure 4.4a

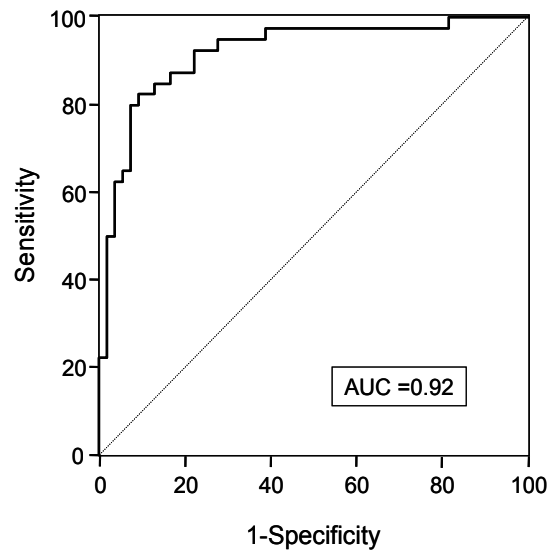


Figure 4.4b

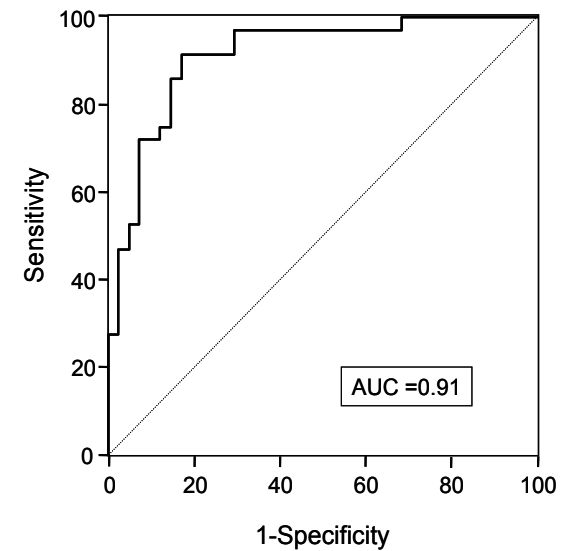


Figure 4.4c

Figure 4.4. Receiver Operating Characteristic curves to show accuracy of 3% ODI for diagnosis of sleep-disordered breathing in all chronic heart failure (CHF) patients (n = 171; Figure 3a), in CHF patients in whom %VLFI was not measurable (n = 94; Figure 3b) and CHF patients included in the heart rate variability analysis (n = 77; Figure 3c).

Table 4.11. Diagnostic Accuracy of the 3% Oxygen Desaturation Index for Detection of Sleep-Disordered Breathing in Patients with Chronic Heart Failure

	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	Positive Likelihood Ratio	Negative Likelihood Ratio	Area under ROC curve
All CHF patients* (n = 171)	97 (91 – 100)	32 (22 – 41)	53 (45 – 62)	94 (79 – 99)	1.42 (1.24 – 1.64)	0.08 (0.02 – 0.34)	0.92 (0.88 – 0.96)
CHF patients unsuitable for %VLFI measurement* (n = 94)	98 (87 – 100)	24 (13 – 35)	49 (38 – 60)	93 (66 – 100)	1.28 (1.10 – 1.50)	0.10 (0.01 – 0.76)	0.92 (0.86 – 0.98)
CHF patients included in HRV analysis* (n = 77)	97 (85 – 100)	41 (26 – 57)	59 (47 – 72)	94 (73 – 100)	1.66 (1.28 – 2.16)	0.07 (0.01 – 0.48)	0.91 (0.85 – 0.98)

*Diagnostic accuracy values were assessed using the a priori cutoff of >7.5 desaturations/hour for diagnosis of sleep-disordered breathing, and are presented with 95% confidence intervals

ROC = receiver operating characteristic; CHF = chronic heart failure; %VLFI = % very low frequency increment of heart rate variability; HRV = heart rate variability

The diagnostic accuracy of the $\geq 4\%$ ODI measured from the pulse oximeter was also assessed in 171 CHF patients. The $\geq 4\%$ ODI had an AUC of 0.89 (95% C.I. 0.84 to 0.94) for diagnosis of SDB in CHF. At a threshold of >7.5 dips/hour, sensitivity was 86%, specificity 78%, positive likelihood ratio 3.87 and negative likelihood ratio 0.19. At a threshold of ≥ 10 dips/hour, the $\geq 4\%$ ODI specificity increased to 91% with positive likelihood ratio 8.19, whilst sensitivity decreased to 78% with negative likelihood ratio 0.25.

4.3.4. Pulse Rate Rise Measured from the Pulse Oximeter for Detection of Sleep-Disordered Breathing in Chronic Heart Failure

In 77 CHF patients included in the HRV analysis who were also suitable for analysis of pulse oximetry, the median frequency of pulse rate rises ≥ 6 bpm (PRRI-6) was 21.7 (10.3 to 30.5)/hour, and the median frequency of pulse rate rises ≥ 10 bpm (PRRI-10) was 5.8 (2.9 to 10.9)/hour. There was a weak but statistically significant correlation between the PRRI-6 and the AHI (Spearman's rho = 0.32; $p = 0.005$), and the PRRI-6 had an AUC of 0.68 (95% C.I. 0.56 – 0.80) for diagnosis of SDB in CHF. However, the PRRI-6 was not significantly correlated with sleep efficiency ($r = 0.18$; $p = 0.13$), arousal index ($r = 0.17$; $p = 0.14$) or PLM index ($r = -0.1$; $p = 0.29$). The PRRI-10 was also weakly correlated with the AHI ($r = 0.27$; $p = 0.02$) with AUC of 0.65 (95% C.I. 0.53 to 0.77) for diagnosis of SDB, but there was no significant correlation between the PRRI-10 and sleep efficiency ($r = 0.13$; $p = 0.25$) or arousal index ($r = 0.14$; $p = 0.24$). A weak inverse correlation was found between the PRRI-10 and PLM index ($r = -0.23$; $p = 0.04$).

4.3.5. Diagnostic Accuracy of Heart Rate Variability Analysis versus Overnight Pulse Oximetry

To compare the diagnostic accuracy of HRV analysis and overnight pulse oximetry, the AUC for %VLFI and 3% ODI were compared in the 77 CHF patients in whom both parameters were measurable. In this subgroup, the AUC for the 3% ODI was 0.91 (Table 4.11; Figure 4.4c) which was significantly greater ($p < 0.001$) than the AUC for the %VLFI (Table 4.9; Figure 4.2).

4.4.1. Discussion

The main finding of this study is that the %VLFI component of HRV was unable to discriminate between the presence or absence of SDB in CHF. Moreover, the %VLFI was measurable in only 78 (45%) patients with CHF as cardiac pacing and rhythm disturbances prevented analysis of HRV in a significant proportion of patients. In those CHF patients in whom HRV was measured, the %VLFI ROC curve was 0.50 suggesting that the %VLFI was no better at diagnosing SDB in CHF than tossing a coin. At a cutoff of $\geq 2.23\%$, the %VLFI had a low positive likelihood ratio and high negative likelihood ratio indicating that it is neither sufficiently sensitive nor specific to be of clinical use to rule in or rule out SDB in patients with CHF.

In contrast, the 3% ODI was measurable with a wrist worn oximeter in 99% of CHF patients. The area beneath the ROC curve indicated that the 3% ODI had a high diagnostic accuracy for detection of SDB in CHF. When evaluated in all 171 CHF patients, at a cutoff of > 7.5 dips/hour, the 3% ODI had a high sensitivity and low negative likelihood ratio. Therefore, measurement of overnight pulse oximetry would be of greatest use to rule out SDB in CHF patients.

As discussed in Section 4.1, clinical symptoms may be of little use when trying to identify CHF patients with SDB. Moreover, in clinical trials of treatment for SDB in CHF, the AHI is the principle criterion used to diagnose SDB and recruitment does not depend on the presence of symptoms (Bradley, 2005). This contrasts with treatment of obstructive sleep apnoea hypopnoea syndrome in the general population where symptoms are of great importance in determining whether treatment is indicated (Scottish Intercollegiate Guidelines Network, 2003; National Institute for Health and Clinical Excellence, 2008). Therefore, diagnosis and decisions about treatment of SDB in CHF may be determined exclusively by a metric of SDB.

Polysomnography is recommended for diagnosis of SDB in CHF (Kushida, 2005), but there are insufficient resources to be able to screen all CHF patients by this method. Portable monitors can be used to diagnose OSA in otherwise healthy adults with a high pretest probability of OSA (Collop, 2007), and they may be a simple and cost effective alternative to polysomnography (Pietzsch, 2011).

The simplest portable monitors recording one or two physiological parameters have a high accuracy for diagnosis of OSA (Vazquez, 2000; Roche, 2002; Erman, 2007), and they may be suitable to screen for SDB in CHF. However, the utility of these monitors to identify SDB in patients with cardiovascular comorbidities is uncertain, and this has been identified as a research priority in a recent international workshop report addressing the ambulatory management of adults with OSA (Kuna, 2011a).

4.4.1. Analysis of Heart Rate Variability to Detect Sleep-Disordered Breathing in Chronic Heart Failure

HRV analysis has been proposed as a simple screening test for diagnosis of SDB (Guilleminault, 1984). The very low frequency (VLF) spectral parameter of HRV reflects

oscillations in heart rate occurring at $<0.04\text{Hz}$, which are increased by voluntary periodic breathing (Francis, 2000), CSA (Leung, 2003) and OSA (Shiomi, 1996). Measurement of the %VLFI component of HRV has been reported to be of value to screen for OSA in adults without CHF; at a threshold of $\geq 2.4\%$, %VLFI has been reported to have sensitivity of 78 to 91% and specificity of 34 to 70% for diagnosis of OSA (see Table 8.4) (Roche, 2002; Roche, 2004; Roche, 2007).

The %VLFI has also been evaluated for detection of SDB in CHF. Vazir et al., (2006) measured HRV in 33 male patients with systolic heart failure and found that the %VLFI was significantly correlated with the AHI ($r = 0.52$), with AUC of 0.82 for diagnosis of SDB in CHF (Vazir, 2006). At an optimum threshold of $\geq 2.23\%$, %VLFI had a sensitivity of 85%, specificity 65%, with negative predictive value of 87% for SDB diagnosis, and the authors recommended that it may be suitable to rule out SDB in CHF.

The findings of the current study do not agree with the study by Vazir et al. Whilst studies that have evaluated the utility of %VLFI to screen for OSA in adults without heart failure have reported the optimum diagnostic cutoff to be $\geq 2.4\%$ (Roche, 2002; Roche, 2004; Roche, 2007), there was no improvement in the sensitivity, specificity or the likelihood ratios when this cutoff was used to identify SDB in CHF. Our results show that %VLFI has no ability to identify SDB in patients with CHF. Moreover, our findings are in agreement with a report evaluating the utility of HRV to screen for SDB in CHF which was published whilst this study was being conducted. Damy et al., (2009) studied 54 CHF patients with low ejection fraction heart failure and also found that the %VLFI had poor diagnostic accuracy for SDB, with an AUC of 0.53 (Damy, 2009).

Why is %VLFI Inaccurate for Identification of Sleep-Disordered Breathing in Chronic Heart Failure?

The poor diagnostic accuracy of %VLFI in patients with CHF may be a result of reduced HRV and impaired autonomic cardiac reactivity that occurs in association with heart failure (Saul, 1988; Casolo, 1989; Patel, 2010). The results of the current study may also have been influenced by the inclusion of a number of older patients, as the cardiovascular response to arousal is known to be reduced with ageing (Goff, 2008). Cardiac autonomic regulation and spectral components of HRV are also significantly reduced by ageing (Stein, 1997; Fukusaki, 2000; Singh, 2006) and the median age of CHF patients in this study was higher than participants in previous studies. Autonomic function can also be impaired by medical comorbidities, particularly diabetes. Whilst some previous studies of the diagnostic utility of %VLFI have excluded patients with comorbidities associated with autonomic dysfunction (Roche, 2002; Roche, 2004), 26% of patients in the current study reported a diagnosis of diabetes. Finally, cardiovascular medications may have significantly altered HRV in CHF. Beta blockers were prescribed to 73% of CHF patients and these can increase vagal cardiac modulation, preferentially increasing the high frequency component of HRV (Cook, 1991; Mortara, 2000). ACE inhibitors or ARB medications were prescribed to 91% of patients and these may also increase HRV through enhanced vagal modulation of cardiac rate (Binkley, 1993).

The %VLFI can increase in association with other sleep related conditions, and this may cause false positive results when it is used to screen for SDB. Concomitant sleep disorders such as insomnia and excessive sleep fragmentation (unrelated to SDB) are prevalent in CHF (Redeker, 2006) and have been reported to increase %VLFI (Roche, 2007). Periodic limb movements (PLM) occur frequently in CHF (Javaheri, 2006c) and these can also significantly increase the %VLFI (Roche, 2007; Sforza, 2007). In the current study, there was a high prevalence of PLM, with 111 (64%) CHF patients

having a periodic limb movement index (PLMI) ≥ 5 /hour and 81 (49%) having a PLMI ≥ 15 /hour. However there was no correlation between %VLFI and PLMI (Spearman's rho = 0.01) or arousal index (Spearman's rho = 0.034). Median %VLFI was not significantly different in CHF patients with PLMI ≥ 5 /hour compared to those without PLM.

Therefore, it appears unlikely that these factors contributed to the present findings.

Why is the Diagnostic Accuracy of %VLFI for Sleep-Disordered Breathing in Chronic Heart Failure Different in this Study from our Previous Report?

It is unlikely that the reasons discussed above account in full for the discrepancy in findings between the current study and those reported by Vazir et al. (Vazir, 2006). In addition, the mean age, AHI and frequency of prescription of beta blockers and ACE inhibitors/ARB medication were similar in both studies. The inclusion of female CHF patients in the current study may have weakened any association between %VLFI and SDB as HRV has been reported to be poorly correlated with indices of SDB in females (Wang, 2008). However, the majority of patients enrolled were male (86%) and there was no significant change in the area under the %VLFI ROC curve when the analysis was performed following exclusion of female patients (AUC = 0.49; 95% C.I. 0.36 to 0.63).

The current study has enrolled a heterogeneous population of CHF patients with both systolic myocardial dysfunction and HFPEF. It is possible that inclusion of a diverse cohort of CHF patients may have influenced the diagnostic accuracy of %VLFI.

Therefore, a further analysis was undertaken to investigate whether diagnostic accuracy of %VLFI was enhanced following exclusion of CHF patients with HFPEF. In a subgroup of 66 male CHF patients with LVEF <50%, selected to match the inclusion criteria of Vazir et al., HRV could be measured in 29 (44%) patients and SDB (AHI >20/hour) occurred in 9 (31%) of these patients. The median %VLFI was 1.23% (0.58

to 4.31) in patients with SDB, and 2.95% (1.78 to 4.86; $p = 0.15$) in CHF patients without SDB, with AUC for %VLFI of 0.33 (95% CI 0.07 to 0.58). Thus it is unlikely that the poor diagnostic accuracy of %VLFI in this thesis can be explained by the inclusion of CHF patients with HFPEF.

Moreover, whilst our study and the study by Vazir et al., appear to report discrepant results for the diagnostic accuracy of %VLFI, comparison of the AUC under the curve suggests that the results of the two studies are not statistically significantly different. Using the same threshold of $AHI \geq 15$ /hour for SDB diagnosis as the current study, Vazir et al., reported the %VLFI AUC was 0.72 (standard error of 0.100). In the current study, the area under the %VLFI AUC was 0.50 (standard error 0.067) and the difference in area beneath the two ROC curves was 0.22 (95% C.I. -0.02 to 0.46) which did not reach statistical significance ($p = 0.07$). It is likely that the larger sample size and greater statistical power of this study has provided a more precise measure of the diagnostic accuracy of %VLFI showing that it has poor sensitivity and specificity for diagnosis of SDB in CHF. This finding also highlights the need for adequately powered trials of portable monitors (Kuna, 2011a).

Association of Other Heart Rate Variability Parameters with Sleep-Disordered Breathing in Chronic Heart Failure

Whilst %VLFI was not increased in CHF patients with SDB compared to those without SDB, there were significant differences in pNN50, RMSSD and absolute LF power. RMSSD and SDNNI time domain parameters of HRV (indicating rapid changes in heart rate through vagal modulation) have previously been reported to be significantly increased in non CHF patients with OSA during nocturnal (midnight to 0700) recordings of HRV (Roche, 1999). The difference between day and night measurements of these parameters was a significant predictor of OSA (Roche, 1999; Roche, 2002). However,

the association of these parameters with SDB in CHF can not be examined in this study as daytime recording of HRV was not performed. Furthermore, subsequent studies with longer duration of HRV recording of 12 to 24 hours have reported no significant alteration of time domain parameters of HRV in patients with OSA (Roche, 2007).

Whilst absolute LF power was increased in CHF patients with OSA in this study, other authors have found LF power was reduced in CHF patients with OSA (Damy, 2009). Moreover, in patients without CHF, differing effects of OSA on spectral components of HRV have been reported, including increased VLF power (Shiomi, 1996; Roche, 2007), increased normalised LF power (Narkiewicz, 1998a) and increased LF/HF ratio (Narkiewicz, 1998a; Hilton, 2001; Gula, 2003).

Therefore, whilst the current study has shown the pNN50, RMSSD and absolute LF power to have a greater AUC than %VLF1 for diagnosis of SDB, there are conflicting observations on the utility of time domain and spectral components of HRV for diagnosis of SDB. This study is not adequately powered to address differences in diagnostic accuracy between these different parameters.

4.4.2. Overnight Pulse Oximetry for Detection of Sleep-Disordered Breathing in Chronic Heart Failure

It has previously been reported that the utility of HRV to screen for SDB in CHF may be limited by the high prevalence of atrial fibrillation and cardiac pacing (Vazir, 2006). An alternative test would therefore be required to screen for SDB in patients unsuitable for HRV analysis. Measurement of the frequency of 2% or 4% oxygen desaturations from overnight pulse oximetry has been reported to have a high sensitivity to detect SDB in patients with low ejection fraction CHF. Series et al., (2005) reported the $\geq 2\%$ ODI had

a sensitivity of 85% and specificity of 93% when pulse oximetry was used to detect SDB in 50 patients with systolic heart failure (Series, 2005). In 41 CHF patients, Staniforth et al., (1998) reported the 4% ODI had a sensitivity of 87% with specificity of 81% to identify SDB (Staniforth, 1998a).

Whilst oximetry is commonly used to diagnose OSA in many sleep clinics, it is traditionally used as a rule in test. However, pulse oximetry can not distinguish between central or obstructive sleep apnoea (Series, 2005) and in CHF, a positive oximetry result may require further investigation by polysomnography or polygraphy sleep study to classify SDB as OSA or CSA. Therefore, in this study oximetry was evaluated as a rule out test with greater emphasis placed on the utility of a negative result to exclude SDB. To optimise the sensitivity of oximetry to rule out SDB, a conservative 3% ODI threshold of >7.5 dips/hour was selected a priori. At this threshold, the 3% ODI had a high sensitivity of 97% and clinically useful negative likelihood ratio of 0.08, suggesting that an overnight oximetry test can provide clinically meaningful information. For example, in an asymptomatic CHF patient undergoing screening for SDB, their pretest probability is likely to be 50%, based on the prevalence of SDB reported in many studies. Using Fagans' nomogram (Fagan, 1975), it can be shown that a negative overnight pulse oximetry result (3% ODI <7.5 dips/hour) would reduce the post test probability of SDB to 7% (Figure 4.5; see also Appendix 8.7.2).

Whilst a negative oximetry result is highly useful to reduce the clinical probability of SDB, a positive oximetry result (3% ODI > 7.5 dips/hour) is of less clinical utility as indicated by the specificity of 32% and positive likelihood ratio of 1.43. Whilst false positive results are undesirable with any diagnostic test, in the context of screening for SDB in CHF they may not lead to adverse clinical consequences as subsequent more detailed sleep studies which would be used to classify SDB as OSA or CSA should identify false positive oximetry results.

Moreover, in a post hoc analysis of the pulse oximetry data from the current study, the optimum 3% ODI cutoff for diagnosis of SDB in CHF was >11.6 dips/hour. With this cutoff the specificity of 3% ODI improved to 67% (95% C.I. 56 to 76%) whilst sensitivity remained high at 96% (95% C.I. 89 to 99%) and negative likelihood ratio was lowered to 0.06 (95% C.I. 0.02 to 0.18) The reduction in false positive oximetry results using the >11.6 dips/hour cutoff would have saved 33 more detailed sleep studies at the expense of only 1 additional false negative result, compared to the >7.5 dips/hour threshold.

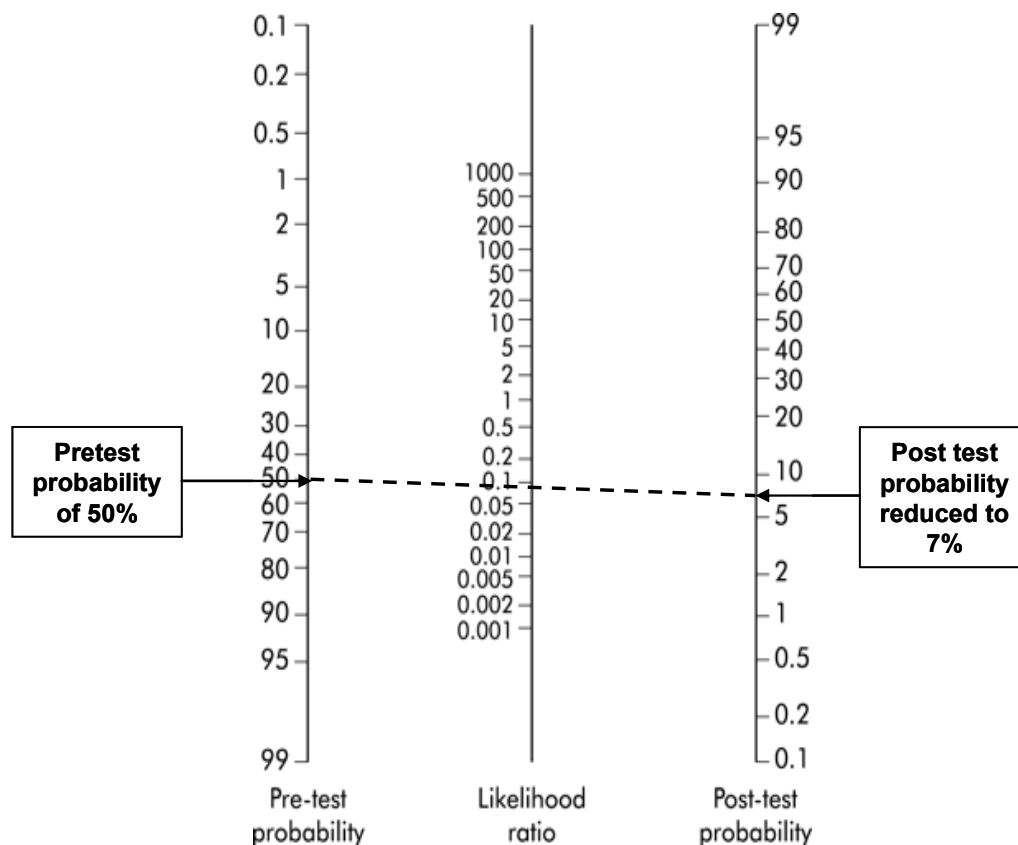


Figure 4.5. Fagan's nomogram. In an asymptomatic CHF patient undergoing overnight oximetry, the probability of SDB is reduced from 50% to 7% if the 3% ODI is <7.5 dips/hour.

(Nomogram adapted from Fagan TJ. Letter: Nomogram for Bayes theorem. N Engl J Med. 1975 Jul 31;293(5):257)

4.4.3. Alternative Portable Monitors for Identification of Sleep-Disordered Breathing in Chronic Heart Failure

Alternative single channel portable monitors including measurement of nasal pressure have also been suggested as a convenient method for detection of SDB. In patients without CHF, measurement of nasal pressure has been reported to have high sensitivity and specificity for diagnosis of OSA, (Erman, 2007; Grover, 2008; Ragette, 2010; Rofail, 2010b). In 41 CHF patients, nasal pressure measurement had a sensitivity of 87% and negative likelihood ratio of 0.14 for detection of Cheyne-Stokes respiration (Weinreich, 2009) which is similar to the diagnostic accuracy of the 3% ODI in the current study. In addition, Rofail et al., (2010) have reported that there is no difference in diagnostic accuracy between 3 nights of overnight pulse oximetry and nasal pressure monitoring for diagnosis of OSA in adults without CHF (Rofail, 2010a). However, the rate of failed studies may be lower with pulse oximetry. A comparative effectiveness study reported a higher rate of technically adequate studies during a single night of overnight pulse oximetry (91.8%), compared to nasal pressure monitoring (77.6%) (Rofail, 2010a).

4.4.4. Strengths of this Study

A strength of this study is the recruitment of a heterogeneous cohort of CHF patients, including 59 (34%) with LVEF >50%. Many studies investigating SDB in CHF have used a minimum ejection fraction recruitment criterion to enrol patients with low ejection fraction heart failure. However, up to 50% of CHF patients may have HFPEF (Hogg, 2004). SDB is important in HFPEF as it may contribute to cardiac dysfunction and treatment of OSA with continuous positive airway pressure has been reported to

prevent progression or reverse abnormalities in diastolic function (Arias, 2005; Bitter, 2009b).

In addition, this study has included patients with common comorbidities and self reported COPD or asthma was present in 20% of this cohort. Despite the inclusion of patients with pulmonary disease which may influence overnight oxygen saturation independent of SDB (Catterall, 1983), the diagnostic accuracy of the 3% ODI was high as demonstrated by the AUC of 0.92. However, this may have contributed to the low specificity of overnight pulse oximetry at the a priori cutoff of >7.5 desaturations/hour

A further strength is the use of polysomnography as the reference standard for diagnosis of SDB. Polysomnography provides the most complete information about sleep architecture, sleep fragmentation and periodic limb movements that have been reported to confound HRV measurement (Sforza, 2007). In addition, the simultaneous recording of polysomnography, ambulatory ECG and overnight oximetry has avoided any potential for night to night variability of AHI to have influenced the results (Le Bon, 2000; Bittencourt, 2001).

Whilst the use of home polysomnography has previously been validated in community living individuals in the Sleep Heart Health Study (Iber, 2004), the current study shows that it can be successfully used and is acceptable to the majority of CHF patients, with a low number of technical failures.

Finally, this is the largest study to date to investigate the accuracy and utility of single channel portable monitoring for diagnosis of SDB in CHF.

4.4.5. Limitations of this Study

Some important limitations of this study are acknowledged. The first relates to the recruitment of patients from a tertiary care heart failure clinic, who may not be

representative of typical heart failure patients. Thus, the finding that a paced cardiac rhythm prevented HRV measurement in 26% of CHF patients was predominantly due to the use of cardiac resynchronisation therapy (CRT). HRV may be measurable in a greater proportion of CHF patients in centres where CRT is less frequently implanted. In addition, HRV analysis can be performed in patients with CRT who are not atrial paced; however, the results of this study suggest this would be of no value to screen for SDB in CHF.

Another consideration is that we did not meet our desired sample size as HRV could not be analysed in all 180 CHF patients recruited. Whilst this study has therefore not achieved the desired statistical power for investigation of the diagnostic accuracy of the %VLFI to detect SDB in CHF, it is the largest study to date to evaluate this parameter in CHF patients. Moreover, the results of this study suggest a sample size of over 780 CHF patients would have been needed to be adequately powered ($1-\beta = 80\%$) to exclude a difference in %VLFI of $>0.5\%$ between CHF patients with and without SDB, at a significance level (α) of 0.05.

Whilst polysomnography was used as the reference standard for diagnosis of SDB, this was not attended and periods of data loss occurred in some patients during the recordings. Two CHF patients required a second night of overnight monitoring due to inadequate polysomnography data. The signals most commonly affected were the nasal pressure airflow trace and polysomnography oxygen saturation. During periods where nasal pressure recording was inadequate or mouth breathing was suspected, reductions in thoracoabdominal excursions could be used to score apnoeas and hypopnoeas (Gould, 1988).

Periods of poor quality pulse oximetry signal may also have contributed to the high proportion of time asleep with oxygen saturation $<90\%$ that was recorded in some patients. This problem was resolved following a change to an oximeter probe which

could be secured to the finger after study number 91. However, SDB may have been underestimated in a small number of CHF patients during periods when the nasal pressure or oximetry signal was poor.

4.4.6. Summary

In summary, in a large sample of heterogeneous CHF patients recruited from a cardiology setting, the %VLFI was measurable in only 45% of patients and it had a poor diagnostic accuracy for SDB. The %VLFI component of HRV can not be recommended to screen for SDB in patients with CHF. In contrast, the 3% ODI had a high sensitivity of 97% and low negative likelihood ratio of 0.08 for diagnosis of SDB in CHF patients. Overnight pulse oximetry would be of greatest clinical use to rule out SDB in patients with CHF, and could be used as part of a phased testing approach to help prioritise those patients who may require more detailed sleep studies.

**CHAPTER 5: THE IMPACT OF SCORING
CRITERIA ON DIAGNOSIS AND CLASSIFICATION
OF SLEEP-DISORDERED BREATHING IN
CHRONIC HEART FAILURE**

5.1. Introduction

Sleep-disordered breathing (SDB) has been reported to occur in 24% to 81% of chronic heart failure (CHF) patients (see Introduction Table.1.2). Differences in clinical characteristics of the patients in these studies may account for some of the variation in prevalence. However, the type of sleep study and differences in the criteria used for respiratory event scoring (see Introduction Table 1.8) may also account for some of the variation in prevalence. As discussed in Section 4.1, clinical symptoms are a poor indicator of SDB in CHF, and metrics of SDB severity such as the apnoea hypopnoea index (AHI) may be of greater importance for clinical decision making. It is important to understand the impact of methodological differences in respiratory event scoring on the diagnosis of SDB in CHF.

One source of disagreement is the criteria used to define hypopnoea. In adults and children, the use of different criteria to score hypopnea can significantly alter the measured AHI, influencing the reported prevalence and severity of obstructive sleep apnoea (OSA) (Tsai, 1999; Redline, 2000; Manser, 2001; Tang, 2002). The first definitions of hypopnoea required a reduction in respiratory effort or airflow signals (Bradley, 1985; Gould, 1988) but later scoring criteria required the reduction in ventilation to be associated with an oxygen desaturation or electro-encephalographic (EEG) arousal (AASM Task Force Report, 1999). Recent guidelines published to standardise the scoring of respiratory events during sleep still list a 'recommended' and 'alternative' rule for scoring hypopnoea, but the use of these two different criteria can result in significant differences in the measured AHI in adults with OSA (Rueland, 2009).

A number of definitions have been used to score hypopnoea in studies of SDB in CHF (Table 5.1). The effect of these different criteria on SDB diagnosis in CHF has not been examined. The first aim of this study was to investigate the impact of two different

Table 5.1. Hypopnoea Scoring Criteria Used in Studies Reporting the Prevalence of Sleep-Disordered Breathing in Chronic Heart Failure

Author, Year	Number of Patients	Type of sleep study	SDB Diagnostic criteria (AHI)	Hypopnoea Scoring Criteria	SDB (%)	OSA (%)	CSA (%)
Javaheri, 1998	81	NPSG	≥ 15 /hour	Reduction in airflow with $\geq 4\%$ desaturation or arousal	51	11	40
Ferrier, 2005	53	NPSG	> 10 /hour	Reduction in breathing signal with $> 3\%$ desaturation or arousal	68	53	15
Oldenburg, 2007	700	PG	> 15 /hour	$\geq 50\%$ reduction in breathing signal with $\geq 4\%$ desaturation	51	19	32
Vazir, 2007	55	NPSG	> 15 /hour	$\geq 50\%$ reduction in airflow with $\geq 4\%$ desaturation	53	38	15
MacDonald, 2008	108	PG	≥ 15 /hour	$\geq 50\%$ reduction in airflow with $\geq 4\%$ desaturation or heart rate defined arousal	61	30	31
Hagenah, 2008	50	NPSG	> 10 /hour	No definition reported	64	20	44
Yumino, 2009	218	NPSG	≥ 15 /hour	$> 50\%$ reduction in airflow	47	26	21
Paulino, 2009	316	PG	≥ 10 /hour	$> 30\%$ reduction in airflow with $> 4\%$ desaturation	81	56	25

SDB = Sleep-disordered breathing; AHI = Apnoea hypopnoea index; OSA = obstructive sleep apnoea; CSA = central sleep apnoea; NPSG = nocturnal polysomnography; PG = respiratory polygraphy

hypopnoea scoring criteria on the measured AHI and prevalence of SDB in CHF. I tested the hypothesis that a significantly greater number of CHF patients would be diagnosed with SDB when hypopnoeas were scored with a corroborative $\geq 3\%$ oxygen desaturation or EEG arousal rule, compared to hypopnoeas scored with a corroborative $\geq 4\%$ oxygen desaturation rule.

As well as the frequency of apnoeas and hypopnoeas, the classification of SDB as OSA or central sleep apnea (CSA) is important when considering the treatment options for CHF patients (Javaheri, 2007a). It is unknown if the use of different hypopnoea definitions may systematically bias the number of central or obstructive hypopnoeas scored. Central apnoeas are reported to be associated with less marked oxygen desaturation than obstructive and mixed apnoeas (Series, 1990; Fletcher, 1991; Szollosi, 2006b). A hypopnoea definition requiring a higher oxygen desaturation could favour the scoring of obstructive hypopnoeas. In CHF patients in whom CSA is prevalent (Javaheri, 1998b), this would influence the classification of SDB as CSA or OSA. Therefore, the second aim of this study was to evaluate whether the use of different hypopnoea scoring criteria would result in preferential scoring of central or obstructive events, resulting in a shift in classification of SDB from CSA to OSA, or vice versa.

Another area of controversy in scoring SDB relates to the categorisation of mixed apnoeas, where there are features of both central and obstructive apnoea in the same event. Mixed apnoeas are considered to be part of the obstructive sleep apnoea hypopnoea syndrome (AASM Task Force Report, 1999). However, some studies of SDB in CHF, have considered mixed apnoeas as central apnoeas (Tkacova, 2001; Vazir, 2007). The impact of these differences in categorising mixed apnoeas on classification of SDB has not been investigated. Therefore, a third aim of this study was to evaluate the impact of scoring and categorisation of mixed apnoeas on the classification of SDB in CHF. The following hypothesis was tested: categorization of

mixed apnoeas as central or obstructive apnoeas in CHF does not significantly change the overall classification of SDB as CSA or OSA.

5.2. Methods

The recruitment of CHF patients for this study is described in Chapter 3 (Section 3.3.1), and the measurement techniques used in this chapter are described in the General Methods chapter (Sections 2.3.1 and 2.3.2).

5.2.1. Respiratory Event Scoring

All polysomnography (PSG) studies were analysed twice by the same scorer, using different hypopnoea scoring criteria on each pass of the study. Hypopnoeas were initially scored when the amplitude of the nasal airflow signal decreased by $\geq 50\%$ for ≥ 10 seconds, in association with a $\geq 4\%$ oxygen desaturation (hereafter referred to as 'hypopnoea rule 1'). Hypopnoeas were categorised as obstructive in origin when snoring, flattening of the nasal pressure signal or out of phase deflections on the thorax and abdomen movement signals were seen during the event. In the absence of all of these findings, a central hypopnoea was scored. After calculation of the AHI using hypopnoea rule 1 the PSG was then reanalysed and hypopnoeas were scored using the same airflow criteria, but requiring an associated $\geq 3\%$ oxygen desaturation or an EEG arousal from sleep for an event to be marked (hereafter referred to as 'hypopnoea rule 2').

Hypopnoea scoring rule 2 was used for the mixed apnoea analysis.

Apnoea was scored when a $\geq 90\%$ reduction in the amplitude of the nasal airflow signal was observed for ≥ 10 seconds. Obstructive apnoea was scored in the presence of

continued respiratory effort on the thorax or abdominal movement signals. Central apnoea was scored when respiratory effort was absent throughout the event and there were less than 3 obstructed breaths before resumption of nasal airflow. Mixed apnoea was scored when respiratory effort was absent during the initial portion of the apnoea but ≥ 3 obstructed breaths occurred before resumption of airflow (Takasaki, 1989).

SDB was defined as an AHI ≥ 15 events/hour and classified as CSA or OSA according to the predominant type of respiratory event. Mixed apnoeas were then categorised as obstructive apnoeas and the classification of SDB reassessed. Finally, mixed apnoeas were recategorised as central apnoeas and the classification of SDB reassessed.

As the quality of the pulse oximeter signal was fundamental to differentiating hypopnoeas scored by each rule, participants with less than 240 minutes of technically adequate oximetry monitoring during sleep were excluded from the hypopnoea analysis. However, as apnoeas did not require an associated oxygen desaturation to be scored, these participants were not excluded from the mixed apnoea analysis.

5.2.2. Statistical Analysis

Non parametric statistical analyses are used in this chapter, as the respiratory event indices were highly right skewed. Results are presented as median (interquartile range) or number and percent (n, %) of patients. Where the distribution of the data could not be indicated using the interquartile range due to occurrence of events in $<25\%$ of patients, values are presented as median and range, or mean and standard deviation [SD].

Comparison of continuous variables between two independent groups was performed with the Mann-Whitney test. The Wilcoxon signed rank test was used to compare repeated measurements of the AHI, hypopnoea index and proportion of respiratory

events measured with each hypopnoea rule. Categorical variables were compared using the chi-square test or Fisher's exact test. McNemars test was used to compare the number of CHF patients diagnosed with SDB using each hypopnoea rule. The proportion of CHF patients classified as having CSA and OSA was compared using the chi square test.

5.3. Results

5.3.1. Hypopnoea Analysis

180 CHF patients were studied with overnight polysomnography. 10 patients with <240 minutes of technically adequate pulse oximetry monitoring during sleep were excluded from this analysis.

170 CHF patients were included in the hypopnoea analysis, with median (interquartile) age 70.5 (59.2 to 76.7) years, BMI 29.1 (25.5 to 32.7) kg/m² and 86% male (Table 5.3). 130 (76%) patients were asymptomatic or had mild symptoms of heart failure (NYHA class I or II), the median left ventricle ejection fraction in all patients was 41% (28 to 58%), and BNP concentration 125 (55 to 245) pg/ml. Most patients were not excessively sleepy during the day with median Epworth Sleepiness Scale (ESS) score of 7 (5 to 11) and OSLER duration of 40 (24.8 to 40) minutes.

5.3.2. Diagnosis and Prevalence of Sleep-Disordered Breathing in Chronic Heart Failure using Different Hypopnoea Scoring Rules

Using hypopnoea scoring rule 1, the median 4% hypopnoea index was 5.1 (2.4 to 11.7) events/hour (Table 5.2). When hypopnoea scoring rule 2 was applied, the median hypopnoea index increased to 9.9 (5.8 to 17.3) events/hour. The 3% hypopnoea index was significantly greater than the 4% hypopnoea index ($p < 0.001$) with a median difference of 3.9 (2.2 to 6.5) events/hour.

The mean difference in AHI scored using each hypopnoea rule was 4.6 events/hour with 95% limits of agreement of -1.9 to 11.2 events/hour (Figure 5.1). With increasing SDB severity up to a mean AHI of 40/hour, the difference in AHI tended to increase. In patients with a mean AHI > 40 /hour, the difference in AHI measured with the two hypopnoea scoring rules was less marked.

50 (29%) CHF patients were diagnosed with SDB ($\text{AHI} \geq 15$ /hour) with hypopnoea rule 1. The number of CHF patients diagnosed with SDB significantly increased to 78 (46%) when hypopnoea rule 2 was applied ($p < 0.001$ by McNemar test; Figure 5.2)

Table 5.2. Comparison of Respiratory Event Frequency and Diagnosis of Sleep-Disordered Breathing in Chronic Heart Failure Patients Using Different Hypopnoea Scoring Criteria (n=170)

Parameter	Hypopnoea Rule 1 (4% Scoring Criteria)	Hypopnoea Rule 2 (3% Scoring Criteria)	p value*
Hypopnoea Index (hour⁻¹)	5.1 (2.4 – 11.7)	9.9 (5.8 – 17.3)	<0.001
Apnoea Hypopnoea Index (hour⁻¹)	9.3 (4.0 – 19.3)	13.8 (7.5 – 26.3)	<0.001
Obstructive hypopnoea Index (hour⁻¹)	3.1 (0.6 – 8.0)	6.5 (2.1 – 12.6)	<0.001
Central Hypopnoea Index (hour⁻¹)	0.4 (0 – 2.2)	1.1 (0 – 4.2)	0.007
Proportion of events obstructive (%)	86 (50 – 98)	85 (46 – 98)	0.60
Proportion of events central (%)	12 (1 – 50)	14 (2 – 51)	0.77
Patients with SDB (n, %)	50 (29)	78 (46)	<0.001
Patients with OSA (n, %)	32 (19)	54 (32)	<0.001
Patients with CSA (n, %)	18 (11)	24 (14)	<0.03

* p value shown for difference between hypopnoea rule 1 and hypopnoea rule 2.

Values shown are median (interquartile range), or number (percent) of patients (n, %)

SDB = sleep-disordered breathing; OSA = obstructive sleep apnoea; CSA = central sleep apnoea

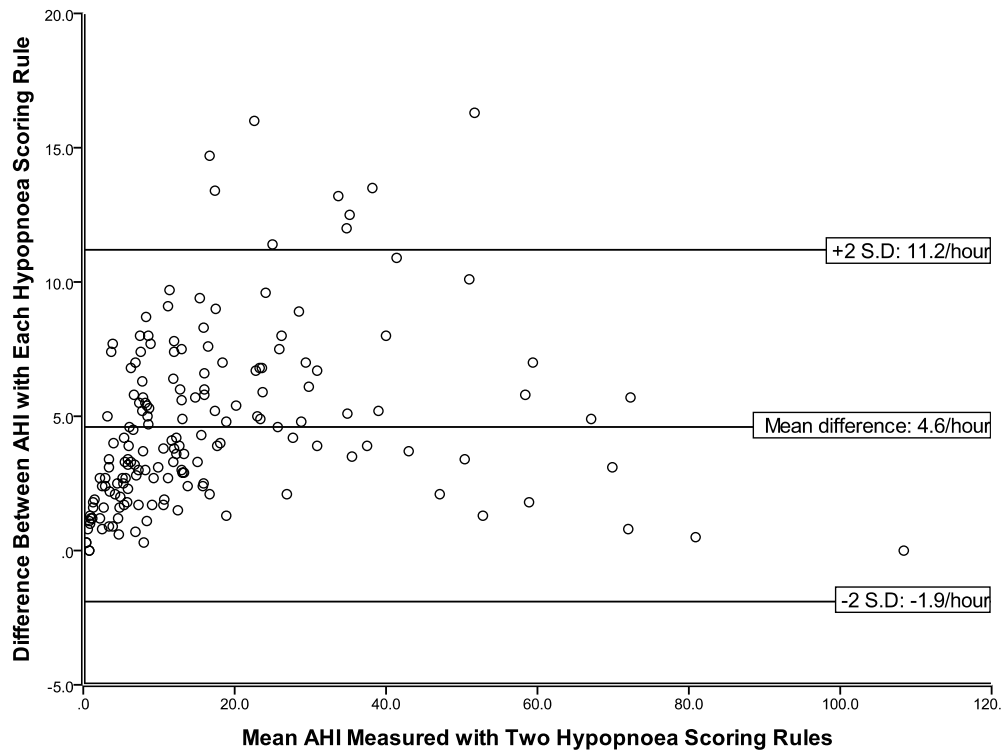


Figure 5.1. Difference versus Average Plot to Show Difference between Apnoea Hypopnoea Index (AHI) Scored with Different Hypopnoea Rules as a Function of Mean AHI

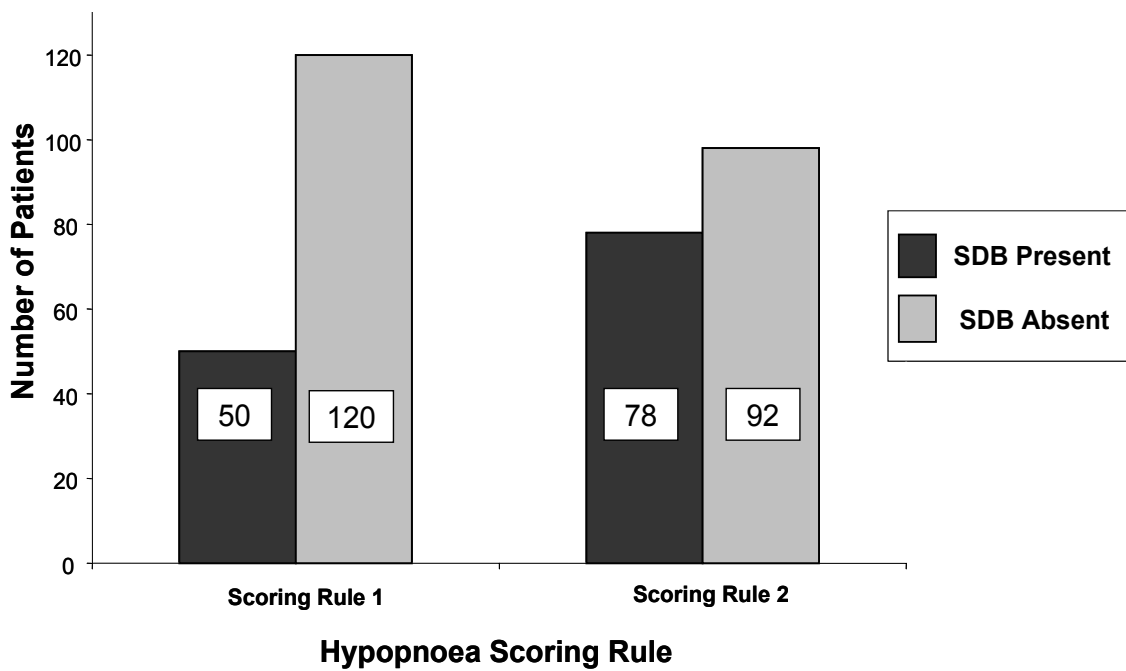


Figure 5.2. Number of Chronic Heart Failure Patients Diagnosed with Sleep-Disordered Breathing Using Different Hypopnoea Scoring Criteria (n = 170)

5.3.3. Impact of Different Hypopnoea Scoring Rules on Classification of Sleep-Disordered Breathing in Chronic Heart Failure

Both the obstructive and central hypopnoea index increased significantly when hypopnoeas were scored using rule 2 (both $p < 0.001$; Table 5.2); the median increase in the obstructive hypopnoea index was 2.5 (0.8 to 4.6) events/hour and the central hypopnoea index increased by 0.4 (0 to 2.0) events/hour.

In accordance with the greater number of patients diagnosed with SDB using hypopnoea rule 2, there was a significant increase in the absolute number of CHF patients diagnosed with OSA ($p < 0.001$) and CSA ($p < 0.03$) using this rule. However, the proportion of patients with SDB classified as having OSA or CSA did not differ significantly with either hypopnoea scoring rule; 64% of CHF patients with SDB were classified as having OSA with rule 1 and 69% were classified as OSA with rule 2 ($\chi^2 = 0.18$, $p = 0.67$). Moreover, in the 50 CHF patients diagnosed with SDB using hypopnoea rule 1, the classification of SDB as OSA or CSA did not change in any patient when hypopnoeas were rescored using rule 2.

5.3.4. Comparison of Patients Included and Excluded from the Hypopnoea Analysis

Anthropometric and clinical characteristics in the 10 excluded patients were similar to patients included in the hypopnoea analysis, except for a significantly smaller waist hip ratio (0.96; $p=0.01$) and lower ESS (5; $p=0.03$) (Table 5.3). However, despite the lower ESS, CHF patients excluded from the hypopnoea analysis had poorer sleep architecture than included patients, with significantly greater stage 1 and 2 light sleep (both $p = 0.03$), and a non significant ($p = 0.15$) higher arousal index (Table 5.4).

In keeping with their poorer quality oximetry data, excluded patients had a significantly greater proportion of sleep time with oxygen saturation less than 90% (34.6%; $p<0.001$) (Table 5.4). The 3% and 4% hypopnoea index were significantly lower in patients excluded from this analysis (both $p<0.001$) and there was a commensurate difference in the 3% and 4% AHI between included and excluded patients, although this did not reach statistical significance ($p=0.08$ and 0.15 respectively).

Table 5.3. Clinical Characteristics of Chronic Heart Failure Patients Included and Excluded from Hypopnoea Analysis

Clinical Characteristic	Included (n=170)	Excluded (n=10)	p value
Age (years)	70.5 (59.2 – 76.7)	63.3 (56.3 – 75.2)	0.37
Male (n, %)	146 (86)	8 (80)	0.64
BMI (kg/m²)	29.1 (25.5 – 32.7)	28.1 (23.9 – 33.6)	0.57
Neck circumference (cm)	40.0 (38.0 – 43.0)	39.0 (37.0 – 41.0)	0.17
Waist:Hip ratio	1.02 (0.98 – 1.06)	0.96 (0.93 – 1.00)	0.01
Diabetes (n, %)	42 (25)	4 (40)	0.28
Ischaemic cardiomyopathy (n, %)	88 (52)	4 (40)	0.53
COPD/Asthma (n, %)	35 (21)	2 (20)	1.0
Atrial Fibrillation (n, %)	52 (31)	3 (30)	1.0
Cardiac pacing (n, %)	48 (28)	3 (30)	1.0
Beta blocker therapy (n, %)	125 (74)	5 (50)	0.14
ACEI/ARB therapy (n, %)	153 (90)	9 (90)	1.0
ESS Score	7 (5 – 11)	5 (3 – 7)	0.03
OSLER duration (minutes)	40.0 (24.8 – 40.0)	40.0 (40.0 – 40.0)	0.19
HADS	11 (6 – 16)	17 (8-21)	0.23
NYHA class(I/II/III/IV)	23/107/38/2	1/6/3/0	0.93
Left ventricle EF (%)	41 (28 – 58)	43(31 – 57)	0.68
BNP (pg/ml)	125 (55 – 245)	100 (45 – 251)	0.65

Values shown are median (interquartile range), or number (percent) of patients (n, %)

BMI = Body mass index; COPD = Chronic obstructive pulmonary disease; ACE/ARB = angiotensin converting enzyme inhibitor/angiotensin receptor blocker; ESS = Epworth Sleepiness Scale; OSLER = Oxford sleep resistance test; HADS = Hospital and Anxiety Depression Score; EF = ejection fraction; NYHA = New York heart association classification, BNP = B-type natriuretic peptide

Table 5.4. Polysomnographic Measurements During Sleep in Chronic Heart Failure Patients Included and Excluded from Hypopnoea Analysis

Parameter	Included (n=170)	Excluded (n=10)	P value
Total Sleep Time (mins)	351 (276 – 402)	314 (278 – 349)	0.37
Stage 1 sleep (% TST)	26 (16 – 43)	41 (30 – 58)	0.03
Stage 2 sleep (% TST)	39 (26 – 50)	28 (9 – 35)	0.03
Deep sleep (% TST)	10 (6 - 18)	11 (5 – 19)	0.75
REM sleep (% TST)	19 (14 – 24)	14 (5 – 23)	0.13
Sleep efficiency (%)	72 (59 – 81)	74 (60 – 78)	0.84
Arousal Index (events/hour)	19.0 (13.5 – 26.3)	26.3 (17.0 – 34.1)	0.15
4% AHI (events/hour)	9.3 (4.0 – 19.3)	5.3 (0.9 – 12.5)	0.15
3% AHI (events/hour)	13.8 (7.5 – 26.3)	7.3 (3.3 – 15.8)	0.08
Time SpO ₂ <90% (% TST)	2.5 (0.3 – 19.1)	34.6 (17.4 – 60.4)	<0.001
PLMI (events/hour)	13.7 (2.6 – 40.4)	12.5 (3.1 – 55.8)	0.97
Cheyne-Stokes resp ⁿ (%TST)	0 (0 – 0)	0 (0 – 5.0)	0.48
Apnoea index (hour ⁻¹)	1.7 (0.3 – 7.2)	4.6 (0 – 12)	0.92
4% Hypopnoea index (hour ⁻¹)	5.1 (2.4 – 11.7)	0.9 (0 – 2.1)	<0.001
3% Hypopnoea index (hour ⁻¹)	9.9 (5.8 – 17.3)	3.3 (2.8 – 5.7)	<0.001
Patients with SDB (n, %)	92 (54)	2 (20)	0.19
Patients with OSA (n, %)	54 (32)	1 (10)	0.16
Patients with CSA (n, %)	24 (14)	1 (10)	0.69

Values shown are median (interquartile range), or number (percent) of patients (n, %)

TST = total sleep time; REM = rapid eye movement; AHI = apnoea hypopnoea index; PLMI = periodic limb movement index; SDB = sleep-disordered breathing; OSA = obstructive sleep apnoea; CSA = central sleep apnoea

5.3.5. Mixed Apnoea Analysis

180 CHF patients had adequate polysomnography data and were included in the mixed apnoea analysis. The median (interquartile) age of patients was 69.6 (58.9 to 76.6) years, BMI 29.1 (25.4 to 32.7) kg/m², and 86% were male (Table 5.5). 137 (76%) patients had no symptoms or mild symptoms of chronic heart failure (NYHA class I and II). Most patients were not subjectively or objectively excessively sleepy during the day, with median ESS of 7 (4 to 10) and OSLER duration of 40 (27.5 to 40) minutes.

The median total sleep time in all CHF patients was 348 (279 to 399) minutes, with predominantly light sleep and a median arousal index of 19.2 (13.5 to 26.7)/hour (Table 5.6). Periodic limb movements during sleep occurred frequently, with an index of 13.3 (2.6 to 42.9)/hour.

The median 3% AHI in all CHF patients was 13.4 (7.2 to 25.8) events/hour. SDB was diagnosed in 80 (44%) patients and classified as OSA in 55 (31%), and CSA in 25 (14%) patients (Table 5.6).

Table 5.5. Clinical Characteristics of Chronic Heart Failure Patients Included in the Mixed Apnoea Analysis (n=180)

Clinical Characteristic	Value
Age (years)	69.6 (58.9 – 76.6)
Male (n, %)	154 (86%)
BMI (kg/m²)	29.1 (25.4 – 32.7)
Neck circumference (cm)	40.0 (38.0 – 43.0)
Waist:Hip ratio	1.02 (0.98 – 1.06)
Diabetes (n, %)	46 (26)
Ischaemic cardiomyopathy (n, %)	92 (51)
COPD/Asthma (n, %)	37 (21)
Atrial Fibrillation (n, %)	55 (31)
Cardiac pacing (n, %)	51 (28)
Beta blocker therapy (n, %)	130 (72)
ACEI/ARB therapy (n, %)	162 (90)
Epworth Sleepiness Scale Score	7 (4 – 10)
OSLER duration (minutes)	40.0 (27.5 – 40.0)
NYHA classification (I/II/III/IV)	24/113/41/2
Left ventricle ejection fraction (%)	41 (29 – 58)
BNP (pg/ml)	125 (55 – 247)

Values shown are median (interquartile range), or number (percent) of patients (n, %)

For definition of abbreviations, see Table 5.3

Table 5.6. Polysomnographic Measurements During Sleep, and Classification of Sleep-Disordered Breathing in Chronic Heart Failure Patients Included in the Mixed Apnoea Analysis (n=180)

Parameter	Value
Total Sleep Time (mins)	348 (279 – 399)
Stage 1 sleep (% TST)	28 (17 – 44)
Stage 2 sleep (% TST)	38 (26 – 48)
Deep sleep (%)	11 (6 - 18)
REM sleep (% TST)	19 (14 – 24)
Sleep efficiency (%)	72 (59 – 80)
Arousal Index (events/hour)	19.2 (13.5 – 26.7)
3% AHI (events/hour)	13.4 (7.2 – 25.8)
Time SpO₂ <90% (% TST)	3.3 (0.5 – 20.5)
PLMI (events/hour)	13.3 (2.6 – 42.9)
PLM with arousal index (/hour)	1.1 (0.1 – 5.1)
Patients with Sleep-Disordered Breathing (n, %)	80 (44)
Patients with Obstructive Sleep Apnoea (n, %)	55 (31)
Patients with Central Sleep Apnoea (n, %)	25 (14)

Values shown are median (interquartile) or number (percent) of patients (n, %).

For definition of abbreviations, see Table 5.4

The median apnoea index in CHF patients was 1.9 (0.3 to 7.2) events/hour (mean [standard deviation] 6.6 [12.3] events/hour) and the majority of apnoeas were obstructive (83%) (Table 5.7). Mixed apnoeas occurred in 40 (22%) patients, but there was a low frequency of these events with median mixed apnoea index 0/hour (mean index 0.3 [1.1]/hour, range 0 to 10.6/hour) (Table 5.7; Figure 5.3). They accounted for a small proportion of all apnoeas and the mean proportion of apnoeas classified as mixed apnoea was 1% [2.7] (range 0 to 15%).

Table 5.7. Frequency of Respiratory Events in Chronic Heart Failure Patients Included in the Mixed Apnoea Analysis (n=180)

	Index (events/hour)*	Percentage
3% Apnoea hypopnoea Index[†]	13.4 (7.2 – 25.8)	N/A
Apnoeas	1.9 (0.3 – 7.2)	18 (4 – 37) [§]
Obstructive Apnoeas	1.1 (0.1 – 4.6)	83 (11 – 100) [‡]
Central Apnoeas	0 (0 – 0.5)	0 (0 – 33) [‡]
Mixed Apnoeas	0 (0 to 10.6) [#]	0 (0 to 15) ^{#‡}
3% Hypopnoeas[†]	9.2 (5.2 – 16.7)	82 (63 – 96) [§]
Obstructive Hypopnoeas	6.1 (1.9 – 12.0)	86 (36 – 100) [‡]
Central Hypopnoeas	1.1 (0 – 4.0)	14 (0 – 64) [‡]
All Obstructive Events	8.4 (3.3 – 16.3)	84 (43 – 97) [‡]
All Central Events	1.6 (0.2 – 5.8)	16 (2 – 56)
All Mixed Events	0 (0 to 10.6) [#]	0 (0 to 15) [#]

*Values shown are median (interquartile range), or where indicated #Value is median (range)

[†]Hypopnoeas scored using hypopnoea rule 2 (associated with 3% desaturation or arousal); [§]percentage of the apnoea hypopnoea index; [‡]percentage of all apnoeas or hypopnoeas as appropriate

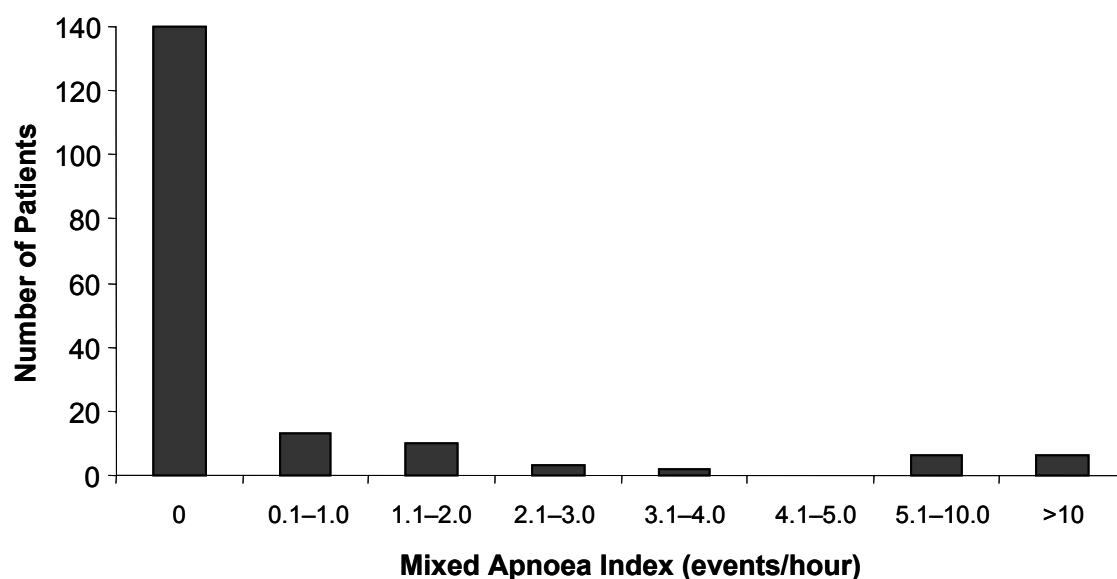


Figure 5.3. Frequency of Mixed Apnoeas in Chronic Heart Failure Patients

5.3.6. Impact of Categorisation of Mixed Apnoeas as Central or Obstructive Apnoeas

Categorisation of mixed apnoeas as obstructive or central apnoeas caused minimal change in the frequency or percentage of these respiratory events (Table 5.8). The classification of SDB as OSA or CSA was unchanged in any patient when mixed apnoeas were recategorised as obstructive apnoeas (Table 5.9). However, when mixed apnoeas were recategorised as central apnoeas, the classification of SDB was changed from OSA to CSA in one patient; this patient had an AHI of 59.8/hour, and was initially classified as having OSA with 47% obstructive, 44% central and 9% mixed respiratory events.

Table 5.8. Impact of Mixed Apnoea Categorisation on Respiratory Event Frequency in Chronic Heart Failure Patients (n=180)

Parameter	Mixed Apnoeas Categorised as Obstructive		Mixed Apnoeas Categorised as Central	
	Index (events/hour)	Percentage	Index (events/hour)	Percentage
Obstructive Apnoeas	1.2 (0.2 – 5.0)	89 (17 – 100)	1.1 (0.1 – 4.6)	83 (11 – 100)
Central Apnoeas	0 (0 – 0.5)	0 (0 – 33)	0.1 (0 – 0.7)	3 (0 – 36)
Obstructive Events*	8.4 (3.4 – 16.4)	84 (44 – 98)	8.4 (3.3 – 16.3)	84 (43 – 97)
Central Events*	1.6 (0.2 – 5.8)	16 (2 – 56)	1.7 (0.3 – 6.3)	16 (3 – 57)

*Events refers to sum of apnoeas and hypopnoeas

Values shown are median (interquartile range)

Table 5.9. Impact of Mixed Apnoea Categorisation on Classification of Sleep-Disordered Breathing in Chronic Heart Failure Patients (n=180)

	Mixed Apnoeas Categorised as Obstructive	Mixed Apnoeas Categorised as Central
Patients with SDB	80 (44)	80 (44)
Patients with OSA	55 (31)	54 (30)
Patients with CSA	25 (14)	26 (14)

Values shown are number (percent) of patients

For definition of abbreviations, see Table 5.3

The frequency of mixed apnoeas was analysed in the 80 CHF patients in whom SDB was diagnosed; the mixed apnoea index remained low with a mean of 0.6 [1.5] (range 0 to 10.6) events/hour and mixed apnoeas comprised a mean of 1% [2.5] (range 0 to 15%) of all respiratory events. Mixed apnoeas occurred in a significantly greater proportion of CHF patients with CSA (56%) compared to patients with OSA (27%; $p = 0.03$), with a higher mixed apnoea index in patients with CSA (Table 5.10).

Table 5.10. The Occurrence of Mixed Apnoeas in Chronic Heart Failure Patients with Obstructive or Central Sleep Apnoea (n = 80)

	Obstructive Sleep Apnoea (n = 55)	Central Sleep Apnoea (n = 25)	p value
Number of Patients with Mixed Apnoeas (n, %)	15 (27)	14 (56)	0.03
Proportion of Apnoeas mixed (%)	0 (0 – 2.3)	1.0 (0 – 3.1)	0.045
Mixed Apnoea Index (hour⁻¹)	0 (0 – 0.2)	0.2 (0 – 0.6)	0.035

Values shown are number (percent) of patients (n, %) or median (interquartile range)

5.4. Discussion

5.4.1. Hypopnoea Analysis

The main finding of this study is that the criteria used to define hypopnoea can significantly influence the number of respiratory events scored and the diagnosis of SDB in CHF. When hypopnoeas were scored using rule 2 ($\geq 50\%$ reduction in nasal airflow with a $\geq 3\%$ oxygen desaturation or EEG arousal), the AHI was significantly higher compared to hypopnoeas scored using rule 1 (associated $\geq 4\%$ oxygen desaturation). Use of hypopnoea rule 2 resulted in a significantly greater number of CHF patients being diagnosed with SDB, with an absolute increase of 28 (16%) patients compared to hypopnoea rule 1. Furthermore, the criteria used to score hypopnoea had no impact on the classification of SDB as OSA or CSA.

The clinical importance of hypopnoeas is highlighted by their association with the obstructive sleep apnoea hypopnoea syndrome (Gould, 1988). However, the definition of hypopnoea is controversial and there has been considerable variation in the rules used to score hypopnoea (Moser, 1994; Manser, 2002). Some authors have defined hypopnoeas solely as a reduction in oronasal airflow (Bradley, 1985) or thoracoabdominal movement (Gould, 1988; Whyte, 1992). Other definitions require the reduction in breathing to be associated with perturbations such as a reduction in oxygen saturation or arousal from sleep (AASM Task Force Report, 1999; Duran, 2001).

Current guidelines from the American Academy of Sleep Medicine require all hypopnoeas to be associated with a corroborative oxygen desaturation, but there are two different rules by which hypopnoea can be scored (Iber, 2007). The recommended scoring rule requires a $\geq 30\%$ reduction in nasal pressure signal amplitude with a $\geq 4\%$

oxygen desaturation. The alternative rule requires a $\geq 50\%$ reduction in nasal pressure signal with a $\geq 3\%$ oxygen desaturation or arousal from sleep.

The importance of a uniform definition of hypopnoea is emphasised by reports of significant differences in the measured AHI and prevalence of OSA with the use of different scoring criteria (Tsai, 1999; Redline, 2000; Manser, 2001; Rueland, 2009). Using data from a community based cohort, Redline et al., (2000) reported that the median AHI increased from 5.4/hour when hypopnoeas were scored as a $\geq 30\%$ reduction in airflow with a $\geq 4\%$ oxygen desaturation, to 29.3/hour when hypopnoeas were scored as the same reduction in airflow without requiring a corroborative oxygen desaturation or arousal (Redline, 2000).

The impact of hypopnoea scoring rules may differ between a community cohort and a clinical sample in which the severity of SDB would be greater. In a population of patients recruited from a sleep clinic, the use of different hypopnoea criteria has also been reported to increase the prevalence of OSA (AHI ≥ 15 /hour) by between 7 to 19% (Tsai, 1999; Manser, 2001). Rueland et al., (2009) have evaluated the impact of the two hypopnoea rules recommended in the current guidelines from the AASM. In a sample of patients from a sleep clinic, the median AHI measured with the recommended hypopnoea scoring rule was 8.3/hour compared to 14.9/hour with the alternative rule, and the prevalence of OSA (AHI ≥ 15 /hour) increased from 38 to 50% with the alternative hypopnoea scoring rule (Rueland, 2009).

To date, no study has evaluated the impact of hypopnoea scoring criteria on SDB diagnosis in CHF patients, in whom CSA occurs commonly. The results of this chapter confirm that hypopnoea scoring rules can significantly influence the prevalence and severity of SDB in CHF. The 16% increase in SDB prevalence in the current study is within the bounds of the 7 to 19% increase in prevalence of OSA reported by studies in adults without CHF (Tsai, 1999; Manser, 2001). Moreover, the two hypopnoea scoring

rules evaluated in the current study were almost identical to those evaluated by Ruehland et al., who reported a similar increase in the median AHI and prevalence of OSA as we observed in CHF patients.

5.4.2. Clinical Significance of Different Hypopnoea Scoring Criteria

The optimum definition for hypopnoea that identifies clinically important events remains uncertain. The requirement for hypopnoeas to be associated with changes in oxygen saturation or arousal may identify clinically relevant reductions in ventilation, by which OSA may predispose to cardiovascular or metabolic disease (McNicholas, 2007).

However, some authors argue that the requirement for a corroborative oxygen desaturation to score hypopnoeas results in under-detection of clinically relevant events (Guilleminault, 2009). Clinical characteristics including baseline oxygen saturation, BMI and resting lung volume will influence the degree of oxygen desaturation associated with periods of reduced ventilation (Bradley, 1985; Peppard, 2009). Hypopnoeas requiring a corroborative oxygen desaturation may be scored more readily in overweight adults than in lean individuals (Guilleminault, 2009). Moreover, sleep fragmentation associated with frequent arousals from sleep is associated with cardiovascular and metabolic morbidity independent of SDB (Morrell, 2000; Stamatakis, 2010). An hypopnoea definition that relies exclusively on a corroborative oxygen desaturation may underestimate the severity of SDB in individuals who have frequent arousals related to respiratory events that do not cause desaturation (Guilleminault, 1993).

Epidemiological studies such as the Wisconsin Sleep Study, Sleep Heart Health Study (SHHS) and Busselton Health Study may help address the question of a clinically relevant definition of hypopnoea. All of these studies have used a hypopnoea definition that requires a corroborative $\geq 3\%$ or $\geq 4\%$ oxygen desaturation (Young, 1993;

Bearpark, 1995; Young, 2002b). In community based samples, these studies have reported an association between the AHI and clinically important outcomes including sleepiness (Baldwin, 2001), neurocognitive impairment (Kim, 1997) and mortality (Marshall, 2008; Young, 2008; Punjabi, 2009). In addition, hypopnoeas associated with a $\geq 4\%$ oxygen desaturation were associated with prevalent cardiovascular disease (Nieto, 2000; Shahar, 2001), whilst hypopnoeas associated with a lesser oxygen desaturation or associated arousal were not (Punjabi, 2008). However, it remains unclear if the requirement for hypopnoeas to be associated with a corroborative oxygen desaturation is the optimum definition to identify those at risk of developing cardiovascular disease. A longitudinal analyses planned by the SHHS may help address this question, but their results may not be applicable to clinical patients seen by a sleep service, or to patients with established cardiovascular disease such as CHF.

5.4.3. Limitations of the Hypopnoea Scoring Analysis

Several limitations of the hypopnoea analysis described in this chapter are recognised. It would have been informative to record how many of the additional hypopnoeas scored with rule 2 were because they met the lower corroborative oxygen desaturation requirement or because they were associated with an arousal without $\geq 3\%$ oxygen desaturation. This may have allowed some inferences from this study to be made about the impact of using respiratory polygraphy to diagnose SDB in CHF (Quintana-Gallego, 2004; Smith, 2007a) as this can only measure hypopnoeas corroborated by oxygen desaturations and not by EEG arousals.

A further limitation relates to our methodology for applying the two hypopnoea scoring rules. The use of the same scorer to analyse all polysomnograms in this study has excluded variability in hypopnoea scoring due to interscorer variability, but the polysomnographer was not blinded to the hypopnoea index scored on the first pass of

the polysomnogram. Moreover, the hypopnoea rules were not applied in a random order, introducing the possibility of a systematic bias in the scoring of hypopnoeas with rule 2. However, our results are consistent with previous studies showing that the measured AHI increases when hypopnoeas are scored with a lower corroborative oxygen desaturation (Redline, 2000).

The sensors used to monitor breathing can also influence the measured hypopnoea frequency. The most commonly used airflow sensors are nasal pressure transducers and thermal devices but these have differing sensitivity for detection of hypopnoeas (Ballester, 1998; Series, 1999). Thermistors and thermocouples are insensitive to small changes in airflow and their use is associated with under-detection of hypopnoeas (Farre, 1998b). Nasal pressure monitoring has a high sensitivity for detection of hypopnoeas (Norman, 1997; Series, 1999) but the non linearity of the relationship between nasal pressure and nasal airflow (see General Methods Section 2.3.1) can result in overestimation of the number of apnoeas (Redline, 2007).

In the current study, only nasal pressure measurement was used to measure airflow and this may have resulted in some hypopnoeas being misclassified as apnoeas. The current AASM guidelines recommend the use of two airflow sensors during sleep studies, with a thermistor used to detect apnoea and a nasal pressure transducer for detection of hypopnoea (Iber, 2007).

The hypopnoea rule 2 used in the present study is the same as the alternative hypopnoea rule recommended by the AASM guidelines. However, a small difference in airflow amplitude criteria means that our hypopnoea rule 1 differs subtly from the AASM recommended rule (Iber, 2007). The requirement for a $\geq 50\%$ reduction in airflow amplitude in hypopnoea scoring rule 1 is greater than the $\geq 30\%$ reduction required in the AASM recommended hypopnoea scoring rule, although the corroborative oxygen desaturation required by both is the same. The significance of this difference may be

limited due to the difficulty of determining baseline breathing amplitude in patients without a stable breathing pattern or with frequent respiratory events (AASM Task Force Report, 1999). Therefore, the difference between a $\geq 30\%$ and $\geq 50\%$ reduction in breathing amplitude may be difficult to accurately measure, particularly with semi quantitative airflow sensors.

The criteria used to differentiate central and obstructive hypopnoeas have not been systematically evaluated, and it is possible that some hypopnoeas have been misclassified. However, the criteria used in the current study have been used in a number of other studies evaluating SDB in CHF (Takasaki, 1989; Naughton, 1993) and were chosen as the most suitable non invasive means to classify hypopnoea in the current study. The gold standard for distinguishing central from obstructive hypopnoeas is oesophageal manometry (Iber, 2007) but this was not practical in view of the high number of polysomnography investigations required for this study, particularly with their use in the home setting. Measurement of pulse transit time may be an alternative technique for distinguishing obstructive from central respiratory events (Argod, 1998).

5.4.4. Mixed Apnoea Analysis

The second finding in this study was that mixed apnoeas occurred in only 22% of CHF patients, and the frequency of these events was low. The categorisation of mixed apnoeas as obstructive or central apnoeas did not alter the classification of SDB as OSA or CSA in 99% of CHF patients.

Few studies have systematically examined the frequency of mixed apnoeas in CHF patients under investigation for SDB. In the one of the earliest report of CHF patients with SDB, Javaheri (1998) reported a mean [SD] frequency of mixed apnoeas of 1 [2]/hour (Javaheri, 1998b). Vazir et al., (2007) evaluated men with mild symptomatic

CHF and observed that the median (IQR) mixed apnoea index was 0.6 (0 – 3)/hour (Vazir, 2007). In a cohort of 20 CHF patients selected for the presence of CSA, Szollosi et al., (2006) reported that the mean mixed apnoea index was 3.2 [1.6]/hour (Szollosi, 2006b). The results of the current study are in agreement with these earlier reports showing that most CHF patients have a low frequency of mixed apnoeas during sleep.

Definition of Mixed Apnoea

The findings of this study may have been influenced by the criteria used to define mixed apnoea. We used a definition of mixed apnoea that required respiratory effort to be absent in the initial portion of the apnoea, followed by ≥ 3 obstructed breaths before the end of the apnoea (Takasaki, 1989). However, other definitions of mixed apnoea have not specified a minimum number of obstructed breaths before the end of the event. The 2007 AASM respiratory event scoring guidelines define mixed apnoea as an apnoea with absent inspiratory effort in the initial portion of the event, followed by resumption of inspiratory effort in the second portion of the event (Iber, 2007). Other authors have specified the minimum duration for the central component of the mixed apnoea must be more than the first half of the apnoea (Vazir, 2007), whilst in another definition, neither the central or obstructive component of the apnoea could exceed 75% of the total duration of the event (Bliwise, 1984). The influence of these different definitions on the measured frequency of mixed apnoea requires systematic examination.

Pathogenesis of Mixed Apnoeas

Mixed apnoeas comprise features of both obstructive and central apnoea within the same event. There have been conflicting reports about their pathogenesis with some

studies reporting that they are caused by upper airway collapse during central apnoea (Alex, 1986; Badr, 1995). Alternatively, mixed apnoeas may occur as a consequence of obstructive apnoea. Hyperventilation during the recovery breaths after obstructive apnoea may cause the arterial CO₂ to fall below the apnoeic threshold, leading to cessation of respiratory drive and upper airway collapse (Iber, 1986). In support of this latter observation, it has recently been reported that ventilatory instability in patients with OSA can increase the propensity to central apnoea (Salloum, 2010).

5.4.5. Clinical Significance and Treatment of Mixed Apnoeas in Chronic Heart Failure Patients

It is unclear from the proposed pathogenetic mechanisms if mixed apnoeas should be treated as obstructive apnoeas or central apnoeas. Uncertainty about the origin and treatment of mixed apnoeas may explain the discrepancy in categorisation of these events as obstructive apnoeas (AASM Task Force Report, 1999) or central apnoeas (Tkacova, 2001; Vazir, 2007). The results from the current study suggest that mixed apnoeas are infrequent events in most CHF patients. The classification and treatment of SDB in CHF patients with mixed apnoeas may therefore be best determined by the frequency and proportion of the other respiratory events.

5.4.6. Limitations of the Mixed Apnoea Analysis

A limitation of this aspect of the current study is our use of nasal pressure monitoring without a thermistor for detection of apnoeas (see Section 5.4.3). Use of nasal pressure alone for measurement of airflow may overestimate the total number of apnoeas (Redline, 2007). Moreover, this may have resulted in overscoring of mixed apnoeas, as low tidal volume breaths or mouth breathing after central apnoea may not

have been detected by nasal pressure monitoring giving the appearance of a mixed apnoea. However, this is unlikely to have significantly altered the findings of this study as this would mean the true prevalence and frequency of mixed apnoeas is even lower than we have observed.

5.4.7. Summary

The classification of SDB as OSA or CSA was not influenced by the two hypopnoea scoring rules used. Moreover, mixed apnoeas were observed in only a small proportion of CHF patients and the low frequency of these events meant that they had minimal impact on the classification of SDB as OSA or CSA.

In patients with CHF, the criteria used to define hypopnoea can significantly influence the AHI and prevalence of SDB. In the current study the number of CHF patients diagnosed with SDB increased by 16% with the use of hypopnoea rule 2.

Understanding the impact of different hypopnoea scoring criteria is potentially of greater clinical relevance in CHF as decisions about diagnosis and treatment of SDB may be recommended exclusively on the basis of the measured AHI (as discussed in Section 4.4.1). This contrasts with treatment of OSA in adults without CHF where both symptoms and the metric of SDB severity are important when determining the need for therapy (Scottish Intercollegiate Guidelines Network, 2003; National Institute for Health and Clinical Excellence, 2008). Whilst it is evident that the criteria used to define hypopnoea can significantly influence the diagnosis of SDB in CHF, whether the different definitions are associated with differences in clinically relevant outcomes or response to therapy requires further evaluation.

CHAPTER 6: DISCUSSION

6.1. Summary of Aims

Sleep-Disordered Breathing (SDB) is prevalent in chronic heart failure (CHF) but it is undiagnosed in the majority of patients. This thesis has evaluated aspects relating to the diagnosis of SDB in CHF with the aim of improving identification of this comorbidity, and to understand how differences in scoring criteria can influence the diagnosis, classification and ultimately treatment of SDB. The principle aim of the thesis was to evaluate the diagnostic utility of two simple portable monitors for the detection of SDB in CHF. The second aim was to compare the characteristics of CHF patients with and without SDB, in order to identify clinical features which may help detect SDB in CHF. The third aim was to investigate the impact of two different hypopnoea scoring rules on the measured apnoea hypopnoea index (AHI), and the impact of mixed apnoea categorisation on classification of SDB in CHF.

6.2. Summary of Main Findings

To evaluate the diagnostic accuracy of Heart Rate Variability (HRV) analysis and overnight pulse oximetry, 180 CHF patients underwent overnight polysomnography for diagnosis of SDB. Simultaneous monitoring with ambulatory electrocardiography and overnight pulse oximetry was performed, to allow investigation of the diagnostic accuracy of these portable monitors. The results of this study showed that the %VLF1 component of HRV was unable to discriminate between the presence and absence of SDB in CHF, and was measurable in less than half of all CHF patients. Therefore, I have argued that HRV analysis is of no utility to identify SDB in patients with CHF.

In contrast, the 3% oxygen desaturation index (ODI) was measurable in 99% of CHF patients, with an AUC of 0.92 indicating a high accuracy for diagnosis of SDB in CHF. At the pre-specified cutoff of >7.5 dips/hour, the 3% ODI had a low number of false

negatives, with high sensitivity and a low negative likelihood ratio. However, at this cutoff, a high number of false positive results occurred with a low specificity. In a post hoc analysis, an optimum 3% ODI cutoff of 11.6 dips/hour was identified that had an increased specificity without any deterioration in the sensitivity or negative likelihood ratio. Therefore, I have argued that overnight pulse oximetry would be of greatest value to rule out SDB in CHF. If used as part of a phased testing approach, a CHF patient with negative overnight oximetry may not need further investigation for SDB. This could reduce pressure on sleep services for more detailed sleep studies, whilst allowing resources to be prioritised to CHF patients with positive oximetry studies.

In a heterogeneous cohort of 180 patients receiving contemporary medical and device therapy for heart failure, the clinical characteristics of 80 CHF patients with SDB were compared to those of 100 CHF patients without SDB. As may be expected, CHF patients with obstructive sleep apnoea (OSA) had significantly higher body mass index (BMI), neck circumference and waist:hip ratio compared to CHF patients without SDB. In addition, CHF patients with CSA also had a significantly greater neck circumference than patients without SDB.

The odds ratio for SDB was increased in CHF patients who reported witnessed apnoeas, but the sensitivity of this symptom was low. There was a small increase in the odds ratio for OSA in CHF patients who reported snoring >4 days/week. As has previously been reported, CHF patients did not complain of excessive daytime sleepiness when assessed subjectively by the Epworth Sleepiness Scale (ESS), or objectively with the OSLER test. Moreover, the ESS score was unable to discriminate CHF patients with SDB from those without SDB.

Measurements of heart failure severity, including the New York Heart Association classification, left ventricle ejection fraction (LVEF) and B-Type Natriuretic Peptide (BNP) were similar irrespective of the presence or absence of SDB. There was a trend

towards a lower LVEF and higher BNP concentration in CHF patients with CSA. However, as there were only 25 CHF patients with CSA, the current study may have been underpowered to detect a true difference in LVEF or BNP between patients with CSA and patients without SDB. Interestingly, CHF patients with OSA had a significantly higher LVEF and BNP concentration than patients with CSA, and I have argued that this may represent important differences in heart failure severity which could have implications for the benefits of treatment.

The impact of two different rules for scoring hypopnoea was evaluated in 170 CHF patients who were investigated for the presence of SDB. As may be expected, scoring hypopnoeas with a lower threshold for the associated oxygen desaturation or the presence of an arousal, resulted in a significant increase in the measured AHI and number of patients diagnosed with SDB. The use of hypopnoea rule 2 (corroborative $\geq 3\%$ oxygen desaturation or arousal) resulted in a median increase in the measured AHI of 3.9 events per hour, and an increase of 16% in the number of CHF patients diagnosed with SDB, compared to rule 1 (corroborative $\geq 4\%$ oxygen desaturation). The impact of the different hypopnoea scoring criteria on clinical outcomes remains to be determined (see below). In addition, the use of a hypopnoea scoring rule requiring a lower associated oxygen desaturation did not alter the classification of SDB as obstructive or central sleep apnoea in any patient.

The effect of mixed apnoea categorisation on SDB classification was studied in 180 CHF patients. Mixed apnoeas occurred in 44 CHF patients. I have argued that the categorisation of mixed apnoeas as obstructive or central events does not significantly influence the classification of SDB in CHF patients. However, the frequency of these events was low in this study.

6.3. Future Directions

This thesis has determined that overnight pulse oximetry has a high diagnostic accuracy for SDB in CHF. A negative result with overnight pulse oximetry can be used to rule out SDB with high confidence. The emphasis of studies to evaluate the utility of portable monitors for diagnosis of SDB has evolved since the current study was conceived (Kuna, 2011a). Instead of comparing the metric of SDB measured by the monitor under investigation and a reference standard, studies are now evaluating the utility of portable monitors as part of a clinical management pathway (Mulgrew, 2007; Antic, 2009; Kuna, 2011b). This approach could be adopted to evaluate the use of overnight pulse oximetry in the diagnosis and clinical management of SDB in CHF patients.

A randomised clinical trial could be used to evaluate the utility of overnight pulse oximetry as part of a clinical management pathway, and a potential study design is shown in Figure 6.1. The challenge with this study would be the choice of outcome. As previously discussed (see Section 1.4.1), SDB in CHF may be asymptomatic or minimally symptomatic. However, treatment of OSA with CPAP even in minimally symptomatic adults is associated with a significant reduction in the ESS (Craig, 2011) and in CHF patients with SDB, treatment with adaptive servo ventilation has also been reported to reduce the median ESS from 9 to 5 (mean difference [SD] 4 [3]) (Hastings, 2010). Therefore, the change in ESS may be suitable as an outcome measure in a study comparing overnight pulse oximetry to polysomnography/polygraphy for initial diagnosis and management of SDB in CHF. If the minimal clinically important difference in the change in ESS is assumed to be 1 point, a sample size of 143 CHF patients in each group would be adequately powered ($1 - \beta = 0.8$), with $\alpha = 0.05$, to exclude a difference in the change in ESS of more than 1 point. As the prevalence of

SDB in CHF is approximately 50%, and assuming a study dropout rate of 10%, a total of 630 CHF patients would need to be recruited and randomised for this study.

A study using endpoints such as hospital admissions or mortality would provide information on more clinically relevant outcomes, but this is also likely to require a large sample size and may take many years to collect sufficient data on these endpoints.

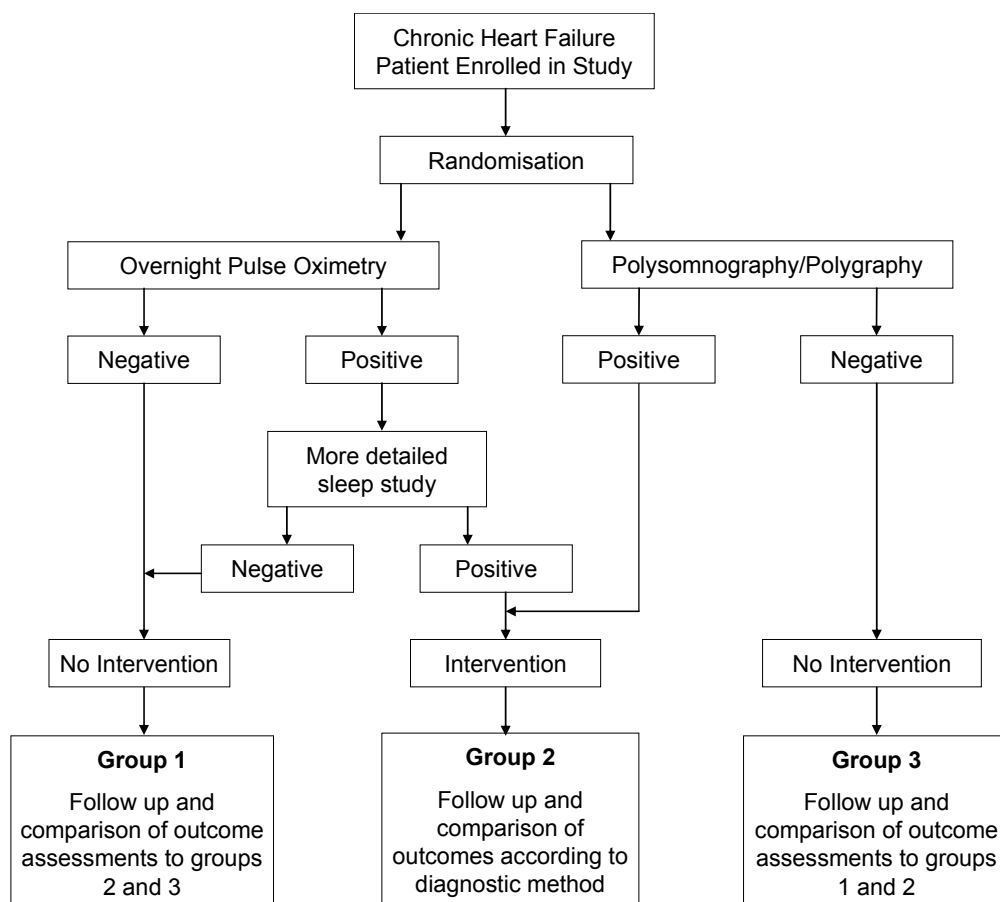


Figure 6.1. Proposed Study Design for a Randomised Controlled Trial to Evaluate the Utility of Overnight Pulse Oximetry for the Investigation and Management of Sleep-Disordered Breathing in Chronic Heart Failure

A further study of overnight pulse oximetry may also be required to evaluate the post hoc 3% ODI cutoff of 11.6 dips/hour, which was determined in the current study to be the optimal threshold for identification of SDB in CHF. As I have shown with the %VLF1 component of HRV, prospective evaluation of diagnostic thresholds is important to confirm or challenge the findings of previous studies.

Another area of investigation relates to the identification of clinical characteristics or symptoms to help identify SDB in CHF. The findings of this thesis confirm previous reports of the inability of the ESS to discriminate between the presence and absence of SDB in CHF. However, this may reflect the poor sensitivity of the ESS to detect symptoms related to SDB in CHF patients, many of whom are elderly (see Section 3.4.3). There may be other symptoms which have higher predictive value for SDB in CHF, such as fatigue or insomnia. For example, research in patients with neurological disease has reported that symptoms of fatigue are more strongly associated with OSA than daytime sleepiness (Kaminska, 2009; Kaminska, 2011). Qualitative research may help establish if the symptoms associated with SDB in CHF differ from those in adults with OSA, with the aim of developing questionnaires which may be more sensitive for SDB in CHF.

An additional approach to improving identification of SDB in CHF may be to try to develop a risk calculator. The presence of individual symptoms such as snoring or witnessed apnoeas is associated with a small increase in the odds of SDB. The combination of a number symptoms or readily observed clinical characteristics e.g. BMI, neck circumference or presence of atrial fibrillation, may have a greater predictive value for SDB in CHF. This would require evaluation of symptoms and anthropometric characteristics in a large cohort of CHF patients who would then be investigated for the presence or absence of SDB.

A third line of future research is related to our investigation of the impact of scoring criteria on SDB diagnosis in CHF. In this thesis, I have shown that the rule used to score hypopnoea can significantly influence the measured AHI and number of patients diagnosed with SDB. However, the results of this study do not determine if there is a difference in clinical outcomes associated with the use of different scoring rules. The optimum definition of hypopnoea would identify SDB that is associated with morbidity, mortality or is responsive to treatment.

Evidence from community based epidemiological cohorts suggests that a hypopnoea scoring criteria requiring a corroborative $\geq 4\%$ oxygen desaturation is most strongly associated with prevalent cardiovascular disease (Punjabi, 2008). It remains uncertain whether these findings apply to clinical populations, to patients with pre-existing cardiovascular disease, or to older adults. There remains the need for further evaluation of respiratory event scoring criteria in patients with CHF, to identify definitions that are most strongly associated with clinically relevant outcomes.

An alternative and potentially simpler approach would be to investigate whether a signal recorded by single channel portable monitor may provide information about SDB which is of clinical or prognostic relevance (Pinna, 2009). Intermittent hypoxaemia which is implicated in the pathogenesis of the cardiovascular consequences of SDB (Tamisier, 2009) could be readily quantified by overnight pulse oximetry. Autonomic arousals may also contribute to cardiovascular and metabolic morbidity (Morrell, 2000; Stamatakis, 2010). Whilst the %VLF component of HRV was not correlated with the AHI, other surrogate markers of autonomic arousals occurring in SDB such as pulse transit time (Pitson, 1994), peripheral arterial tone (Pillar, 2002) or pulse rate rise index (Adachi, 2003) could also be evaluated for clinical and prognostic relevance.

This approach would require a well characterised cohort of CHF patients to undergo baseline measurements by the single channel portable monitors being evaluated, with longitudinal follow up to assess clinically relevant outcomes.

A novel observation of this thesis was that a significantly lower proportion of CHF patients with SDB reported a diagnosis of COPD or asthma. This may be an area for future research to establish whether there is a true difference in the prevalence of COPD or asthma in CHF patients with SDB. If confirmed, investigation may help establish mechanisms by which COPD or asthma may protect against SDB, including possible changes in eupneic carbon dioxide levels and chemosensitivity.

In addition, this study has also found a high prevalence of periodic limb movements (PLM) during sleep in CHF patients. Whilst this is not a new finding, (Hanly, 1996; Javaheri 1998), the impact of PLM on sleep structure, daytime symptoms and quality of life in CHF requires further investigation. Moreover, reports of an association between PLM and incident cardiovascular disease (Koo, 2011) suggest that their impact on cardiovascular morbidity and mortality requires further evaluation.

6.4. Conclusion

In conclusion, I think future studies should concentrate on investigating whether the data recorded by single channel portable monitors such as overnight pulse oximetry can provide prognostic or other clinically relevant information. In addition, the utility of overnight pulse oximetry for identification of SDB in CHF now needs to be evaluated as part of a clinical management pathway.

CHAPTER 7: REFERENCES

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CHAPTER 8: APPENDIX

8.1. Monitor Validation Tables

Table 8.1. Results of Validation Studies of Type 3 Portable Monitors

PORTABLE MONITOR SYSTEM	REFERENCE	NO OF PTS	PARTICIPANTS	AGE (YRS) $\pm$ SD	% MALE	BMI	SETTING	FAILURE RATE %	CORRELATION BETWEEN NPSG AND PORTABLE MONITOR AHI	AHI CUTOFF	SENSITIVITY %		SPECIFICITY %		PPV%		NPV%	
											Manual scoring	Automatic scoring	Manual scoring	Automatic scoring	Manual scoring	Automatic scoring	Manual scoring	Automatic scoring
APNOE-SCREEN II	Quintana-Gallego et al. Eur Respir J 2004; 24: 443-448	75	Cardiology outpatients with stable CHF	56.1 $\pm$ 11.7	87	28.6 $\pm$ 4.4	NPSG in sleep lab, then home PG	9		>5 >10 >15	82.5 79.3 68.4		88.6 97.8 94.6					
BEDBUGG (now NovaSom QSG)	Claman et al. Otolaryngol Head Neck Surg 2001;125: 227-30.	42	Referrals with suspected OSA	54 $\pm$ 12.9	74	30.6 $\pm$ 6.7	Synchronous NPSG and PM recording in sleep lab	0	r=0.96	>15		85.7		95.2		94		88
BITMED NGP 140	Candela et al. Arch Bronconeumol 2005;41(2):71-7	92	Referrals with suspected sleep disordered breathing	52.4 $\pm$ 11.8	78	31.8 $\pm$ 6.6	Synchronous recording in sleep lab	4	r=0.945	>10 >15 >20 >30	97 96 96 98	97 92 92 98	82 94 97 98	85 97 97 93	93 96 98 98	94 98 98 94	92 94 95 98	92 90 90 98
EDENTEC 3711	Whittle et al. Thorax 1997; 52;1068-1073	23	Sleep clinic referrals with suspected OSA	50 $\pm$ 9	83	31 $\pm$ 5	NPSG in sleep lab, home PM following night	13	r=0.8									
EDENTEC 4700	Redline et al. Chest 1991; 100;1281-1286	25	Sleep clinic referrals and relatives of patients with OSA	53 $\pm$ 13.7	83	31.4 $\pm$ 5.8	Synchronous NPSG and PM recording in sleep lab	0	r=0.96									

Table 8.1. (continued) Results of Validation Studies of Type 3 Portable Monitors

PORTABLE MONITOR SYSTEM	REFERENCE	NO OF PTS	PARTICIPANTS	AGE (YRS) $\pm$ SD	% MALE	BMI	SETTING	FAILURE RATE %	CORRELATION BETWEEN NPSG AND PORTABLE MONITOR AHI	AHI CUTOFF	SENSITIVITY %		SPECIFICITY %		PPV%		NPV%	
											Manual scoring	Automatic Scoring	Manual scoring	Automatic scoring	Manual scoring	Automatic scoring	Manual scoring	Automatic scoring
EDENTRA CE II	Álvarez et al. Arch Broncon 2008;44:22-8	45	Referrals with suspected OSA	52.3 $\pm$ 11	87	28.5 $\pm$ 4	Home PM followed by in hospital NPSG	0	r=0.727	<7.2 >13.7	90.5 61.9		54.2 95.8		63.3 92.9		87 74	
EDENTRA CE II	Parra et al. Eur Respir J 1997; 10: 1720–1724	89	Referrals with suspected OSA	54 $\pm$ 12	82	29 $\pm$ 4	Hospital NPSG before or after home PM	0 - 10*	89% Agreement in therapeutic decision between NPSG and PM studies	$\geq$ 10	90		57					
EMBLETTA	Dingli et al. Eur Respir J 2003; 21: 253–259	40	Referrals with suspected OSA	46 $\pm$ 10	83	32 $\pm$ 6	In lab NPSG and PM	3	r=0.98 (Kappa=0.62 for agreement in clinical diagnosis between Embletta and PSG)									
		61		50 $\pm$ 11	77	31 $\pm$ 6	Home PM before or after hospital NPSG	18	r=0.74 (Kappa=0.54 for agreement in clinical diagnosis between Embletta and PSG)									
EMBLETTA	Smith et al. J. Sleep Res. 2007;16, 428–435	20	Cardiology outpatients with stable CHF	61 $\pm$ 10	70	29 $\pm$ 6	Synchronous NPSG and PM in hospital	0	r=0.92 (Kappa=0.63 for agreement in clinical diagnosis between Embletta and PSG)									
							Home PM after NPSG	15	r=0.54 (Kappa=0.27 for agreement in clinical diagnosis)	$\geq$ 15					83		57	

* Failure rate 10 % when monitoring equipment attached by patient at home, no failures when technician attached monitoring equipment in patients home

Table 8.1. (continued) Results of Validation Studies of Type 3 Portable Monitors

PORTABLE MONITOR SYSTEM	REFERENCE	NO OF PTS	PARTICIPANTS	AGE (YRS) $\pm$ SD	% MALE	BMI	SETTING	FAILURE RATE %	CORRELATION BETWEEN NPSG AND PORTABLE MONITOR AHI	AHI CUTOFF	SENSITIVITY %		SPECIFICITY %		PPV%		NPV%	
											Manual scoring	Automatic Scoring	Manual scoring	Automatic scoring	Manual scoring	Automatic scoring	Manual scoring	Automatic scoring
MERLIN	Calleja et al. Eur Respir J 2002; 20: 1505–1510	86	Referrals with suspected OSA	52 $\pm$ 11.1	89	30.1 $\pm$ 4.4	Synchronous NPSG and PM in hospital	8		≥ 5 ≥ 10 ≥ 15 ≥ 20 ≥ 30	97 91 91 91 89	82 63 64 60 63	91 87 81 85 91	64 87 73 59 57				
MICRODIG ITRAPPER-S	Zucconi et al. Eur Respir J., 1996, 9, 1251–1256.	30	Referrals with suspected OSA	53 $\pm$ 12	70	30.7 $\pm$ 6.7	Synchronous NPSG and PM in hospital	3		≥ 10 ≥ 20 ≥ 40	100 94 91	100 94 55	100 92 94	100 100 95	100 94 91	100 100 86	100 92 77	100 93 94
NIGHT-WATCH	White et al. Sleep 1995. 18(2): 115-126	30	Referrals with suspected OSA	51.1 $\pm$ 2.9	77	33.0 $\pm$ 1.5	Synchronous NPSG and PM in hospital	0	r=0.94	>10 >20	100 77		64 88		87 83		100 83	
		70		47.9 $\pm$ 1.6	74	31.0 $\pm$ 1.0	Home PM before or after NPSG	3	r=0.92	>10 >20	91 86		70 83		87 79		84 89	
NOVASOM QSG	Reichert et al. Sleep Medicine 4 (2003) 213–218	51	Referrals with suspected OSA	52.2 $\pm$ 2.1	75	30 $\pm$ 1.0	Synchronous NPSG and PM in hospital	14		≥ 15		95		91		91		96
							Home PM after NPSG	12		≥ 15		91		83		83		91
POLY G	Man et al. Chest 1995;108;388-393	104	Referrals with suspected sleep disorders	47 $\pm$ 11.5	78	29.7	Synchronous NPSG and PM in sleep laboratory	0	r=0.97	≥ 15	86		95		86		95	

Table 8.1. (continued) Results of Validation Studies of Type 3 Portable Monitors

PORTABLE MONITOR SYSTEM	REFERENCE	NO OF PTS	PARTICIPANTS	AGE (YRS) $\pm$ SD	% MALE	BMI	SETTING	FAILURE RATE %	CORRELATION BETWEEN NPSG AND PORTABLE MONITOR AHI	AHI CUTOFF	SENSITIVITY %		SPECIFICITY %		PPV%		NPV%	
											Manual scoring	Automatic Scoring	Manual scoring	Automatic scoring	Manual scoring	Automatic scoring	Manual scoring	Automatic scoring
POLY-MESAM	Verse et al. <i>Chest</i> 2000;117;1613-1618	53	Patients with sleep related respiratory disorders and snorers	48.1 $\pm$ 10.8	92	27.4 $\pm$ 4.9	Synchronous inpatient NPSG and PM	ND	r=0.965	≥ 10 ≥ 15 ≥ 20	92 87 71		96 97 97					
SIBEL HOME -300	Ballester et al. <i>Eur Respir J</i> 2000; 16: 123 $\pm$ 127	116	General population	47 $\pm$ 12	56	26 $\pm$ 4	Synchronous NPSG and PM in sleep laboratory	ND		≥ 10 ≥ 30	89 100		92 97		78 79		96 100	
SNAP	Su et al. <i>Otolaryngol Head Neck Surg.</i> 2004;131:844-50	60	Referrals for NPSG	45.2 $\pm$ 12.3	42	35.6 $\pm$ 10	Simultaneous NPSG and PM in sleep laboratory	2	r=0.92	≥ 5 ≥ 10 ≥ 15		98 88 84		40 74 76		89 88 79		80 74 82
STARDUS T II	Yin et al. <i>Otolaryngology-Head and Neck Surgery</i> (2006) 134, 204-209	44	Referrals with suspected OSA	52.3 $\pm$ 13.5	91	26.7 $\pm$ 5.3	Home PM then inpatient NPSG	6	r=0.845	≥ 5 ≥ 15 ≥ 30 ≥ 50		100 94 79 90		- 25 70 97		93 77 76 90		- 60 74 97.

BMI = Body mass index; NPSG = nocturnal polysomnography; PM = Portable monitor; AHI = Apnoea hypopnoea index; PPV = Positive predictive value; NPV = negative predictive value; CHF = Chronic heart failure; OSA = Obstructive sleep apnoea;

**Table 8.2. Results of Validation Studies of Type 4 Portable Monitors for Diagnosis of Sleep-Disordered Breathing
(excluding oximeters and heart rate variability monitors)**

PORTABLE MONITOR SYSTEM	REFERENCE	NO OF PTS	PARTICIPANTS	AGE (YRS) +SD -SD	% MALE	SETTING	FAILURE RATE (%)	CORRELATION BETWEEN NPSG AND PORTABLE MONITOR AHI	AHI CUTOFF	SENSITIVITY%		SPECIFICITY%		PPV%		NPV%	
										Manual scoring	Automatic scoring	Manual scoring	Automatic scoring	Manual scoring	Automatic scoring	Manual scoring	Automatic scoring
Airflow and oximetry signals only (Pro-Tech Portable Sleep Data Recorder)	Ayappa et al. Sleep 2004;27: 1171-79	59	Referrals with suspected OSA	ND	ND	NPSG in sleep lab and different night PM study in research centre	5%	89% agreement in diagnostic classification when NPSG AHI cutoff =15	18	88		92					
ApneaLink	Erman et al. J Clin Sleep Med 2007;3:387- 392	63	Diabetic patients in OSA prevalence study	57.3 ±12	49	Same night NPSG and PM study in hospital, second PM study at home on different night	6.3	r=0.89	>5 >10 >15 >20	85 82 91 83		50 84 95 93		80 82 91 83		60 84 95 93	
ARES	Westbrook et al. Chest 2005; 128:2166- 2175	299	Referrals with suspected OSA (210), general medical patients (36) and healthy volunteers (53)	48 ±11	62	Same night NPSG and PM study in lab (299)	5	Correlation between ARES RDI and NPSG AHI, Kappa = 0.85	>10		97		86		94		94
						Hospital NPSG and home PM on different nights (191)	2	Correlation between home ARES RDI and NPSG AHI, Kappa = 0.77	>5 >10 >15 >30		96 92 86 79		59 86 84 100		92		86

Table 8.2. (continued) Results of Validation Studies of Type 4 Portable Monitors for Diagnosis of Sleep-Disordered Breathing (excluding oximeters and heart rate variability monitors)

PORTABLE MONITOR SYSTEM	REFERENCE	NO OF PTS	PARTICIPANTS	AGE (YRS) $\pm$ SD	% MALE	SETTING	FAILURE RATE %	CORRELATION BETWEEN NPSG AND PORTABLE MONITOR AHI	AHI CUTOFF	SENSITIVITY%		SPECIFICITY%		PPV%		NPV%	
										Manual scoring	Automatic Scoring	Manual scoring	Automatic scoring	Manual scoring	Automatic scoring	Manual scoring	Automatic scoring
ApnoeScreen I	Golpe et al. Chest 2002; 122:1156-1161	55	Referrals with suspected OSA	52.7 $\pm$ 13	96	Home PM study then NPSG in hospital	20*	Concordance in diagnosis (AHI>10) = 75% Agreement in treatment decision = 77%	10								
Autoset	Rees et al. Eur Respir J 1998;12: 764–769	20	Referrals with suspected OSA	48 $\pm$ 11	100	Same night NPSG and PM study in hospital	0	r=0.9									
MESAM IV	Esnaola et al. Eur Respir J 1996 ;9 :2597–2605	152	Referrals with suspected OSA	57 $\pm$ 11	89	Same night NPSG and PM study in hospital	1	r=0.57	>5 >10 >15 >20	66 69 68 52		96 98 97 98		87 98 96 95		80 67 75 71	
OxiFlow	Baltzan et al. Sleep 2000; 23:1-9	97	Referrals with suspected OSA	51.8 $\pm$ 15	74	Same night NPSG and PM study in hospital	8	r=0.75	>15	100	73	52	83				
						Home PM study on different night to NPSG	8.7	r=0.58	>15	88	55	62	88				
Reggie	Overland et al. Respiration 2005;72:600-605	53	Referrals with suspected OSA	ND	ND	Same night NPSG and PM study in hospital	ND	r=0.98									

* Failure rate 7% when Apnoescreen I attached by technician at home, and 33% when patient attached the portable monitor following printed instructions.

Table 8.2 (continued) Results of Validation Studies of Type 4 Portable Monitors for Diagnosis of Sleep-Disordered Breathing (excluding oximeters and heart rate variability monitors)

PORTABLE MONITOR SYSTEM	REFERENCE	NO OF PTS	PARTICIPANTS	AGE (YRS) $\pm$ SD	% MALE	SETTING	FAILURE RATE %	CORRELATION BETWEEN NPSG AND PORTABLE MONITOR AHI	AHI CUTOFF	SENSITIVITY%		SPECIFICITY%		PPV%		NPV%	
										Manual scoring	Automatic Scoring	Manual scoring	Automatic scoring	Manual scoring	Automatic scoring	Manual scoring	Automatic scoring
SleepStrip	Pang et al. Otolaryngol Head Neck Surg 2006;135:265-268	39	Referrals with suspected OSA	52.1 $\pm$ 12	44	NPSG in hospital, home PM study night after	14	Kappa Coefficient 0.139	>15 >25 >40		55 44 33		70 81 95				
SleepStrip	Shochat et al. Eur Respir J 2002;19:121-126	402	Referrals with suspected OSA	ND	ND	Same night NPSG and PM study in sleep lab	26.5	r=0.73	>10 >20 >40		86 80 80		57 70 86				
Somnocheck	Ficker et al. Respiration 2001;68:307-312	51	Referrals with suspected OSA	53.4 $\pm$ 13	86	Same night NPSG and PM study in sleep lab	ND	r=0.98 (manual analysis) r=0.83 (automatic analysis)	>5 >10 >20 >40	94 97 76 69	83 83 71 61	100 100 100 100	87 95 93 100	100 100 100 100	94 96 88 100	88 96 86 90	68 81 82 88
WatchPAT 100	Ayas et al. Sleep Medicine 2003;4:435-442	30	Referrals with suspected OSA	47 $\pm$ 14	63	Same night NPSG and PM study in sleep lab	0	r=0.87 and concordance in clinical diagnosis =87%	>10 >15 >20 >30		83 93 91 83		71 73 84 92				
WatchPAT 100	Bar et al. Chest. 2003;123:695-703	102	Referrals with suspected OSA (69) and healthy volunteers (33)	41.4 $\pm$ 15	76	Same night NPSG and PM study in sleep lab	1	r=0.88									

Table 8.2. (continued) Results of Validation Studies of Type 4 Portable Monitors for Diagnosis of Sleep-Disordered Breathing (excluding oximeters and heart rate variability monitors)

PORTABLE MONITOR SYSTEM	REFERENCE	NO OF PTS	PARTICIPANTS	AGE (YRS) $\pm$ SD	% MALE	SETTING	FAILURE RATE %	CORRELATION BETWEEN NPSG AND PORTABLE MONITOR AHI	AHI CUTOFF	SENSITIVITY%		SPECIFICITY%		PPV%		NPV%	
										Manual scoring	Automatic Scoring	Manual scoring	Automatic scoring	Manual scoring	Automatic scoring	Manual scoring	Automatic scoring
WatchPAT 100	Penzel et al. Physiol Meas 2004;25:1025-103	21	Referrals with suspected OSA and patients with OSA on CPAP	ND	ND	Same night NPSG and PM study in sleep lab	19	$r=0.89$									
WatchPAT 100	Pittman et al. Sleep 2004;27:923-33	30	Referrals with suspected OSA	43.2 $\pm$ 10	72	Same night NPSG and PM study in sleep lab	3	$r=0.89$	>10 >15 >20 >30	96 91 90 92		100 86 89 82					
						PM study at home on different night	0	$r=0.72$	>10 >15 >20 >30	82 96 80 92		100 90 100 96					
WatchPAT 100	Zou et al. Sleep 2006;29:367-374	106	Hypertensive and control participants in Skaraborg Sleep Study	60 $\pm$ 7	56	Unattended home NPSG and PM study	7	$r=0.90$									

ND = No data; RDI = Respiratory disturbance index. CPAP = Continuous positive airway pressure therapy. See Table 8.1 for additional abbreviations

Table 8.3. Studies Evaluating Pulse Oximetry for the Diagnosis of Obstructive Sleep Apnoea

Study	Oximeter	No of pts	Participants	Failure rate %	Setting	Outcome Measure	Reference Standard Cutoff	Sensitivity%	Specificity%	Other findings	
Chiner et al. Thorax 1999;54:968-71	N-200 (Nellcor Inc, USA)	275	Sleep clinic referrals	ND	Simultaneous NPSG and oximetry in sleep lab	ODI 4%	AHI $\geq 15/h$ vs ODI $\geq 5/h$ ODI $\geq 10/h$ ODI $\geq 15/h$	82 71 62	76 90 93	PPV	NPV
										93	54
										96	46
Epstein et al. Chest 1998;113:97-103	NPSG oximeter data	100	Sleep clinic referrals	ND	In lab NPSG with blinded NPSG oximeter reanalysis	oxygen desaturation $\geq 4\%$ to $<90\%$ Visual analysis	AHI $\geq 20/h$ vs ODI 4% Visual analysis	74 96	89 53	PPV	NPV
										89	75
										71	93
Golpe et al. Sleep 1999;22:932-937	AVL-Minolta Pulsox -7 (AVL Medical Instruments, Switzerland)	125	Sleep clinic referrals	7.2	Home oximetry then NPSG	Cumulative Time SaO ₂ $<90\%$ ODI 4% Visual analysis	AHI 10/h vs CT $\leq 90\%$ ODI 4%	84 32	48 97	62% incorrectly or inconclusively classified by oximetry	
Jobin et al. Thorax 2007;62:422-427	Oximax Durasensor DS-100A (Tyco Healthcare, USA)	104	Sleep clinic referrals	10	Simultaneous home oximetry and limited channel PM	ODI 4%	PM RDI $>15/h$	63	96	81% patients correctly classified	

Table 8.3. (continued) Studies Evaluating Pulse Oximetry for the Diagnosis of Obstructive Sleep Apnoea

Study	Oximeter	No of pts	Participants	Failure rate %	Setting	Outcome Measure	Reference Standard Cutoff	Sensitivity%	Specificity%	Other findings
Levy et al. Chest 1996;109:395-99	Biox 3700 or 3740 (Ohmeda, USA)	301	Sleep lab referrals	ND	In lab	Delta (Δ) index.	AHI $\geq$ 15/h Vs Δ index 0.6 Δ index 0.8	98 90	46 75	Correlation with RDI and Δ index $r=0.72$
Magalung et al. Chest 2003;124:1694-1701	ND	292	Sleep clinic referrals	ND	Lab NPSG oximeter recording used	Change (Δ) index ODI 2/3/4%	AHI $\geq$ 15/h vs Δ index $\geq$ 0.61 ODI 4%	91 94	59 44	Accuracy Δ index = 0.881 ODI 4% =0.852 (2, 3% ODI as accurate as 4%)
Oeverland et al. Sleep Med 2002;3:133-138	Nonin 8500 (Nonin Medical Inc, USA)	100	ENT clinic	7	Simultaneous NPSG and oximetry in sleep lab	ODI 2,3,4,5 %	AHI $\geq$ 5/h vs ODI 2% ODI 3% ODI 4% ODI 5% AHI $\geq$ 15/h vs ODI 2% ODI 3% ODI 4% ODI 5%	100 91 73 57 100 86 64 52	0 67 100 100 27 88 100 100	

Table 8.3. (continued) Studies Evaluating Pulse Oximetry for the Diagnosis of Obstructive Sleep Apnoea

Study	Oximeter	No of pts	Participants	Failure rate %	Setting	Outcome Measure	Reference Standard Cutoff	Sensitivity%	Specificity%	Other findings
Olson et al. J Sleep Res 1999;8:51-55	Biox 4700 (Ohmeda, USA)	793	Sleep clinic referrals	ND	Home oximetry before NPSG	Cumulative Time SaO ₂ <90% Δ index	AHI > 15/h vs CT < 90% Δ index ≥ 0.4	75 88	46 40	Correlation coeff CT < 90 r = 0.36 Δ index 0.4 r = 0.59
Series et al. Ann Int Med 1993;119:449-453	Biox IVA (Ohmeda, USA)	240	Sleep clinic referrals	ND	Home oximetry then lab NPSG	Visual inspection	AHI ≥ 10/h AHI ≥ 20/h	98 100	48 39	
Vazquez et al. Thorax 2000;55:302-307	Healthdyne 202-11 (Healthdyne technologies)	245	Sleep clinic referrals	1.6	Simultaneous NPSG and oximetry in sleep lab	Oximeter RDI (automated)	AHI ≥ 15/h AHI ≥ 20/h	98 97	88 85	NPSG AHI and oximeter RDI correlation r = 0.97
Whitelaw et al. AJRCCM 2005;171:188-193	Snoresat with Nonin OEM II oximeter (Sagatech, Canada)	288	Sleep lab refs	ND	Home snoresat or in lab NPSG	4% Desaturation > 10s				NPSG no better than oximetry helping predict likelihood of success of CPAP treatment

Table 8.3. (continued) Studies Evaluating Pulse Oximetry for the Diagnosis of Obstructive Sleep Apnoea

Study	Oximeter	No of pts	Participants	Failure rate %	Setting	Outcome Measure	Reference Standard Cutoff	Sensitivity%	Specificity%	Other findings
Wiltshire et al. Chest 2001; 120:384-389	Biox 3740 (Ohmeda, UK)	100	Sleep clinic referrals	ND	Home oximetry then NPSG in sleep laboratory	ODI 4% (automated)	NPSG ODI ≥10/h ≥15/h	41 35	100 100	.
Yamashiro et al. Sleep 1995;18:167-71	Biox 3740 (Ohmeda, USA)	300	Sleep clinic referrals	10.3	In lab NPSG with blinded NPSG oximeter reanalysis	ODI 3%	NPSG AHI ≥5/h	94	74	PPV = 79% NPV = 92%

ODI = oxygen desaturation index; See Tables 8.1 and 8.2 for additional abbreviations

Table 8.4. Studies Evaluating Heart Rate Variability Analysis for Diagnosis of Sleep-Disordered Breathing

Author Reference	Study population	No of Pts	AHI diagnostic criteria	Prevalence of SDB	Age $\pm$ S.D.	Male (%)	HRV measures	Best Outcome Measure	(%) Sensitivity	(%) Specificity	AUC	Notes
Adachi et al. Sleep Med 2003;4:537-42	Suspected OSA	33	>5/hr or >10/hr breathing related arousals	94%	49 $\pm$ 13	88	Oximeter pulse rate rise index (PRRI) (from 4 – 10bpm)	PRRI-6 >40/hour	88	86	84	PRRI overestimates arousals due to causes other than SDB
Aydin et al. Tex Heart Inst J. 2004;31: 132-6	OSA and healthy controls	60	>5/hr	60	45	100	Time and Frequency domain	ND				Decrease in all time domain measures in OSA. Increased ULF, VLF and LF power in OSA
Dingli et al. Eur Resp J 2003;22:943-50	OSA and healthy controls	21	ND	67	51 $\pm$ 9	ND	Time and Frequency domain analyses					Increased LF power and total power around end of apnoeas/ hypopnoeas
Gula et al. ANE 2003;8: 144-9	Suspected OSA	20	10/hr	ND	47 $\pm$ 12	75	LF, HF power and LF:HF ratio	Increased LF:HF ratio in moderate OSA compared to severe OSA and no OSA				
Hilton et al. Med Biol Eng Comput 1999;37:760-9	Suspected OSA and healthy volunteers	40	>5/hr	53	47	ND	Frequency and Time-Frequency Analysis, with Discrete Harmonic Wavelet Transform (DHWT)	0.019-0.036 Hz band power				15 min ECG recordings in NREM and REM sleep used. DHWT superior to Fourier transform for diagnosis OSA in NREM sleep. Both less discriminatory in REM sleep.

AUC = Area under receiver operating characteristic curve; ND = No data in report; ULF = Ultra low frequency; VLF = Very low frequency; LF = Low frequency; HF = High frequency; ECG = Electrocardiogram; NREM = Non rapid eye movement; REM = Rapid eye movement sleep.

Table 8.4.(continued) Studies Evaluating Heart Rate Variability Analysis for Diagnosis of Sleep-Disordered Breathing

Author Reference	Study population	No of Pts	AHI diagnostic criteria	Prevalence of SDB	Age $\pm$ S.D.	Male (%)	HRV measures	Best Outcome Measure	(%) Sensitivity	(%) Specificity	AUC	Notes
Hilton et al. Eur Resp J 2001;17: 1258-66	OSA and healthy controls	29	>15/hr	52	47	100	Frequency domain	HF power and LF/HF ratio.				Reduced vagal tone in waking hours in OSA compared to control
Narkiewicz et al. Circulation 1998;98:1071-77	OSA and normal controls	49	<20/hr = mild; >20/hr = moderate-severe	30% mod severe OSA 37% mild OSA 33% no OSA	41 $\pm$ 9 45 $\pm$ 10 40 $\pm$ 9	78	Mean RR, RR variance, LF,HF,LF/HF	mean RR, normalised LF, normalised HF, LF/HF ratio				Severity of cardiovascular variability derangement linked to the severity of OSA.
Penzel et al. Med Biol Eng Comput 2002 ;40:402-7	OSA and healthy controls	70	15/hr	71	ND	78	Comparison of different algorithms	Frequency domain based algorithms most reliable for diagnosis of SDB				Comparison of published algorithms.
Roche et al. Circulation 1999;100; 1411-15	Suspected OSA	143	>10/hr	44	55 $\pm$ 11	79	Time domain	1. Δ (D/N) SDNN index 2. Night SDNN index 3. Δ (D/N) SDNN 4. Night SDNN				

Definitions as per Table on previous page. In addition, RR = RR interval on ECG; Δ (D/N) = Change between day and night; SDNN = Standard deviation of all normal – normal intervals (see also Table 2.3)

Table 8.4.(continued) Studies Evaluating Heart Rate Variability Analysis for Diagnosis of Sleep-Disordered Breathing

Author Reference	Study population	No of Pts	AHI diagnostic criteria	Prevalence of SDB	Age $\pm$ S.D.	Male (%)	HRV measures	Best Outcome Measure	Sensitivity (%)	Specificity (%)	AUC	Notes
Roche et al. PACE 2002;25: 1192-1199	Suspected OSA	124	>10/hr	44	54 $\pm$ 12	79	VLFI power, %VLFI (also time and frequency domain and day night differences in measures)	%VLFI >2.4%	87	52		Repeat HRV measured in 18 patients after 3 months CPAP treatment and decrease in %VLFI, Δ [D/N] SDNN index, Δ [D/N] RMSSD
								Δ [D/N] SDNN index	87	55		
								Δ [D/N] RMSSD	91	48		
Roche et al. Eur Resp J 2003;22:937-42	Suspected OSA	147	10/hr	45	55 $\pm$ 11	50	Wavelet analysis	Wv32	92	90	0.76	
Roche et al. Clin Sci 2004 ;107:105–10	Suspected OSA	28	10/hr	71	58 $\pm$ 12	82	VLFI power and %VLFI	%VLFI $\geq$ 2.4%	78	70	0.85	Hourly AHI and %VLFI significantly correlated. Validated in a second study with 35 pts
Roche et al. ERJ 2007;29:1206-11	Suspected OSA	150	>15/hr	66%	51 $\pm$ 10	79	Time and frequency domain, including %VLFI	%VLFI >2.4	91	34		Sleep fragmentation index also strongly correlated with %VLFI; i.e. other causes of sleep fragmentation also increase %VLFI
								%VLFI >4	64	69		
Shiomi et al. Sleep 1996; 19:370-77	OSA patients	12	ND	100%	53 $\pm$ 12	83	Time and frequency domain: HF, LF,VLF, ULF	VLF power and visual identification of peak in VLF component				VLF power reduced in 2 of 3 OSAS pts who were adequately treated by dental device

Definitions as per Tables on previous pages. In addition, VLFI = Very low frequency increment; RMSSD = Square root of the mean of the squares of differences between adjacent NN intervals (see also Table 2.3); HRV = Heart rate variability; Wv = Wavelet;

8.2. Copy of Ethical Approval Letter



National Research Ethics Service

Brompton, Harefield & NHLI Research Ethics Committee

2nd Floor, Block A
50 Eastbourne Terrace
LONDON
W2 6LG

Telephone: 020 7725 3409
Facsimile: 020 7725 3465

11 May 2007

Dr Mary J Morrell
Reader in Respiratory Physiology
Imperial College
Clinical and Academic Unit of Sleep and Breathing
Royal Brompton Hospital
Sydney Street
SW3 6NP

Dear Dr Morrell

Full title of study: Screening for sleep apnoea in chronic heart failure
REC reference number: 07/Q0404/32

Thank you for your letter of 11 May 2007, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chairman.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised.

Ethical review of research sites

The favourable opinion applies to the research sites listed on the attached form.

Conditions of approval

The favourable opinion is given provided that you comply with the conditions set out in the attached document. You are advised to study the conditions carefully.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	Version	Date
Application	1	22 March 2007
Investigator CV		01 March 2007
Protocol	1	19 March 2007
Covering Letter		19 March 2007
Summary/Synopsis	1	19 March 2007
Letter from Sponsor		20 March 2007

This Research Ethics Committee is an advisory committee to London Strategic Health Authority
The National Research Ethics Service (NRES) represents the NRES Directorate within
the National Patient Safety Agency and Research Ethics Committees in England

Statistician Comments		01 August 2006
Compensation Arrangements		14 March 2007
Questionnaire		19 March 2007
Questionnaire		19 March 2007
Letter of invitation to participant	2	08 May 2007
GP/Consultant Information Sheets	1	19 March 2007
Participant Information Sheet	3	08 May 2007
Participant Information Sheet	3	08 May 2007
Participant Consent Form	1	19 March 2007
Participant Consent Form	1	19 March 2007
Response to Request for Further Information	email	11 May 2007
Letter from Funder	BHF Grant Award	11 December 2006

R&D approval

All researchers and research collaborators who will be participating in the research at NHS sites should apply for R&D approval from the relevant care organisation, if they have not yet done so. R&D approval is required, whether or not the study is exempt from SSA. You should advise researchers and local collaborators accordingly. Guidance on applying for R&D approval is available from <http://www.rdforum.nhs.uk/rdform.htm>.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

Feedback on the application process

Now that you have completed the application process you are invited to give your view of the service you received from the National Research Ethics Service. If you wish to make your views known please use the feedback form available on the NRES website at: <https://www.nresform.org.uk/AppForm/Modules/Feedback/EthicalReview.aspx>

We value your views and comments and will use them to inform the operational process and further improve our service.

07/Q0404/32

Please quote this number on all correspondence

With the Committee's best wishes for the success of this project

Yours sincerely

Rosalind Cochrane

On behalf of
Dr Derek Gibson
Chairman

Enclosures:

Standard approval conditions
Site approval form

Copy to:

Imperial College
R&D office for Brompton hospital ✓

Brompton, Harefield & NHLI Research Ethics Committee
LIST OF SITES WITH A FAVOURABLE ETHICAL OPINION

For all studies requiring site-specific assessment, this form is issued by the main REC to the Chief Investigator and sponsor with the favourable opinion letter and following subsequent notifications from site assessors. For issue 2 onwards, all sites with a favourable opinion are listed, adding the new sites approved.

REC reference number: 07/Q0404/32 Issue number: 0 Date of issue: 11 May 2007

Chief Investigator: Dr Mary J Morrell

Full title of study: Screening for sleep apnoea in chronic heart failure

This study was given a favourable ethical opinion by Brompton, Harefield & NHLI Research Ethics Committee on 11 May 2007. The favourable opinion is extended to each of the sites listed below. The research may commence at each NHS site when management approval from the relevant NHS care organisation has been confirmed.

Principal Investigator	Post	Research site	Site assessor	Date of favourable opinion for this site	Notes (1)
Dr Mary J Morrell	Senior Lecturer	Royal Brompton Hospital	Brompton, Harefield & NHLI Research Ethics Committee	11/05/2007	

Approved by the Chair on behalf of the REC:

 (Signature of Co-ordinator)
 Rosalind Cooke

8.3. Patient Information Sheet

V4: 12/01/08

REC Reference: 07/Q0404/32

Neil Ward
Department of Sleep and Ventilation, Royal Brompton Hospital
Sydney Street, London, SW3 6NP
n.ward@imperial.ac.uk
020 7351 8027

Patient Information Sheet

Screening for sleep apnoea in chronic heart failure

We invite you to consider taking part in our research project; you have been asked because you have been diagnosed as having heart failure.

What we wish to find out in this study

From our previous research we have found that quite a number of heart failure patients like yourself have breathing irregularities at night; a disorder called sleep apnoea. Unfortunately, it may not be obvious that heart failure patients have sleep apnoea and it often goes unrecognised and untreated. Once it is recognised it can be treated.

The overall aim of this proposal is to establish a cost-effective method of screening for sleep apnoea in heart failure patients.

Specifically we will test the idea that overnight changes in the rate at which the heart beats, plus changes in the amount of oxygen in the blood can be used in a general cardiology clinic to rule out sleep apnoea in patients with chronic heart failure.

What will be required of you if you decide to take part and why?

If you agree to take part in our study, we will invite you to complete some questionnaires and to have some tests to monitor your breathing and sleep during the night. The next morning we would like to take a blood sample and to do a test to measure how sleepy you are (OSLER test). You can choose to have the tests in your own home or to stay overnight in the sleep laboratory at the Royal Brompton Hospital, London. On the evening of the study, an experienced research doctor will ask you to fill out the questionnaires before fitting the equipment which will monitor your breathing and sleep. This would take between 2 and 3 hours. Once the monitoring equipment has been fitted you can go to bed when you wish. In the morning it will take about 1 hour to remove the equipment, and finish the tests. If your heart function has not been assessed recently we will arrange for this to be tested again.

If you have the tests in hospital we would ask you to arrive at about 6pm on the evening of the study and you will usually be able to leave by 10am the following morning. If you have the tests in your home, the research doctor will visit you at approximately 6pm for 2 to 3 hours. He would return the next morning at approximately 9am for 1 hour. The research doctor is a male doctor who will usually be working on his own. If you prefer, he can arrange to be accompanied by a female workmate as a chaperone.

Test of sleepiness: The OSLER test is routinely used in our sleep clinic to assess sleepiness levels. For this test we will ask you to sit upright in bed, or on a comfortable chair in a dark, silent room. You will be asked to press a button every time that you see a red light flash on a small electronic box which will be placed about 2 metres away from you. This test will last approximately 40 minutes.

Tests of breathing during sleep: During the sleep study a few simple measurements will be made. These will include your sleep state via the wires attached to your head, and the level of oxygen in your blood via a small clip placed on your finger. We will also monitor your breathing via two elastic bands placed around your chest and stomach. All these measurements are non-invasive and are used in normal clinical practice.

We will also show you how to use a “watch-like” device that you will be asked to wear on your other hand during the same night. This device also measures the oxygen in your blood over the period in which it is worn. On the same night we would also like you to wear 5 sticky electrodes (about the size of a 10p piece) on your chest which can be attached to a heart rate monitor. The monitor (match box size) will then be tucked inside a pouch worn round the neck under the clothing

Tests of cardiac function: If you have not had your heart tested in the previous 6 months we would like to test it again. We will do this in 3 different ways 1) by doing an echocardiogram, which tests how well your heart is pumping blood 2) by taking a small amount of blood (about 20ml, about 2 tablespoons) from your veins. This will be used for routine blood tests, which you may have had in the past in the cardiology clinic.

We would also like to store your venous blood within the freezer, so we can use it for possible further research at a future date, when new techniques or a new test may be available. Your blood will be anonymised before it is stored; it will not be identifiable except by a special list that will be kept in a locked draw and will be accessible only to identified individuals. We will NOT contact you again for further permission before doing this. If you agree to take part in the study, you will be giving consent for possible future use of your blood sample; any future project will have been approved by an NHS Research Ethics Committee.

Additional tests: We would also like you to fill in two short questionnaires to assess your sleepiness and mood. Finally we would like to measure your height, weight, neck size, and ask you about your alcohol and coffee consumption, and years of education.

Risks of the study

It is extremely unlikely that you will come to any harm taking part in this study. Taking the venous blood sample may be uncomfortable when the needle picks the skin, and may cause bruising at the needle site. In the 5 plus years we have been using the sleep monitoring devices we have never had an adverse incident (over 200 patients). As with the wearing of any new fabric next to the skin there is a potential risk of skin irritation through the wearing of the devices for long periods of time. If this occurs you should remove them and inform us. It is possible that the 'clip' that is applied to the finger as part of the oximeter may be uncomfortable during the night. If this occurs we ask you to swap the clip to a different finger. All equipment used will be cleaned or sterilized as appropriate, and all electrical equipment used is checked routinely for electrical safety.

Imperial College London holds insurance policies which apply to this study. If you experience harm or injury as a result of taking part in this study, you will be eligible to claim compensation without having to prove that Imperial College is at fault. This does not affect your legal rights to seek compensation.

If you are harmed due to someone's negligence, then you may have grounds for a legal action. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been treated during the course of this study then you should immediately inform the Investigator (*Mary Morrell*). The normal National Health Service complaints mechanisms are also available to you. If you are still not satisfied with the response, you may contact the Imperial College Clinical Research Office.

Benefits of taking part in this study

This study is an observational study and will not directly benefit your health in any way. It will lead us to a greater understanding of heart failure and sleep apnoea in older people which may be of benefit to future treatment regimes. If we find you have sleep apnoea we will, with your consent, inform your GP and we will also inform the consultant chest doctor and your cardiac doctor involved in this study. If you, your GP or the hospital consultants would like to have our findings of sleep apnoea investigated further, and possibly treated, we will make an appointment for you to be seen by a specialist doctor in the sleep clinic at the Royal Brompton Hospital, or in a Sleep Clinic local to you.

Payment

You will be reimbursed for any additional travel expenses incurred through participating in this study.

Refusal to participate in this study will in no way affect your future treatment.

You may withdraw from this study at any time without giving any reason and without any prejudice regarding your future treatment.

A contact number can be found at the end of this document should you need to contact us for any reason during the study.

Thank you for your kindness in considering this project

Contact details: **Dr Neil Ward**

Work Tel: 0207 351 8027

Email: n.ward@imperial.ac.uk

Principal Investigator: **Dr Mary Morrell**

Department of Sleep and Ventilation, Royal Brompton Hospital

Sydney Street, London, SW3 6NP

Work Tel: 020 7352 8121 (ext 4023)

Email: m.morrell@imperial.ac.uk

8.4. Study Consent Form

V1: 19/03/2007

REC Reference: 07/Q0404/32



Mary J Morrell
Department of Sleep and Ventilation, Royal Brompton Hospital
Sydney Street, London, SW3 6NP
m.morrell@imperial.ac.uk
020 7352 8121 (ext 4023)

Screening for sleep apnoea in chronic heart failure

(The volunteer should complete the whole of this sheet him/herself)

Have you read the information sheet?

Have you had the opportunity to ask questions and discuss the study?

Have you received satisfactory answers to all of your questions?

Have you received enough information about the study?

Who have you spoken to? (write name) _____

Do you understand that you are free to withdraw from the study at any time without having to give a reason, and without affecting the quality of your present or future medical care?

Do you agree to take part in this study?

I understand that the Local Ethics Committee may review this form as a part of a monitoring process.

NAME IN BLOCK LETTERS: _____

Signature: _____ Date: _____

Address _____

GP:

Address _____

SIGNATURE OF PERSON OBTAINING CONSENT:

Signature: _____ Date: _____
Position: _____

8.5. Epworth Sleepiness Scale

Epworth Sleepiness Scale

(Version 1.0; 19/03/2007 REC: 07/Q0404/32)

Participant Number _____

Please rate how likely you are to fall asleep in the following situations. Your answers should reflect how you have been in the past week:

0= Would never doze

1= Slight chance of dozing

2= Moderate chance of dozing

3= High chance of dozing

Situation	Score
Sitting & reading	
Watching television	
Sitting inactive in a public place eg. Theatre, meeting	
As a passenger in a car for an hour without a break	
Lying down to rest in the afternoon	
Sitting & talking to someone	
Sitting quietly after lunch (when you've had no alcohol)	
In a car, while stopped at traffic	
Total	

8.6. Hospital Anxiety and Depression Scale

Please read the following statements and indicate which of the 4 possible responses is closest to how you feel at the moment.

I feel tense or 'wound up': *Score*

Most of the time	☐	3
A lot of the time	☐	2
From time to time, occasionally	☐	1
Not at all	☐	0

I still enjoy the things I used to enjoy:

Definitely as much	☐	0
Not quite so much	☐	1
Only a little	☐	2
Hardly at all	☐	3

I get a sort of frightened feeling as if something awful is about to happen:

Very definitely and quite badly	☐	3
Yes, but not too badly	☐	2
A little, but it doesn't worry me	☐	1
Not at all	☐	0

I can laugh and see the funny side of things:

As much as I always could	☐	0
Not quite so much now	☐	1
Definitely not so much now	☐	2
Not at all	☐	3

Worrying thoughts go through my mind: **Score**

A great deal of the time	☐	3
A lot of the time	☐	2
From time to time, but not too often	☐	1
Only occasionally	☐	0

I feel cheerful:

Not at all	☐	3
Not often	☐	2
Sometimes	☐	1
Most of the time	☐	0

I can sit at ease and feel relaxed:

Definitely	☐	0
Usually	☐	1
Not often	☐	2
Not at all	☐	3

I feel as if I am slowed down:

Nearly all the time	☐	3
Very often	☐	2
Sometimes	☐	1
Not at all	☐	0

I get a sort of frightened feeling like 'butterflies' in the stomach:

Not at all	☐	0
Occasionally	☐	1
Quite often	☐	2
Very often	☐	3

I have lost interest in my appearance:

Definitely	☐	3
I don't take as much care as I should	☐	2
I may not take quite as much care	☐	1
I take just as much care as ever	☐	0

I feel restless as I have to be on the move: **Score**

Very much indeed	☐	3
Quite a lot	☐	2
Not very much	☐	1
Not at all	☐	0

I look forward with enjoyment to things:

As much as I ever did	☐	0
Rather less than I used to	☐	1
Definitely less than I used to	☐	2
Hardly at all	☐	3

I get sudden feelings of panic:

Very often indeed	☐	3
Quite often	☐	2
Not very often	☐	1
Not at all	☐	0

I can enjoy a good book or radio or TV program:

Often	☐	0
Sometimes	☐	1
Not often	☐	2
Very Seldom	☐	3

8.7. Assessment of the Accuracy of a Diagnostic Test

8.7.1. Sensitivity, Specificity and Predictive Values

The usefulness of a diagnostic test may be determined by its ability to correctly detect the presence or absence of the condition under investigation. Assessment of the accuracy of a diagnostic test usually requires a gold standard or reference standard in order to ascertain a definitive diagnosis. The table below shows the possible outcomes with such a comparison.

		Gold Standard	
		Positive	Negative
Diagnostic test result	Positive	True Positive	False Positive
	Negative	False Negative	True Negative

The sensitivity of a test measures the proportion with the condition in whom the diagnostic test is positive (true positive) and is calculated as follows:

$$\text{Sensitivity} = \frac{\text{true positives}}{(\text{true positives} + \text{false negatives})}$$

A diagnostic test with high sensitivity is most useful to rule out a condition as a negative result is very unlikely to be a false negative. In contrast, sensitivity provides no information about the probability of the condition being present if the test is positive.

The specificity of a test measures the proportion without the condition in whom the diagnostic test is negative (true negative).

$$\text{Specificity} = \frac{\text{true negatives}}{(\text{true negatives} + \text{false positives})}$$

A diagnostic test with high specificity is most useful to rule in a condition as a positive test is very unlikely to be a false positive. Specificity provides no information on the diagnostic accuracy of a negative test.

The diagnostic accuracy of a positive and negative test result can be expressed as a predictive value. The positive predictive value measures the probability of the condition being present in those who have a positive result with the diagnostic test.

$$\text{Positive Predictive Value} = \frac{\text{true positives}}{(\text{true positives} + \text{false positives})}$$

The negative predictive value measures the probability of the condition being absent in those who have a negative result with the diagnostic test

$$\text{Negative Predictive Value} = \frac{\text{true negatives}}{(\text{true negatives} + \text{false negatives})}$$

However, the predictive value of a diagnostic test is dependent on the prevalence of the condition. As prevalence increases, so positive predictive value increases whilst negative predictive value decreases, and vice versa as prevalence decreases. Thus, the utility of a diagnostic test may be influenced by the prevalence of the condition under investigation.

8.7.2. Likelihood Ratios

An alternative method of assessing the accuracy of a diagnostic test is to quantify how much the test result changes the probability of the condition being present or absent.

The change in probability associated with a particular test result can be quantified by the likelihood ratio, which is defined as follows:

$$\text{Likelihood ratio} = \frac{\text{Probability of test result (e.g. positive) in patient with the condition}}{\text{Probability of same test result in patient without the condition}}$$

The positive likelihood ratio quantifies the change in probability of the condition being present, if the diagnostic test is positive:

$$\text{Positive Likelihood Ratio} = \frac{\text{sensitivity}}{(1 - \text{specificity})}$$

The negative likelihood quantifies the change in probability of the condition being absent if the diagnostic test is negative.

$$\text{Negative Likelihood Ratio} = \frac{(1 - \text{sensitivity})}{\text{specificity}}$$

Likelihood ratios are not influenced by the prevalence of a condition and conveniently circumvent the difficulties associated with use of a diagnostic test in populations where prevalence differs. However, if the prevalence of a condition is known, likelihood ratios can be used to quantify the change in diagnostic certainty with a positive or negative result. When used with Bayes theorem, they can be used to calculate the post test odds, as follows:

$$\text{Post test odds} = \text{Pretest odds} \times \text{likelihood ratio}$$

A likelihood ratio >1 will increase the post test probability of the condition being present, whilst a likelihood ratio <1 will decrease the probability. A positive likelihood ratio >10 and negative likelihood ratio <0.1 are considered to indicate a clinically useful diagnostic test (Jaeschke, 1994), respectively increasing or decreasing the probability of the condition by approximately 45% (McGee, 2002).

Likelihood ratios are reported to be underused in clinical medicine despite their usefulness in assessing the utility of a diagnostic test, and this may be because they require the user know or calculate the odds of a condition or disease. Many clinicians may be more familiar with using the probability of a condition (McGee, 2002). However, odds can be converted to probability with the following formulas:

$$\text{Pretest odds} = \frac{\text{Pretest probability}}{(1 - \text{Pretest probability})}$$

$$\text{Post test probability} = \frac{\text{Post test odds}}{(1 + \text{Post test odds})}$$

An alternative approach is to use Bayes nomogram, (Figure 8.1 and see also Discussion in Section 4.4.2) which avoids the need to convert probability to odds (Fagan, 1975).

The pretest probability may be estimated from the known prevalence of the condition, or this probability may be modified depending on the presence or absence of clinical symptoms and physical examination findings. For example, the prevalence of sleep-

disordered breathing in CHF is approximately 50% and in the absence of clinical information to alter this estimate, pretest probability would be 0.5. Pretest odds would therefore be 1 ($0.5/(1-0.5) = 1$).

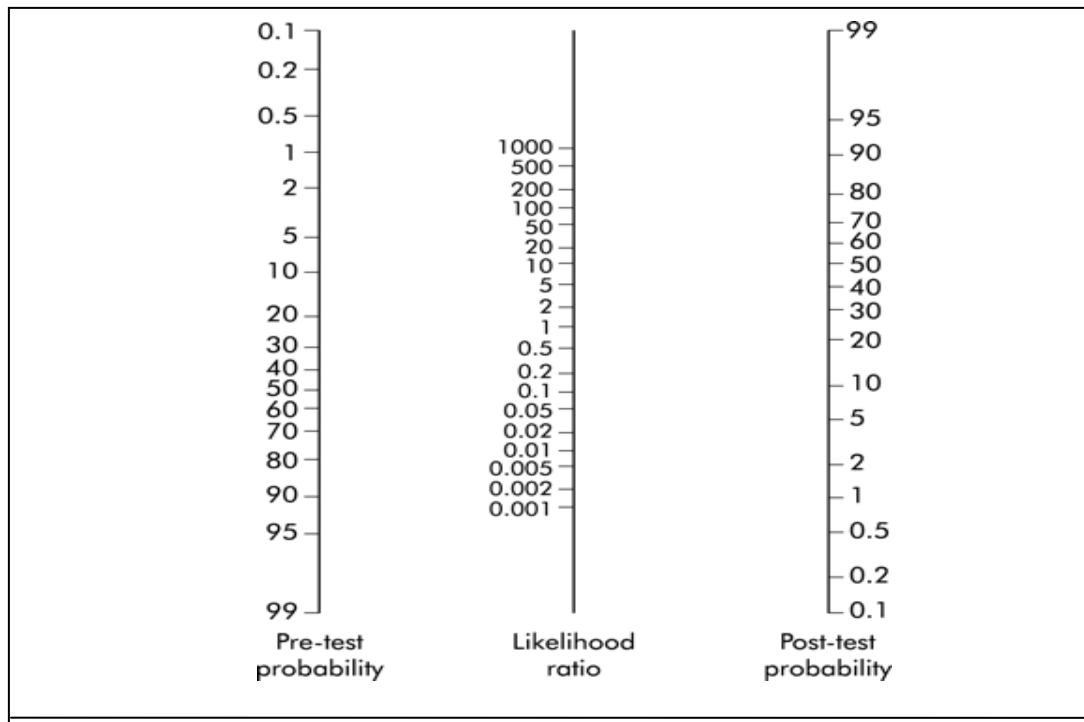


Figure 8.1. Fagan's Nomogram. Pretest probability is located on the first axis and joined to the appropriate likelihood ratio on the middle axis. The post test probability is then read from the third axis. Adapted from Fagan 1974.

If a diagnostic sleep study, with a positive likelihood ratio of 10 and negative likelihood ratio of 0.1, were used to diagnose SDB in a patient with CHF, the post test probability would be 0.91 with a positive test, and 0.09 with a negative test. Thus, a diagnostic sleep study with this level of accuracy would be extremely useful in refining the likelihood of the presence or absence of SDB in such a patient.

8.7.3. Receiver Operating Characteristic Curves

Receiver operating characteristic (ROC) curves can also be used to quantify the accuracy of a diagnostic test (Figure 8.2). The ROC curve is created by plotting the probability of a positive test in those with the condition (sensitivity) against the probability of a positive test in those without the condition ($1 - \text{specificity}$) for all different cut off values of the diagnostic test. The closer the curve lies to the upper left corner of the plot, the better the diagnostic accuracy of the test (Figure 8.2b). A ROC curve that lies close to the line of identity (the diagonal line from the bottom left to top right corner) identifies a diagnostic test that has no ability to discriminate between the presence of absence of disease (i.e. as accurate as tossing a coin; Figure 8.2a).

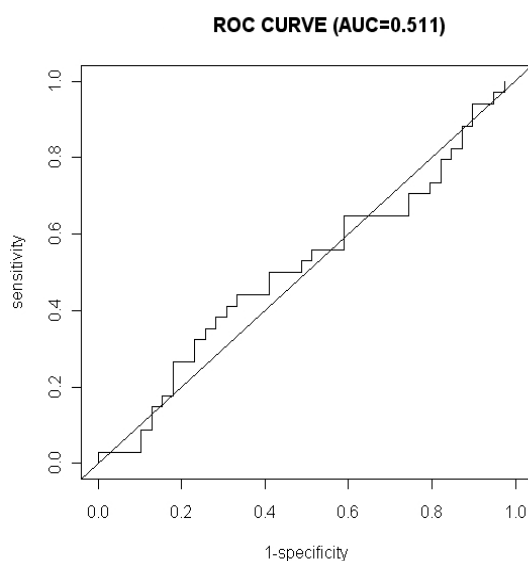


Figure 8.2a

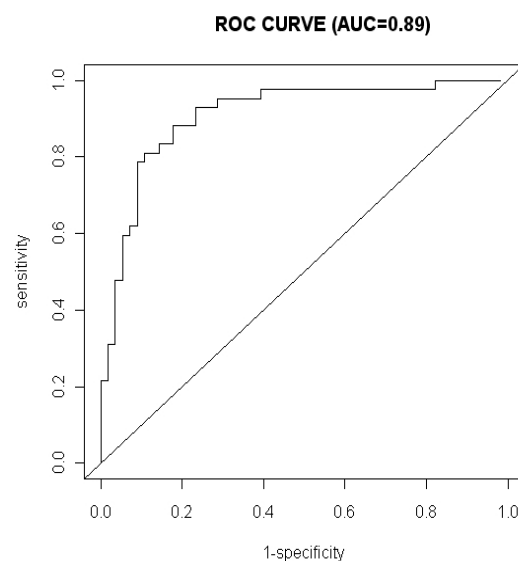


Figure 8.2b

Figure 8.2. Receiver Operating Characteristic (ROC) Curves for Assessment of the Accuracy of a Diagnostic Test. Figure 8.2a shows a ROC curve for a test with poor diagnostic accuracy indicated by area under curve (AUC) = 0.511. Figure 8.2b shows the ROC curve for a test with a high diagnostic accuracy indicated by AUC = 0.89

ROC curve analysis provides a rapid visual assessment of the usefulness of a diagnostic test, whilst measurement of the area under the curve provides an objective measurement of the accuracy and allows comparison between different diagnostic tests (Baker, 2003). The ROC curve can also be used to determine the optimal cut-off value that minimises the number of false positive or false negative results, depending on the implications of an incorrect test result.

8.7.4. Difference Versus Average Plots

Whilst the above metrics are useful to measure the accuracy of a diagnostic test when there is a binary outcome (e.g. condition present or absent) it may also be useful to consider agreement between the diagnostic test and gold standard, when the outcome is a continuous variable. For example, many of the studies which have evaluated a portable monitor for diagnosis of SDB have reported a measure of agreement between the AHI recorded by the new monitor and the AHI measured by the reference standard (in nearly all cases, a polysomnogram). In most cases, the agreement is reported as the Pearson correlation coefficient, but this does not provide information on the accuracy of the measurements or if there is a systematic difference between the two measurements. It is more useful to assess the agreement in such studies by plotting a difference versus average plot, also called a Bland-Altman plot (See Chapter 2, Figure 2.3). This provides a graphical illustration of the magnitude of difference between the two measurements across a range of values and can indicate if there is a systematic bias between the two measurements. If the 95% limits of agreement between the two measurements are very broad, this also indicates poor agreement.

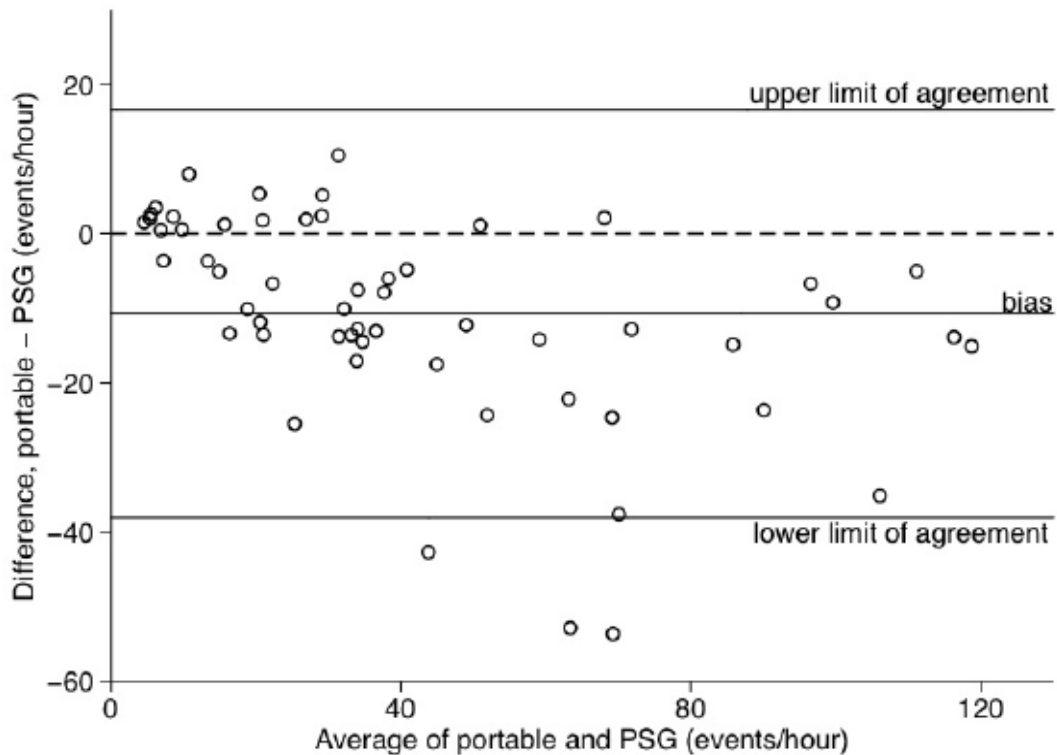


Figure 8.3. Difference versus average plot for AHI recorded by a portable monitor and polysomnography (modified from Ayappa, 2004). The portable monitor was reported to underestimate AHI by a mean of 11 events/hour with limits of agreement ± 27 events/hour. Note asymmetry of differences with small bias when AHI is low, but increasing bias as AHI exceeds 30 events/hour.

When comparing the AHI from portable monitors and polysomnography, difference versus average plots have some limitations. Firstly, the use of the average of the two measurements as the ‘true’ value assumes that neither measurement is better than the other, but as discussed in Section 1.5, in many cases polysomnography is likely to provide a more accurate measure of the AHI. Secondly, if the differences are not evenly scattered across the plot, the mean difference and 95% limits of agreement will be misleading (Figure 8.3). This is often the case when comparing the AHI from portable monitors and polysomnography as differences are usually small when the AHI is low but may become much larger when the AHI is high. Logarithmic transformation can be used to overcome uneven distribution of the differences.