SLEEP DISORDERED BREATHING IN CHRONIC HEART FAILURE: CAUSES, CONSEQUENCES AND TREATMENT

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A thesis submitted for the degree of Doctor of Philosophy

August 2012

ABSTRACT

Chronic heart failure (HF) is a prevalent clinical syndrome in which both central and obstructive sleep disordered breathing (SDB) have been described. The aim of this research was to investigate the mechanisms causing central SDB, their consequences with reference to sleep and physical activity, and the way in which treatment modalities may modify these.

The first study of this thesis is the SERVE-HF study, a randomised controlled trial of adaptive servoventilation (ASV) to treat central SDB in patients with CHF. This study is ongoing and aims to test the hypothesis that patients randomised to ASV will have a reduction in mortality compared to controls. Data regarding those randomised at the Royal Brompton Hospital are presented alongside data on ventilator compliance in the ASV group.

The second study investigated ventilatory control, in HF patients both with and without SDB. It tested the hypothesis that those with central SDB had heightened chemosensitivity (assessed by the hypercapnic ventilatory response, HCVR) compared to those with no SDB and older healthy controls.

The third study explored the effect of treatment on ventilatory control by testing the hypothesis that the implantation of a cardiac-resynchronisation therapy pacemaker would be associated with a reduction in the HCVR from baseline to 3 months post implantation.

The fourth study investigated the consequences of SDB in CHF. Physical activity, subjective sleepiness and sleep were assessed in patients with CHF and older healthy controls to test the hypothesis that physical activity would be reduced in those with central SDB compared to those without SDB, and reduced in both patient groups compared to the controls.

In summary, this thesis investigated the mechanisms underlying central SDB in patients with HF, to elucidate their consequences, both by day and night and to address the ways in which treatment modalities may modify these pathophysiological mechanisms.

DECLARATION

I declare that the work presented in this thesis is the result of my own work, except where otherwise acknowledged. The study presented in chapter 3 is an international randomised controlled trial which was conceived and designed by the SERVE-HF study steering committee. My involvement in this study was at a local level, implementing the study protocol, collecting, collating and analysing data, and coordinating study visits. The studies presented in chapters 4, 5 and 6 were created and designed by myself with the valued assistance of my supervisors. I benefited from the statistical assistance of Mr. Winston Banya for the sample size calculations in chapters 4 and 5.

Data collection for the study presented in chapter 4 was the result of collaboration with my colleague Mr. Tom Carlisle using the same laboratory protocols. Tom and I both carried out the laboratory tests on HF patients and healthy subjects and pooled the resulting HCVR data. The analysis and statistical testing of the resultant data are different.

No part of this thesis has previously been submitted for consideration for a higher degree. Part of the data from the study presented in chapter 6 has been presented in abstract form and the details are given in the next section.

PUBLICATIONS ARISING FROM THIS WORK

Published abstracts

Atalla A., Carlisle T.W., Ward N.W., Hastings P.C., Morrell M.J., Simonds A.K., Cowie M.R. Subjective Sleepiness And Activity Levels In Heart Failure Patients With Sleep Disordered Breathing. Am J Respir Crit Care Med 185;2012:A6707

Presentations

Sleepiness in Heart Failure Patients with Sleep Disordered Breathing. 5th Annual National Heart and Lung Institute Postgraduate Research day. Winner of Best Clinical Presentation. June 2011

Sleep disordered breathing in heart failure. The next big thing? Advances in Respiratory Medicine course, National Heart and Lung Institute, Imperial College London. April 2010.

Understanding Heart Failure and Sleep Disordered Breathing-The Story of Loop Gain. Physiology Society International Workshop. Imperial College, London. December 2009.

ACKNOWLEDGEMENTS

Sincerest thanks are due to my supervisors, Professor Martin Cowie, Professor Mary Morrell and Professor Anita Simonds for their advice and encouragement. Thanks are due also to the patients and subjects who took part in this research. I benefited enormously from the help of the Sleep and Ventilation Team and wish to thank Steve Heather, Anna Hanak, Vitor Roldao, Rachel Pickersgill and the entire team for their time and help, not to mention entertainment, along the way. I would also like to thank the heart failure specialist nurses Laura Fallon and Hayley Pryse-Hawkins for their advice and assistance with recruitment. My thanks to Lisa Trembath for her friendship, particularly in the early days of my research, and to Professor Doug Corfield for his encouragement and assistance. I was part of the Health Services Research Group and am grateful to the other researchers in that group.

Particular thanks must go to Zarrin Shaikh, Jay Jaye, Lizzy Goff, Lydia Paniccia, Neil Ward, and Thomas Carlisle; you witnessed the recruitment dance, shared in the endless Haribos, and offered much needed and appreciated help and advice throughout. I salute you. Thanks also to Alison McMillan, Martin Glasser, Julia Kelly, Alana Hare and Annette Woods.

I would also like to extend my deepest thanks to Pam Copeland from the Chelsea and Westminster hospital, for her help and friendship during my research time; to Dr. Emma Watson, for her help and encouragement and to Professor John Trinder, for showing me that sleep research and jazz are, happily, not mutually exclusive.

As I have moved around the UK during the last few years I have been cheered on by friends at South West London Vineyard church, Bristol Vineyard Church and Belfast City Church to whom I am enormously grateful. Particular thanks to my close friends Liesl Wandrag, Sarah Bennett, Fiona Hunter, Michael Hunter and Rebecca Dunlop.

My family share this achievement with me, as without the love and support of my brothers Ash and Andrew, of whom I am immensely proud, and that of my parents, Albert and Adele, none of this would have been possible. Thank you, thank you, thank you.

And finally, to my husband, Chris. You have been my tower of strength and my best friend. There are simply no words sufficient to thank you.

I dedicate this thesis to my parents, my brothers and my husband; with all my love.

Now, upon what has been said, the physicians may determine whether sleep be so necessary that our lives depend upon it: for we read that King Perseus of Macedon, being prisoner at Rome, was killed by being kept from sleep; but Pliny instances such as have lived long without sleep. Herodotus speaks of nations where the men sleep and wake by half-years, and they who write the life of the sage Epimenides affirm that he slept seven-and-fifty years together.

Montaigne, Michel de. “Of sleep.” Trans. Charles Cotton. 1574. *Quotidiana.* Ed. Patrick Madden. 23 Sep 2006. 25 Aug 2012

TABLE OF CONTENTS

ABSTRACT **3**

DECLARATION **4**

PUBLICATIONS ARISING FROM THIS WORK **5**

ACKNOWLEDGEMENTS **6**

TABLE OF CONTENTS **9**

LIST OF TABLES **17**

LIST OF FIGURES **20**

ABBREVIATIONS **23**

CHAPTER ONE: GENERAL INTRODUCTION **26**

1.1 Heart failure **27**

1.1.1 Definition of heart failure 27

1.1.2 Classification of heart failure 28

1.1.3 Epidemiology of heart failure 29

1.1.4 Aetiology of heart failure 31

1.1.5 Pathogenesis of heart failure 34

1.1.6 Diagnosis of heart failure 42

1.1.7 Management of heart failure 48

1.1.8 Prognosis of heart failure 53

1.1.9 Summary 56

1.2 Sleep disordered breathing **57**

1.2.1 The classification of sleep disordered breathing 57

1.2.2 Obstructive sleep disordered breathing 58

1.2.3 Central sleep disordered breathing 60

1.3 Sleep disordered breathing in patients with heart failure **61**

1.3.1 Prevalence of sleep disordered breathing in heart failure 62

1.3.2 Variability in severity and type of sleep disordered breathing 65

1.3.3 Summary 66

1.4 Symptoms of sleep disordered breathing in heart failure **67**

1.4.1 The effect of ageing on sleep, sleepiness and daytime activity 68

1.4.2 The effect of heart failure on sleep and daytime activity 69

1.4.3 The effect of sleep on the failing heart 70
1.4.4 Subjective and objective sleepiness in patients with HF and SDB 71
1.4.5 Sympathetic nerve activity and subjective sleepiness 72
1.5 Breathing during sleep in healthy subjects 74
1.5.1 Changes in breathing during sleep 74
1.5.2 The effect of sleep on the upper airway 74
1.5.3 The apnoeic threshold 75
1.5.4 The model of loop gain 75
1.5.5 Controller, plant and feedback gains 78
1.5.6 Summary 80
1.6 Pathophysiology of sleep disordered breathing in heart failure 82
1.6.1 The effect of heart failure on controller gain 82
1.6.2 The effect of heart failure on plant and feedback gains 83
1.6.3 The effect of heart failure on the upper airway 83
1.6.4 Summary 85
1.7 The treatment of central SDB in heart failure 86
1.7.1 Continuous positive airways pressure 86
1.7.2 The use of CPAP for the treatment of CSA in patients with HF 87
1.7.3 The CANPAP Study 87
1.7.4 Adaptive servoventilation 89
1.7.5 Nocturnal oxygen, carbon dioxide and other treatments 92
1.7.6 Cardiac resynchronisation therapy 94
1.7.7 Summary 97
1.8 Summary of the main themes and overall aims of this thesis 98
1.8.1 Summary of main themes of this thesis 98
1.8.2 Overall aims of this thesis 99
CHAPTER TWO: GENERAL METHODS 102
2.1 Overview of ethical approvals 103
2.2 Questionnaires 104
2.2.1 Epworth sleepiness scale 104
2.2.2 Minnesota Living with Heart Failure Questionnaire 104
2.2.3 EQ-5D questionnaire 104

2.3 Six minute walk test 106

2.4 Spirometry 107

2.5 Measurement of the hypercapnic ventilatory response 108

2.5.1 Theory of the Read rebreathe test 108

2.5.2 Rebreathing protocol 109

2.5.3 Calibration 111

2.5.4 Data analysis 111

2.5.5 Rebreathe versus steady state techniques 112

2.5.6 The repeatability of the Read rebreathe method over time 112

2.6 Respiratory sleep studies 114

2.6.1 ApneaLink™ with oximeter 114

2.6.2 Respiratory polygraphy 115

2.7 Polysomnography 117

2.7.1 Placement of EEG, EMG and EOG electrodes 117

2.7.2 Signal acquisition, quality and calibration 119

2.8 Adaptive servoventilation 120

2.9 Activity monitoring 123

2.9.1 Technology 123

2.9.2 Instructions to subjects 125

2.9.3 Actograms 126

2.9.4 Limitations of actigraphy 127

2.10 Data analysis 128

2.10.1 Scoring of sleep and respiratory events 128

2.10.2 Statistical analysis 130

CHAPTER THREE: THE USE OF ADAPTIVE SERVOVENTILATION IN PATIENTS WITH HEART FAILURE AND CENTRAL SLEEP DISORDERED BREATHING - THE SERVE-HF STUDY AT THE ROYAL BROMPTON HOSPITAL 133

3.1 INTRODUCTION 134

3.2 METHODS 135

3.2.1 Study objectives and endpoints 135

3.2.2 Study population and enrolment 136

3.2.3 Respiratory polygraphy scoring rules 138

3.2.4 Randomisation and study schedule 140
3.2.5 Adaptive Servoventilation 141
3.2.6 Statistical analysis 142
3.4 RESULTS 143
3.4.1 Baseline characteristics and polygraphy 144
3.4.2 ASV titration and serial polygraphy 147
3.4.3 Compliance with ASV treatment 150
3.4.4 Serial data over 24 months 153
3.5 DISCUSSION 155
3.5.1 The effects of ASV on SDB and HF 155
3.5.2 Recruiting and retaining patients; local and international hurdles 156
3.5.3 The issue of compliance 158
3.5.4 Methodological issues 162
3.5.5 Summary 164
CHAPTER FOUR: THE INFLUENCE OF SLEEP DISORDERED BREATHING ON THE HYPERCAPNIC VENTILATORY RESPONSE IN PATIENTS WITH CHRONIC HEART FAILURE 167
4.1 INTRODUCTION 168
4.2 METHODS 169
4.2.1 Subjects 169
4.2.2 Protocol 170
4.2.3 Analysis 170
4.3 RESULTS 172
4.3.1 Differences in hypercapnic ventilatory response between HF patients with central SDB and those without SDB. 176
4.3.2 Differences in hypercapnic ventilatory response between HF patients and healthy controls 181
4.3.3 Factors influencing the hypercapnic ventilatory response 188
4.4 DISCUSSION 189
4.4.1 The effect of heart failure on the hypercapnic ventilatory response 190
4.4.2 Factors affecting the hypercapnic ventilatory response and how these might explain differences between this and previous work 191
4.4.3 Methodological considerations 195
4.4.4 Summary 196

CHAPTER FIVE: THE EFFECT OF CARDIAC RESYNCHRONISATION THERAPY ON SLEEP IN PATIENTS WITH CHRONIC HEART FAILURE **199**

5.1 INTRODUCTION **200**

5.2 METHODS **201**

5.2.1 Subjects 201

5.2.2 Protocol 202

5.2.3 Analysis 204

5.3 RESULTS **205**

5.3.1 Baseline characteristics 205

5.3.2 The effect of CRT on heart failure 207

5.3.3 The effect of CRT on sleep 209

5.3.4 The effect of CRT on chemosensitivity 211

5.3.5 Changes in sleep and chemosensitivity 211

5.4 DISCUSSION **216**

5.4.1 The effect of CRT on chemosensitivity 217

5.4.2 The effect of CRT on sleep 218

5.4.3 Methodological considerations 218

5.4.4 Summary 220

CHAPTER SIX: SUBJECTIVE SLEEPINESS AND ACTIVITY LEVELS IN HEART FAILURE PATIENTS WITH AND WITHOUT SLEEP DISORDERED BREATHING **223**

6.1 INTRODUCTION **224**

6.2 METHODS **225**

6.2.1 Subjects 225

6.2.2 Protocol 226

6.2.3 Analysis 226

6.3 RESULTS **228**

6.3.1 The effect of SDB on subjective sleepiness, sleep and physical activity in HF patients 228

6.3.2 The effect of central SDB on subjective sleepiness, sleep and physical activity in HF patients 233

6.3.3 The effect of heart failure on subjective sleepiness, sleep and physical activity 236

6.4 DISCUSSION **241**

6.4.1 The effect of heart failure on activity levels, subjective sleepiness 241

and sleep 241
6.4.2 Differences between the current study and previous work 244
6.4.3 Subjective and objective sleepiness 247
6.4.4 Methodological considerations 248
6.4.5 Summary 249
CHAPTER SEVEN: GENERAL DISCUSSION 253
7.1 Summary of the main findings of this thesis 254
7.2 Potential direction of future work 257
7.2.1 Explaining the absence of central SDB in some HF patients; the potential role of pre-morbid ventilatory stability. 257
7.2.2 Objective and subjective sleepiness in HF patients 258
7.2.3 The relationship between ventilatory instability and cardiac function 258
7.2.4 The effect of age on the evening to morning change in hypercapnic ventilatory response 259
REFERENCES 262
APPENDICES 287
APPENDIX ONE 288
Ethical approvals for the SERVE-HF study 288
Research and Development office approval 293
APPENDIX TWO 294
Ethical approval for the Control of Ventilation study (chapter 4) 294
Consent forms 297
Patient information sheet 299
Healthy subject information sheet 306
APPENDIX THREE 312
Ethical approval for the Cardiac Resynchronisation Study (chapter 5) 312
Research and Development office approval 315
Consent form 316
Patient information sheet 317
APPENDIX FOUR 322
Ethical approval for the Activity Study (chapter 6) 322

APPENDIX FIVE **324**

Minnesota Living with Heart Failure questionnaire 324

APPENDIX SIX **325**

Epworth Sleepiness Scale 325

APPENDIX SEVEN **326**

EQ5D questionnaire 326

APPENDIX EIGHT **329**

Actiwatch instructions given to subjects 329

APPENDIX NINE **331**

Sleep diary used with Actiwatch 331

APPENDIX TEN **332**

Individual patient HCVR results, x intercepts and resting carbon dioxide levels (chapter 4) 332

APPENDIX ELEVEN **335**

Night time actigraphy data for 3 comparisons (chapter 6) 335

APPENDIX TWELVE **337**

Additional analysis for the Activity study (chapter 6) 337

APPENDIX THIRTEEN **340**

Data for all 4 patient groups in the Activity study (chapter 6) 340

APPENDIX FOURTEEN **344**

Instructions given to patients using the ApneaLink™ device 344

LIST OF TABLES

Table 1.1	Two frequently used classification systems for HF	34
Table 1.2	The causes of the HF syndrome	38
Table 1.3	The differential diagnoses of heart failure	52
Table 1.4	Summary of key medications used in the management of chronic heart failure	56
Table 1.5	Risk factors for sudden cardiac death in HF	59
Table 1.6	Prevalence of SDB in HF populations with stable left ventricular systolic impairment on optimised medical treatment	68
Table 1.7	Prevalence of SDB in different populations of patients with heart failure	69
Table 2.1	Predicted normal values for spirometry	112
Table 2.2	Individual control subject data for the change in evening to morning HCVR from baseline to follow-up.	118
Table 2.3	Group data for hypercapnic ventilatory response at baseline and follow up in 6 control subjects	118
Table 2.4	Channels recorded by the Embletta^{TM} device	121
Table 2.5	Definitions of terms used in actigraphy	129
Table 2.6	Key features seen in the EEG, EMG and EOG channels for wake and each stage of sleep	134
Table 3.1	Inclusion and exclusion criteria for the SERVE-HF study	141
Table 3.2	Definitions of respiratory events using in scoring polygraphy in the SERVE-HF study.	143
Table 3.3	Schedule for Baseline visit and subsequent annual follow up visits	145
Table 3.4	Baseline characteristics for the control and ASV groups	148
Table 3.5	HF characteristics for the control and treatment (ASV) groups	149
Table 3.6	Baseline polygraphy for the control and treatment (ASV) groups	150
Table 3.7	Baseline, titration and 3 month polygraphy data for 10 patients randomised to ASV	152
Table 3.8	The number of patients on ASV with data available by study visits.	154
Table 3.9	Baseline characteristics for persistent ASV users and ASV drop-outs	155
Table 3.10	Serial AHI and ASV download data for persistent ASV users and ASV drop-outs	155
Table 3.11	Number of patients with data available by study visits	157

Table 4.1	Baseline demographics for HF patients and healthy controls	178
Table 4.2	Results from nocturnal polysomnography for HF patients and healthy controls	179
Table 4.3	Baseline characteristics for the HF-CSA and HF-noSDB groups	181
Table 4.4	Nocturnal polysomnography data for the HF-CSA and HF-noSDB groups	182
Table 4.5	Baseline characteristics of HF-CSA, HF-noSDB and control groups	186
Table 4.6	Nocturnal polysomnography data for the HF-CSA and HF-noSDB groups	188
Table 5.1	Clinical criteria for implantation of Cardiac resynchronisation	205
Table 5.2	Characteristics of individual patients at baseline	210
Table 5.3	Group patient characteristics at baseline and follow-up visits	211
Table 5.4	Individual patient characteristics at Baseline and follow up	212
Table 5.5	Results of in laboratory nocturnal polysomnography in HF patients before and after CRT implantation; group data	213
Table 5.6	Results of in laboratory nocturnal polysomnography in HF patients before and after CRT implantation; group data	214
Table 5.7	Resting CO_2 levels, X intercept and HCVR data in HF patients at baseline and follow-up; group data	216
Table 6.1	Patient characteristics of all HF patients with and without SDB	234
Table 6.2	Nocturnal polysomnographic data for the HF-SDB and HF-noSDB groups	235
Table 6.3	Daytime activity in HF patients with and without SDB	236
Table 6.4	Patient characteristics of the HF-CSA and HF-noSDB groups	238
Table 6.5	Nocturnal polysomnographic data for the HF-CSA and HF-noSDB groups	239
Table 6.6	Daytime activity in HF patients with and without central SDB	240
Table 6.7	Characteristics of HF patients without SDB and age matched healthy controls	241
Table 6.8	Nocturnal polysomnographic data for the HF-noSDB and control groups	242
Table 6.9	Daytime activity in HF patients without SDB and healthy control subjects	243
Table A.1	HF-CSA group (n=14)	338
Table A.2	HF-noSDB group (n=15	339
Table A.3	Control group (n=14)	340
Table A.4	Comparison of HF-SDB and HF-noSDB groups	341
Table A.5	Comparison of HF-CSA and HF-noSDB groups	341
Table A.6	Comparison of HF-noSDB and control groups	342
Table A.7	Characteristics of HF patients without SDB (BMI <30kg/m^2) and age matched healthy controls	343
Table A.8	Nocturnal polysomnographic data for the HF-noSDB (BMI <30kg/m^2) and	

	control groups	344
Table A.9	Daytime actigraphy data from HF patients without SDB (BMI <30kg/m^2) and healthy control subject	345
Table A.10	Night time actigraphy data from HF patients without SDB (BMI <30kg.m2) and healthy control subjects	345
Table A.11	Baseline Characteristics	346
Table A.12	Polysomnography	347
Table A.13	Actigraphy- Daytime activity	348
Table A.14	Actigraphy- Night time activity	349
Table A.15	Nocturia data (from sleep diary)	349

LIST OF FIGURES

Figure 1.1	The incidence of HF in a West London population by age and gender	35
Figure 1.2	Aetiology of heart failure in a West London population	36
Figure 1.3	Relationship between preload and stroke volume in a normal heart	39
Figure 1.4	Relationship between afterload and stroke volume in a normal heart	39
Figure 1.5	The response of the heart to various aetiologies of HF	41
Figure 1.6	The relationship between left ventricular end diastolic volume (preload) and stroke volume in heart failure of varying severity	44
Figure 1.7	The relationship between afterload and stroke volume in heart failure of varying severity.	45
Figure 1.8	Summary of the pathophysiology of systolic heart failure	45
Figure 1.9	Summary of the management of the heart failure syndrome	53
Figure 1.10	One year survival rates for HF compared with major cancers, mid 1990s, England and Wales	58
Figure 1.11	Features of obstructive and central apnoeas	62
Figure 1.12	15 minute epoch of respiratory polygraphy from a patient with HF and central SDB	66
Figure 1.13	A basic feedback loop	80
Figure 1.14	Ventilatory control conceptualised as a feedback loop	81
Figure 1.15	Quantifying loop gain; a stable (panel A) and an unstable (panel B) system	82
Figure 1.16	Seven minute epoch of polysomnogram showing periodic breathing occurring after a cortical arousal	82
Figure 1.17	The components of loop gain and the factors which influence them	83
Figure 1.18	HCVR measured in the evening in 2 healthy male subjects	84
Figure 1.19	The hyperbolic relationship between alveolar carbon dioxide and ventilation	85
Figure 1.20	Transplant free survival in the CPAP and control groups of the CANPAP study	93
Figure 1.21	Kaplan-Meier survival plots demonstrating an improved transplant free survival in CPAP suppressed patients compared with both the CPAP unsuppressed and the control groups	94
Figure 2.1	Apparatus used for the Read rebreathe	115
Figure 2.2	Schedule used for the measurement of the hypercapnic ventilatory response	115
Figure 2.3	Raw data from HCVR test in a healthy subject	116

Figure 2.4	Evening HCVR at healthy controls at baseline and follow-up, 3-4 months	118
Figure 2.5	Seven minute epoch of respiratory polygraphy from a patient with HF and central SDB	120
Figure 2.6	Electrode placement using the 10-20 system	122
Figure 2.7	Patient set up for nocturnal polysomnography and ready for bed	123
Figure 2.8	Illustration of the pressure support generated by the device and the respiratory flow to the patient.	126
Figure 2.9	ASV takes measurements at 12 points of the flow wave	126
Figure 2.10	Eight minute epoch from a polygraphy study with patient wearing ASV	127
Figure 2.11	Photograph of the Actiwatch 4 mounted on wrist strap	130
Figure 2.12	Annotated actograms for a healthy subject	131
Figure 2.13	Actogram from a healthy subject.	132
Figure 3.1	Patient screening and recruitment numbers for the first 28 months of recruitment at the Royal Brompton Hospital	147
Figure 3.2	Polygraphy data to show changes from baseline to titration and 3 month study	153
Figure 3.3	Two week download data; differences between ASV users and drop-outs	156
Figure 3.4	Correlations between hours ASV device used during titration study and 2 week download data	156
Figure 3.5	Serial data collected over 24 hours (a) control subjects and (b) ASV users	158
Figure 3.6	Distribution of recruitment of patients into the SERVE-HF study at the Royal Brompton Hospital.	161
Figure 4.1	Subjects studied and included in study analysis	176
Figure 4.2	Resting carbon dioxide levels in the HF-CSA and HF-noSDB groups	183
Figure 4.3	Scatter graph to show the relationship between resting CO_2 levels and the apnoea hypopnoea index in the combined patient group	183
Figure 4.4	Scatter graph to show the relationship between resting CO_2 and BMI in the combined HF group	183
Figure 4.5	Scatter graph to show the relationship between resting CO_2 and BMI in the HF-CSA group only	183
Figure 4.6	Scatter graphs showing individual HCVR for each of HF-CSA and HF-noSDB groups	184
Figure 4.7	Group data for resting CO_2 levels for HF-CSA, HF-noSDB and the controls	189
Figure 4.8	Scatter graph to show the relationship between resting CO_2 and morning HCVR in the total study population	189

Figure 4.9 Scatter graphs to show individual evening and morning HCVR data with overnight change in HF-CSA, HF-noSDB and control groups 190
Figure 4.10 Graphs to show group data for evening and morning HCVR and overnight change in the three groups studied 191
Figure 4.11 Distribution of HCVR tests according to season 197
Figure 5.1 CRT study flow chart 206
Figure 5.2 Periodic limb index from baseline to follow-up in HF patients 215
Figure 5.3 HCVR slopes for each patient able to complete the protocol 217
Figure 5.4 Changes in HCVR (solid line) and resting CO_2 (dotted line) at baseline and follow up 218
Figure 5.5 Figure 5.5; Changes in HCVR (solid line) and carbon dioxide (dotted line) alongside changes in SDB and sleep 219
Figure 6.1 Typical actograms from each group over 14 days 236
Figure 6.2 Relationships between BNP and time in bed assessed by polysomnography and actigraphy 244
Figure 6.3 Relationships between left ventricular ejection fraction and stage 1 and stage 2 sleep expressed as a percentage of total sleep time 244
Figure 6.4 Proportion of total sleep time spent in slow wave sleep for each group in the current study 250
Figure 6.5 Proportion of total sleep time spent in slow wave sleep for both groups in the Hastings study 250

ABBREVIATIONS

ASV	Adaptive Servoventilation
ACC	American College of Cardiology
AHA	American Heart Association
AASM	American Academy of Sleep Medicine
AHI	Apnoea Hypopnoea Index
AI	Apnoea Index
ArI	Arousal Index
AF	Atrial Fibrillation
ACE	Angiotensin Converting Enzyme
ARB	Angiotensin Receptor Blocker
BP	Blood Pressure
BMI	Body Mass Index
BNP	B-type natriuretic peptide
CSA	Central Sleep Apnoea
CSR	Cheyne-Stokes Respiration
CO_2	Carbon dioxide
CT	Computed Tomography
CMR	Cardiac Magnetic Resonance Imaging
CRT	Cardiac Resynchronisation Therapy
CPAP	Continuous Positive Airways Pressure
EEG	Electroencephalogram
EOG	Electooculogram
EMG	Electromyogram
ESC	European Society of Cardiology
ECG	Electrocardiogram
EQ5D	EuroQol quality of life questionnaire
EEP	End Expiratory Pressure
$ETCO_2$	End Tidal Carbon Dioxide
ESS	Epworth Sleepiness Score
EPR	Electronic Patient Record
HF	Heart Failure
HFNEF	Heart Failure with Normal Ejection Fraction
HFSS	Heart Failure Survival Score
HCVR	Hypercapnic Ventilatory Response
HI	Hypopnoea Index
ICSA	Idiopathic Central Sleep Apnoea
LV	Left Ventricle/Left Ventricular

LVH	Left Ventricular Hypertrophy
LVEF	Left Ventricular Ejection Fraction
LVESD	Left Ventricular End Systolic Diameter
LVESD	Left Ventricular End Systolic Diameter
MLHFQ	Minnesota Living with Heart Failure Questionnaire
MRI	Magnetic Resonance Imaging
NICE	National Institute of Clinical Excellence
NYHA	New York Heart Association
NHS	National Health Service
NREM	Non Rapid Eye Movement (sleep stage)
NIV	Non Invasive Ventilation
OSA	Obstructive Sleep Apnoea
ODI	Oxygen Desaturation Index
OSLER	Oxford Sleep Resistance Test
PAP	Positive Airway Pressure
PG	Polygraphy
PSG	Polysomnography
PLM	Periodic Leg Movement
PSQI	Pittsburgh Sleep Quality Index
PCWP	Pulmonary Capillary Wedge Pressure
REM	Rapid Eye Movement (sleep stage)
RAAS	Renin-Angiotensin-Aldosterone System
RLS	Restless Legs Syndrome
RIP	Respiratory Inductance Plethysmography
REC	Research Ethics Committee
SDB	Sleep Disordered Breathing
SNA	Sympathetic Nerve Activity
SE	Sleep Efficiency
S1	Stage 1 sleep
S2	Stage 2 sleep
S3	Stage 3 sleep
S4	Stage 4 sleep
SWS	Slow Wave Sleep
SL	Sleep Latency
SPSS	Statistical Package for the Social Sciences
TST	Total Sleep Time
T<90%	Time spent with oxygen saturations less than 90%
WASO	Wake After Sleep Onset
VT	Ventricular Tachycardia
VF	Ventricular Fibrillation
6MWT	Six Minute Walk Test

We are such stuff

As dreams are made on, and our little life

Is rounded with a sleep.

The Tempest (4.1.168-170)

by William Shakespeare (1564-1616)

CHAPTER ONE:

GENERAL INTRODUCTION

Chapter one provides an introduction to this thesis. The first section describes the clinical syndrome of heart failure (HF), particularly as it pertains to the diagnosis of sleep disordered breathing (SDB), which will be described in the second section. Sleep disordered breathing in HF patients will then be described followed by a discussion of symptoms in HF patients with central SDB. The fifth section describes breathing during sleep in healthy subjects which is followed by an account of the pathophysiology of central SDB in patients with HF. Finally; the treatment of central SDB in this group is considered.

1.1 Heart failure

HF is a complex clinical syndrome characterised by a mismatch between the perfusion requirements of the body and the ability of the heart to meet them. Its high prevalence places a substantial burden on health care services in terms of acute admissions, outpatient care and the use of devices plus other interventions, such as transplantation. The first descriptions of HF date back to ancient Egyptian times where early physicians recorded "*blood that has got itself fixed and does not circulate"* (Saba et al., 2006). The HF syndrome is the final common pathway of a number of cardiac conditions and as such represents an aetiologically heterogeneous condition with a variety of clinical phenotypes and this has implications for diagnosis, management and prognosis. This section will give a general introduction to the subject with an emphasis on the pathophysiology which underlies the syndrome and is linked to the emergence of SDB in some, but not all, patients with HF (Vazir et al., 2007, Javaheri, 2006b). For the most part this section will refer to chronic HF rather than acute HF.

1.1.1 Definition of heart failure

The clinical symptoms and signs of the HF syndrome are due largely to a mismatch between the perfusion requirements of the body and the ability of the heart to fulfil them. The European Society of Cardiology (ESC) guidelines (Dickstein et al., 2008) provide a practical definition of HF as the presence of symptoms at rest or on exertion (shortness of breath, fatigue); signs of fluid retention (pulmonary congestion, peripheral oedema); and objective findings of an abnormality of the heart structure or function. Other symptoms or signs of HF may relate to the diverse underlying causes of the syndrome, or be related to its treatment, but are not a requirement for its diagnosis. The clinical diagnosis of HF should never be made in isolation; the underlying cause of the syndrome should be sought as this may change management. A discussion of aetiology will now follow but it is noteworthy that this lack of accepted definition has implications for clinical diagnosis, the ascertainment of the incidence and prevalence of HF and the comparability of different research.

1.1.2 Classification of heart failure

The classification of HF permits a better understanding of what is an aetiologically diverse condition. HF may be classified by mode of onset, duration (ie. acute vs. chronic), severity (ie. mild, moderate or severe) or type of ventricular impairment (ie systolic vs. diastolic) but these descriptive terms are falling from favour due to their often ambiguous use (Dickstein et al., 2008). A frequently used classification of clinical severity is the New York Heart Association (NYHA) functional classification originally devised in 1964 and updated in 1994 (Kossman, 1964) which grades symptoms according to the level of activity (see table 1.1). While straightforward to apply the NYHA is subject to considerable inter-observer variability (Goldman et al., 1981) due to its lack of objective parameters and this may limit its usefulness, particularly in clinical research. The American College of Cardiology and American Heart Association (ACC/AHA) Staging system is shown in table 1.1. Heart failure is often described in terms of the severity of impairment of the left ventricle (LV) although this may not correlate with the severity of the clinical syndrome, and left ventricular systolic dysfunction is not seen in all cases of clinical heart failure. Heart failure with preserved (or normal) ejection fraction (HFNEF) is increasingly recognised and more common in older patients, females and those with hypertension and diabetes (Vasan et al., 1995). Rather than systolic impairment it is characterised by impaired LV filling in diastole which reduces cardiac output. The remainder of this section will focus on systolic dysfunction.

Table 1.1: Two frequently used classification systems for HF.

Classification by functional status; the New York Heart Association functional classification (REF)	
Class I	No limitation of physical activity.
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 with any physical activity without discomfort. Symptoms at rest. Any physical activity results in an increase in discomfort.

Classification by Stage of heart failure based on structure and damage to heart muscle (REF)	
Stage A	At high risk of developing heart failure.No identified structural or functional abnormality; no signs or symptoms.
Stage B	Developed structural heart disease that is strongly associated with the development of heart failure, but without signs or symptoms.
Stage C	Symptomatic heart failure associated with underlying structural heart disease.
Stage D	Advanced structural heart disease and marked symptoms of heart failure despite maximal medical therapy.

1.1.3 Epidemiology of heart failure

Given the lack of a universally accepted definition, measuring the true incidence and prevalence of HF within a population poses certain challenges. Different epidemiological studies have used different definitions of HF, rendering their results difficult to compare. Patients may erroneously be labelled as having HF in primary care, where specialist investigations may not be done, or alternatively an incorrect diagnosis may be given, particularly in certain groups, such as the obese (Mathew et al., 2008), in whom diagnosis may be more difficult.

In the United Kingdom 878,000 people have definite or probable HF, with a similar number of individuals with structural cardiac damage which is not yet causing symptoms (Petersen et al., 2002) as only 50% of those with LV dysfunction are thought to have symptoms (Ho et al., 1993). The prevalence of HF is anticipated to increase as the population ages, primary prevention of the causes of HF improves and more patients with coronary artery disease survive to develop its sequelae, although data to support this are lacking. Hospitalisation rates for patients with HF have also increased; however, co-morbidities are often the primary reason for admission (Brown and Cleland, 1998) and it seems likely that the manner in which admissions are coded has changed over time (Murdoch et al., 1998). Prevalence rates unadjusted for age are misleadingly low as cases before the age of 45 are unusual (Cowie et al., 1999). In a West Midlands prevalence study of 3960 adults (aged 45 years or older) 1 in 35 people aged 65 to 74 years old had HF, 1 in 15 of those aged 75 to 84 and 1 in 7 of those

aged 85 and above (Davies et al., 2001). This group used the ESC guidelines for diagnosis and their assessment included echocardiography.

A study investigating the incidence of HF in a West London population, also using the ESC guidelines and echocardiography, found the median age of presentation to be 76 with a similar sharp increase in incidence with age; 0.02 per 1000/year in those aged 25 to 34 up to 11.6 in those aged 85 years or more (Cowie et al., 1999). The incidence data from this study by age and gender are shown in figure 1.1. The Framingham study too found an increase in incidence of HF with age, with this increase being more pronounced in women than men (Lloyd-Jones et al., 2002).

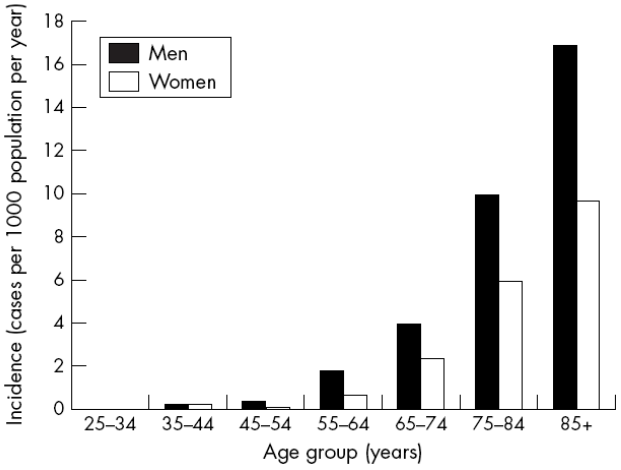


Figure 1.1: The incidence of HF in a West London population by age and gender. (Cowie et al., 1999)

There is a well established gender difference in the incidence of HF; women are less frequently affected (Ho et al., 1993), reflecting the higher rates of ischaemic heart disease found in men. However, after the age of 70 the incidence rates equalise between the genders. Ethnicity too plays a role; the incidence of HF in black patients is significantly higher than it is in white patients (Bibbins-Domingo et al., 2009).

Heart failure is a major economic burden on the health systems of developed countries (Lee et al., 2004) with UK expenditure on HF health care costs estimated at around 2% of annual National Health Service (NHS) expenditure, of which 70% relates to the costs of hospitalisation (Petersen et al., 2002). The annual cost of HF to the NHS is estimated to be over £625 million (Petersen et al., 2002). HF admissions account for 1 million of all NHS inpatient bed days and 5% of all emergency medical admissions to hospital; admissions are anticipated to increase by 50% over the next 25 years due, for the most part, to the ageing of the population (Petersen et al., 2002). The median admission is 7 to 8 days, with the vast majority of patients being discharged by day 10 (Nicol et al., 2008).

1.1.4 Aetiology of heart failure

Establishing the relative aetiology of HF in clinical studies is also difficult; although ischaemic heart disease is the commonest cause of HF in UK based studies (Cowie et al., 1999) and other work in the developed world, it often coexists with hypertension creating uncertainty as to which factor is truly causal. Absolute blood pressure readings often fall in the latter stages of HF in patients previously documented as hypertensive and this may further confuse the issue. Finally; atrial fibrillation is common in those presenting with HF, but may not be its sole contributor. In many cases there is no single identifiable factor but rather a combination of contributing factors. The aetiology of HF in the West London incidence study previously discussed is shown in figure 1.2 (Cowie et al., 1999).

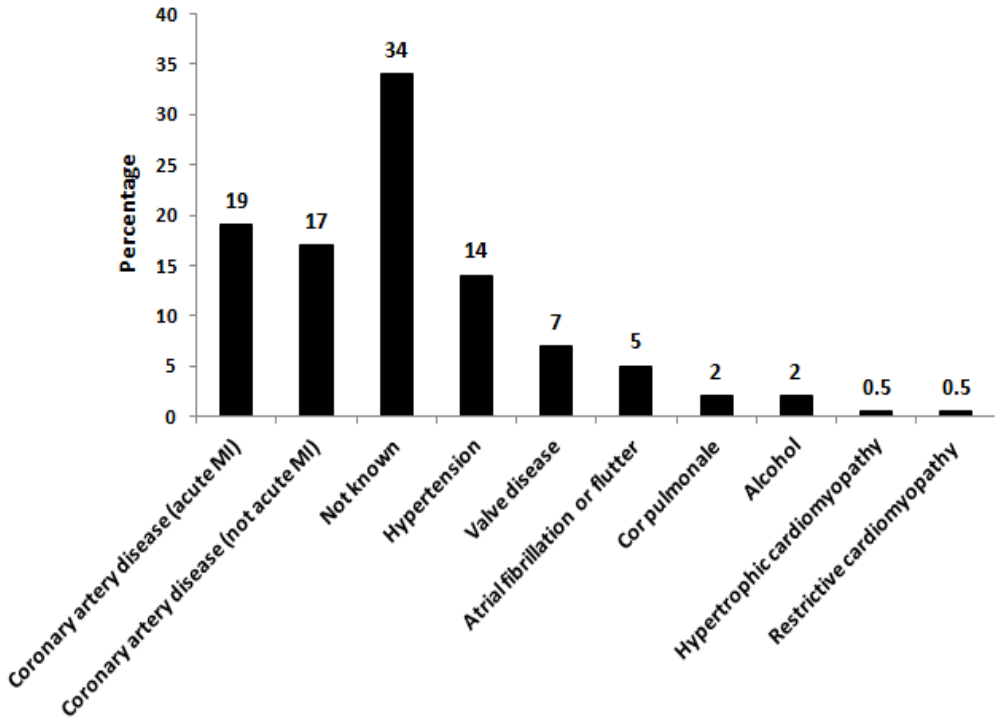


Figure 1.2: Aetiology of heart failure in a West London population. (Cowie et al., 1999).
MI- myocardial infarction.

Broadly speaking the functional capacity of the heart may be compromised by acute or chronic ischaemia, injury to the heart muscle itself (cardiomyopathy), damage to the valves, an increase in vascular resistance (as with hypertension) or as a consequence of a tachyarrhythmia (such as atrial fibrillation- AF). The pathophysiological consequences of this damage will be considered later but while the HF syndrome has many causes, the pattern of aetiology varies by population and with time. In the past valvular (particularly rheumatic) heart disease was a common cause of HF in the developed world where ischaemic and hypertensive cardiomyopathy now predominate as the population ages

and more patients with ischaemic heart disease survive after myocardial infarction (Kannel et al., 1994). Alongside ischaemic heart disease, diabetes is also increasingly implicated as a cause of the HF syndrome (Kannel et al., 1994). Dilated cardiomyopathy is also common in the developed world and may be genetic in origin or the sequela of a viral or other toxic insult to the heart. There is often a significant proportion of cases where the cause is unclear, as in figure 1.2, when investigated only half of such cases were truly idiopathic Table 1.2 provides a list of the causes of HF.

In a study of over 13,000 men and women followed for almost 20 years in the United States risk factors for the development of HF were coronary heart disease, hypertension, obesity, diabetes, cigarette smoking and valvular heart disease (He et al., 2001).

The aetiological pattern of HF for a given population reflects its socioeconomic development and, to a certain extent, its health care provision. Those affected in developing countries are younger and more often have nutritional deficiencies or communicable diseases as the cause of their HF syndrome (Mendez and Cowie, 2001). Rheumatic heart disease remains prevalent on the African and Asian continents and Chagas disease (American trypanosomiasis) remains endemic in South America. As developing countries undergo “epidemiological transition” (Mendez and Cowie, 2001) the aetiological pattern changes and reflects a population with fewer communicable and nutritional diseases but more diseases of an ageing population such as hypertension and IHD.

Table 1.2: Causes of the HF syndrome. Modified from Kearney *et al.*, (Kearney, 2008)

Ischaemic heart disease		
Hypertrophic cardiomyopathy	**Systemic hypertension**	
	Inherited hypertrophic cardiomyopathy	
Restrictive cardiomyopathy	**Infiltration**	Amyloidosis
		Sarcoidosis
		Neoplasm
	Storage disorders	Haemochromatosis
		Glycogen storage diseases
		Fabry disease
	Endomyocardial disease	Radiotherapy
		Endomyocardial fibrosis
		Carcinoid
Dilated Cardiomyopathy	**Inherited Cardiomyopathy**	
	Toxins	Alcohol
		Chemotherapy
		Cocaine
	Metabolic disorders	Endocrine disease
		Nutritional deficiency
		Autoimmune disease
	Peripartum cardiomyopathy	
	Neuromuscular disease	Friedreich's ataxia
		Muscular dystrophy
	Infections	Parasitic
		Viruses e.g. HIV
		Bacteria
Other	**Valve disease**	
	Pericardial disease	
	Arrhythmia	

1.1.5 Pathogenesis of heart failure

Heart failure is a whole body syndrome because the vasculature of every organ system is dependent on the cardiac pump. When considering the pathophysiology of the HF syndrome the importance of aetiology again deserves mention as it is likely to determine the speed with which it develops; a slowly failing valve may culminate in HF very gradually whereas a sudden ischaemic insult (such as a large infarct) may produce HF much more quickly. The speed of onset of HF determines the body's response; more gradual changes in the heart permit time for compensatory changes to occur, whilst sudden ones may overwhelm the body's ability to compensate and so precipitate an acute presentation. Elucidating the aetiology of HF may not only reveal abnormalities which may be reversible, but it may also determine the response to management. For example; those with coronary artery disease may also have atherosclerosis of the renal vasculature which will likely limit the use of diuretic, ACE (angiotensin converting enzyme) inhibitor or aldosterone antagonist therapy. This section will give an account of the heart in health, then patterns of response to cardiac injury before considering the pathophysiology of the established HF syndrome. Emphasis will be given to those aspects of pathophysiology most pertinent to the pathogenesis of SDB and also to the manner in which the resultant compensatory responses to HF are maladaptive and so magnify the effect of the initial insult and propagate the syndrome: in this way HF begets HF.

The heart in the healthy state

A full account of the physiology of the heart is beyond the scope of this thesis however its remarkable adaptive qualities deserve mention here as they pertain to the discussion of the pathophysiology which follows. The cardiac cycle is a product of the heart's intrinsic rhythmogenesis and contractile ability which together permit the sequential contraction of the atria then the ventricles. Valve competency means that these pressure changes direct the flow of blood through the heart with ventricular filling being initially passive (with increasing atrial pressure) and then active (with atrial systole). The volume of blood ejected by the left ventricle into the systemic circulation is the stroke volume (the difference between end diastolic and end systolic volumes) and is predominantly determined by 3 key factors: preload, myocardial contractility and afterload.

Preload is the pressure the heart is filled with, or the left ventricular end diastolic volume. An increase in left ventricular volume at end diastole increases cardiac fibre stretch and so sarcomere length, which due to the relationship of actin and myosin within the sarcomere will increase the force generated, up to a point. The relationship between preload and stroke volume was described in the classic work often attributed to Otto Frank and Ernest Starling, but which in fact was the culmination

of observations made by several others (Katz, 2002). Starling's hypothesis was that "the mechanical energy set free in the passage from the resting to the active state is a function of the length of the fibre". Figure 1.3 shows the Frank-Starling curves; the relationship between preload (left ventricular end diastolic volume -or pressure, as the two are closely linked in health) and the stroke volume in health, between which there is a positive relationship.

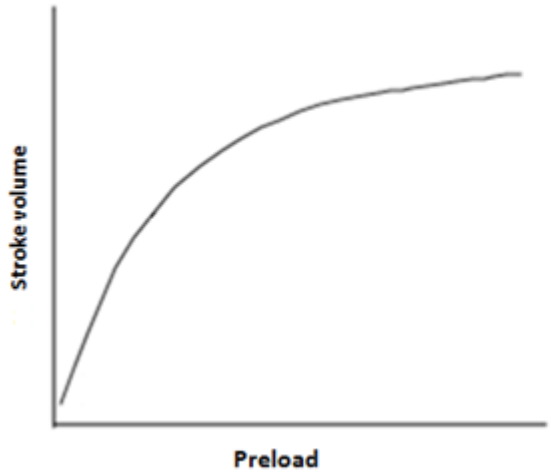


Figure 1.3: Relationship between preload and stroke volume in a normal heart.

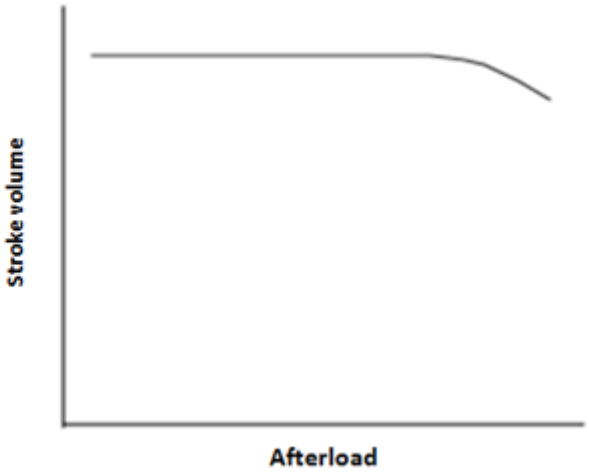


Figure 1.4: Relationship between afterload and stroke volume in a normal heart.

Myocardial contractility is determined by the tension generated by the cardiac muscle cells which is related to the binding of intracellular calcium to the myofibrills, the basic unit of the cardiac muscle.

Afterload describes the resistance which the heart pumps against. This force acts on the ventricular wall and is defined by the force acting on the ventricular wall (wall stress). Therefore changes in ventricular geometry (volume of the cavity and thickness of the wall) will play a part here. The normal heart can maintain a similar stroke volume against an increasing afterload to a point, but this ability to compensate is lost in HF and is discussed later. The relationship between stroke volume and afterload is illustrated in figure 1.4 and allows the heart to alter stroke volume on a beat by beat basis.

Each of these three determinants of stroke volume may be affected by the HF syndrome, by the body's response or by treatments for heart failure.

In health there a swift cardiovascular response to a change in the body's work load and so to its perfusion requirement which utilises the physiological reserve of the heart which, on exertion, may increase cardiac output significantly from its resting level. The heart's ability to adapt is well illustrated by its response to situations of extreme (but non-pathological) increases in work load such as in endurance athletes in whom an increase in left ventricular end diastolic volume and cardiac hypertrophy optimise cardiac output by increasing preload, stroke volume and a reduction in afterload

to meet the work load required of it: a physiological process called cardiac remodelling which is histologically distinct from that seen in HF.

Beyond the heart itself various control mechanisms play a pivotal role in regulating pre- and after-load, as well as having effects directly on the heart. Such mechanisms include neurohumoral influences (such as the renin-angiotensin-aldosterone system) and the sympathetic nervous system; these bring about peripheral vasoconstriction, an increase in heart rate and force of contraction (chronotropic and ionotropic effects).

The healthy heart therefore has a number of highly complex compensatory mechanisms which ensure that it is able to adapt to changing needs and so maintain a cardiac output appropriate to the requirements of the body. In health, demands on the heart must be great before it is unable to fulfil them due to its significant physiological reserve.

The heart's response to injury

There are a limited number of ways in which the heart can be damaged, and a limited number of way in which it will respond. Cardiac injuries may be classified according to the effect they have on the heart and broadly speaking fall into three categories; those increasing the preload on the heart, those causing damage to the myocardium itself, and those increasing the afterload on the heart. Examples of the conditions which cause each of these and their effect on the heart are illustrated in figure 1.5.

Maladaptive compensatory responses; the heart failure syndrome

Whatever the underlying cause, a reduction in cardiac output precipitates a number of physiological changes and these compensatory responses may initially maintain cardiac output and delay or attenuate clinical symptoms which may only become apparent during exertion. These may serve to restore cardiac output in the short term but are ultimately maladaptive compensatory mechanisms which have both cardiac and systemic sequelae and may ultimately fail to maintain cardiac output. The nature of the compensatory changes which occur is determined by the time course and magnitude of the cardiac insult. Rapid falls in cardiac output (such as in acute myocardial infarction) are less well tolerated and result in more symptoms acutely than those with more gradual onset. The greater the physiological reserve available to accommodate it that insult, the more completely the reduction in cardiac output may be corrected. In severe cardiac dysfunction, where compensatory mechanisms are necessary to maintain the cardiac output required at rest, only minimal exertion will precipitate symptoms.

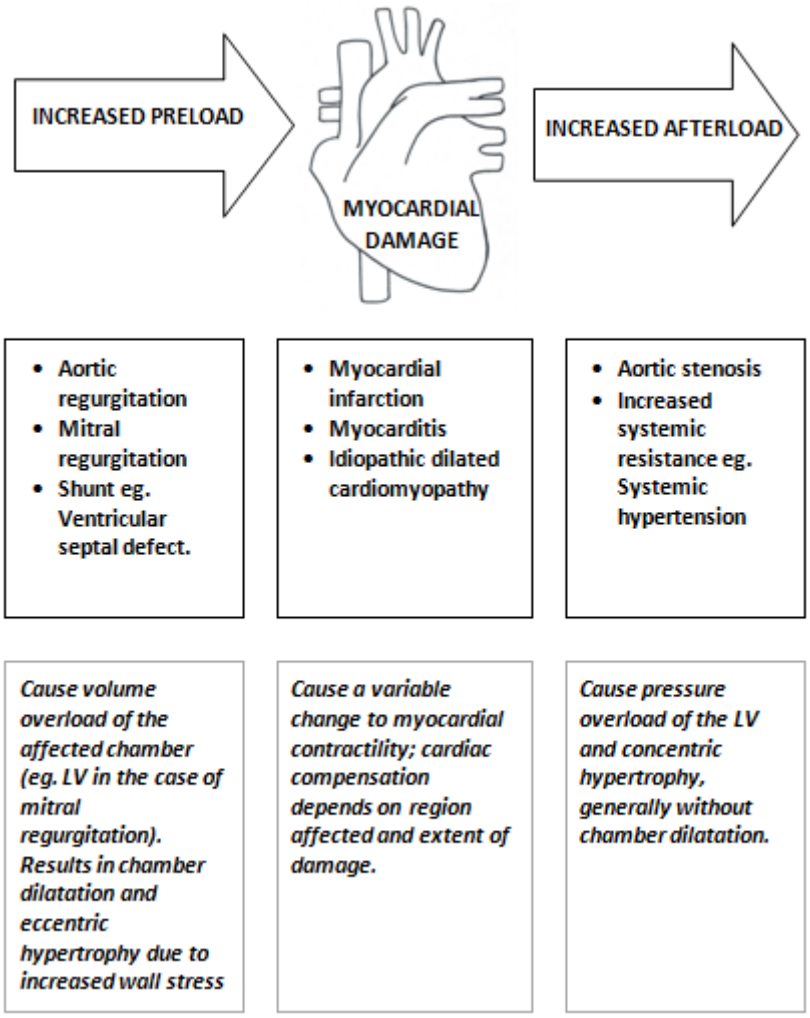


Figure 1.5: The response of the heart to various aetiologies of HF. (Original figure)

Maladaptive compensatory responses; the heart failure syndrome

Whatever the underlying cause, a reduction in cardiac output precipitates a number of physiological changes and these compensatory responses may initially maintain cardiac output and delay or attenuate clinical symptoms which may only become apparent during exertion. These may serve to restore cardiac output in the short term but are ultimately maladaptive compensatory mechanisms which have both cardiac and systemic sequelae and may ultimately fail to maintain cardiac output. The nature of the compensatory changes which occur is determined by the time course and magnitude of the cardiac insult. Rapid falls in cardiac output (such as in acute myocardial infarction) are less well tolerated and result in more symptoms acutely than those with more gradual onset. The greater the physiological reserve available to accommodate that insult, the more completely the reduction in cardiac output may be corrected. In severe cardiac dysfunction, where compensatory mechanisms are necessary to maintain the cardiac output required at rest, only minimal exertion will precipitate symptoms.

An acute fall in cardiac output will cause activation of the sympathetic nervous system as well as the renin-angiotensin-aldosterone system (RAAS). The sympathetic nervous system increases myocardial contractility and heart rate, so shortening diastole and the time available for coronary blood flow. Its chronic activation also causes myocyte hypertrophy and interstitial fibrosis, resulting in changes of ventricular geometry. Furthermore, ongoing adrenergic stimulation causes a down regulation of adrenoreceptors such that that these mechanisms are less efficacious in increasing cardiac output if required subsequently. The sympathetic nervous system, along with a reduction in renal perfusion, also causes activation of the RAAS and this increases circulating volume via the mineralocorticoid hormone, aldosterone and causes vasoconstriction, via the peptide hormone, angiotensin II, which also increases noradrenaline levels. Natriuretic peptides are released in response to myocardial stretch and in part counter the effects of sympathetic nervous system and the RAAS. Like many chronic conditions, the HF syndrome is recognised as an inflammatory state in which levels of circulating cytokines are increased and play a role in the pathophysiology of the syndrome.

The increase in circulating volume serves to increase preload and so cardiac contractility via the Frank-Starling mechanism (an increase in chamber stretch producing a greater contractile shortening). Systemic vasoconstriction will maintain blood pressure but increase the resistance against which the heart must pump and both this increase in afterload and the increase in preload reduce compensatory reserve and so the threshold before which HF symptoms will emerge.

Figure 1.6 shows the effect of the HF syndrome on the relationship between stroke volume and left ventricular end diastolic pressure (preload). The reduction in stroke volume in mild cardiac dysfunction (middle curve) may be compensated for by an increase in circulating volume (via the RAAS system), but this increase in left ventricular end diastolic pressure (preload) comes at a cost as it reduces the physiological reserve available to respond to further demands on the heart. In severe cardiac dysfunction the reduction in stroke volume is such that increases in preload cannot fully compensate and the increase in circulating volume contributes to the clinical syndrome, with no physiological benefit. In addition to these neurohumoral mechanisms there are others which perpetuate the HF syndrome such as the cellular effects of reactive oxygen species and cytokines and the role played by anti-diuretic hormone (ADH) and endothelin which both increase preload.

Depending on its cause, HF will also affect myocardial contractility. Myocardial infarction may result in an akinetic region of the heart which, depending on its size and location, may significantly reduce stroke volume. Infiltrative cardiac disease will affect myocardial contractility by distrupting the normal microscopic architecture of the myocardium; for example, granulomatous infiltration in cardiac sarcoid or hyaline deposits in cardiac amyloid.

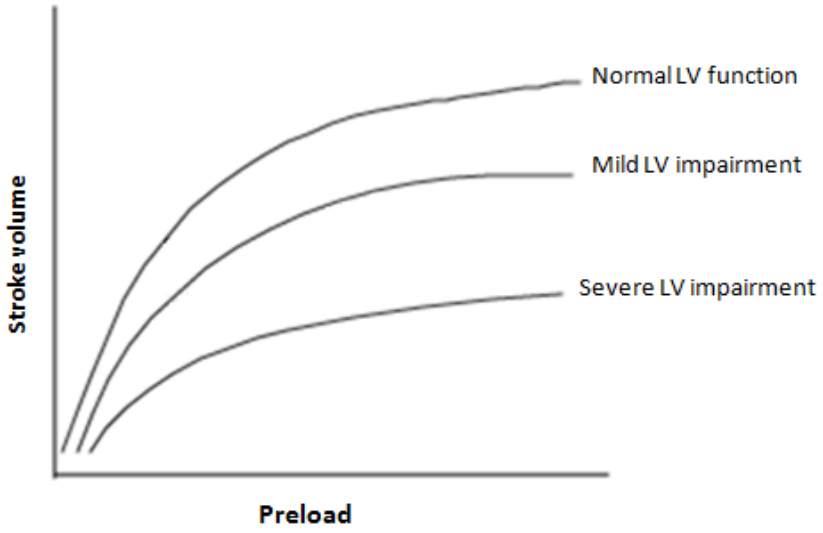


Figure 1.6: The relationship between left ventricular end diastolic volume (preload) and stroke volume in heart failure of varying severity. *LV- left ventricular.*

Figure 1.7 shows the effect of the HF syndrome on the relationship between stroke volume and afterload and the deleterious effect of even mild cardiac dysfunction on the heart's response to increasing afterload. Structural changes in the heart compensate for wall stress with chamber dilatation and wall hypertrophy, changes accelerated by angiotensin II and aldosterone. Therapy to reduce afterload not only improves stroke volume but may also slow the progression of heart failure. Key factors involved in the pathogenesis of the HF syndrome are summarised in figure 1.8.

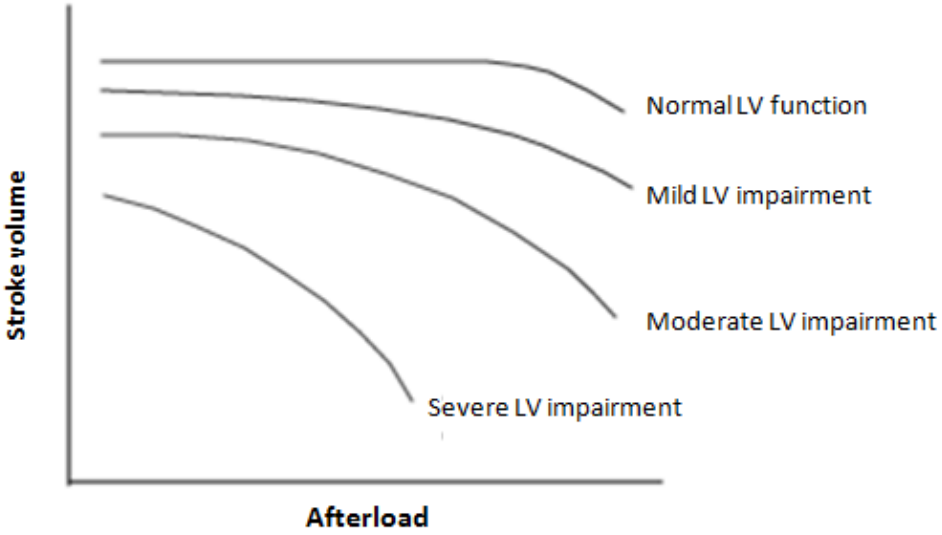


Figure 1.7: The relationship between afterload and stroke volume in heart failure of varying severity. *LV- left ventricular.*

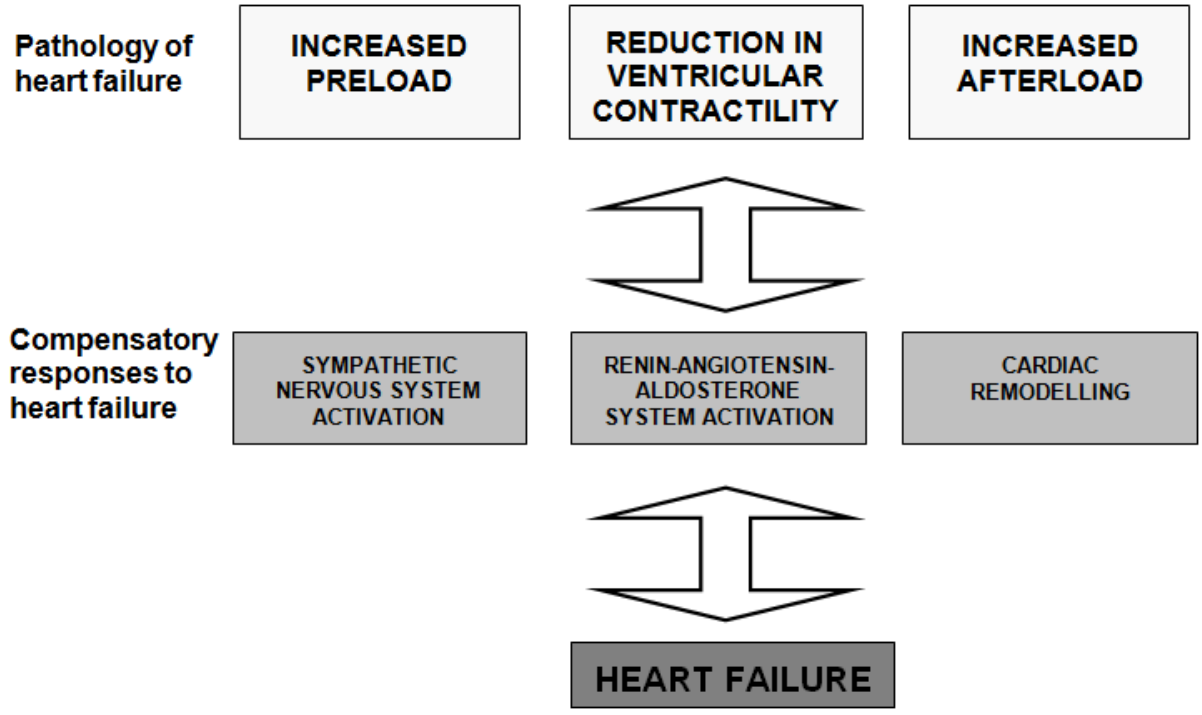


Figure 1.8: Summary of the pathophysiology of systolic heart failure. (Original figure)

Aside from pathology relating to preload, myocardial contractility and afterload, there are other changes which contribute to the HF syndrome and have implications for treatment. Cellular changes which result in structural changes can adversely affect the functional integrity of the heart by changing its mechanical properties. For example, a dilating LV will have implications for the competence of the mitral valve, the annulus of which may be affected resulting in functional mitral regurgitation. Discrete areas of poorly contractile myocardium, such as those caused by myocardial infarction, might cause a regional wall motion abnormality which disrupts the normal pattern of myocardial contraction and so further impairs cardiac output. A large area of akinetic myocardium brings a risk of intracardiac thrombus and systemic embolisation. Conduction abnormalities which disrupt the synchronous contraction of both sides of the heart may be seen; left bundle branch block is one such abnormality and may result in ventricular dyssynchrony which is now well established as a worthwhile therapeutic target (Moss et al., 2009); see section 1.7.6. Downstream of the failing heart each organ vessel bed is at risk of hypoperfusion, particularly at times when the heart is under pressure, such as during exertion. Some are more sensitive to this than others; renal impairment in the HF syndrome may not only be due to a fall in cardiac output and renal perfusion, but also a side effect of the medications aimed to reduce circulating volume and so preload.

There are several pulmonary changes seen as part of the HF syndrome which deserve mention. These have been summarised in a review by Kee and Naughton (Kee and Naughton, 2010). As the left ventricle fails so left atrial pressure rises resulting in pulmonary hypertension and, depending on the speed of this process, pulmonary oedema ensues due to increased hydrostatic capillary pressures. Chronic HF brings with it a range of changes to the pulmonary vasculature which hinder the development of pulmonary oedema despite high pressure in the pulmonary vasculature and these include capillary basement membrane thickening, muscularisation of arterioles and venules and circumferential fibrosis of arteries and veins, alveolar haemosiderin deposition, small airway compression by increased volume of connective tissue and hypertrophy of bronchial smooth muscle (Kee and Naughton, 2010). As with the compensatory mechanisms illustrated before, this increased resistance to the development of pulmonary oedema comes at a price; it both reduces the reserve available to cope with further stress on the heart and also exposes the pulmonary vasculature to ongoing high pressures, without the “pressure release” of pulmonary oedema. Chronic HF is associated with a restrictive pattern on spirometry, compared to healthy controls, and impaired gas exchange across the alveolar capillary membrane (Torchio et al., 2006).

1.1.6 Diagnosis of heart failure

A diagnosis of HF should never be made in isolation but should prompt a search for its underlying cause as this will direct subsequent management, however it will not be found in approximately a third of cases (Cowie et al., 1999). The tools used to establish a patient's diagnosis of HF are also used to monitor its progression, response to treatment and to detect any adverse effects of therapy; a summary of these will now follow. The combination of features from the history and examination along with results from investigations are helpful in determining which patients require further assessment and with what level of urgency. For example; the most recent NICE guidelines for HF recommend that primary care patients suspected of having HF with a history of MI should be referred urgently for echocardiography; whereas a similar patient *without* a history of MI should have measurement of B-type natriuretic peptide (BNP) in the first instance (Mant, 2010).

Diagnostic tools will be divided into (i) Clinical assessment; (ii) Bedside and ambulatory; (iii) Imaging and (iv) Invasive tests.

Clinical assessment

A thorough history and examination may satisfy two out of three of the ESC conditions for the definition of HF. Patients will characteristically complain of shortness of breath and fatigue, both worse on exertion and fluid retention depending on the type, severity and speed of onset of their HF. They may additionally describe orthopnoea, paroxysmal nocturnal dyspnoea, palpitations, anginal pain, syncope, abdominal distension or anorexia, depending on the underlying aetiology of their HF syndrome. Symptoms however, and particularly exercise capacity correlate poorly with the severity of cardiac impairment (Volterrani et al., 1994) and the way they are communicated are subject to numerous other factors such as language barriers and health care literacy. Symptoms which persist despite the initiation and titration of treatment should prompt a reconsideration of the original history and diagnosis.

Features on examination may similarly include clues as to the underlying cause (eg evidence of peripheral vascular disease) as well as permitting a clinical assessment of severity. Features suggestive of HF include peripheral or pulmonary oedema, elevated central venous pressure, displaced apex beat (with LV enlargement), pulsus alternans and a third or "extra" heart sound. Where the right ventricle is predominantly affected patients may have a more prominently elevated jugular venous pressure on examination, more marked peripheral and sacral oedema, ascites and hepatosplenomegaly. Where the left ventricle is more predominantly affected pulmonary oedema might be seen in acute onset HF or where HF becomes rapidly worse.

In a systematic review of studies of symptomatic patients in primary care dyspnoea was the only symptom or sign to have a high sensitivity for the diagnosis of HF (89%) but this was coupled with a specificity of only 51%. Other features had higher specificities; history of MI (89%), orthopnoea (89%), oedema (72%), raised jugular venous pressure (70%), cardiomegaly (85%), added heart sounds (99%), lung crepitations (81%) and hepatomegaly (97%) but the sensitivity of these was too low to be of real value (all less than 53%) (Mant et al., 2009).

Bedside and ambulatory assessment

As with the assessment of symptoms and signs, the electrocardiogram (ECG) is useful in diagnosis and monitoring of the HF patient and may reveal a number of abnormalities such as tachyarrhythmias (particularly AF), evidence of ischaemia/infarction or hypertension. ECG has a sensitivity of 89% but is poorly specific for HF (Mant et al., 2009). Assessment of heart rate (particularly ventricular rate in the context of AF) is useful in guiding management.

Ambulatory ECG (holter) monitoring permits a prolonged assessment of rhythm and rate and in the context of suspected or proven HF may identify and quantify a rhythm treatable by drug therapy, cardioversion or ablation, such a AF or non-sustained ventricular tachycardia.

Laboratory tests permit the exclusion of other diagnoses (discussed later) rather than providing definitive evidence for the diagnosis of HF. Such tests are invaluable in monitoring treatment (and, indirectly, compliance) as treated patients may demonstrate pre-renal renal impairment, hyperkalaemia and hyponatraemia. Hyperglycaemia and suggestive urinalysis may point to diabetes as a co-diagnosis; similarly an abnormal lipid profile provides a further therapeutic target. Liver function tests may be abnormal in the presence of hepatic congestion. Co-morbid disease or precipitating/exacerbating illnesses may be detected or monitored; for example, infections may exacerbate HF, thyrotoxicosis may precipitate AF and HF. Iron levels may suggest a diagnosis of haemachromatosis.

B-type natriuretic peptide (BNP) is a natriuretic peptide hormone released from myocardial cells in response to an increase in wall stress and volume and as such it is a marker of increased filling pressures and is homeostatic in function. BNP is released primarily from the left ventricle and is the product of cleavage of the inactive NT-proBNP from the precursor peptide proBNP. NT-proBNP is released into the circulation at levels proportional to the biologically active BNP, hence the use of both BNP and NT-proBNP in diagnostic assays, however there is no difference in their diagnostic accuracy (Mant et al., 2009). A sudden change in filling pressure may not be mirrored by an immediate increase in natriuretic peptides and they have moderately long half lives so circulating levels may lag a little behind the clinical picture.

A normal level of BNP in an untreated patient has a high negative predictive value making it a useful rule-out test, particularly in primary care (Zaphiriou et al., 2005). However while an elevated BNP has a sensitivity of 94% (Mant et al., 2009) it is not specific to HF and can be raised in left ventricular hypertrophy (LVH), myocardial ischaemia, pulmonary hypertension, hypoxia, pulmonary embolism, right ventricular strain, COPD, liver failure, sepsis, diabetes and renal failure. Female gender and age over 70 may also increase baseline levels of natriuretic peptides (McDonagh et al., 2004). The level of natriuretic peptide does not distinguish between systolic impairment and HF characterised by a preserved ejection fraction; indeed amongst patients with diastolic dysfunction on echocardiogram natriuretic peptides are elevated and are highest in those with symptoms (Lubien et al., 2002). Natriuretic peptide levels are of prognostic value as baseline levels predict both the risk of subsequent admission to hospital and mortality (Kubanek et al., 2009) and NICE guidelines (Mant, 2010) suggest a referral within 2 weeks where levels are very high. Natriuretic peptides have also shown to be an independent prognostic factor at the point of discharge from hospital after an episode of acute HF (Metra et al., 2007). Natriuretic peptide measurement is a more accurate diagnostic test than ECG (Mant et al., 2009) and the latter is now no longer recommended as part of the NICE diagnostic algorithm. Additionally, ECG has been shown to add little in the way of diagnostic value to the measurement of natriuretic peptides in the exclusion of HF in primary care (Zaphiriou et al., 2005).

Troponins are regulatory proteins essential for cardiac muscle contraction and are a complex of three protein subunits I, T and C of which I and T are specific to cardiac muscle. Troponins I and T are released from cardiac myocytes in the event of necrosis and so are highly sensitive and specific for cardiac damage. Like natriuretic proteins, and many other biomarkers, they are not 100% specific and an increase in troponin I and/or T is also seen acute myocarditis as well as other, non-cardiac, conditions. In the context of HF troponin has a place in the investigation of the patient suspected to have underlying cardiac ischaemia but may also be elevated in decompensated HF in the absence of myocardial ischaemia. Like natriuretic peptides, a detectable cardiac troponin level is an independent prognostic factor at the point of discharge from hospital after an episode of acute HF (Metra et al., 2007).

Exercise testing is useful for quantifying function, assessing clinical stability, monitoring of the response to treatment and progression of heart failure. Sub-maximal exercise testing in the form of the six minute walk test (6MWT) is easily undertaken without specialist equipment and with limited staff training. Measurement of maximal oxygen uptake (VO_2max) during more formal exercise testing is more demanding of time, equipment and staff expertise but gives objective information, which is

prognostically useful, for example, in a patient undergoing assessment for transplantation. Performance on exertion may be limited by numerous other factors, eg. musculoskeletal or pulmonary disease.

Imaging

The chest radiograph is an important investigation in the assessment of suspected HF. In support of the diagnosis of HF it gives information about the pulmonary vasculature and cardiothoracic ratio (the latter increased with cardiomegaly on a posterior-anterior projection). It may reveal evidence of an alternative (or co-existing) pathology such as chronic obstructive pulmonary disease, pleural or pericardial effusion, or infection. The chest radiograph has a reasonable sensitivity for HF of 76-83% but a lower specificity of 67-68% (Mant et al., 2009). It is worth noting that a normal cardiothoracic ratio does not preclude left ventricular dysfunction.

Trans-thoracic echocardiography (used here to include all Doppler technologies) is the most available, least invasive and most practical of all the imaging modalities used in the diagnosis and assessment of HF. Echocardiography permits the examination of both the structure and function of the heart and so may diagnose the underlying cause of the HF syndrome, for example, by assessment of valve, the pericardium and detection of any regional wall motion abnormalities. Echocardiography may also quantify severity by means of the LVEF, detection of any regional wall motion abnormalities and other parameters such as diastolic and systolic measurements. Left atrial dilation may be readily measured on echo and has been found to correlate with mortality in the context of HF (Rossi et al., 2009). Echocardiography may also detect abnormalities of diastolic filling or function in a patient with preserved systolic function but symptoms of heart failure. Echocardiography has the advantage of being free of radiation and relatively available (unlike other, more specialist modalities) but image quality may be impaired by obesity or tachycardia, the patient is required to change position to permit different views to be achieved and a skilled operator is necessary to acquire and interpret quality images. Trans-oesophageal echocardiography can be used when trans-thoracic echocardiography is impractical, impossible or insufficient; such as in the ventilated or obese patient or when a detailed assessment of valve structure and function is necessary. Echocardiography may also be used with exercise or dobutamine (“stress echo”) in order to assess ventricular function under conditions of potential stress induced ischaemia.

Computed tomography (CT) scanning provides a non-invasive alternative to coronary angiography for the visualisation of the coronary vasculature with the use of contrast. It provides evidence of coronary artery atherosclerosis and calcification, but, unlike radionucleotide perfusion scanning it does not

provide information regarding myocardial perfusion and viability. Computed tomography may also be used to non-invasively image the coronary vasculature (CT angiography).
Radionucleotide perfusion scanning is often combined with ventriculography and is useful in the assessment of possible coronary artery disease where its use may detect reversible ischaemia which may respond to revascularisation therapies.

Cardiac magnetic resonance imaging (CMR) is an evolving imaging modality which utilises a magnetic field to magnetise the hydrogen ions of which the body is principally composed and in this way obtain images of any tissue in the body. CMR is now considered the gold standard to assess myocardial structure, viability and function and as such may both assess HF severity as well as establish the underlying cause, and compared to echocardiography has better inter-study reproducibility for the assessment of dilated, hypertrophic and normal hearts (Grothues et al., 2002). The use of intravenous gadolinium-chelated contrast agents permits the identification of areas of infarct and fibrosis. CMR is useful for assessing the myocardium when an infiltrative process (such as amyloid, sarcoid or haemachromatosis) is suspected. CMR is not widely available and its use is limited in claustrophobic or orthopnoeic patients and precluded in morbidly obese patients and those with pacemakers or similar devices. Like CT, MRI may also be used to image the coronary anatomy (CMR angiography).

Invasive tests

Coronary angiography (or left heart catheterisation) allows both assessment of coronary patency with the use of contrast materials as well as interventions such as stenting of critically narrowed regions either acutely during an episode of acute coronary syndrome, or subsequently. In the context of HF such revascularisation may improve the function of viable myocardium and so improve cardiac function. LV ventriculography is often done concurrently and provides an estimation of LVEF as well as potentially revealing any regional wall motion abnormalities. While the significant risks of this procedure are extremely low (1 in 1000 risk of stroke, myocardial infarction or death) the volume of contrast given may upset the delicate fluid balance of some with HF as well as be potentially nephrotoxic.

Other investigations

Where the aetiology of HF is unknown, as discussed above, endomyocardial biopsy may be considered in a scenario where the result may alter management and where the potential benefit is thought to outweigh the risks, which include myocardial perforation and tamponade, tricuspid valve damage and

venous thromboemblic disease. Genetic testing may be considered in cases of dilated cardiomyopathy of unknown aetiology, of which a quarter may have familial disease.

Differential diagnoses

In approaching the diagnosis of HF an appreciation of the potential alternative diagnosis is essential, particularly given the age of the population in question. Table 1.3 gives a list of the key differential diagnoses to be considered in the evaluation of a patient with suspected heart failure.

Table 1.3: The differential diagnoses of heart failure

Other causes of dyspnoea

- chronic obstructive pulmonary disease or other chronic pulmonary disease
- pneumonia
- arrhythmia
- myocardial ischaemia

Other causes of fatigue

- depression
- physical deconditioning
- sleep disordered breathing

Other causes of peripheral oedema

- deep vein thrombosis
- drug side effects
- liver failure

1.1.7 Management of heart failure

The management of HF requires a multidisciplinary, multifaceted approach which reflects the complexity of the clinical syndrome. The aims of treatment are to improve symptoms, to reduce clinical worsenings (episodes of HF decompensation) and hospitalisations and to reduce morbidity and mortality. Establishing the underlying cause of the HF is an important part of management as this allows treatments and other interventions targeted at that disease entity; eg. revascularisation where appropriate in cases of HF due to coronary artery disease. A summary of the different components of management is given in figure 1.9.

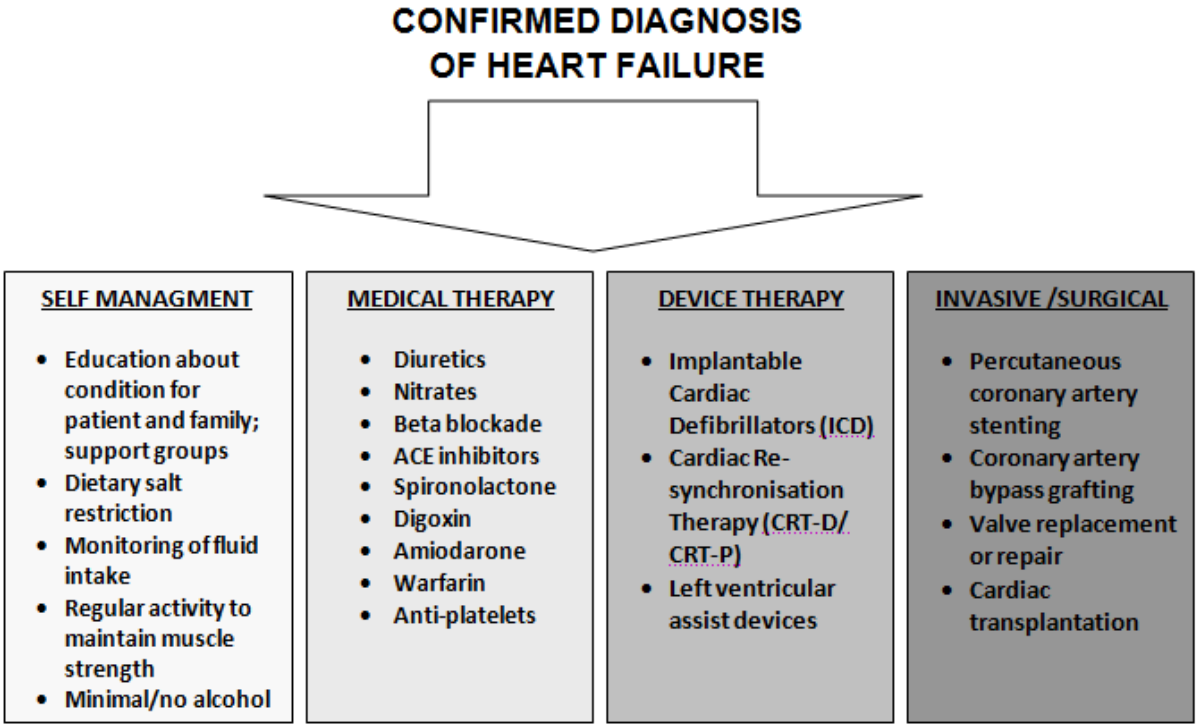


Figure 1.9: Summary of the management of the heart failure syndrome. (Original figure)
ACE- angiotensin converting enzyme; ICD- implantable cardioverter defibrillator; CRT D/P- cardiac resynchronisation therapy defibrillator/pacemaker.

Self management and non-pharmacological treatments

Self management is the cornerstone of non-pharmacological treatments and describes measures such as lifestyle modification, compliance with medication, self monitoring and timely contact with specialist services in event of clinical worsening. Lifestyle measures are important in addressing issues such as smoking cessation, reduction or cessation of alcohol intake, exercise, dietary changes to control salt intake and the maintenance of an appropriate body weight. Patient education, and that of partners and relatives, is of paramount importance in self management. Measures to improve self

efficacy, such as educational programs using group, individual or telephone based interventions, have been shown to benefit HF patients (Yehle and Plake, 2010, Du et al., 2012). Heart failure support groups are a means of improving patient education and allowing a regular interface with members of the multidisciplinary team. The development of a written, tailored plan for and with individual patients allows an increased or decreased diuretic dose to be taken within set boundaries in response to changes in weight, blood pressure or other agreed parameters, and also sets out criteria for seeking help. Home monitoring may be facilitated by novel approaches such as telemonitoring which have been shown to reduce emergency department and clinic visits, and re-admissions with HF (Dar et al., 2009) and in a meta analysis was also shown to reduce mortality without a reduction in patient quality of life or satisfaction (Polisena et al., 2010)

The management of HF is best undertaken by a multidisciplinary team approach including input from cardiologists, specialist nurses, dieticians, occupational therapists, physiotherapists, pharmacists and palliative care practitioners. The multidisciplinary approach has been associated with a mortality benefit (McAlister et al., 2004) and is of particular benefit in the management of advanced HF.

As well as education about HF itself patients should be advised, wherever possible, to avoid medications which may worsen their condition (such as non-steroidal anti-inflammatory drugs, systemic steroids) and also of the importance of vaccination (pneumococcal and annual influenza) in the community.

Pharmacological treatments and device therapy

Treatment of the underlying cause of HF may include anti-platelets, anti-anginals and, where possible, revascularisation in the case of coronary artery disease or tailored treatment of hypertension in others.

Many drug treatments both improve symptoms and have been shown to improve survival (diuretics, beta-blockers, ACE inhibitors, angiotensin II receptor blockers, aldosterone antagonists and the combination of hydralazine and a nitrate) while others, such as digoxin, have only symptomatic benefit. A full discussion of the pharmacotherapy of the HF syndrome is beyond the scope of this thesis but the key medication classes are given in table 1.4, along with their mode of action in relation to the pathophysiology discussed in section 1.1.5 and main side effects and benefits of their use.

Appropriate treatments must also be directed at conditions which may worsen HF of any cause, such as atrial fibrillation or other arrhythmia, venous thromboembolic disease, thyroid dysfunction, diabetes, anaemia and SDB (discussed later, see section 1.3). Conditions such as gout are common due to the combination of loop diuretics and renal impairment and prompt treatment (avoiding non-

steriodal analgesia where possible) followed by prophylaxis is important both for future compliance with diuretic treatment and patient quality of life.

Medications must be tailored to the patient; their severity of disease, fluid balance and response to treatment. It has been suggested ACE inhibitor use in female patients may not have the same survival benefit as their use in male patients; but there seems to be no gender difference associated with beta-blocker use (Shekelle et al., 2003). Ethnicity too determines response; black patients respond less well to ACE inhibitors and better to the combination of hydralazine and a nitrate than white patients (Exner et al., 2001, Carson et al., 1999), a finding common to the treatment of hypertension.

Implanted devices are an established part of the management of patients with HF, in whom conduction abnormalities are common and may be poorly tolerated due to a reduction in the physiological reserve of the heart, as discussed. The use of implantable cardioverter defibrillators (ICDs) is recommended for selected groups for the primary and secondary prevention of life threatening arrhythmias (Barnett, 2006). The use of cardiac resynchronisation therapy (CRT) is now also an integral part of HF management and these devices are discussed in section 1.7.6.

Left ventricular assist devices, valve surgery, coronary artery bypass grafting and cardiac transplantation are further treatment options for advanced HF in some patients. Palliation of symptoms is an important target and palliative care teams are increasingly part of the multidisciplinary team to assist in the management of dyspnoea and other disabling symptoms, as well as other issues around the end of life (Goodlin, 2009). The prognosis of HF is discussed in the next section.

Table 1.4: Summary of key medications used in the management of chronic heart failure.

Drug class and examples	Mode of action	Key side effects	Benefits
Loop diuretics eg. frusemide	Reduce fluid retention by inhibiting reabsorption from renal tubule (ascending loop of Henlé) and so reduce left ventricular end diastolic volume and so preload. Can be used synergistically with thiazide diuretics (eg. metolazone).	• hypovolaemia • hypotension • electrolyte imbalance • renal impairment • hearing impairment with high doses or rapid intravenous doses • hyperuricaemia and gout	• Reduction in risk of death • Reduction in risk of worsening HF • Improvement in exercise capacity (Faris et al., 2012)
Angiotensin receptor enzyme (ACE) inhibitor eg. ramipril, enalapril	Inhibit conversion of angiotensin I to angiotensin II and so reduce preload and afterload. May be used in addition to an ARB	• Hypotension • Renal impairment • Dry cough • Angioedema	• Improvement in survival (CONSENSUS trial study group, 1987, SOLVD investigators, 1991) • Reduction in hospitalisation (SOLVD investigators, 1991)
Angiotensin receptor blocker (ARB) eg. losartan	Block the angiotensin II receptor and so reduce preload and afterload. Unlike ACE inhibitors do not inhibit bradykinin breakdown therefore tend not to cause dry cough as a side effect.	• Hypotension	• Equivalent reduction in mortality to ACE inhibitor (captopril vs. losartan) (Konstam et al., 2005) • Reduction in combined endpoint of morbidity and mortality, reduction in hospitalisation with use of valsartan in addition to standard treatment (including ACE inhibitors) (Cohn and Tognoni, 2001) • Reduction in cardiovascular death and hospitalisation for CHF when candesartan used with an ACE inhibitor (Pfeffer et al., 2003)
Aldosterone antagonists eg. Spironolactone, eplerenone	Competitively antagonise aldosterone (therefore reduce preload and afterload). Augment the effect of thiazides and loop diuretics. Reduces adrenocortical biosynthesis of aldosterone.	• Hypotension • Hyperkalaemia • Gastro-intestinal disturbance • Gynacomastia (spironolactone)	• Reduction in mortality with spironolactone (Pitt et al., 1999) • Reduction in death and combined endpoint of death from cardiovascular cause or hospitalisation for cardiovascular events in patients post myocardial infarction (Pitt et al., 2003)

	Eplerenone is a selective aldosterone receptor antagonist which does not bind to hormone receptors.		
Beta blockers eg. bisoprolol	Competitively antagonise beta adrenoceptors and counter effect of adrenergic stimulation.	• Bradycardia • Hypotension • Worsening of peripheral vascular disease • Bronchospasm in some with chronic airways disease • Fatigue • Impotence	• Improvement in functional status with bisoprolol (CIBIS Investigators, 1994) • Reduction in hospitalisations due to worsening HF and all cause mortality (CIBIS Investigators, 1999) • Reduction in mortality due to both pump failure and sudden arrhythmic cardiac death (MERIT-HF Study group, 1999) with metoprolol • Reduction in all cause mortality, sudden cardiac death and hospitalisation with decompensated HF
Digoxin	Increases intracellular calcium resulting in increased myocardial contractility and so LV systolic function. Inhibits sympathetic outflow so attenuating effect of adrenergic overdrive. Augments parasympathetic tone and slows ventricular rate in AF.	• Nausea and vomiting • Diarrhoea • Xanthopsia (yellow vision- in toxic range) • Arrhythmias	• Improvement in clinical symptoms, quality of life (Digitalis Investigation group, 1997) • No effect on survival

ACE- angiotensin converting enzyme.

1.1.8 Prognosis of heart failure

Prognostication in HF, as with many chronic conditions, is an important part of management in that it allows appropriate and timely discussion of life expectancy with patients and their families. Patients with HF tend to be older and so comorbidities are common in this group and may affect the patient's prognosis. These may be the underlying cause of the HF itself (eg. diabetes, hypertension or ischaemic heart disease), a consequence of HF (eg. atrial fibrillation, depression), a result of the treatment of HF (eg. gout, renal impairment) or other related conditions (eg. SDB, anaemia). This section will first address the prognosis of HF patients, then the mode of death and finish by presenting information on prognostic scoring systems.

The prognosis of HF is poor; in the Hillingdon incidence study 38% of patients had died one year from diagnosis (Cowie et al., 1999). A study of over 6000 subjects in the UK reported a mortaility rate of 9% per annum (Hobbs et al., 2007). The development of new therapies, both pharmacological and device based, means that the prognosis of HF is improving (Mehta et al., 2009), however, it still compares unfavourably with many common malignancies, as shown in figure 1.10 (Petersen et al., 2002), despite its relatively low profile in the public eye as an important condition.

A comparison of survival between two cohorts of newly diagnosed patients with HF (1994-5 and 1995-7) employing analogous methodology, found mortality at 1, 3 and 6 months to be 16%, 22 and 26% respectively in the earlier cohort, but 6%, 11 and 14% in the later cohort (Mehta et al., 2009). The authors found the severity of HF at baseline to be comparable but found an increased use of neurohumoral antagonists in the later cohort.

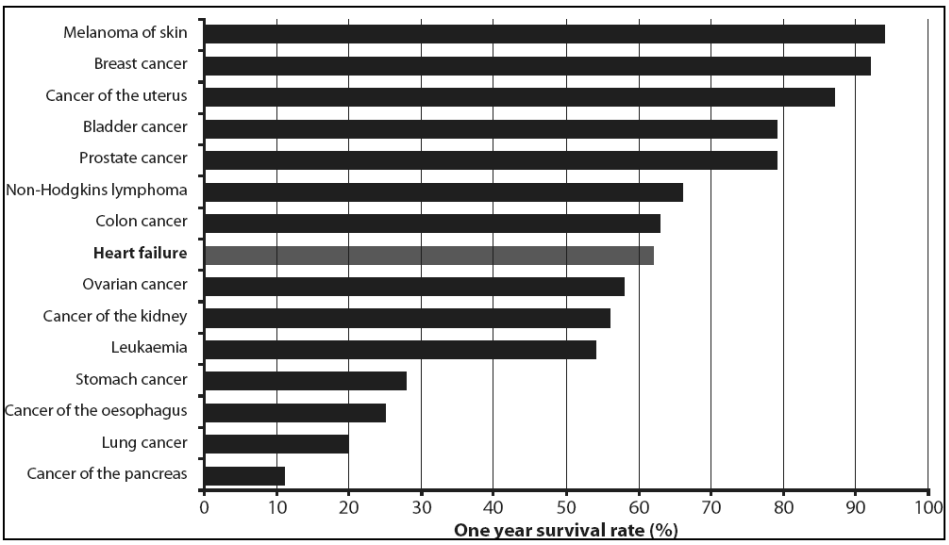


Figure 1.10: One year survival rates for HF compared with major cancers, mid 1990s, England and Wales (Petersen et al., 2002).

Estimating the number of deaths due to HF is difficult as guidance on death certificates unequivocally discourages doctors from assigning "heart failure" as the cause of death, instead listing the (sometimes presumed) underlying cause of the HF syndrome. A retrospective analysis of Scottish death certificates from 1979 to 1992 found that of 833,622 deaths only 1.5% had HF coded as the cause; however HF was coded as having been contributory in a further 14.3% of deaths (Murdoch et al., 1998). In the year 2000 just less than 10,000 deaths were attributed to HF. However, the British Heart Foundation (Petersen et al., 2002), using data from incidence studies (Cowie et al., 1999), believe the true figure to be at least 24,000 and so account for at least 5% of deaths in the UK.

In those newly diagnosed with HF in the general population 6 month mortality is 14% (Mehta et al., 2009) with 52% dying of progressive HF, 22% with sudden cardiac death (SCD), 12% dying another cardiovascular death and 14% dying a non-cardiovascular death (Mehta et al., 2008). Almost a third of patients hospitalised for HF will be readmitted to hospital within three months (Rich and Freedland, 1988).

HF patients may die from progressive pump failure, when a decision to palliate or escalate treatment may be more easily made, or from a life threatening arrhythmia which is less easy to predict. Pump failure is more common amongst those with a worse NYHA class while an arrhythmic death tends to be seen in those with less affected NYHA class.

Table 1.5 Risk factors for sudden cardiac death in HF (Lane et al., 2005)

- **NYHA**
- **Syncope**
- **Left ventricular systolic dysfunction**
- **QRS duration on ECG- a longer duration is associated with a higher risk**
- **Non-sustained ventricular tachycardia on holter monitor**
- **Natriuretic peptides- thought to have good negative predictive value for SCD**
- **Reduced heart rate variability (in the early period post MI)**

NYHA- New York Heart Association; ECG- electrocardiogram; SCD- sudden cardiac death; MI- myocardial infarction.

Approximately half of those with HF will die suddenly and of assumed "Sudden cardiac death" (SCD); generally thought to be the degeneration of monomorphic ventricular tachycardia (VT) to ventricular fibrillation (VF). It is for this reason that, in selected patients, ICDs are a cost effective way of reducing mortality (both primary and secondary prevention). Factors thought to contribute to the risk of SCD in HF patients are listed in table 1.5.

Strategies aimed at both the primary and secondary prevention of SCD in HF patients are now part of clinical guidelines (Mant, 2010) and take the form of pharmacotherapy (ACE inhibitors, beta blockers, aldosterone receptor antagonists and antiarrhythmics) and device therapy (ICDs and CRT devices).
A predictive model incorporating what is known about prognosis has obvious appeal both in terms of planning future clinical management (treatment escalation or symptom management) as well as supporting patients and their families with the best possible information on which to make decisions about their care. One such model is the Heart Failure Survival Score (HFSS) an American score devised to assess risk in ambulatory HF patients referred for consideration of cardiac transplantation (Aaronson et al., 1997). This score incorporates HF aetiology, systolic function, mean arterial pressure, heart rate, serum sodium concentration, a measure of interventricular conduction and peak VO_2, amongst others. Further work has found that measurement of peak oxygen uptake could be replaced by the 6MWT without affecting the prognostic accuracy of the model (Zugck et al., 2001). Interestingly however, the same authors found that the HFSS was inferior to a new model incorporating only LVEF and either peak VO_2 or the 6MWT, which has obvious advantages. A study from the Netherlands on a population enrolled in a randomised controlled trial found that diabetes mellitus, a history of renal dysfunction, NYHA functional class III or IV, lower body weight, lower blood pressure, ankle oedema and a higher score on the Minnesota "living with heart failure" questionnaire were all independent predictors of mortality (Bouvy et al., 2003). The use of beta blockers in the same model was associated with a better prognosis. More recently another prognostic model was constructed with 21 variables of which the most powerful were older age (>60 years), diabetes and LVEF (<45%) (Pocock et al., 2006).

Coupled with clinical judgement such models may assist the decision to directly involve palliative care specialists in the care of HF patients, which is increasingly recognised as an important part of the multidisciplinary team approach (Goodlin, 2009). Given the poor prognosis of this group and its heterogeneous nature with regards to aetiology, interventions which may improve prognosis may be less likely to be broadly applicable to the entire HF population. It is in this context that the understanding of SDB in HF has progressed and offers the possibility of a targeted intervention which it is hoped may improve prognosis in a sub-group of these patients.

1.1.9 Summary

In summary, chronic HF is a clinical syndrome of enormous economic and public health importance given its prevalence and prognosis. There is marked heterogeneity in its cause, classification and in research methodologies to investigate its epidemiology. Its identification in a patient should prompt a search for its underlying cause which, along with treatments aimed at improving symptoms, are a target of treatment. In health the heart has significant capacity to increase cardiac output in response to an increase in demand, for example, during exercise. In HF this capacity is reduced or lost as compensatory mechanisms are overwhelmed. The management of HF requires a multifaceted, multidisciplinary approach and at its centre is self management which encompasses patient education, compliance and lifestyle modification.

1.2 Sleep disordered breathing

The sleeping state presents the cardio-respiratory system with a unique physiological challenge due to the loss of the wakefulness drive, changes in the control of ventilation to the upper airway and pump muscles, as well as the mechanical difficulties of breathing in the supine position. The presence of cardio-respiratory disease, such as HF, may not only augment these physiological challenges, but also has implications for the clinical features of the resultant condition. Sleep disordered breathing, its classification, clinical features and treatment in a non-HF population will be described here.

1.2.1 The classification of sleep disordered breathing

Sleep Disordered Breathing is an umbrella term used to describe several separate conditions. It is traditionally classified into obstructive SDB (or obstructive sleep apnoea; OSA) and central SDB (or central sleep apnoea; CSA) however these two conditions share several pathophysiological features and might be better considered as a spectrum or continuum of disease rather than separate clinical entities.

Obstructive SDB is characterised by recurrent pharyngeal airway occlusion or narrowing during sleep in the presence of ongoing respiratory effort which causes apnoeas or hypopnoeas respectively. In contrast, central SDB is characterised by cessation of ventilatory effort during which airway patency is maintained (at least at the onset of the event). Figure 1.11 illustrates the key polygraphic features of an obstructive and a central apnoeic event. Central SDB is related to abnormalities in the control of ventilation and the term Cheyne-Stokes Respiration (CSR) is used to describe central SDB where there is a classical cycling crescendo-decrescendo pattern of ventilation, after the Scottish and Irish physicians who first described it in the 19th century.

The pathophysiological links between obstructive and central SDB are increasingly being appreciated and include the ventilatory instability seen in some patients with OSA (Wellman et al., 2004, Younes et al., 2001) and the airway closure seen at the termination of central events in some patients with CSA (Badr et al., 1995).

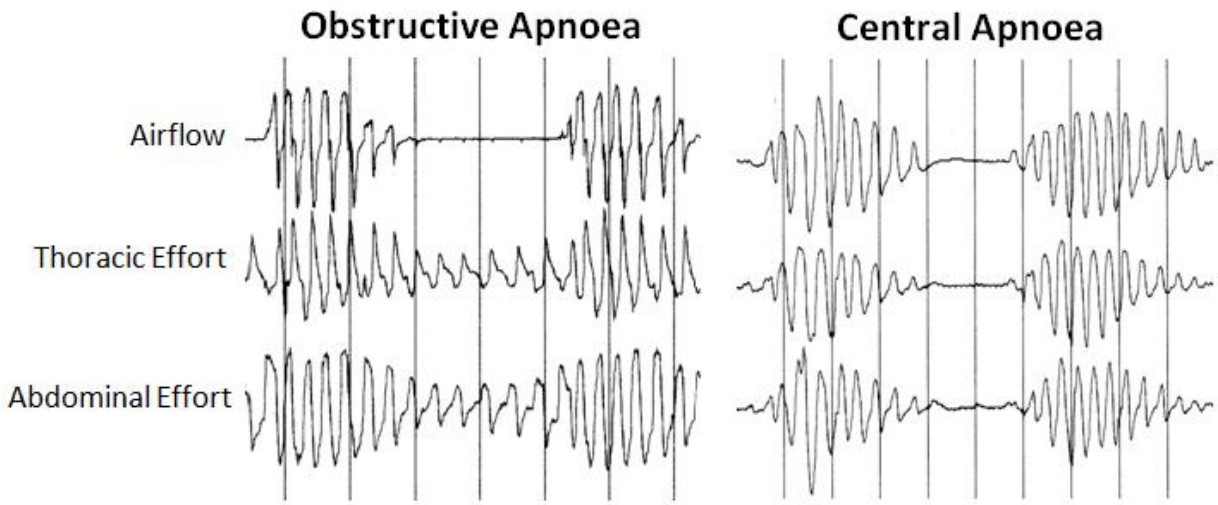


Figure 1.11: Features of obstructive and central apnoeas. (Vazir, 2005). Note absence of flow but the presence of ongoing thoracic and abdominal movement in the obstructive apnoea. In contrast note the absence of flow coupled with an absence of respiratory effort in the central apnoea.

1.2.2 Obstructive sleep disordered breathing

Obstructive SDB is prevalent in the general population with many cases remaining undiagnosed on account of the non-specific clinical features that patients may suffer from. Prevalence studies suggest that approximately 2% of women and 4% of men in western societies have SDB with hypersomnolence (Young et al., 1993). Obstructive SDB is most commonly associated with obesity and body mass index (BMI) has been positively associated with the severity of oxygen desaturations (Peppard et al., 2009). Less common causes of obstructive SDB include an anatomically susceptible airway such as those seen with retrognathia and micrognathia (Rachmiel et al., 2012); the effect of sedating drugs and the sequelae of some neurological conditions such as muscular dystrophies (Pincherle et al., 2012). Obstructive SDB may also occur in older people in the absence of these risk factors as airway compliance is thought to increase with age (Eikermann et al., 2007, Kostikas et al., 2006) although some work suggests this only occurs in males but not females (Huang et al., 1998). The difference in prevalence between the genders is incompletely understood. It seems likely there are hormonal influences involved as premenopausal women and postmenopausal women on HRT have a lower prevalence of obstructive SDB when compared to men (Bixler et al., 2001) suggesting that progesterone might be protective. This hypothesis is further supported by the observation that premenopausal women with obstructive SDB tend to have a higher BMI than a man of the same age (Redline et al., 1994).

Patients with obstructive SDB have repetitive narrowing or occlusion of the upper airway resulting in hypopnoeas and apnoeas respectively. These events tend to be more frequent whilst in the supine, rather than the lateral, position due to gravitational effects on the upper airway (Cartwright, 1984, Brown et al., 1987, Walsh et al., 2008). Each respiratory event is usually, but not always (Younes, 2003), terminated with an arousal from sleep which returns airway tone to waking levels and so increases airway calibre. During an apnoeic event, high levels of negative intrathoracic pressure result from airway occlusion in the face of ongoing respiratory effort. The resultant arousal is associated with a surge in blood pressure (BP) and adrenergic activity. Repeated over the night these events cause sleep fragmentation which the patient is often unaware of. Clinical presentation is often with marked daytime somnolence, difficulty concentrating at work, or apnoeas witnessed by a bed partner. Patients with undiagnosed obstructive SDB, or those not adequately treated, are at increased risk of road traffic accidents (Mulgrew et al., 2008) and driving simulation studies suggest that these skills are particularly impaired in scenarios when the view of the upcoming road is restricted (Juniper et al., 2000). Patients with undiagnosed or untreated obstructive SDB and have a significantly higher level of health care utilisation than age and gender matched controls (Kapur et al., 1999) due in part to the increased cardiovascular risk now recognised in this group (Shahar et al., 2001). Objective assessment of complex skills such as driving suggests that the effects of obstructive SDB are more akin to those seen in sleep deprivation than those seen due to alcohol intoxication (Hack et al., 2001).

The diagnosis is supported by a suggestive overnight oximetry trace (repetitive increases in heart rate with dips in oxygen saturations) in association with a compatible clinical history. However definitive evidence requires nocturnal polysomnography (PSG) or polygraphy (PG), although a suggestive history, and oximetry trace together with an improvement in both in response to treatment are acceptable in many departments. The Epworth score provides a numerical value with which to assess subjective sleepiness based on the self reported likelihood of dozing in eight different scenarios but this score is not diagnostic and does not correlate with the severity of OSA where it is present.

Treatment with Continuous Positive Airways Pressure (CPAP), a positive airways pressure device worn overnight, remains the gold standard for obstructive SDB but should be accompanied with measures to aid weight loss and improve sleep hygiene where necessary. Effective CPAP use has been shown to improve twenty-four hour mean BP (Pepperell et al., 2002); excessive daytime sleepiness, vigilance, cognitive performance, mood and self reported health status (Engleman et al., 1994, Jenkinson et al., 1999) as well as driving performance in a controlled study (Hack et al., 2000). Other interventions for obstructive SDB might be used in mild disease, or where CPAP is not tolerated and includes the use of

mandibular advancement splints (Lim et al., 2006) or measures to modify sleeping position to reduce supine respiratory events, where these predominate.

1.2.3 Central sleep disordered breathing

Central SDB is much less prevalent in the general population than obstructive SDB. It is seen in the rare genetic condition congenital central hypoventilation syndrome (previously called "Ondine's curse") which is characterised by abnormalities of the autonomic nervous system and severe hypoventilation with resultant hypercapnia and hypoxaemia in both wakefulness and sleep (Weese-Mayer et al., 1999). Central SDB is also seen in Idiopathic Central Sleep Apnoea (ICSA) , another rare condition, the exact prevalence of which remains unknown. An interventional study of a sleep centre population found a prevalence of 4.3% (DeBacker et al., 1995) amongst a group of 327 patients referred because of suspicion of a sleep-related breathing disorder, although the cardiac status of these patients was not known. It is characterised by recurrent central apnoeas and hypopnoeas during sleep in the absence of cardiac, neurological or respiratory disease. It is of interest in the context of HF patients in that patients with ICSA tend to be hypocapnic and have heightened chemosensitivity (Xie et al., 1994, Xie et al., 1995) when compared with healthy controls and as such provide a useful model of ventilatory instability with therapeutic implications (Xie et al., 1997). Central SDB in the context of patients with HF will be discussed in the sections which follow.

1.3 Sleep disordered breathing in patients with heart failure

Both SDB and HF are conditions increasingly prevalent in western societies (Young et al., 2009, Cowie et al., 1997) and both have several aetiologies in common, with obesity being the most notable link with western lifestyles. There are well established epidemiological links between obesity and HF (Kenchaiah et al., 2002) and hypertension and HF (McKee et al., 1971). As well as aetiological links, SDB and HF share pathophysiological links with both conditions causing sleep fragmentation and autonomic dysfunction in the form of sympathetic activation (Carlson et al., 1993, Leimbach et al., 1986). Figure 1.12shows a 15 minute epoch of respiratory PG (discussed in 2.6.2) from a patient with HF and central SDB.

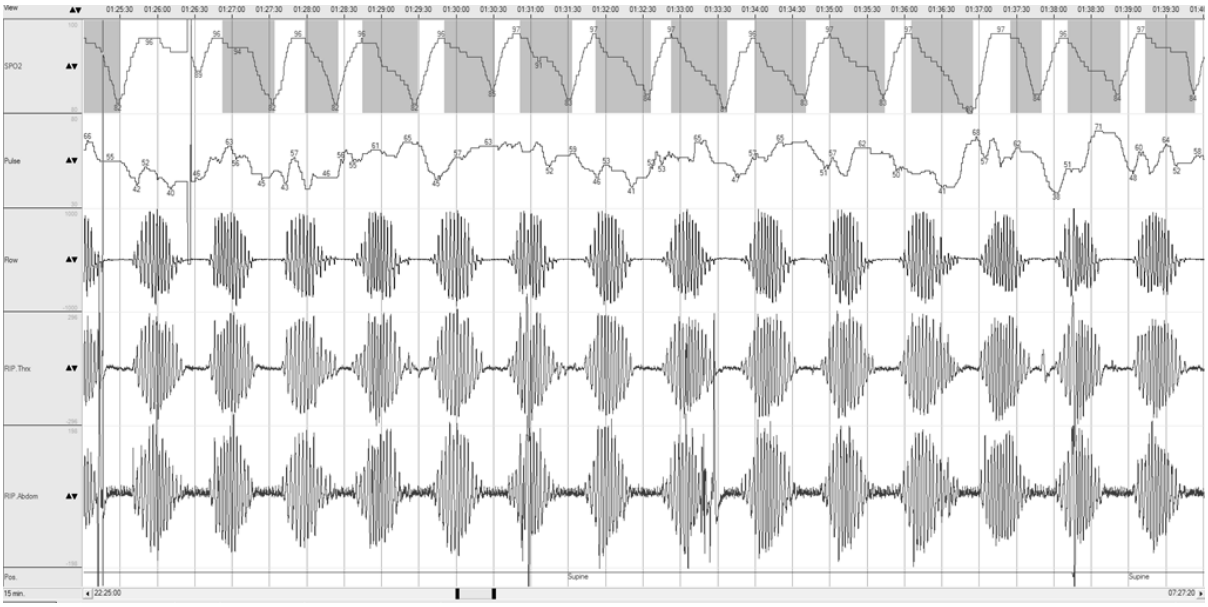


Figure 1.12: 15 minute epoch of respiratory polygraphy from a patient with HF and central SDB. The channels, from the top, are pulse oximetry, heart rate, flow (from nasal pressure), thoracic movement (effort band), abdominal movement (effort band) and position sensor. Recurrent desaturations are associated with a crescendo-decrescendo pattern of ventilation with recurrent central apnoeas (absent flow, absent effort) which is characteristic of Cheyne-Stokes respiration.

1.3.1 Prevalence of sleep disordered breathing in heart failure

The prevalence and type of SDB seen in HF patients has been the subject of much scrutiny and table 1.6 summarises some of the key prevalence studies in this area. All of these were prospective studies which investigated the prevalence of SDB (with a breakdown for SDB type) in stable patients with left ventricular systolic impairment and each studied only patients established on optimised medical treatment. It is noteworthy that the methodology of these studies varies in several ways but most importantly perhaps in the apnoea hypopnea index (AHI) cut-off used to define SDB; this is indicated on table 1.6 to allow comparison. The overall prevalence of SDB in patients with systolic HF is around 70% with around 40% of these having central SDB and between 20 and 40% having obstructive SDB. Prevalence studies which have specifically investigated SDB in patients with symptomatically mild HF have found a similar prevalence (Vazir et al., 2007). As well as differences in AHI cut-off the differences in the prevalence estimates in table 1.6 are likely to reflect differences in the population sampled, ie. severity of LV dysfunction. Yumino *al al.* (Yumino et al., 2009) looked at the change in prevalence of SDB between 1997 and 2004 and found no difference, despite the increased use of medications such as beta blockers, ACE inhibitors and angiotensin receptor blockers.

Table 1.7 gives details of prevalence studies looking at subgroups of HF patients. Most (Tremel et al., 1999, Padeletti et al., 2009), but not all (Khayat et al., 2009), studies looking at the prevalence of SDB in those admitted with decompensated HF found more central than obstructive SDB than in a stable population as well as a low rate of resolution of SDB after medical treatment. In those patients awaiting cardiac transplantation there was also more central than obstructive SDB (Lofaso et al., 1994, Villa et al., 2003) and SDB remains prevalent when patients with HF but a preserved LVEF are studied (Chan et al., 1997, Bitter et al., 2009, Herrscher et al., 2011).

Table 1.6: Prevalence of SDB in HF populations with stable left ventricular systolic impairment on optimised medical treatment.

Author	Country	Sample size	Population	Type of study	AHI criteria	Prevalence (%) *		
						Total SDB	Obstructive	Central
Ferrier (Ferrier et al., 2005)	New Zealand	53	Mean age 60.1 yrs, males 77% LVEF 34±8.5 %	PSG	>10	**68**	**53**	**15**
Javaheri (Javaheri, 2006b)	USA	100	Mean age 64 yrs , males 100% , mean LVEF 24%	PSG	>15	**49**	**37**	**12**
Zhao (Zhao et al., 2007)	China	126	Males 81%, mean age 56 yrs NYHA II-IV	PSG	≥10	**71**	**25**	**46**
Schulz (Schulz et al., 2007)	Germany	203	Mean age 65.3 ± 1.1, males 75% NYHA II (55%), III (45%) Mean LVEF 28± 1 %	PG	>10	**71**	**43**	**28**
Oldenburg (Oldenburg et al., 2007d)	Germany	700	Mean age 64.5±10.4yrs, males 80% Mean NYHA 2.7±0.5 Mean LVEF 28.3±6.8 %	PG	>5	**76**	**36**	**40**
Vazir (Vazir et al., 2007)	UK	55	Mean age61±12, males 100% NYHA II, mean LVEF 60.6±10.1	PSG	>15	**53**	**15**	**38**
MacDonald (MacDonald et al., 2008)	USA	108	Mean age 57.5 yrs, males 85% LVEF 20 (15-30) %, NYHA II-IV	PG	≥15	**61**	**30**	**31**
Paulino (Paulino et al., 2009)	France	316	Median age 59±13 yrs, Males 83% Mean LVEF 30±11%, NYHA 2.5±0.8	PG	≥10	**81**	**56**	**25**
Yumino (Yumino et al., 2009)	Canada	218	Mean age 55.6±12.7 yrs, males 77% Mean LVEF 24.7±10.0%, NYHA class II-IV	PSG	≥15	**47**	**26**	**21**

LVEF- left ventricular ejection fraction; NYHA- New York Heart Association functional class; PSG- polysomnography; PG- polygraphy. *percentages given are of total sample.

Table 1.7: Prevalence of SDB in different populations of patients with heart failure.

Author	Country	Sample size	Population	Type of study	AHI criteria	Prevalence (%)*		
						Total SDB	Obstructive	Central
Tremel (Tremel et al., 1999)	France	34	**Within 1 month of acute pulmonary oedema** Mean age 69 ±9 yrs, males 82% LVEF 30 ±10 %, NYHA IV	PSG	>15	**83**	**21**	**62**
Padeletti (Padeletti et al., 2009)	USA	29	**Studies done within 48hrs of admission with acute decompensated HF** Mean age 57 ±17 yrs, males 62% LVEF20 ±5.6 %, NYHA III/IV	PSG	>15	**97**	**0**	**97**
Khayat (Khayat et al., 2009)	USA	395	**Studies done during admission with acute decompensated HF** Mean age 59 ±0.7yrs, males 62% LVEF 33±0.9 %	PSG	≥15	**75**	**57**	**18**
Lofaso (Lofaso et al., 1994)	France	20	**Outpatients awaiting cardiac transplant** Mean age 50 yrs, males 85% Mean LVEF 12.5%	PSG	>10	**45**	**5**	**40**
Villa (Villa et al., 2003)	-	14	**Outpatients awaiting cardiac transplant** Mean age54 yrs, males 100% Mean LVEF 26.7 %	PSG	>10	**21**	**0**	**21**
Chan (Chan et al., 1997)	Hong Kong	20	**Stable symptomatic patients with diastolic** HF **on echo** Mean age 65 ±6 yrs, males 35%	PSG	>10	**55**	**35**	**20**
Bitter (Bitter et al., 2009)	Germany	244	**Stable symptomatic outpatients with HF with Normal Ejection Fraction (HFNEF**). Mean age 65.3 ±1.4 yrs, males 64%	PG	>5	**70**	**40**	**30**
Herrscher (Herrscher et al., 2011)	Norway	44	Stable HF patients with normal EF Mean age 62.8 ±10 yrs, males 70% mean LVEF 51.7±5.2 %, NYHA II-IV	PG	>5	**80**	**62**	**18**

LVEF- left ventricular ejection fraction; NYHA- New York Heart Association functional class; PSG- polysomnography; PG- polygraphy. *percentages given are of total sample.

1.3.2 Variability in severity and type of sleep disordered breathing

Of those HF patients who do have SDB there may be variability in the severity and type of SDB both between nights (Tkacova et al., 2006, Vazir et al., 2008b) and within the same night (Tkacova et al., 2001). Furthermore, some may only exhibit SDB at the time of HF decompensation but not at other times (Tremel et al., 1999, Padeletti et al., 2009). This variability of SDB type and severity within the HF population affords us an understanding of how the underlying spectrum of pathophysiology manifests in a range of clinical phenotypes. The emergence of SDB in a HF patient represents the net effect of a combination of pre-morbid factors (gender, age, genetic influence on chemosensitivity, upper airway anatomy and compliance, body mass index) and disease related factors (cardiac output, circulation time, pulmonary capillary wedge pressure- PCWP). These predisposing factors can be thought of as each contributing to the likelihood of SDB in any one patient, whereas individually they may be insufficient to cause it. These factors are also dynamic and the prevailing type of SDB will depend on the relative contribution of each at a point in time. HF patients studied over a number of years in our institution have shown progression of SDB severity as cardiac function has deteriorated, in keeping with the underlying pathophysiology and the current literature (Javaheri, 2006b, Lanfranchi et al., 1999). As well as being dynamic over time, SDB in HF patients is subject to within night change (Tkacova et al., 2001) which has also been related to an overnight deterioration in cardiac function. Tkacova and co-workers (Tkacova et al., 2001) found a shift in SDB type from predominantly obstructive in the first quartile of the night to predominantly central in the last quartile in association with a reduction in transcutaneous carbon dioxide (CO_2) levels and a concomitant increase in circulation time. The same group found that a subgroup of HF patients had more variability in SDB type over a number of months compared to others (Tkacova et al., 2006). The patient group exhibiting SDB type instability had more marked hypocapnia and longer CSR cycle lengths on nights where central SDB predominated, compared to nights where obstructive SDB predominated. Sleeping position has also been implicated as a cause of within night variability. Szollosi *et al.* found that the lateral position attenuated both event related desaturations (independent of apnoea type) and the AHI in all stages of sleep (Szollosi et al., 2006b).

Similar phenotypes exist in patients classified as having clinically significant obstructive SDB (OSA) but no HF; Wellman and co-workers have reported on such a group and found that ventilatory instability (as measured by loop gain) and upper airway susceptibility (as measured by the critical closing pressure; Pcrit) contributed to a variable degree. In those with a more collapsible airway the correlation between loop gain and AHI was poor, however in those with intermediate near atmospheric Pcrit levels there was a strong correlation between AHI and loop gain (Wellman et al.,

2004). These data suggest that in patients with sleep apnoea syndrome and with an upper airway which is of intermediate susceptibility, ventilatory instability is more likely to play a role.

An understanding of the pathophysiology which contributes to clinical phenotypes of SDB in HF, how these vary between patients and over time, and how they might be modified is likely to have treatment implications in the future. The control of ventilation will be further discussed in section 5.

1.3.3 Summary

Sleep disordered breathing in patients with HF is more prevalent that that seen in the non-HF population and is the result of a diverse range of pathophysiology resulting in a spectrum of disease; some patients have predominantly central SDB, others predominantly obstructive. As well as these differences, the symptomatology of the condition in the HF population is also distinct from that of the non-HF population and this will be addressed in the next section.

1.4 Symptoms of sleep disordered breathing in heart failure

Symptoms in a patient with a diagnosis of SDB and HF may represent any one of a number of factors making it difficult to ascribe specific symptoms to specific pathologies. Firstly these patients have symptoms related to their underlying HF, many of which may overlap with those of SDB. Secondly the symptoms of SDB in HF patients are not typical of those seen in the non-HF population and the potential reasons for this (considered below) include the effect of the HF syndrome itself (which may attenuate subjective sleepiness) as well as lifestyle modifications which may mask some symptoms. Thirdly, in the developed world, the typical HF patient is older and age itself brings with it a gamut of changes to sleep, and daytime activity, which affect the genders differently. Finally, as discussed, the entity of SDB in the HF population is by no means homogeneous and there are differences in clinical characteristics and symptoms between those with predominantly obstructive versus central SDB.
It is noteworthy that the diagnoses of HF and SDB share not only symptoms in common, but also some aspects of pathophysiology; both are associated with heightened sympathetic nerve activity (SNA) and it is possible this contributes to the clinical symptoms, or lack thereof (see section 1.4.5).

The clinical significance of symptomatology in this population relates primarily to the need to identify HF patients with underlying SDB, although its prognostic significance remains unknown. The absence of typical symptoms of SDB presents a diagnostic challenge, as investigation in the non-HF population is often prompted by the presence of subjective sleepiness, snoring and allied symptoms.

Symptoms in the HF patient with predominantly obstructive SDB (or OSA) more closely echo those of the non-HF patient with OSA; they are more often overweight with a large neck circumferences and more likely to snore than their counterparts with predominantly central SDB (or CSA) (Javaheri, 2006b). Those with HF and predominantly central SDB tend to be older (Sin et al., 1999, Vazir et al., 2007) with more severely impaired LVEF, higher BNP (Oldenburg et al., 2007d, Ferrier et al., 2005, Javaheri, 2006b, Paulino et al., 2009), worse reported symptoms on SF-36 questionnaire (Vazir et al., 2007), shorter distance walked during the 6 minute walk test (Oldenburg et al., 2007c), lower resting CO_2 levels (Sin et al., 1999, Tremel et al., 1999) and higher apnoea hypopnoea and oxygen desaturation indices (Ferrier et al., 2005, Paulino et al., 2009). They are also more likely to have left atrial dilatation and atrial fibrillation (Sin et al., 1999, Ferrier et al., 2005, Javaheri, 2006b).

1.4.1 The effect of ageing on sleep, sleepiness and daytime activity

Any discussion of the effect of the HF on sleep and daytime activity is best preceded by reflection on the effect of ageing itself, as HF is predominantly a condition of later years. The process of aging alone involves physiological changes in sleep architecture at a time when there is a concomitant increase in the prevalence of both primary sleep disorders (such as restless legs syndrome and SDB) and co-morbidities which may result in sleep dysfunction by other means. Sleep dysfunction in older adults is common. They may report difficultly initiating or maintaining sleep (35-40%) or trouble falling asleep with early wakening (23-34%) (Foley et al., 1995). The presence of respiratory symptoms, physical disabilities, over the counter medications, features of depression and poorer perceived health have all been associated with sleep dysfunction (Foley et al., 1995), suggesting that factors other than age itself may be causal. Increasing age in men is associated with more light stage 1 and 2 sleep and less deep stage 3 and 4 sleep; the reduction in deep sleep is much less prominent in women and both genders have a modest reduction in rapid eye movement (REM) sleep and an increase in arousal index with ageing (Redline et al., 2004).

The prevalence of periodic leg movements (PLM), without daytime symptoms of the restless legs syndrome (RLS), increases with age (Pennestri et al., 2006). Similarly, the prevalence of the RLS increases with age, being higher in females than males in all age groups; it often remains undiagnosed and untreated (Allen et al., 2005) and so may contribute to sleep disruption in older age groups. When associated with the RLS the presence of PLM at night are associated with more cortical arousals and greater fluctuations in BP in older compared to younger subjects (Pennestri et al., 2007).

A study by Davies *et al.* used movement sensors on the wrists and ankles of HF patients and age matched controls and found them to be lower in the patients. Furthermore there was no difference between the older controls and a group of 20 younger subjects (Davies et al., 1992).

The measurement of subjective sleepiness is not straightforward and is influenced by many different factors including sleep perception which may relate more to sleep latency and the time spent awake after initial sleep onset, than the total time spent asleep. Outlook on life and mindset have been linked to sleep quality; older subjects with higher morale and self confidence had shorter sleep latencies and were less active during the night and in naps than those with lower self confidence and morale although there was no difference in daytime activity levels, sleep duration nor the number of naps taken between the two groups (Shirota et al., 1999).

1.4.2 The effect of heart failure on sleep and daytime activity

Previous work has shown both that HF patients with SDB are no more sleepy than those with HF alone (Hastings et al., 2006) and that HF patients with obstructive SDB are *less* sleepy than community dwelling subjects with obstructive SDB but without HF (Arzt et al., 2006). This latter study found that when the groups were matched for OSA severity, those with HF were significantly less sleepy than those without HF, even when the AHI was <5 (ie. no SDB).

Sleep disruption is common in patients with HF and may be related to the disease itself, medications, anxiety and depression or associated SDB. Sleepiness in HF patients has been associated with medication non-adherence (Riegel et al., 2011b). A questionnaire based survey of 201 HF patients attending a tertiary care clinic found that the presence of paroxysmal nocturnal dyspnoea was associated with complaints of insomnia and sleepiness in both genders; 10% of participants admitted to having fallen asleep at the wheel of a car (Principe-Rodriguez et al., 2005).

A cross-sectional observational study (Riegel et al., 2011a) which used the Pittsburgh Sleep Quality Index (PSQI) in 266 HF patients to identify potentially modifiable factors found that SDB was not a significant determinant of self reported sleep dysfunction, a finding that is in keeping with the objective findings of Artz *et al.* and Hastings *et al.* Redeker *et al.* used 3 days of actigraphy and domiciliary PSG in 170 patients with HF and found worse self reported physical function in the most severe quartile of SDB (classified by AHI) (Redeker et al., 2010). They found neither LVEF nor NYHA to be associated with SDB severity and also that those with central SDB had lower durations of daytime activity than those without SDB. The effect of SDB on daytime activity and subjective sleepiness is considered further in chapter 6.

Lower levels of physical activity in HF (assessed by pedometer) have been associated with death (Walsh et al., 1997) along with cardiac output and NYHA whilst more conventional symptom limited exercise testing was not. Davies *et al.* used movement sensors on the wrists and ankles of 30 patients with HF, and 20 age matched controls and found mean 24 hour activity levels were lower in those with HF (Davies et al., 1992) although the presence of SDB in this group was not ascertained. A prevalence study of 700 patients with HF found peak VO_2 on cardiopulmonary exercise testing and distance walked during the 6 minute walk test to be lower in those HF patients with central SDB, compared to obstructive SDB or no SDB (Oldenburg et al., 2007c).

Factors other than SDB have been associated with sleep disruption in the HF population, although direct causal links are less clear. Redeker and Hilkert (Redeker and Hilkert, 2005) used actigraphy in 61 patients with HF and found a positive relationship between NYHA functional class and sleep quality assessed using the PSQI. They also found that TIB was negatively associated with physical function (assessed by NYHA and daytime activity) and that sleep latency was negatively associated with physical function. Witham *et al.* found that age and NYHA, as well as psychological and attitudinal factors played a role in explaining distance covered in the 6MWT (Witham et al., 2006). Brostrom *et al.* (Brostrom et al., 2001) interviewed 20 patients with HF and found that worries about heart failure, problems in daily life and cardiac symptoms all disturb sleep in HF patients.

Periodic leg movements are common in patients with chronic HF (Hanly and Zuberi-Khokhar, 1996, Skomro et al., 2009, Yumino et al., 2011) and a periodic leg movement index of over 5/hour has been associated with increasing age, more severe HF (assessed by LVEF and NYHA functional class) and worse mortality, even after adjustment for potential confounders (Yumino et al., 2011). Hanly *et al.* found that those with a higher periodic leg index (>10/hr) spent more time in lighter stages 1 and 2 sleep and were more objectively sleepy than those with a lower index (<10) (Hanly and Zuberi-Khokhar, 1996). Interestingly, the presence of periodic leg movements in a group of patients with HF, was not associated with an increase in subjective sleepiness, compared to a group without them (Skomro et al., 2009). Case reports suggest that periodic leg movements improve after implantation of a cardiac resynchronisation device (Shalaby et al., 2005) and cardiac transplantation (Hanly and Zuberi, 1992).

1.4.3 The effect of sleep on the failing heart

The sleeping state can be considered a physiological stress on the failing heart; the horizontal position may place a greater load on the heart by increasing central venous pressure, the atonia associated with REM increases the work of breathing in a position which is mechanically unfavourable for breathing and there are changes in the control of ventilation affecting the drive to the upper airway and pump muscles. The supine position is well known to be associated with more severe obstructive SDB in those without HF (Cartwright, 1984, Oksenberg et al., 2000) which can be explained by gravitational effects on the upper airway. In contrast the left lateral position has been observed to be poorly tolerated during sleep in some HF patients (Wood, 1959, Wood, 1937). A study using heart rate variability found the right lateral position was associated with lower SNA compared with the left (Miyamoto et al., 2001) whilst another found patients with chronic HF spent less time in the left lateral

position (compared to the right) and that this was related to the severity of HF (Leung et al., 2003). Szollosi *et al.* found that the severity of central SDB is attenuated during sleep in the lateral (rather than supine) position (Szollosi et al., 2006b) although the mechanism for this is unclear but seems likely to relate to the role of plant gain (see section 1.6.2). Interpreting these data together it is difficult to draw conclusions about the relative effect of the supine position on SNA. Sympathetic nerve activity is discussed below in the context of subjective sleepiness.

1.4.4 Subjective and objective sleepiness in patients with HF and SDB

Hastings *et al.* measured objective sleepiness using the Oxford Sleep Resistance Test (OSLER; Stowood Scientific Instruments, Oxford, UK) and found that whilst those with HF and SDB were no more subjectively sleepy than those with HF alone, they were significantly more objectively sleepy. Similarly Hanly and Zuberi-Khokhar used the multiple sleep latency test in a group of controls alongside 2 HF groups; one with central SDB and one without. They found a shorter sleep latency in those with HF and central SDB compared to both of the other groups (Hanly and Zuberi-Khokhar, 1995). Objective sleepiness was measured by Pepperell *et al.* as part of a randomised controlled trial of ASV in a group of patients with HF and central SDB (Pepperell et al., 2003). Those authors found a reduction in objective sleepiness, using the OSLER test, with the suppression of SDB by ASV and also found that, like the current study, their patient group (n=30) had a mean ESS which was less than 11. Taken together these data suggest that while SDB may not be associated with subjective sleepiness, it may cause objective sleepiness which is improved with effective treatment of SDB. It is possible that objective sleepiness relates more to the presence of SDB (and improves with its suppression) and that subjective sleepiness relates more to the effect of the HF syndrome. It has been suggested that heightened sympathetic activation seen in HF may explain the lack of subjective sleepiness but this mechanism (discussed in the next section) does not explain the mismatch between objective and subjective sleepiness.

1.4.5 Sympathetic nerve activity and subjective sleepiness

HF patients have heightened SNA (discussed in section 1.1.5) which correlates with mortality (Cohn et al., 1984), and is an ultimately maladaptive physiological response to the failing heart and so is the target of much treatment for heart failure. Measures of SNA are also elevated in patients with obstructive SDB and normal hearts, both overnight and in the daytime (Carlson et al., 1993, Somers et al., 1995) and these levels fall after treatment with CPAP (Somers et al., 1995).

Work investigating SDB in the HF population has found similar elevations in urinary catecholamines (Rao et al., 2006). This might be expected given the effects of arousals from sleep, apnoeic episodes, hypoxia and hypercapnia. Overnight studies have found that in patients with HF and central SDB, SNA is highest in the second half of an apnoea when hypoxia is worst, and that SNA falls during periods of normal breathing (van de Borne et al., 1998). In keeping with this, arousals due to apnoeas and hypoxia correlate with overnight urinary noradrenaline and the same authors found that SNA levels are higher in those HF patients with central SDB compared to those without, even when the LVEF is similar (Naughton et al., 1995a).

As with non-HF patients with obstructive SDB, those with HF and central SDB have elevated overnight urinary and daytime plasma catecholamines (Naughton et al., 1995a) suggesting either a spill over effect of nocturnal disordered breathing and/or an additional mechanism present during waking hours. In support of this are data showing that while HF patients with central SDB have higher cardiac specific markers of SNA than those with HF and obstructive SDB and HF patients without SDB (between whom there was no difference), this difference was not found when the data was controlled for markers of cardiac dysfunction (PCWP and cardiac index). This suggests that elevated SNA in HF patients with central SDB relates to HF severity, rather than entirely to nocturnal disturbances of breathing (Mansfield et al., 2003). Another study from the same group (Solin et al., 2003) in HF patients with obstructive and central SDB found the factors which most influenced urinary catecholamines were PCWP, percentage of REM sleep and mean overnight oxygen saturations, rather than markers of SDB severity per se. Contrary to this, Spaak *et al.* (Spaak et al., 2005) found that waking muscle SNA was higher in HF-CSA patients than HF-OSA patients, and relatively lower in HF patients without SDB; findings which they related to the severity of the underlying SDB rather than the severity of the underling HF. When central SDB is suppressed with positive airways pressure markers of SNA fall (Naughton et al., 1995a, Pepperell et al., 2003) although such devices are known to improve LVEF as well as suppress SDB (Hastings et al., 2008, Philippe et al., 2006).

Heightened SNA may be the mechanism explaining the observation that HF patients with SDB do not report sleepiness. Montemurro *et al.* found an inverse relationship between subjective sleepiness and muscle SNA in 27 patients with HF-OSA suggesting that the heightened SNA has an alerting effect which compensates for the effects of SDB (Montemurro et al., 2012). It is difficult to reconcile these findings with those of previous authors who have reported that that these patients are more objectively sleepy, even if not complaining of subjective sleepiness (Hastings et al., 2006, Pepperell et al., 2003). The effect of HF and SDB on subjective sleepiness is considered further in chapter 6.

1.5 Breathing during sleep in healthy subjects

Breathing during sleep is vulnerable to instability, even in health, for a number of reasons. Understanding the manner in which breathing overnight is controlled and the reasons why breathing remains, despite these vulnerabilities, stable, is helpful in our understanding of what goes wrong in disease and specifically the pathophysiology of SDB in patients with HF.

1.5.1 Changes in breathing during sleep

During wakefulness breathing is under the control of a number of factors, including volitional factors (emotional and behavioural) and the so called "wakefulness drive" described by Fink and others (Fink, 1961, Orem, 1990). Such contributions are lost at sleep onset and there are a characteristic set of changes in breathing with the transition from wake to non-REM (NREM) sleep which include a reduction in minute ventilation as the electroencephalogram frequency slows (Trinder et al., 1997). Tidal volume falls but there is little change in respiratory rate. The resultant rise in CO_2 levels rise does not precipitate an increase in ventilation due to the changes in chemosensitivity occurring at sleep onset (Douglas et al., 1982b) and so sleep is a time of permissive hypercapnia and a dampened ventilatory response to CO_2. The deepest stages of NREM sleep are associated with a reduction in oxygen levels which, like those of CO_2, do not increase ventilation due to the concomitant reduction in the hypoxic ventilatory response with sleep (Douglas et al., 1982a). Both the hypoxic and the hypercapnic ventilatory responses fall with the depth of sleep and are at their lowest in REM sleep (Douglas et al., 1982b, Douglas et al., 1982a). Sleep onset and the transition between sleep stages may precipitate ventilatory instability (Thomson et al., 2005).

1.5.2 The effect of sleep on the upper airway

During wakefulness upper airway patency is maintained, despite the negative pressure caused by the diaphragm, by a combination of factors. Activation of the genioglossus muscle, a key dilator muscle of the upper airway increases in response to negative pressure in the airway (Mathew et al., 1982), respiratory neurons in the medulla (which increase its activation just before that of the diaphragm) (van Lunteren, 1993) and neurons responsible for varying levels of arousal (the so called "wakefulness drive") (Fogel et al., 2003, Orem, 1990, Fink, 1961). All 3 of these activating mechanisms are reduced or lost in sleep. Furthermore the supine position has gravitational effects on the upper airway such that the soft tissues of the palate and tongue are displaced posteriorly so reducing airway cross sectional area (Brown et al., 1987). The supine position also affects the caudal traction on the upper airway present in the upright position (Van de Graaff, 1988, Burger et al., 1992). In health these

factors tend not to result in clinically significant narrowing or occlusion of the upper airway, although upper airway resistance does increase (Hudgel et al., 1988), but in situations of obesity or an anatomically unfavourable upper airway the ability of the compensatory mechanisms are overwhelmed and airway patency is compromised resulting in SDB.

1.5.3 The apnoeic threshold

With the loss of the wakefulness drive and cortical inputs, breathing during sleep becomes dependant on CO_2 levels and their reduction below a critical level, (Skatrud and Dempsey, 1983, Dempsey and Skatrud, 1986) known as the hypocapnic apnoeic threshold, will cause an apnoea until levels have risen above that threshold again. This apnoeic threshold has been measured in healthy controls using NIV to artificially reduce CO_2 levels and precipitate an apnoea at levels of 3-6mmHg below NREM levels and 1-2mmHg below waking eucapnea (Skatrud and Dempsey, 1983).

1.5.4 The model of loop gain

The ventilatory system may be usefully conceptualised as a feedback system where a controller compares the system's sensed output against a reference output and amplifies the error signal such that the system's output is brought closer to the reference output, as illustrated in figure 1.13.

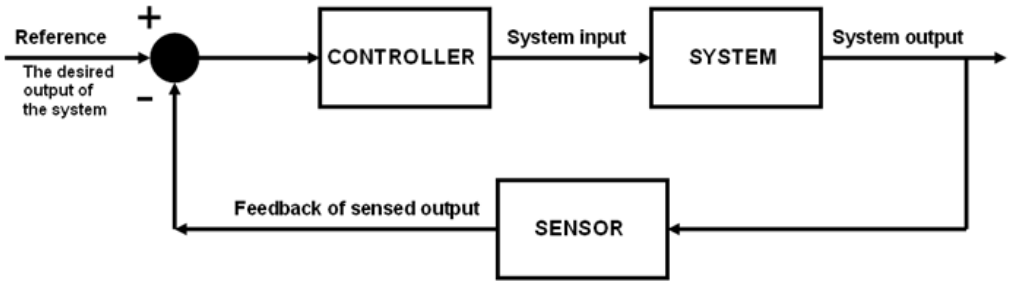


Figure 1.13: A basic feedback loop. Figure adapted from Wikipedia.org./wiki/Control_theory last accessed 19th August 2012. (Wikipedia., 2012)

As with all feedback systems a high level of sensitivity carries a risk of instability, whereas a low or blunted sensitivity may leave a system unable to respond adequately or appropriately. The sensitivity of the system could be considered the way it responds to a disturbance. A rapid and accurate response indicates a system which is both sensitive and does not produce a response out of proportion to the disturbance. An oversensitive system (high gain) responds to a disturbance with a response which is out of proportion (greater than) the disturbance itself and so the system output overshoots and oscillates between an output which is above and then below the desired, reference output. This

theoretical system would be liable to instability as the feedback loop magnifies the initial insult. Conversely, if the system responds to the initial perturbation with a response which is *smaller* in magnitude then the effect of the initial insult is "dampened out", without any system overshoot. This model is known as loop gain and has its origins in Control Theory, a subfield of science with its roots in mathematics and engineering and which historically was pivotal in realising the first manned aircraft flight in the early 1900s.

In the control of ventilation the chemoreceptors, most notably the central (medullary) chemoreceptors, take the role of controller, the system is the lung, or plant, and the signal is fed back by the circulation, as illustrated in figure 1.14.

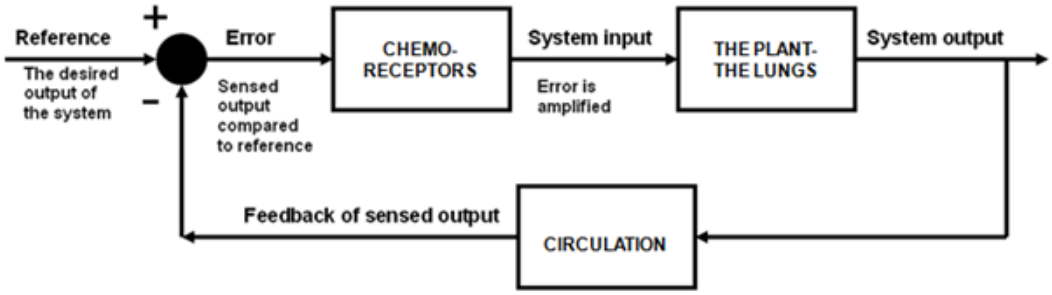


Figure 1.14: Ventilatory control conceptualised as a feedback loop.

The overall stability, or gain, of the system is defined by the ratio of a system's response to a disturbance to the magnitude of the disturbance itself (ie. how sensitive the system is). In terms of ventilation we can define this as the change in ventilation in response to a disturbance, divided by the disturbance itself. In ventilation a disturbance would be an event such as an apnoea or hyperpnoea. The components of the loop (controller, plant and feedback) each contribute to the response of the system and loop gain can therefore be considered as the product of the controller, plant and feedback gains. The more sensitive the system the more likely it will produce a response which is out of proportion to the disturbance, and so initiate instability.

Loop gain may therefore be quantified numerically as the ratio between the system response to the perturbation, and the perturbation itself. It follows that a loop gain over 1 describes a system where the response is greater than the insult and so is prone to instability. A loop gain of less than 1 describes a system where an insult will be dampened or smoothed out by a response smaller than the insult itself. This is illustrated in the 2 panels in figure 1.15 (White, 2005) in which the first panel is a

pictorial representation of a stable system (loop gain<1) and the second panel an unstable system (loop gain=1).

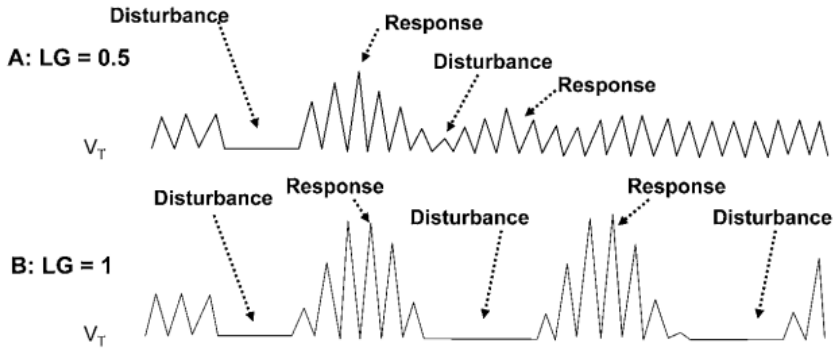


Figure 1.15: Quantifying loop gain; a stable (panel A) and an unstable (panel B) system. Figure taken from D. White; Pathogenesis of Obstructive and Central Sleep Apnoea. (White, 2005)

To illustrate this, figure 1.16 shows an original 7 minute recording from our laboratory illustrating a cortical arousal and increase in ventilation with a reduction in CO_2 levels. This hyperpnoea acts as a disturbance to the ventilatory system which becomes unstable with the resumption of sleep, hence the appearance of ventilation in a crescendo-decrescendo pattern (periodic breathing).

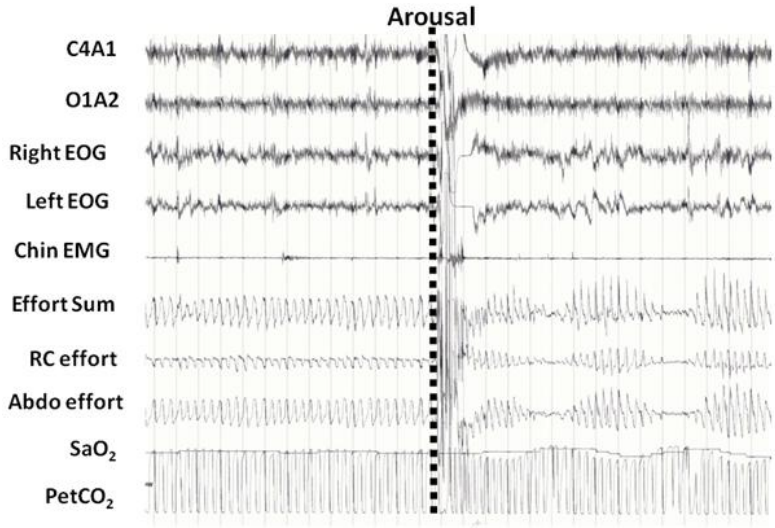


Figure 1.16: Seven minute epoch of polysomnogram showing periodic breathing occurring after a cortical arousal. Reproduced with permission of Prof. M. Morrell.

C4A1, O1A2- electroencephalograms; EOG-electroocculograms; EMG- electromyogram; Effort sum- combined chest and abdominal effort; RC- rib cage; abdo- abdominal; SaO_2- oxygen saturations; $PetCO_2$- end tidal carbon dioxide levels.

1.5.5 Controller, plant and feedback gains

As discussed Loop gain may be considered as the product of the controller, plant and feedback gains and each are illustrated in figure 1.17, (Wellman et al., 2003).

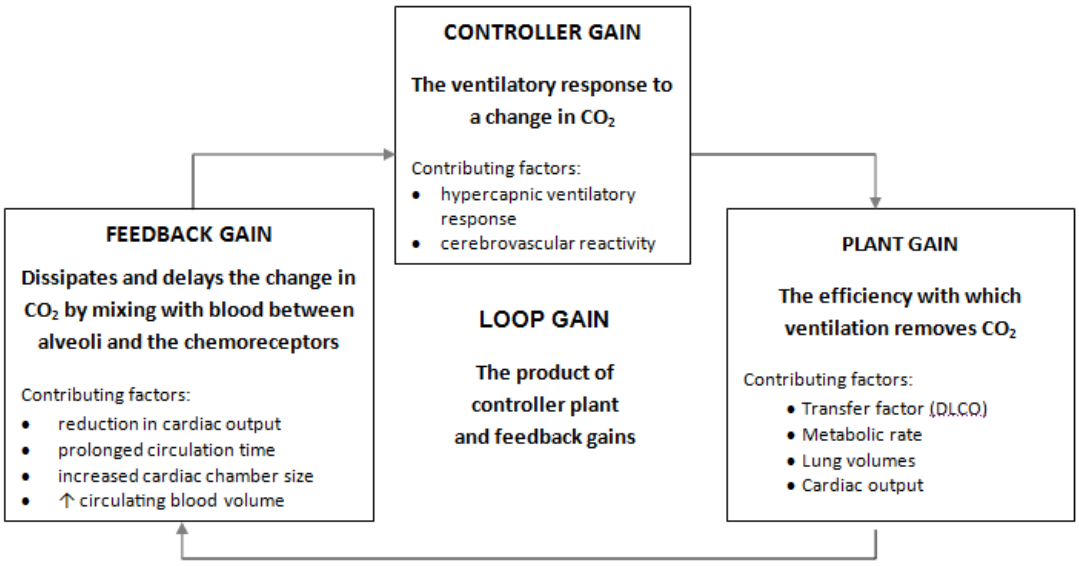


Figure 1.17: The components of loop gain and the factors which influence them. Adapted and reproduced from Wellman *et al.* (Wellman et al., 2003).

The term controller gain describes the chemosensitivity of the ventilatory system and is best described by the hypercapnic ventilatory response (HCVR) which expresses the change in ventilation elicited by a change in CO_2. The HCVR is primarily, but not exclusively, a product of the action of protons at the central (medullary) chemoreceptors (Blain et al., 2010). The slope of the relationship between CO_2 and ventilation describes the sensitivity of the central chemoreceptors and is conventionally plotted as shown in figure 1.18, which shows original data taken from the laboratory measurement of the HCVR in 2 healthy subjects to illustrate between subject variability. An extrapolation of this slope generates the x intercept which is the theoretical CO_2 level at which ventilation would cease and as such is an approximation of the apnoeic threshold.

The HCVR shows a high level of variability between normal subjects (Read, 1967, Jones et al., 1993). Genetic (Weil, 2003) and gender (Aitken et al., 1986) related factors, as well as the effect of age (Brischetto et al., 1984) and personality (Saunders et al., 1972) are also thought to play a role. The HCVR is under the influence of circadian rhythm (Spengler et al., 2000) and is not, as once thought (White et al., 1983b) affected by sleep deprivation or sleep fragmentation (Spengler and Shea, 2000,

Espinoza et al., 1991), at least in the short term. Despite this high level of waking variability the hypercapnic (and hypoxic) ventilatory responses, both fall at sleep onset and are at their lowest during REM sleep (Douglas et al., 1982b, Douglas et al., 1982a). This sleep related fall is not attenuated with age (Browne et al., 2003). Despite this sleep related reduction in HCVR there is a net evening to morning increase in the HCVR in healthy subjects (Cummings et al., 2007). Measurement of the waking HCVR as a means of predicting ventilatory stability when asleep requires the assumption that waking and sleeping HCVR are approximate. Furthermore, the slope of the relationship between ventilation and CO_2 can readily be studied in the hypercapnic range, but a further assumption is required to predict that that this relationship is the same in both the hyper- and hypocapnic ranges.

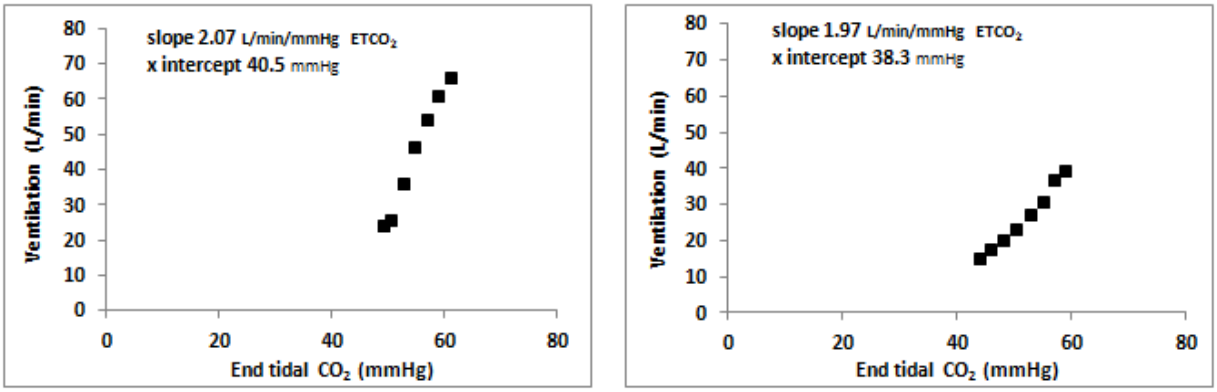


Figure 1.18: HCVR measured in the evening in 2 healthy male subjects. *$ETCO_2$- end tidal carbon dioxide.*

Cerebral blood flow, and specifically that of the central chemoreceptor, serves an important role in maintaining ventilatory stability. Carbon dioxide causes cerebral vasodilatation and so increases cerebral blood flow, increasing clearance of itself, reducing the proton concentration around the central chemoreceptor and so attenuating the ventilatory response to perturbations in arterial CO_2 and avoiding rebound hyperventilation. The opposite is also true in response to a reduction in arterial CO_2 and so cerebral blood flow, and its response to changes in CO_2, play an integral role in ventilatory stability. Cummings *et al.* (Cummings et al., 2007) found, in a study of healthy younger men, that there is an evening to morning increase in the cerebrovascular response to CO_2 which is related to an evening to morning fall in the HCVR and work using indomethacin to reduce cerebrovascular reactivity found a concomitant increase in the HCVR (Xie et al., 2006), again emphasising the relationship between the two.

Plant gain describes the efficiency with which ventilation removes CO_2 from the body and is affected by any factor or disease process which interferes in this process, as happens in patients with HF. Plant gain can be described by the theoretical line which describes the relationship between alveolar

ventilation and alveolar CO_2 levels (Dempsey et al., 2010) assuming that CO_2 production remains stable. This relationship, shown in figure 1.19, is not linear, but rather hyperbolic and it is this property which means that at higher levels of alveolar CO_2 relatively less ventilation is required to reach the apnoeic threshold, whereas at lower levels of CO_2 relatively more ventilation is required to reach the apnoeic threshold. Resting hypocapnia, such as is seen in some HF patients, has a stabilising effect on ventilation for this reason. Plant gain can be changed by anything which affects the nature of the relationship between alveolar CO_2 and ventilation, or which causes hypoventilation such that the resting CO_2 is higher, thus promoting instability.

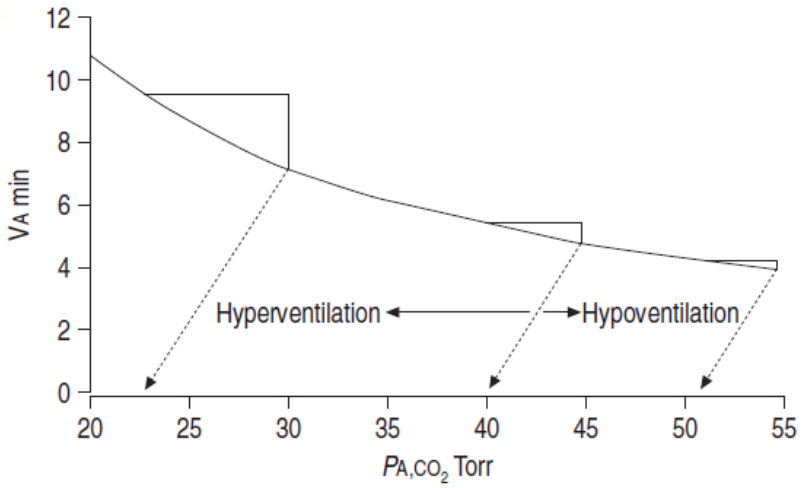


Figure 1.19: The hyperbolic relationship between alveolar carbon dioxide and ventilation. Adapted from Dempsey *et al.* (Dempsey et al., 2010). *V_A- Alveolar ventilation; $PaCO_2$- alveolar carbon dioxide levels.*

Feedback gain describes the delay, intrinsic to any feedback system, between the physiological change occurring and the transmission of that change to the central controller which then elicits a response. This component of loop gain plays the smallest role in contributing to instability in disease states; it is further considered in the sections which follow.

1.5.6 Summary

Breathing during sleep in healthy subjects is usually stable because any transient disturbance to ventilation is "dampened out" and stable breathing resumes. Chemosensitivity (which can be measured by the hypercapnic ventilatory response) shows considerable variability between normal individuals which is thought to be due to genetic, gender, age and personality related factors, the latter relevant only to testing during wakefulness.

The ability to compensate for ventilatory disturbances is compromised in HF patients in whom several abnormalities of the components of loop gain result in an elevated loop gain and a system vulnerable to instability. This is discussed in the section which follows.

1.6 Pathophysiology of sleep disordered breathing in heart failure

The syndrome of HF can affect every component of the loop gain system and result in ventilatory instability. It was once thought that such instability resulted only in central SDB but it is now understood that ventilatory instability plays a role in both obstructive and central SDB (Wellman et al., 2004). Here emphasis will be given to the pathophysiology relevant to central SDB.

1.6.1 The effect of heart failure on controller gain

The potential for ventilatory instability already described in health is magnified in patients with HF, which in part explains the prevalence of central SDB in patients with HF, as outside of this group it is rare. Studies in HF patients have shown ventilatory instability in response to brief exposure to hypoxia during sleep (Ahmed et al., 1994) and subsequent studies have shown brisker hypercapnic ventilatory responses which contribute to an increased controller gain, and so instability (Javaheri, 1999, Topor et al., 2001, Solin et al., 2000).

The cause of the brisk ventilatory response to CO_2 is unclear. Several factors such as gender, genetics and age may contribute independently of the HF state however it is also possible that some aspect of SDB (sleep disruption or nocturnal hypoxaemia), or indeed the HF syndrome itself, are causal. Javaheri found that the elevated HCVR in patients with central SDB correlated with the AHI (Javaheri, 1999), suggesting that the SDB itself, or something about its effect on sleep may be contributing, if not causal. Early studies found that 24 hours of sleeplessness in 13 healthy men caused a decrease in the HCVR (White et al., 1983b), however subsequent studies using longer, more controlled periods of sleep deprivation found no such difference (Spengler and Shea, 2000) and studies using 2 consecutive nights of sleep fragmentation (more akin to the effect of SDB on sleep) again found no effect on HCVR (Espinoza et al., 1991).

Solin *et al.* (Solin et al., 2000) have investigated the relative pathophysiological contributions of the peripheral and the central chemoreceptors. They found that both are likely to be implicated with both eliciting a heightened ventilatory response to CO_2. Their findings suggest that the central chemoreceptors are more specifically responsible for causing the metabolic environment likely to promote central SDB by causing hypocapnia; and the peripheral chemoreceptors are more likely to determine the severity of central SDB as determined by the proportion of central events and the

overall AHI. Using canine models others have found the peripheral and central chemoreceptors to interact in the sensing of and response to hypocapnia (Smith et al., 2007).

A study of 50 patients with HF found their cerebrovascular responses to CO_2 were reduced compared to both age matched and younger controls, although the presence or absence of SDB was not established (Georgiadis et al., 2000). The same study found a significant relationship between cerebrovascular reactivity and LVEF, as well as differences associated with NYHA class IV, compared to classes II and III. Xie *et al.* found that patients with HF and central SDB have a reduced cerebrovascular response to CO_2 compared to HF patients with no SDB, but this is particularly significant in the hypocapnic range (Xie et al., 2005) suggesting this may be a mechanism by which ventilatory instability, and so CSR is initiated and propagated.

1.6.2 The effect of heart failure on plant and feedback gains

HF patients with central SDB tend to have a resting hypocapnia (Sin et al., 1999) and do not have the same rise in CO_2 at sleep onset (Xie et al., 2002) meaning that their sleeping levels are closer to the apnoeic threshold. Notably, their resting hypocapnia acts to stabilise breathing because of the relationship between alveolar CO_2 and ventilation (section 1.5.5). Low cardiac output, reduced lung volumes and low oxygen and CO_2 reserve contribute to an increased plant gain. Alveolar water and chronic parenchymal changes may also affect diffusion capacity (Szollosi et al., 2008) and so increase plant gain and contribute to instability.

Prolonged circulation time causes an increase in feedback gain, although this is not thought to be a major cause of ventilatory instability (Francis et al., 2000) given than experimentally induced periodic breathing in a canine model (Crowell et al., 1956) required an increase in circulation time beyond that seen in humans.

1.6.3 The effect of heart failure on the upper airway

The prevalence of obstructive SDB in the HF population exceeds that of the general population, despite having levels of obesity which are less than those of the general population. Much work has sought to explain this discrepancy. In the Western world HF is a clinical syndrome of older adults and Eikerman *et al.*, in a study of healthy individuals of a range of ages, found that age correlated with upper airway closing pressure; as age increased so the pressure required to close the airway became less negative (Eikermann et al., 2007). It is plausible therefore that the older HF patient has a more compliant, easily collapsible airway. This hypothesis has not yet been tested in a HF population.

Another possible explanation relates to observations initially made by Shepard and co-workers (Shepard et al., 1996) who found that, in a group of patients with OSA, central venous pressure manipulation by means of leg raising and use of blood pressure cuff inflation on the legs influenced upper airway cross sectional area. Subsequently a series of studies have developed this concept. Chiu and co-workers (Chiu et al., 2006) demonstrated that the use of lower body positive pressure in the form of anti-shock trousers in healthy individuals resulted in both an increase in neck circumference and pharyngeal resistance. The same group (Shiota et al., 2007) showed that lower body positive pressure was associated with a reduction in leg fluid volume and a decrease in upper airway cross sectional area with further work (Su et al., 2008) demonstrating an increase in critical closing pressure (Pcrit) which was more pronounced in men than in women (62). Redolfi *et al.* (Redolfi et al., 2009) from the same group explored this phenomenon in patients with obstructive SDB and found that the change in leg fluid volume that occurred overnight correlated with the increase in neck circumference, AHI and subjective reports of time spent sitting, an effect reversed in a subsequent study which applied compression stockings (Redolfi et al., 2011). Whilst another group were able to replicate measurement of fluid from the lower limbs to the neck, they did not find this shift was associated with a worsening of obstructive SDB (Jafari and Mohsenin, 2011). Kasai *et al.* correlated sodium intake with the AHI in patients with HF and obstructive SDB, suggesting that this relates the fluid shift mechanism to abnormal fluid balance and retention in patients with HF (Kasai et al., 2011). Furthermore, it has been suggested that the theory of fluid shift may explain central, as well as obstructive SDB in patients with HF by contributing to pulmonary congestion and driving down CO_2 levels (Yumino et al., 2010).

Also notable is the observation that patients treated with tracheostomy for OSA in the past have continued to have SDB in the form of central events (Weitzman et al., 1980). More recently Younes and co-workers (Younes et al., 2001) and Wellman and co-workers (Wellman et al., 2004, Wellman et al., 2008) have found that ventilatory instability (as measured by loop gain) is implicated in a sub-group of patients with OSA (without HF). As discussed, HF patients are known to have ventilatory instability and it is recognised that as ventilatory drive fluctuates, so does drive to the upper airway (Hudgel et al., 1987), an observation further supported by the finding that airway closure may occur before the termination of a central apnoea- a “mixed apnoea” (Badr et al., 1995, Alex et al., 1986). A mixed apnoea is central in aetiology but terminates in breaths taken against an occluded airway and it remains to be seen if this combination of pathologies carries any clinical or prognostic significance.

1.6.4 Summary

The HF syndrome is associated with a range of pathophysiological changes which increase the likelihood of ventilatory instability which has been implicated in both obstructive and central SDB in HF patients. Patients with HF and central SDB have more brisk ventilatory responses to CO_2, lower resting CO_2 and less rise in CO_2 at sleep onset that those without SDB. Furthermore, they have reduced cerebrovascular reactivity to CO_2, in contrast to their ventilatory response. The model of loop gain can be used to conceptualise these factors; HF is associated with increases in controller, plant and, to a lesser extent, feedback gains. The upper airway may also be affected by the HF syndrome via the mechanism of fluid shift from the legs up to the neck when recumbent and the effect of this fluid shift on pulmonary congestion may also contribute to central SDB.

1.7 The treatment of central SDB in heart failure

As the considerable prevalence of SDB in the HF population has become better understood, research into possible treatments has intensified, although the prognostic significance of the condition remains unknown. This section will focus primarily on treatments aimed at central SDB as this is the subject of the remainder of this thesis.

Interventions for the treatment of predominantly central SDB have included oxygen, CO_2, pacing devices and pharmacological agents as well as devices which deliver positive airway pressure (PAP) in order to stabilise breathing and these will be discussed in the sections that follow.

1.7.1 Continuous positive airways pressure

Continuous Positive Airways Pressure is a well established treatment for OSA in non-HF populations and has been investigated as an intervention in the HF population in both obstructive and central SDB. CPAP is a PAP device which delivers a constant level of pressure to the patient via a mask interface which is worn by the patient overnight. In the case of obstructive SDB this acts as a pneumatic splint to support the upper airway and prevent airway narrowing or closure. The pressure delivered is set by the clinician or sleep technician setting up the machine initially and is usually measured in cm of water. The pressure delivered by the machine (measured in centimetres of water; cmH_2O) must be sufficient to overcome the pressures acting on the upper airway which would cause it to narrow or become occluded. Where the pressures acting on the upper airway are higher, a greater pressure is required. In practice this pressure is selected by the clinician or sleep technician based on a knowledge of the patient's BMI/neck circumference and experience and the pressure can be titrated in response to the clinical response to therapy (e.g., a persistence of somnolence despite compliance might require an increase in pressure). A more objective estimate of the pressure required can be made by using an auto-titrating CPAP machine which, within certain limits, will automatically alter the pressure delivered such that airway patency is maintained. The 95^{th} percentile of pressure required overnight can then be used to set up a standard CPAP machine for the patient to use thereafter. Compliance and treatment efficacy can be monitored by means of a removable chip in the device, via download directly from the device or can be retrieved over the phone line for remote monitoring.

1.7.2 The use of CPAP for the treatment of CSA in patients with HF

In patients with HF and central SDB therapy with CPAP has been shown to effectively suppress central respiratory events, reduce urinary and plasma catecholamines (Naughton et al., 1995a, Naughton et al., 1995b), increase heart rate variability (Butler 1995), improve the left ventricular ejection fraction and improve quality of life (Naughton et al., 1995b).

A prospective study of CPAP use in 29 men with HF and either obstructive or central SDB found that it suppressed SDB in only 9 out of 21 with central SDB (but in 7 out of 8 with obstructive SDB) (Javaheri 2000). The same study found a reduction in nocturnal ventricular arrhythmias in those patients responding to treatment, but not in those that didn't. Twelve weeks of CPAP use were found to improve ventilatory efficiency during symptom limited cardiopulmonary exercise testing (Arzt 2005).

In a study comparing the efficacy of CPAP with other treatments in terms of its ability to suppress respiratory events, CPAP outperformed oxygen therapy, but not bi-level ventilation or adaptive servo-ventilation (Teschler et al., 2001), although some authors have reported CPAP and oxygen to be equivalent (Krachman 1999). CPAP achieved similar results to oxygen therapy with respect to attenuation of the arousal index but was outperformed by both bi-level ventilation and ASV with both achieving a greater reduction (Teschler et al., 2001).

1.7.3 The CANPAP Study

The CANPAP study (Bradley et al., 2005) was undertaken to investigate if there was a survival benefit associated with the use of CPAP in HF patients with predominantly central SDB. It was designed as a randomised controlled trial and the primary outcome was transplant free survival. Patients were randomised to either standard medical care (the control group) or to nocturnal CPAP therapy with standard medical care (the intervention group). Other outcome measures included LVEF, quality of life (as assessed by the Chronic Heart Failure Questionnaire), 6MWT, hospitalisation and neurohormones (plasma noradrenaline levels and atrial natriuretic hormone; ANP). Eligibility criteria included an AHI of ≥15 events/hr with >50% central events; LVEF <40%; NYHA functional class II-IV and optimal medical therapy. Eleven centres were involved in the anticipated recruitment of 204 patients in each group however the study was stopped at only 50% recruitment due to an early divergence in transplant free survival in favour of the control group. Mean follow up at this stage was 2 years and statistical analysis could detect no difference in the primary outcome between the two groups. The investigators concluded that their data could not support the use of CPAP to prolong survival in patients with

predominantly CSA. Additionally they commented that the observed rate of death and transplantation was lower than they had anticipated. Figure 1.20 shows transplant free survival in both groups.

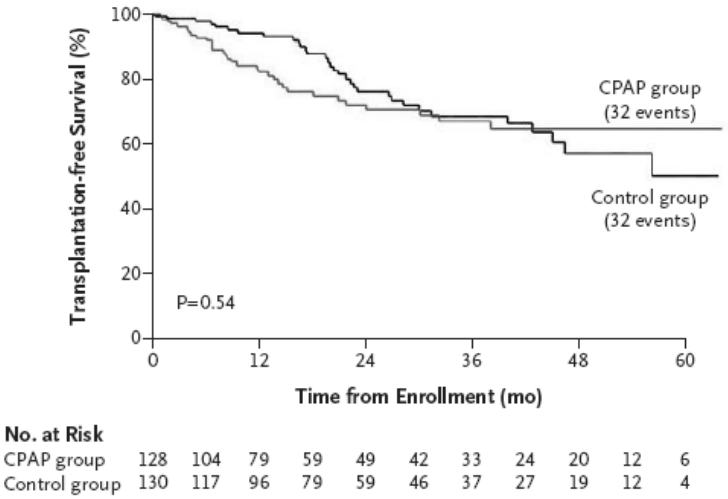


Figure 1.20: Transplant free survival in the CPAP and control groups of the CANPAP study. (Bradley et al., 2005)

Analysis of the 3 month data revealed differences with respect to the secondary outcomes. In terms of secondary outcomes, the CPAP group showed a reduction in AHI, an improvement in mean and minimum oxygen saturations overnight, plasma noradrenaline, 6MWT and a modest improvement in LVEF (2.2%) when compared to the control group. It is noteworthy that although the AHI was reduced by 53%, and the LVEF improved by 2.2% these changes were smaller in magnitude than had been achieved in other work (Naughton et al., 1995b). There was no difference the hospitalisation rate nor the ANP levels between the two groups, nor was the use of CPAP associated with a change in sleep time, sleep stage distribution or arousal frequency and this was the subject of a subsequent post hoc analysis.

The original CANPAP data was published at the end of 2005 and a post hoc analysis published in 2007 investigated the outcome of a subgroup of patients in whom the use of CPAP was associated with better suppression of the AHI (Arzt et al., 2007b). Fifty-seven out of 100 patients had suppression of their AHI to <15 and this group had a greater improvement in LVEF and transplant free survival. Those with an AHI ≥15 despite CPAP had a non-significant trend to worsening of LVEF and primary outcome. Figure 1.21 illustrates the unadjusted transplant free survival rates for the CPAP suppressed (ie. improved SDB), CPAP unsuppressed (ie. persistent SDB) and the control group.

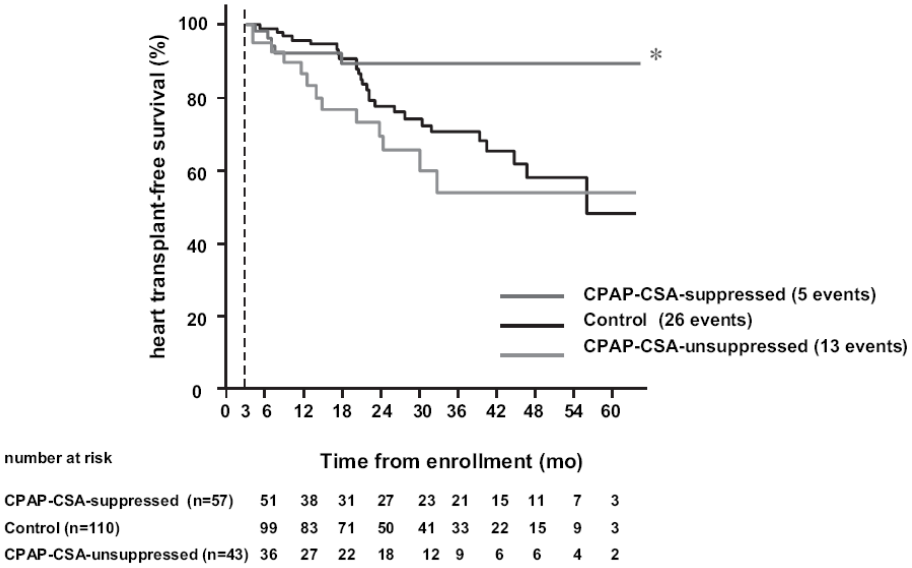


Figure 1.21: Kaplan-Meier survival plots demonstrating an improved transplant free survival in CPAP suppressed patients compared with both the CPAP unsuppressed and the control groups. Taken from Arzt *et al.* (Arzt et al., 2007a)

A further post-hoc analysis was published in 2009 (Ruttanaumpawan et al., 2009) found that even in those patients with an AHI suppressed below 15 the use of CPAP was not associated with a significant change in sleep structure; specifically the arousal index in this group was not reduced and this is in keeping with other work (Teschler et al., 2001). The authors speculate that arousals in central SDB may have a protective role in a similar way as is seen in OSA where arousals (in most cases (Younes, 2003)) serve to terminate a respiratory event.

1.7.4 Adaptive servoventilation

Adaptive servoventilation (ASV) is a novel form of positive pressure ventilation characterised by delivery of a variable level of pressure support to the patient which is the reciprocal of the patient's own respiratory effect. This variable pressure support is superimposed on low levels of EPP which serves to stabilise the upper airway and remove airflow limitation. Further details on the technical aspects of the device are given in chapter 2, section 2.8.

Much work has shown that ASV both suppresses the AHI and so improves nocturnal oxygenation (Teschler et al., 2001, Pepperell et al., 2003, Philippe et al., 2006, Hastings et al., 2008), and also reduces sleep fragmentation so improving sleep architecture (Hastings et al., 2008, Allam et al., 2007, Zhang et al., 2006, Teschler et al., 2001). Pepperell *et al.* found a reduction in objective, but not subjective, sleepiness after 1 month of ASV use compared to sub-therapeutic ASV (Pepperell et al.,

2003), while other authors have found a near significant change in subjective sleepiness (using the Epworth sleepiness score; ESS) after 6 months of ASV (Philippe et al., 2006) and still others found a significant change after 36 ± 18 months (Carnevale et al., 2011). Oldenburg *et al.* found an improvement in NYHA functional class and distance walked in 6 minutes after 6.7+/- 3.2 months of ASV use (Oldenburg et al., 2011b) and Hastings *et al.* found reduction in nocturia and an improvement in quality of life after 6 months of ASV use (Hastings et al., 2008). A recent meta-analysis of ASV use concluded that ASV was an effective treatment for central SDB, improving the AHI, LVEF and the distance walked in 6 minutes (Sharma et al., 2012).

Studies measuring LVEF found no change after 1 month of ASV (Pepperell et al., 2003) but an increase after 6 months (Hastings et al., 2008, Philippe et al., 2006, Hastings et al.) and improvements in cardiac function (assessed by both LVEF and BNP) have been found regardless of the severity of SDB (Takama and Kurabayashi, 2011) suggesting that ASV has an effect on the heart which is not dependent on the suppression of SDB. In support of this is the observation that 12 months of ASV use is associated with an improvement in renal function which correlates with the improvement in LVEF (Koyama et al., 2011b) suggesting the improvement may be related to end organ perfusion. Furthermore, improvement in LVEF has been found in more compliant patients compared to those rejecting or poorly compliant with treatment (Oldenburg et al., 2011b), suggesting a dose response relationship.
Several studies have investigated the neuroendocrine effects of ASV. The use of ASV is associated with a reduction in markers of SNA measured by heart rate variability (D'Elia et al., 2012), muscle sympathetic nerve activity (Harada et al., 2011), urine and plasma catecholamines (Pepperell et al., 2003, Yoshihisa et al., 2012). Both atrial natriuretic peptide (a marker of atrial stretch) and BNP have fallen in association with ASV use (Pepperell et al., 2003, Koyama et al., 2010, Oldenburg et al., 2011b, Yoshihisa et al., 2011) as has the cardiac enzyme troponin T (Yoshihisa et al., 2012).

Like nocturnal CSR, oscillation of ventilation during exercise is thought to be a marker of ventilatory instability and perhaps associated with a worse prognosis. The use of ASV over several months has been shown to reverse or reduce ventilatory oscillation in exercise (Kazimierczak et al., 2011, Oldenburg et al., 2011b) and also, to reduce the heightened ventilatory response to CO_2 (Oldenburg et al., 2011b) previously described in these patients (Javaheri, 1999). However one night of ASV was not associated with a change in the evening to morning cerebrovascular response to CO_2 (Morrell et al., 2007); the longer term effects of ASV are unknown.
Acutely, the application of ASV causes a fall in BP (Haruki et al., 2011), particularly in those with a lower baseline BP (Oldenburg et al., 2011a), along with an increase in stroke volume and cardiac

output in association with a reduction in the systemic vascular resistance (Haruki et al., 2011). Longer term (24 weeks) use of ASV has been found to reduce left atrial volumes, left ventricular volumes and the severity of mitral regurgitation as well as improving markers of diastolic function (Haruki et al., 2011). There is a case report of a patient who had measurement of pulmonary artery pressure and PCWP before and 10 minutes after the initiation of ASV therapy; both parameters fell significantly from baseline (Higashi et al., 2012).

As previously observed with CPAP use in patients with obstructive SDB (without HF) (Weaver et al., 2007), a dose response relationship exists with ASV use; higher levels of use were associated with a reduction in subjective sleepiness and an improvement in blood gas markers of chronic hyperventilation, whereas lower levels of use were not (Carnevale et al., 2011). Compliance is discussed considered further in chapter 3.

A study comparing one night of ASV to CPAP, NIV and oxygen have found it to more effectively reduce the AHI and also to improve sleep architecture by reducing the arousal index and increasing slow wave and REM sleep; this study of 14 patients found all preferred the ASV device over the other positive pressure devices (Teschler et al., 2001). A retrospective chart review of 100 patients at the Mayo clinic found comparable results (Allam et al., 2007) and a randomised controlled trial of CPAP versus ASV found ASV to be superior both in terms of efficacy (reduction in AHI) but also compliance, which was similar in both groups at 3 months but higher in the ASV group at 6 months (Philippe et al., 2006). The same study found LVEF increased only in the ASV group. A 3 month study investigating CPAP vs. ASV in a group of HF patients with both obstructive and central SDB found similar results with respect to efficacy, compliance and LVEF, as well as a greater improvement in quality of life (using the SF-36 questionnaire) with ASV over CPAP (Kasai et al., 2010). ASV has been found to be more efficacious at reducing the AHI and respiratory related arousals than bi-level ventilation, in a 3 month randomised study that found no difference in sleep architecture between the two modalities (Morgenthaler et al., 2007b). ASV has also been found more effective than nocturnal oxygen at reducing the AHI over one night (Yoshihisa et al., 2012) and 8 weeks (Campbell et al., 2011), although the latter study found oxygen therapy was better accepted by patients.

Epidemiological work using Medicare data from the United States suggests that those HF patients tested, diagnosed and treated for sleep apnea (type unspecificed) have a better survival than those not tested, or who were tested, diagnosed but not treated (Javaheri et al., 2010). Furthermore, work

looking at HF patients with SDB and ICD devices found that the AHI and severity of nocturnal hypoxia correlated with the appropriate ICD discharge (Tomaello 2010), suggesting that SDB in this population may increase the risk of life threatening arrhythmia. Uncontrolled work looking at event free survival over 1 year in HF patients using ASV compared with those not using, or poorly compliant, suggests survival is better in those using the device, particularly those using it for more than 4 hours a night (Takama and Kurabayashi, 2012, Koyama et al., 2011a).

The SERVE-HF study is the first randomised controlled study to investigate the effect of ASV on mortality in patients with systolic left ventricular impairment and predominantly central SDB. Data from patients randomised into that study at the Royal Brompton Hospital can be found in chapter 3.

1.7.5 Nocturnal oxygen, carbon dioxide and other treatments

Nocturnal oxygen has been used in the treatment of central SDB since the early 1900s (Pitt et al., 1907). It has been shown to effectively reduce the AHI in patients with central SDB, specifically the central event rate (Hanly et al., 1989, Walsh et al., 1995, Franklin et al., 1997, Staniforth et al., 1998, Javaheri et al., 1999, Sakakibara et al., 2005, Sasayama et al., 2006, Toyama et al., 2009, Sasayama et al., 2009) and to have little or no effect in obstructive events (Franklin et al., 1997), with some work suggesting a worsening of obstructive events (Sakakibara et al., 2005). Interestingly oxygen has been found to more effectively suppress the AHI in eucapnic than hypocapnic HF patients (Franklin et al., 1997, Javaheri et al., 1999). Oxygen also improved both the mean oxygen saturations overnight, as well as reducing the time spent with oxygen saturations less than 90% (Staniforth et al., 1998, Hanly et al., 1989, Javaheri et al., 1999), it reduced the duration of the night spent in CSR (Staniforth et al., 1998, Andreas et al., 1998, Andreas et al., 1999), reduced the number of Cheyne-Stokes cycles but increased the cycle length (Andreas et al., 1999). Furthermore, nocturnal oxygen improved some aspects of sleep architecture (Hanly et al., 1989, Walsh et al., 1995, Andreas et al., 1996), reducing arousals from sleep (Hanly et al., 1989, Walsh et al., 1995, Franklin et al., 1997) but had no effect on REM sleep. Some work has found a reduction in sleepiness and improvement in subjective sleep quality (Franklin et al., 1997) but this has not been universal (Staniforth et al., 1998) and others found no effect on daytime symptoms (Andreas et al., 1996).

As with CPAP and ASV, the use of nocturnal oxygen also reduced markers of SNA (Staniforth et al., 1998, Toyama et al., 2009) and reduced heart rate (Sakakibara et al., 2005) but it had no effect on the frequency of nocturnal ventricular arrhythmias (Javaheri et al., 1999).

In terms of its effects on the pathophysiology of central SDB, Andreas *et al.* found that 1 week of nocturnal oxygen significantly reduced the HCVR compared to room air in a randomised cross over

trial (Andreas et al., 1998). In a separate study the same author found that that nocturnal oxygen increased resting CO_2 levels in patients but not age matched controls (Andreas et al., 1999), suggesting a mechanism of action which influences chemosensitivity. Peak oxygen uptake during exercise has also been shown to improve (Toyama et al., 2009, Andreas et al., 1996). Longer term use has found oxygen use to reduce BNP levels (Shigemitsu et al., 2007), improve the LVEF and the NYHA functional class (Sasayama et al., 2009), reduce hospitalisation, outpatient and emergency visits (Seino et al., 2007). There have been conflicting results regarding the effect of nocturnal oxygen on cognitive function with some authors reporting an effect (Andreas et al., 1996), whilst others found none (Staniforth et al., 1998).

The administration of CO_2 during sleep effectively suppressed central events and was associated with an increase in both trans-cutaneous CO_2 and oxygen saturations in both patients with idiopathic central sleep apnoea (Xie et al., 1997) and patients with HF and central SDB (Lorenzi-Filho et al., 1999). Adding dead space as another means of raising CO_2 levels, was also shown to significantly reduce the AHI in those with idiopathic central SDB (Xie et al., 1997) and HF patients with central SDB, but in the latter group, when compared to ASV therapy, caused a decrease in total sleep time and an increase in the arousal index (Szollosi et al., 2006a). The use of dynamic CO_2 (timed to specific points of the Cheyne-Stoke ventilation) has been investigated in awake controls and patients and found to reduce periodic breathing (Giannoni et al., 2010) although its use overnight and its effect on sleep architecture have not been tested.

The carbonic anhydrase inhibitor and respiratory stimulant acetazolamide is used to treat periodic breathing associated with altitude and its use in HF patients with central SDB has produced interesting results; several authors have found it reduces central SDB and improved nocturnal oxygenation (Fontana et al., 2011, Javaheri, 2006a) but it had a deleterious effect on exercise capacity and while it decreased hypoxic ventilatory responses, it increased hypercapnic ventilatory responses (Fontana et al., 2011). In a double blind prospective cross over study Javaheri found 6 nights of acetazolamide use were associated with an improvement in subjective perception of sleep quality and daytime sleepiness although had no effect on sleep architecture, arousals or efficiency (Javaheri, 2006a).

The methyl xanthine theophylline has also been investigated in a double blind placebo controlled cross over study. Its use over 1 week was associated with a significant reduction in AHI, central apnoea index and time with oxygen saturations <90%. However, as with acetazolamide, its use was not associated with a change in sleep parameters, nor daytime arterial blood gases or LVEF. Notably, theophyline use was not associated with any increase in ventricular arrhythmias (Javaheri et al., 1996).

An earlier study of theophylline in healthy controls found no effect on the hypoxic or hypercapnic ventilatory responses (Javaheri and Guerra, 1990).

The use of a left ventricular assist device in 3 patients presenting with acutely decompensated HF and central SDB did not result in resolution of central events at follow-up PSG at 7 to 80 days post insertion, despite improved haemodynamics in all three patients (Padeletti et al., 2007). A case report of the same device in similar circumstances was associated with resolution of central events at 10 months post insertion (Vazir et al., 2008a). Cardiac transplantation has been associated with an improvement in central SDB in some, but not all patients (Mansfield 2003).

Medical therapy aimed at the underlying HF syndrome has been associated with an improvement in SDB; a study of ionotropes, oxygen and diuretics found they were associated with such an improvement in a group of patients with decompensated HF (Dark et al., 1987). A group with central SDB treated intensively for HF with diuretics, ACE inhibitors, nitrates and carvedilol (and PAP in some) demonstrated a fall in AHI and a proportional fall in PCWP (Solin et al., 1999). Patients treated with carvedilol or metoprolol had a single sleep study as part of an observational study and were found to have a lower AHI and improved sleep quality, including arousal index (Kohnlein and Welte, 2007).

1.7.6 Cardiac resynchronisation therapy

Cardiac resynchronisation therapy (CRT) is an implantable device used to improve the coordination of cardiac contraction and so improve cardiac output and its use in selected patients with chronic HF is now well established (Barnett et al., 2007, NICE HTA, 2007). This group of patients frequently have asynchronous ventricular contraction due to conduction defects (Shenkman et al., 2002) and these are associated with a poorer prognosis (Kalra et al., 2002). Several large randomised controlled trials have demonstrated that the use of CRT is associated with improved survival and a fall in unplanned hospitalisation (Bristow et al., 2004, Cleland et al., 2005), as well as improvements in quality of life and exercise capacity (Abraham et al., 2002, Cleland et al., 2005). Subgroup analyses have shown the reduction in mortality and hospitalisation is greater in those with an intrinsic QRS duration of ≥150 msec and in those with left bundle branch block (Tang et al., 2010, Moss et al., 2009) and these findings are reflected in criteria for implantation in the current national guidelines (NICE HTA, 2007). Aside from the hard end points (eg. mortality) used in large clinical trials the issue of defining response to CRT is far from straightforward; this makes comparison of research difficult as agreement between criteria is poor (Fornwalt et al., 2010). A review on this subject reported non-response rates of 25 to

30% when functional end points are used, and 40 to 50% when LV remodelling parameters, such as change in left ventricular ejection fraction and end systolic volumes, were used (Birnie and Tang, 2006); a placebo effect is likely to account for this discrepancy. Some work has used a combination of functional measures, maximal and sub-maximal exercise testing and change in LV function to classify response (Oldenburg et al., 2007a). A failure to respond, by whichever criteria, may reflect differences in the degree of mechanical dyssynchrony (Yu et al., 2004), the site of LV lead implantation (Dekker et al., 2004) and the underlying aetiology of the HF syndrome (those with idiopathic DCM seem to derive greater benefit than those with an ischaemic aetiology) (Cleland et al., 2005).

Much work has been done to investigate the effect of CRT on both obstructive and central SDB and a meta analysis has concluded that CRT is effective in reducing the severity of SDB, particularly central SDB (Lamba et al., 2011) and that the presence of SDB may be taken into consideration when selecting patients for CRT implantation, although at the moment this is not part of the current national guidelines (Barnett et al., 2007).

There are various potential mechanisms by which CRT may improve SDB. Correction of electrical dyssynchrony is associated with downstream improvements in left ventricular contractility and myocardial efficiency, and also improves myocardial contractility as the heart rate increases (Vollmann et al., 2006). CRT implantation is also associated with reverse remodelling, as evidenced by a reduction in left ventricular end systolic and diastolic diameters, as well as mitral regurgitant jet (Abraham et al., 2002, Cleland et al., 2005). Furthermore CRT implantation has been found to reduce PCWP (Blanc et al., 1997, Leclercq et al., 1998) and previous authors have found that changes in PCWP are associated with improvements in central SDB in CHF patients (Solin et al., 1999). Interestingly an elevated AHI before CRT has been shown to be an independent risk for death and major cardiac event during medium term follow-up (Sredniawa et al., 2009). Taken together, it seems likely that CRT improves central SDB via a mechanism which includes an improvement in cardiac output given that an improvement in SDB is only seen in those with a positive haemodynamic response to CRT (Oldenburg et al., 2007b).

Gabor *et al.* (Gabor et al., 2005) and Luthje *et al.* (Luthje et al., 2009) found no change in objective sleep quality using PSG 3 to 9 months after CRT implantation, although the same authors found improvements in SDB (see below) suggesting that improvement of one does not depend on improvement of the other. Subjective sleepiness assessed using the Epworth score was found to improve 3 to 4 months after CRT (Luthje et al., 2009, Czarnecka et al., 2010). Pittsburgh sleep quality

index has been found to improve after CRT (Sinha et al., 2004, Czarnecka et al., 2010), with Sinha *et al.* finding a significant correlation between improvement in PSQI and reduction in AHI (r=0.83) in those with central SDB, but not those without. CRT implantation may improve sleep quality by other mechanisms. Skobel *et al.* (Skobel et al., 2005) used the Beck depression inventory and found symptoms of depressive illness in those patients with central SDB at baseline (but not those without SDB) which improved 4 to 6 months after CRT.

Sinha *et al.* (Sinha et al., 2004) used PG in 24 chronic HF patients before and 4 to 6 months after CRT implantation. They found a reduction in AHI in the 14 patients with central SDB at baseline and subjective improvements in sleep quality using the PSQI and these findings have been replicated by others (Skobel et al., 2005, Gabor et al., 2005, Oldenburg et al., 2007a, Luthje et al., 2009). Evidence for a mechanism for this effect can be drawn from 2 observations; only those patients who responded to CRT with improvements in NYHA, VO_2 peak, LV end diastolic diameter (LVEDD), LVEF and 6 minute walk, had a reduction in central SDB (Oldenburg et al., 2007a). Secondly; those with central SDB were relatively hypocapnic and this was corrected after CRT implantation (Gabor et al., 2005, Oldenburg et al., 2007a). Gabor *et al.* found this improvement in hypocapnia to be correlated with the reduction in central AHI. CRT has been shown to reduce PCWP (Blanc et al., 1997, Leclercq et al., 1998) the manipulation of which has been shown to improve central SDB in CHF patients (Solin et al., 1999). Taken together these observations suggest that CRT may improve central SDB by a variety of means including improvements in cardiac function, ventilatory stability and by a reduction in PCWP which has previously been found to be inversely related to arterial CO_2 (Solin et al., 1999).

An improvement in resting, or eucapnic, CO_2 levels may improve ventilatory stability during sleep because of the observation that those HF patients with resting hypocapnia when awake fail to produce a rise in CO_2 levels at sleep onset (Xie et al., 2002); the so called permissive hypercapnia of sleep. It is this therefore narrowed gap between sleeping CO_2 and the apnoeic threshold which contributes to ventilatory instability. Hypocapnia itself is also stabilising because of the hyperbolic relationship between alveolar CO_2 and ventilation previously described in section 1.5.5. A study investigating the effect of CRT implantation on central SDB found a resting hypocapnia in these patients (as previously reported) and a trend to increase in CO_2 after CRT implantation (Oldenburg et al., 2007a). The effect of CRT implantation on the HCVR has not previously been investigated and is the subject of a study presented in chapter 5.

The effect of CRT on obstructive SDB is less clear. Early work suggested that atrial overdrive pacing improved both central and obstructive SDB in patients *without* CHF (Garrigue et al., 2002) but several authors were unable to replicate these findings (Czarnecka et al., 2010, Oldenburg et al., 2007b, Shalaby et al., 2011) and a meta-analysis concluded that there was no evidence for the effect of CRT on obstructive SDB (Lamba et al., 2011). Stanchina *et al.* found that CRT improved obstructive SDB and that this correlated with a reduction in circulation time. They found no additional benefit with an increased atrial pacing rate and concluded that their results might reflect the stabilising effect of an improvement in cardiac output on respiratory loop gain (Stanchina et al., 2007). Although these data appear to be contradictory, they may reflect the previously discussed heterogeneity of obstructive SDB (section 1.3.2), which in some individuals owes as much to ventilatory instability and high loop gain, as an anatomically unfavourable upper airway.

1.7.7 Summary

Several different treatment modalities have been shown to effectively suppress SDB in patients with HF in association with an improvement in cardiac function which serves to emphasise the links between HF and SDB. An improvement in SDB however is not synonymous with an improvement in sleep architecture. Some of these treatments have effects on markers of ventilatory instability, providing further evidence for the mechanisms which underlie central SDB in patients with HF. Until the prognostic implications of central SDB in the HF syndrome are known it is unlikely that these interventions will be widely used.

1.8 Summary of the main themes and overall aims of this thesis

1.8.1 Summary of main themes of this thesis

Chronic HF is a clinical syndrome of enormous epidemiological, and so public health, significance and despite advancement in the understanding of both its causes and consequences its prognosis remains poor. Central to its management is an understanding of its heterogeneity; the HF syndrome is the final clinical pathway of a diverse range of insults to the heart which vary across age groups, continents and through time. Sleep disordered breathing is more common in patients with HF than in the general population and is also a heterogeneous entity, encompassing both obstructive and central phenotypes, with some patients exhibiting overlap between these two.

Many of the pathophysiological sequelae of the HF syndrome contribute to ventilatory instability and central SDB (on which this thesis will focus) and might be considered as exerting a "physiological pressure" for the emergence of central SDB which increases with worsening HF severity over time and during periods of acute worsening. Some patients do not develop central SDB despite this and the reasons for this are unknown.

A range of treatments, including oxygen, positive airways pressure devices and implantable devices, are known to be effective at suppressing central SDB, often with an associated improvement in cardiac function and other markers of ventilatory instability. However despite its prevalence amongst HF patients it is unclear if central SDB is merely a consequence of the failing heart, seen in some but not all patients, or if it contributes to the morbidity and mortality of the syndrome and so has prognostic implications.

1.8.2 Overall aims of this thesis

This thesis aims to investigate the mechanisms underlying central SDB in patients with HF (particularly that of ventilatory instability), to elucidate their consequences, both by day (on physical activity and subjective sleepiness) and night (on sleep architecture and SDB) and to address the ways in which various treatment modalities may modify these pathophysiological mechanisms.

The aims of each chapter are given below.

Chapter 3: The SERVE-HF study. This is an international randomised controlled trial which aims to investigate the effect of adaptive servoventilation on mortality and morbidity in patients with HF and predominantly central SDB. The chapter contained within this thesis presents data from those patients randomised at the Royal Brompton Hospital and with an emphasis on the effect of the device on SDB, factors predicting compliance in this group and the way in which the HF population differ from others using positive pressure devices.

Chapter 4: The influence of SDB on the hypercapnic ventilatory response (HCVR) in patients with chronic HF. The aim of this study was to confirm the mechanism of central SDB in HF patients by measuring the HCVR in HF patients with and without central SDB, and also in a group of older healthy subjects.

Chapter 5: The effect of cardiac resynchronisation therapy on sleep in patients with chronic HF. The aim of this study was to investigate the effect of CRT implantation on SDB, sleep quality and chemosensitivity (assessed by the hypercapnic ventilatory response) on patients with chronic HF.

Chapter 6: Subjective sleepiness and activity levels in HF patients with and without SDB. The aim of this study was to expand the findings of previous work by investigating the effect of central SDB on subjective sleepiness and physical activity levels in patients with chronic HF. A secondary aim was to investigate the effect of HF itself on sleepiness and activity levels by comparing a group of HF patients without SDB with a group of age matched healthy controls.

Beloved, may your sleep be sound
That have found it where you fed.
What were all the world's alarms
To mighty Paris when he found
Sleep upon a golden bed
That first dawn in Helen's arms?

Sleep, beloved, such a sleep
As did that wild Tristram know
When, the potion's work being done,
Roe could run or doe could leap
Under oak and beechen bough,
Roe could leap or doe could run;

Such a sleep and sound as fell
Upon Eurotas' grassy bank
When the holy bird, that there
Accomplished his predestined will,
From the limbs of Leda sank
But not from her protecting care.

"Lullaby", William Butler Yeats,1865-1939)

CHAPTER TWO:

GENERAL METHODS

2.1 Overview of ethical approvals

This section will summarise the ethical approvals gained for each of the studies presented in this thesis. Chapter 3 presents data from the SERVE-HF study, an international randomised trial for which international Research Ethics Committee (REC) approval was gained and can be found in appendix 1. Ethical approval for the study in the United Kingdom was given by the Leeds (West) REC (REC no. 08/H1307/41) in May 2008. The study was also approved by the Royal Brompton and Harefield Research and Development Office (project reference 2008EP001B) and is registered on the clinicaltrials.gov website (NCT00733343). ResMed were the sponsors of this study.

Chapter 4 presents data from a substudy of the SERVE-HF study which investigated the control of breathing and was conducted at the Royal Brompton Hospital only. It received ethical approval in June 2009 from the South West London REC no. 1 (REC no. 09/H0708/35) which can be found in appendix 2**.** It was approved by the local Research and Development Office in the same month. This study included patients recruited into the SERVE-HF study, patients not in the SERVE-HF study and healthy older controls. It is registered on the clinical trials website (NCT00976417) and was sponsored by ResMed.

Chapter 5 presents data from a study investigating the effect of CRT on chemosensitivity. It was granted ethical approval by the West London REC no. 3 in September 2010 (REC no. 10/H0706/50) and was approved by the local Research and Development Office in the same month (project reference 2010C5005B). Documentation can be found in appendix 3. Imperial College, London sponsored this study.

Chapter 6 presents additional data from the local substudy in chapter 4 which investigated subjective sleepiness and physical activity levels in patients with HF and SDB. This data was collected after submission of a substantial amendment to the South West London REC no. 1 in March 2010 (documentation can be found in appendix no 4).

Explanation of each research study and subsequent informed consent was taken by the same person on every occasion (AA) who has been trained in the assessment of capacity and taking consent. The process of informed consent and all contact with participants complied with the principles set out in the General Medical Council's guidance on Good Medical Practice and complied with the standard operating procedures provided by Imperial College.

2.2 Questionnaires

Several questionnaires were used in this work and an account of each will be given here.

2.2.1 Epworth sleepiness scale

This is a self-administered questionnaire which asks the user to rate the likelihood of dozing off in 8 different scenarios as either “no chance”, “low”, “moderate” or “high”. Each response attracts a score of 0, 1, 2 or 3 and the combined score provides an indication of the level of sleepiness, with the highest score possible being 24 (and the lowest 0). A score of over 10 is conventionally used to indicate elevated levels of subjective sleepiness and over 16 is considered to be a high level. It was developed by Dr. Murray Johns in 1990 (Johns, 1991) and updated in 1997. The scale has been shown to be reliable and have good internal consistency when tested over 8 months, and also to be responsive to treatment of obstructive sleep apnoea (Johns, 1992). Although widely used it does not correlate well with measures of sleep apnoea severity nor with measures of objective sleepiness, such as the multiple sleep latency test (Chervin and Aldrich, 1999). The main strength of the ESS is its ease of use, both to administer and to complete. The questionnaire can be found in appendix 6.

2.2.2 Minnesota Living with Heart Failure Questionnaire

The Minnesota Living with Heart Failure Questionnaire (MLHFQ) is a self-administered questionnaire developed in 1984 as a measure of the effect of the HF syndrome on the physical, social, emotional and mental aspects of quality of life. The questionnaire asks the subject to rate if, and to what extent, 21 different factors relating to their HF have prevented them from living as they would have wanted to over the 1 month prior to the test being taken. Subjects are presented with a 0 to 6 scale where 0 is “not at all”, 1 is “very little” and 5 is “very much”. In a meta-analysis the MLHFQ was found to have high reliability, validity and responsiveness (Garin et al., 2009). The questionnaire can be found in appendix 5.

2.2.3 EQ-5D questionnaire

The EQ-5D questionnaire is a self-administered standardised measure of health status available since 1990 and developed by the EuroQol Group, a collaboration of international researchers working in the area of health status assessment and measurement. There are over 120 translated versions of the questionnaire. It has 2 components, the EQ descriptive system and the EQ visual analogue scale. The former consists of questions relating to 5 dimensions; mobility, self care, usual activities, pain/discomfort and anxiety/depression and for each the subject is asked to tick 1 of 3 boxes to

indicate if they have had “no problems” in that area, “some problems” or “extreme problems”. The visual analogue scale is a vertical scale labelled at the top with “best imaginable health state” and at the bottom with “worst imaginable health state”; the subject is asked to indicate with a line where they rate themselves. All responses relate to the health state of the subject at the time of completing the questionnaire (in contrast to the MLHFQ). The overall score is not a sum of the responses but is calculated using the pattern of responses with the use of a formula which attaches values to each possible response of each of the 5 dimensions. The EQ-5D was designed primarily as a health economic tool. It has been shown to have a high level of test-retest reliability (in a British population) (van Agt et al., 1994). When compared to another widely used measure of quality of life, the Short-Form 36, the two were found to broadly agree although the EQ-5D was less sensitive, a fact thought likely due to the fewer dimensions it addresses (Brazier et al., 1993).The questionnaire can be found in appendix 7.

2.3 Six minute walk test

The six minute walk test (6MWT) is a sub-maximal exercise test and as such is a measure of functional capacity which provides an overall assessment of cardiac, respiratory and musculoskeletal function. The test was performed in accordance with the guidance provided by the American Thoracic Society (Crapo, 2002).

For the purposes of data collection for this thesis the test was carried out using a 30 meter route with markers placed at 3 meter intervals. Prior to the test subjects had a 10 minute rest while the test was explained to them. Oxygen saturations and heart rate were measured and recorded (Nellcor, Coviden-Tellcor, Boulder, USA) before the test was started and the patient was instructed to walk as far as possible during the timed period without running, without a practice. All tests were carried out by the same person (AA) and standard instructions were given to each subject, in accordance with the ATS guidance. Laps were counted manually and recorded. At the end of the test subjects were asked to sit and oxygen saturations and heart rate were reassessed. Subjects had the option to terminate the test early if unable to continue. The total distance walked in the time allowed was calculated.

Various equations exist to calculate predicted distance (Jenkins et al., 2009) but serial measurements in the same individual are often used to measure response to treatment or progression of disease and this was the case when the 6MWT was used in this thesis.

The distance walked in 6 minutes has been used in models to predict prognosis in patients with HF (Zugck et al., 2001) and has been shown to be reproducible, to be more sensitive to deteriorations in HF than to improvements (O'Keeffe et al., 1998) and increase after treatment with captopril in older patients with HF (De Bock et al., 1994).

2.4 Spirometry

Spirometry was undertaken in all subjects undergoing measurement of the hypercapnic ventilatory response. Both forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC) were measured according to standard criteria (Miller et al., 2005). A reduction in the FEV_1/FVC ratio is indicative of airways obstruction with the percentage predicted FEV_1 conventionally used to describe its severity.

Spirometry was performed with a hand held device in the sleep laboratory using the Vitalograph 2120 (Vitalograph Ltd, Buckinghamshire) with a pneumotachograph with integration of flow to derive volume (Miller et al., 2005) and this was calibrated with a 1 litre syringe with an accuracy of ±3%. The test was explained and the required manoeuvres described and then demonstrated by the researcher. The best of 3 efforts, with the subject standing, was recorded. The test was terminated in the event of the subject, many of them frail elderly patients, feeling unwell.

Normal values are influenced by age, height, gender and ethnicity. Equations for their calculation are given in table 2.1.

Table 2.1: Predicted normal values for spirometry. Height is in cm, age is in years.

	Males	**Females**
FEV_1	=4.3 x height -(0.029 x age)-2.49	=3.95 x height - (0.025 x age) -2.60
FVC	=5.76 x height - (0.026 x age) -4.34	=4.43 x height - (0.026 x age) – 2.89

FEV1- forced expiratory volume in 1 second; FVC- forced vital capacity.

2.5 Measurement of the hypercapnic ventilatory response

Chemosensitivity was assessed by measurement of the HCVR using the Read rebreathing technique (Read, 1967). The purpose of this test is to measure the ventilatory response to a known concentration of CO_2. This method was developed so allow faster (serial) measurement of chemosensitivity than other steady state techniques permit, without the need for invasive measurements, and so to be suitable for unwell patients. The theory behind the technique will be described, followed by a description of the protocol used, calibration technique, description of data analysis and then a discussion of the advantages and disadvantages of the rebreathe test and how it compares to other techniques.

2.5.1 Theory of the Read rebreathe test

An accurate measurement of the ventilatory response to CO_2 requires that the concentration of CO_2 around the central (medullary) chemoreceptor be known. An approximation is possible by measuring arterial CO_2 although this, while possible, is not practical in many cases. Traditional methods for the measurement of HCVR involve the establishment of a steady state however the Read rebreathe technique involves rebreathing from a bag containing a known volume of CO_2 (with balance O_2) which is close to mixed venous blood (7% is conventionally used). Fowle and Campbell observed that this results in a rapid equilibration between end tidal CO_2 ($ETCO_2$), mixed venous blood, aterial blood and so the CO_2 around the medullary chemoreceptors, and that this occurs within about 15 seconds of the commencement of rebreathing (Fowle and Campbell, 1964). In this way changes in $ETCO_2$ becomes a surrogate of changes in CO_2 at the chemoreceptor. They also observed that $ETCO_2$ rises at a rate of about 6 mmHg every minute for 4 minutes of rebreathing.

For this rebreathe technique to accurately measure the ventilatory response to CO_2 this equilibrium must be achieved rapidly such that a physiological “open loop”, where $ETCO_2$ and the concentration of CO_2 around the central chemoreceptor are not dependant on ventilation, can be established. In this way the rise in CO_2 is a function of time, and not ventilation. This is in contrast to the steady state method, which is a “closed loop” technique and is discussed in section 2.5.5.

The use of hyperoxia (93%) removes the effect of hypoxia on ventilation and was traditionally considered as a means to ensure that only the central, rather than the peripheral chemoreceptors, were involved. As discussed in section 1.6.1 is its now understood that the nature of the relationship between the peripheral and central chemoreceptors is likely to be synergistic and more complex than previously thought (Smith et al., 2007, Solin et al., 2000).

2.5.2 Rebreathing protocol

The test was explained to patients before the day of the laboratory test and again on the day of the test as I observed that this greatly improved tolerance of and compliance with the test. To avoid distractions affecting ventilation during the test every effort was made to keep noise in the laboratory to a minimum, to ensure the subject was comfortable and had emptied their bladder before the start of the test. Subjects were asked to refrain from caffeine from noon on the day of the test and asked not to have their evening meal until after the test was complete. Where the test was done in the morning the patient was asked to refrain from caffeine until after the test, when they were also offered breakfast.

The subject was asked to rest supine in the laboratory for 10 to 15 minutes, at the start of which resting oxygen saturations, non invasive blood pressure measurement and spirometry (see section 2.4) were measured. The patient was closely observed to ensure wakefulness was maintained.

Just prior to the test a 6 litre anaesthetic bag was filled with 7% CO_2 and balance oxygen and the concentration checked to ensure accuracy. To ensure sufficient gas in the bag it was filled with FVC plus 1 litre, as described by Rebuck (Rebuck, 1976). The bag was attached to a 3 way tap and a mouth piece, with a catheter placed within it to measure $ETCO_2$ using an infra-red sensor (CD-3A, AEI Technologies, Illinois, USA). Flow was measured by a pneumotachometer, placed next to the mouthpiece (Series 4700, Hans Rudolph, Kansas, USA). The pressure difference across the pneumotachometer was measured by a differential pressure transducer (MP45, Validynne, USA; range ±2cmH_2O) and this was converted to a voltage and converted to a proportional DC signal. The bag, tap and mouthpiece were suspended above the patient and the patient asked to breathe through the mouthpiece, with the tap turned so they were breathing room air. A nose clip was applied. Oxygen saturations and heart rhythm were measured throughout using digital oximetry (2-3 second averaging time, N-200E, Nellcor® Colorado, USA) and 3 lead electrocardiogram (LifePulse HME, UK). The arrangement of apparatus used is illustrated in figure 2.2.

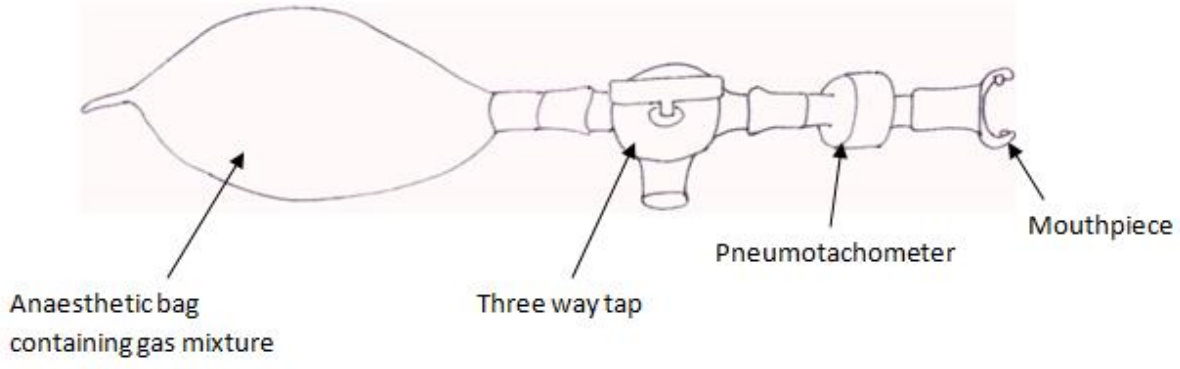


Figure 2.1: Apparatus used for the Read rebreathe. (Original figure)

The test comprised 3 phases as illustrated in figure 2.2. Initially the circuit was left open to room air for approximately 5 minutes to allow the patient to get used to the set up and monitoring (phase 1). When the subject was comfortable and $ETCO_2$ stable the 3 way tap was turned with the subject in held expiration; with the tap turned they were instructed to take 3 larges breaths in and out (Rebuck, 1976) to enhance rapid equilibration as described. The subject was asked to breathe through this circuit for 5 minutes or for as long as was tolerated (phase 2) at the end of which time the circuit was opened again to room air and the subject monitored for approximately 5 minutes (phase 3). A further rest period of 10 to 15 minutes concluded the protocol. Data was acquired in real time for subsequent analysis using a computerised data acquisition system (Micro 1401, Spike 2, CED, Cambridge, UK).

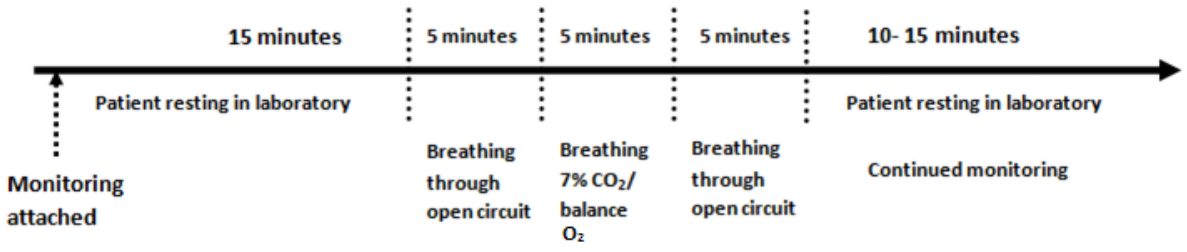


Figure 2.2: Schedule used for the measurement of the hypercapnic ventilatory response.

A screen shot of the raw data obtained in shown in figure 2.3. The x axis is time in seconds, the upper trace is CO_2 (in mmHg) and the lower is ventilation (in volts, before conversion to L/min). This test was performed on a healthy subject in the morning.

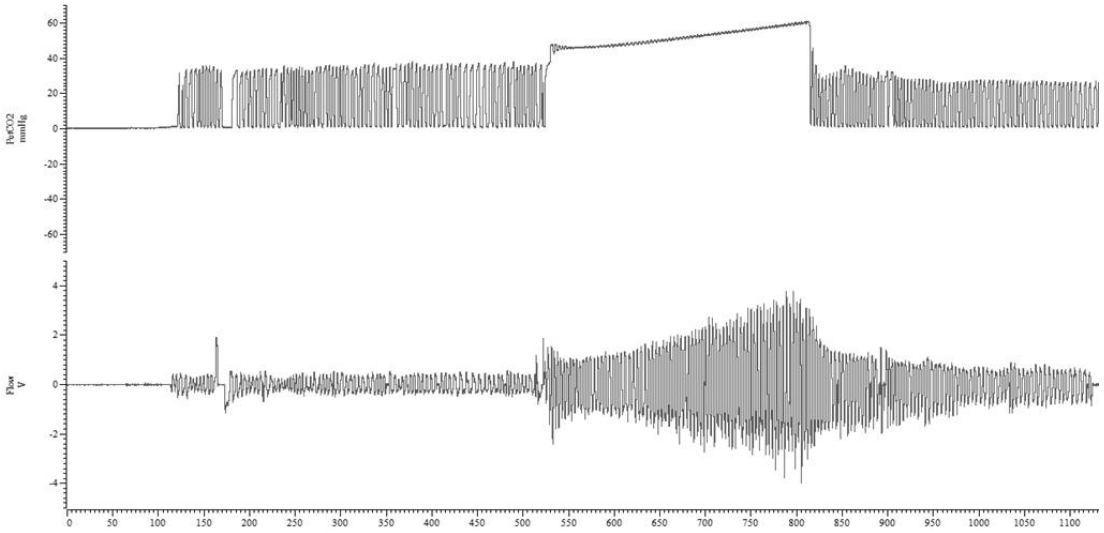


Figure 2.3: Raw data from HCVR test in a healthy subject. (Original figure). The top signal is $ETCO_2$ measured using a sensor in the mouthpiece, as described in the text, and measured in mmHg. The lower signal is flow, measured by a pneumotachometer. Here it is displaced in volts, before its conversion to L/min. The x axis is time in seconds. Rebreathing commenced at 525 seconds and finished at 810 seconds after this recording started.

2.5.3 Calibration

The data acquisition system measures both CO_2 and flow in volts. The infra-red CO_2 sensor was calibrated before every test using first room air (CO_2 0.03%) then alpha grade 5% carbon dioxide (BOC, UK) and the sensor adjusted as necessary. This was used to create a conversion factor to covert volts to mmHg. The pneumotachometer was calibrated using 9 cycles of a 1 litre syringe (accurate to within 3%) at a rate similar to 3 slow breaths, 3 resting breaths and 3 fast breaths. This was later used to create a conversion factor for volts to L/min. Data from the calibrations were viewed in real time and saved for later off-line analysis.

2.5.4 Data analysis

Breath by breath analysis was undertaken using an automated script which measured $ETCO_2$ and minute ventilation and these were plotted to produce a slope of HCVR. The x intercept which is the theoretical CO_2 at which ventilation would cease, was calculated mathematically from the slope describing the relationship between ventilation and CO_2.

2.5.5 Rebreathe versus steady state techniques

The rebreathe method has some clear advantages; it is a quick technique and so may be tolerated better by subjects, particularly in the presence of cardio-respiratory disease. Because it is associated with a rapid rise in CO_2 levels it is associated with a fairly sharp increase in ventilation, particularly in those with a brisk ventilatory response to CO_2, such as those with HF and central SDB (Javaheri, 1999, Solin et al., 2000). For this reason it may be less well tolerated in this group, particularly in patients who are very frail.

The steady state method involves a much longer protocol but involves sequentially increasing concentrations of CO_2 being added to the circuit to allow ventilation to increase gradually and plateau with each concentration. The longer duration of this test may affect its tolerability but the rate of increase in ventilation is less than that with the Read rebreathe method. Berkenbosch *et al.* compared the two methods in ten healthy controls and found the HCVR to be consistently more brisk in the rebreathe, compared to the steady state method (Berkenbosch et al., 1989). A modification of the traditional steady state method, called the Fenn and Craig technique (Fenn and Craig, 1963), involves increasing the concentration of CO_2 every 5 minutes (Nickol et al., 2009).

2.5.6 The repeatability of the Read rebreathe method over time

It is well established that there is a high level of variability in HCVR between individuals who are both healthy (Read, 1967) and in those with HF (Javaheri, 1999). Studies presented in chapters 4 and 5 involve the measurement of the HCVR in HF patients; specifically, in chapter 5 this is done before and after CRT. In order to establish the potential confounding effect of variability in the HCVR over time in each individual, and to investigate the consistency of methodology used, the repeatability of the Read rebreathe technique in healthy controls studied in our laboratory over 3 to 4 months was investigated.

Six healthy older controls (median (IQR) age 64 (61-68) yrs) had evening and morning measurements of HCVR made at both baseline and between 3 and 4 months later. Results for the change in evening to morning HCVR in each of the 6 control subjects at baseline and at follow up is given in table 2.2 and group data are given in table 2.3. The Wilcoxon Signed Rank test was used to compare data from baseline and follow-up. There was no statistically significant difference between evening or morning HCVR, nor overnight change at baseline and follow up, as shown in table 2.3. The evening HCVR at baseline and follow up is shown in figure 2.4.

Table 2.2: Individual healthy subject data for the change in evening to morning HCVR from baseline to follow-up.

subject no.	Overnight change in HCVR at Baseline	Overnight change in HCVR at follow-up
1	-0.476	-0.009
2	-0.182	-0.506
3	-0.461	-0.755
4	2.454	-1.147
5	-0.713	-0.522
6	-0.414	-0.256

HCVR-hypercapnic ventilatory response.

Table 2.3: Group data for hypercapnic ventilatory response at baseline and follow up in 6 healthy subjects.

	Baseline	Follow-up	
Evening HCVR	1.953 (1.812-2.782)	2.006 (1.722-2.269)	p=0.92
Morning HCVR	1.883 (1.210-3.636)	1.512 (0.951-2.119)	p=0.75
Overnight change HCVR	-0.438 (-0.535 - 0.477)	-0.514 (-0.853 - -0.194)	p=0.60

HCVR- hypercapnic ventilatory response.

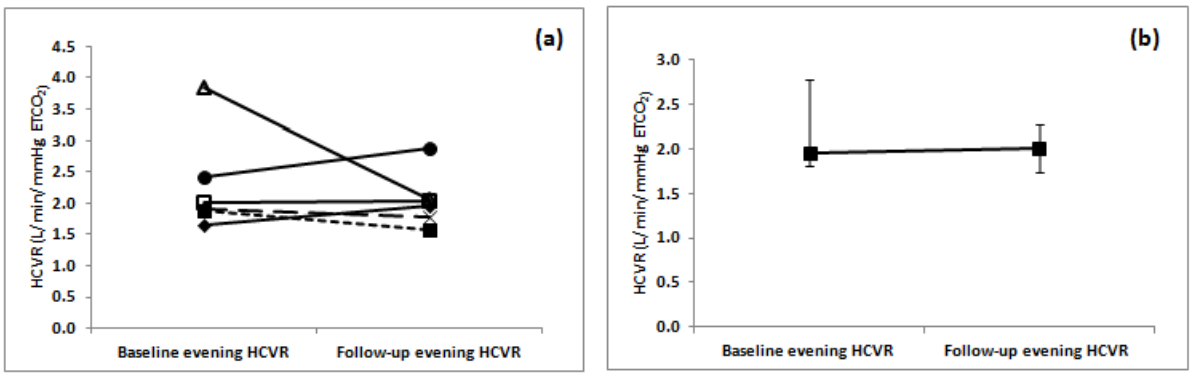


Figure 2.4: Evening HCVR at healthy subjects at baseline and follow-up, 3-4 months later (a) individual data and (b) group data. *HCVR- hypercapnic ventilatory response.*

2.6 Respiratory sleep studies

This section will describe the diagnostic studies used in chapter 3, the SERVE-HF study.

2.6.1 ApneaLink™ with oximeter

The ApneaLink™ with oximeter (ResMed Inc., Sydney, Australia) was used to screen potential participants for the SERVE-HF study. It is a type IV portable monitoring device (ie. measurement of 2 variables) which measures nasal pressure using nasal cannulae (as a surrogate of airflow) and heart rate and oxygen saturations using digital oximetry. The original ApneaLink device measured only airflow. These channels permit calculation of the AHI and the ODI. Because there is no objective measurement of sleep the denominator used to determine these is the total recording time, rather than the total sleep time which would be used in PSG. This tends to result in an underestimation of both the AHI and ODI since total recording time is generally longer than the total sleep time. The ApneaLink™ has been validated against hospital PSG for the diagnosis of obstructive SDB (obstructive sleep apnoea) (Ng et al., 2009). Another validation study using PSG has shown the device to be effective at correctly identifying CSR when used with its associated software which is designed to detect periodicity (Weinreich et al., 2009).

The device was given to patients expressing an interest in the SERVE-HF study but in whom the presence or absence of SDB had to be determined. Patients took the device home after an explanation of how to use it. Additionally, I created written, step by step instructions to assist patients and these are found in appendix 14. The next morning the device was posted it back and the data downloaded to a desktop computer. The device software provides a report including AHI and ODI and also permits inspection of the nasal pressure, oximetry and heart rate traces. I inspected these raw data and patients with evidence of likely central SDB (as evidenced by a periodic pattern or clear CSR) were invited to attend the laboratory for respiratory PG, which is discussed next.

2.6.2 Respiratory polygraphy

Respiratory PG was requirement of entry into the SERVE-HF study (see chapter 3). This was done with the Embletta™ (ResMed Inc., Sydney, Australia), a type III portable monitoring device (ie. measurement of 4 variables) which records nasal and oral airflow, respiratory effort, snore, oxygen saturations, heart rate and body position. Table 2.4 gives details of these channels. Respiratory inductance plethysmography is described in the next section. Each sensor is attached and then connected to the control box which is worn around the waist. Like the ApneaLink™ this device provides no objective measure of sleep and so the denominator used to calculate AHI and ODI is the total recording time.

The Embletta™ device was also able to be used to measure mask pressure and differential pressure on nights when adaptive servoventilation was used. This required the use of an in line differential pressure device (Pneumoflow™, MAP Medizin-Technologie GmbH, Germany) which was customised to connect to the Embletta™ interface and provide a channel on the recording.

The Embletta™ device was connected to a computer the next morning and the data downloaded. Although automated scoring is possible with the device software all data were scored by hand by the same scorer (AA) to determine eligibility. Figure 2.5 shows a screen shot from the Embletta™ software taken from a patient recruited into the SERVE-HF study.

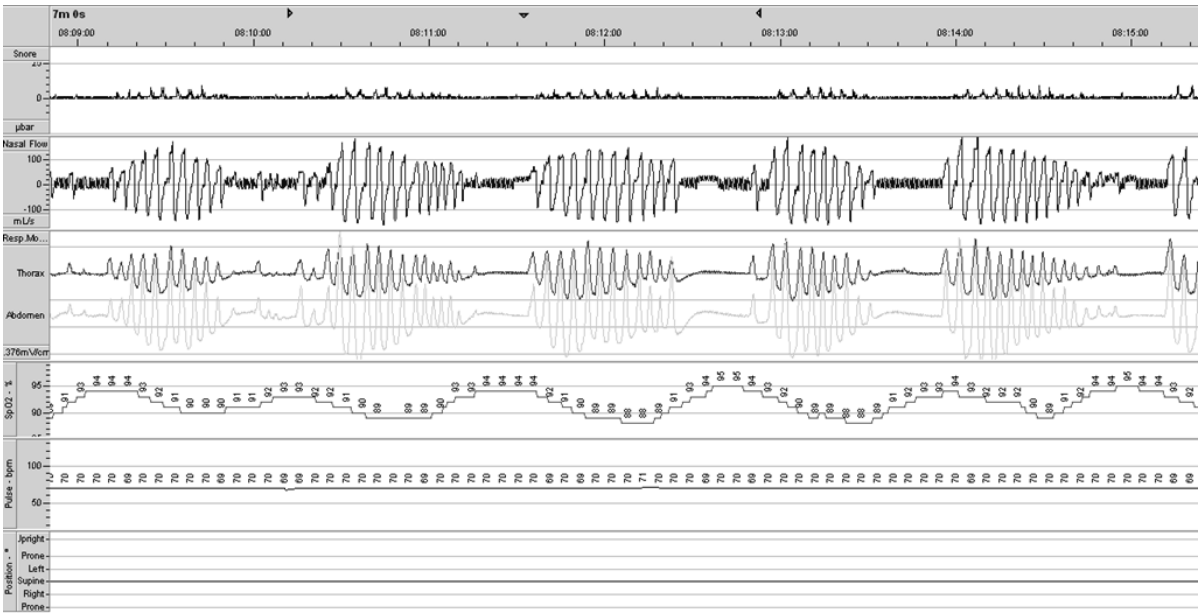


Figure 2.5: Seven minute epoch of respiratory polygraphy from a patient with HF and central SDB. Channels (from the top) are snore, airflow (nasal pressure), thoracic and abdominal movement (effort), oxygen saturation, heart rate and body position. For simplicity oral airflow is not shown in this figure but it was used in the analysis of raw data. Recurrent apnoeas are seen with associated desaturations.

Table 2.4: Channels recorded by the Embletta™ device.

Channel	Measurement
Nasal airflow	• nasal pressure using nasal cannuale (Embla, Colorado, USA) • cannulae connected to differential pressure transducer and converted to a proportional voltage • provide a surrogate of airflow and sensitive to airflow limitation
Snore	• vibration sensor placed medial to carotid region • detection of turbulence in surrogate flow signal
Oral airflow	• oral thermistor; thermally sensitive resistor to detect inhalation (of cooler, ambient air) and exhalation (of warmer air)
Respiratory effort	• thoracic and abdominal bands measure effort using respiratory inductance plethysmography (RIP) • bands cut to size for each patient • attached around patient at level of T4 vertebra and at level of the umbilicus
Oxygen saturation	• digital oximetry • averaging time of 3 seconds • accuracy of ±2% in the 70-100% range, and ±3% in the 50-70% range.
Heart rate	
Body position	• Internal sensor within control box

2.6.3 Respiratory inductance plethysmography

For both the respiratory PG studies (section 2.6.2) and the PSG studies (section 2.7) respiratory effort was measured using bands employing respiratory inductance plethysmography (RIP). This technology uses an alternating current passed through a fine insulated metal wire contained within the band to generate a magnetic field. The changes in the cross-sectional area of this field alter the current and this is converted into a voltage which is proportional to the change in area. Although these bands may be calibrated to provide a quantitative measure of tidal volume, they may also be used without calibration to provide a semi-quantitative measure of respiratory effort.

2.7 Polysomnography

The ability to discern wake from sleep by means of electrical activity from the brain was developed only as recently as 1928. The word polysomnography comes from both Greek (poly-, meaning many and denoting many channels) and Latin (sommus, meaning sleep); hence polysomnography simply means an overnight multi-channel recording of sleep. Conventionally nocturnal PSG involves measurement of electroencephalograms (EEG), electromyograms (EMG) and electrooccculograms (EOG) to enable accurate sleep staging. Respiratory measurements, as discussed in section 2.6, are also included. Polysomnography was carried out using the SOMNOmedics (GmBH, Germany) system which includes both the hardware and the software system.

2.7.1 Placement of EEG, EMG and EOG electrodes

The international 10-20 system of electrode placement, first described in 1974, provides a standardised manner in which EEG electrodes may be applied and is based on measurements taken from the nasion, inion and right and left pre-auricular points (Harner and Sannit, 1974). Figure 2.6 illustrates these landmarks.

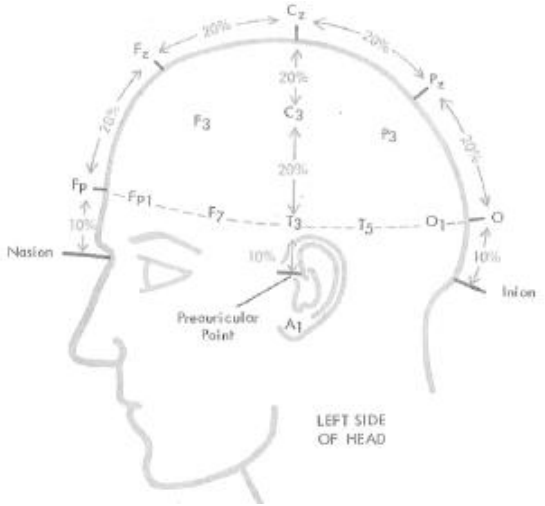


Figure 2.6: Electrode placement using the 10-20 system. Figure shows the main landmarks on the left side of the head and the application of the 10 and 20% measurement rule. Figure taken from Hanner and Sannit, 1974 (Harner and Sannit, 1974).

Gold cup electrodes (Grass instruments, Astro-Med Inc., USA) were applied at the C4 (right) and C3 positions and each were referenced to disposable electrodes at the opposite mastoid (right A2 and left A1). Another gold cup was applied in the O1 (left occipital) position and also referenced to A2. A disposable electrode (Neuroline, Ambu Ltd., UK) was applied to the middle of the forehead as a

ground electode. Electroocculograms were applied 1 cm lateral and inferior to the left outer canthus of the eye and 1cm lateral and superior to the right outer canthus of the eye using disposable electrodes. Electromyograms were applied over the submentalis muscle, under the chin.

After the scalp was measured and each location marked with a chinagraph pencil, the skin at each site was prepared to keep electrical impedance low; it was cleaned with an abrasive gel (Nuprep, D.O., Weaver and Co., USA) and then alcohol swabs. The gold cup electrodes were carefully filled with Ten20 conductive paste (D.O. Weaver and Co., USA), placed on the scalp and secured with Collodion glue (S.L.E. Diagnostics Ltd., UK). The skin was cleaned in the same manner for the disposable Neuroline electrodes, which were self adhesive. Neuroline electrodes at both mastoids (A1 and A2) were also secured with medical tape. All electrodes were connected to the headbox and that to the control box, worn around the subject's waist. Respiratory measurements were also undertaken (as described in 2.6) with digital pulse oximetry, nasal pressure and oronasal thermistor and RIP. All electrodes were attached before the subject retired at their usual bed time. Figure 2.7 shows a patient, with his permission, set up with the equipment just before bedtime.



Figure 2.7: Patient set up for nocturnal polysomnography and ready for bed. Photograph included with patient's permission.

2.7.2 Signal acquisition, quality and calibration

Once the electrodes were in place and the rest of the equipment secured the control box was turned on and a transmitting device attached to permit the amplified electrical signals to be captured in the office next to the sleep laboratory and watched in real time. The data was also recorded onto a flash card within the control box. Electrical impedance was checked to ensure that recording of electrical activity from the brain was favourable; impedance of over or equal to 10 000 ohms was considered unacceptable and if present prompted a search for a cause and /or a repositioning of the electrode.

The EOG and EEG electrical signals were sampled at a rate of 128 Hz and the EMG at a rate of 256 Hz, according to the AASM guidelines (Iber et al., 2007). In order to capture only the electrical frequencies of concern high and low pass filters were set. For EEG these were 0.2 and 35Hz (high and low respectively), for EMG they were 10 and 100 Hz and for EOG they were 0.3 and 10Hz. Because adjacent electrical appliances and power sources can interfere with the signal an additional filter was set at 50 Hz (notch filter) to reduce this artefact.

Finally a series of checks were undertaken on each signal to ensure their validity. The subject was asked to carry out a standardised sequence of activities. The instructions given were as follows;

1. Take large deep breaths in and out
2. Take short, small, panting breaths in and out
3. Hold your breath
4. Blink as fast as you can
5. Look from the floor to the ceiling and repeat
6. Look from side to side and repeat
7. Close your eyes
8. Push your tongue into your lower teeth (to simulate bruxism) and repeat
9. Keeping your heel on the group, tap with your right toes, then repeat with the left.

Recording of EEG activity with the eyes shut and the patient is known to be awake is often useful as a comparison when determining the onset of sleep. The scoring of sleep is discussed in section 2.10.1.

2.8 Adaptive servoventilation

Adaptive Servo-ventilation is a novel form of positive pressure ventilation characterised by delivery of a variable level of pressure support to the patient which is the reciprocal of the patient's own effort (discussed in Chapter 1, section 1.7.4). This variable pressure support is superimposed on a low level of end expiratory pressure (EPP; analogous to CPAP) which serves to stabilise the upper airway and remove airflow limitation. This device is CE certified for marketing in Europe as the Autoset CS2™ and FDA approved in the USA where it is marketed as the VPAP Adapt SV ™. In the UK the Autoset CS2 ™ device retails at £5000 and is available for the treatment of CSA/CSR. For comparison a standard CPAP device now costs in the region of £350-400. During the course of the SERVE-HF study (see chapter 3) a new model was released as the Autoset CS™ (VPAP Adapt™ in the USA). The newer device uses the same, patented, treatment algorithm but is quieter and easier to use, particularly when combined with a humidifier.

The device is mains powered and is comprised of a microprocessor controlled flow generator, tubing for air delivery to the patient and a pressure sensing tube with a mask interface and head gear. It is capable of delivering a pressure support level of between 3cm and 15cm H_2O superimposed on an End Expiratory Pressure of between 4 and 10 cmH_2O. The default settings are an EEP of 5cmH_2O, a minimum inspiratory pressure of 3 cmH_2O and a maximum inspiratory pressure of 10 cmH_2O. The maximum permitted peak inspiratory pressure is 20 cmH_2O.

Conceptually the device is designed around the pathophysiology of central SDB in that it aims to ensure the patient is not over ventilated so that the CO_2 is not allowed to fall below the apnoeic threshold. By preventing respiratory events (therefore theoretically arousals from sleep) it aims to smooth out breathing by providing pressure support when it is needed (e.g. during an apnoea) but not when it's unnecessary (e.g. during a hyperpnoea). Figure 2.8 illustrates the relationship between the device pressure support and the flow delivered to the patient.

ASV measures the patient's stable ventilation over a 100 second period of time and from this calculates a target ventilation which is 90% of the recent ventilation. To do this the device measures the patient's intrinsic respiratory rate including the ratio of inspiration to expiration and the length of the expiratory pause. In the event of a prolonged apnoea the device will initiate a back up rate of

15 breaths per minute until patient effort resumes. In addition measurements of the patient's intrinsic flow are taken at 12 points in the flow wave as illustrated in figure 2.9.

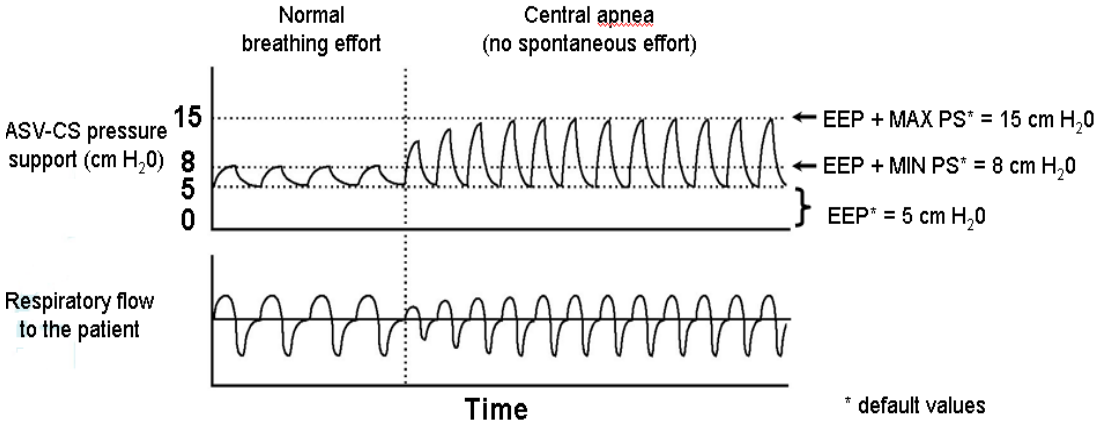


Figure 2.8: Illustration of the pressure support generated by the device and the respiratory flow to the patient. (Illustration taken from ResMed training material)

Should spontaneous ventilation fall below 90% of recent ventilation then pressure is delivered to achieve this level of ventilation. If spontaneous ventilation increases then pressure support is reduced back to the minimum level of 3 cmH_2O over a similar time period. The magnitude and time course of any change in ventilation by the patient is matched by the magnitude and time course of the response from the device. While ventilation remains at the baseline level the support delivered by the device is the minimum of 3 cmH_2O. The target ventilation is constantly monitored so that the physiological changes in ventilation seen in sleep are accommodated. EEP may be adjusted as necessary to abolish airflow limitation.

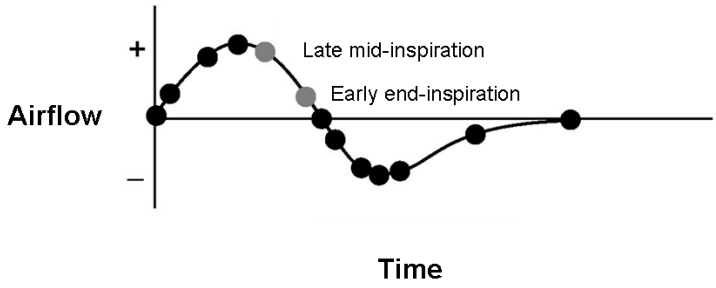


Figure 2.9: ASV takes measurements at 12 points of the flow wave. (Illustration taken from ResMed training material)

Figure 2.10 is raw data from a PG study done with ASV worn by the patient. It shows the classical crescendo-decrescendo pattern of effort in the chest and abdominal bands, but a variable level of pressure support being delivered such that the same pattern is not seen in the flow signal (see figure legend). ASV has been investigated in a number of studies.

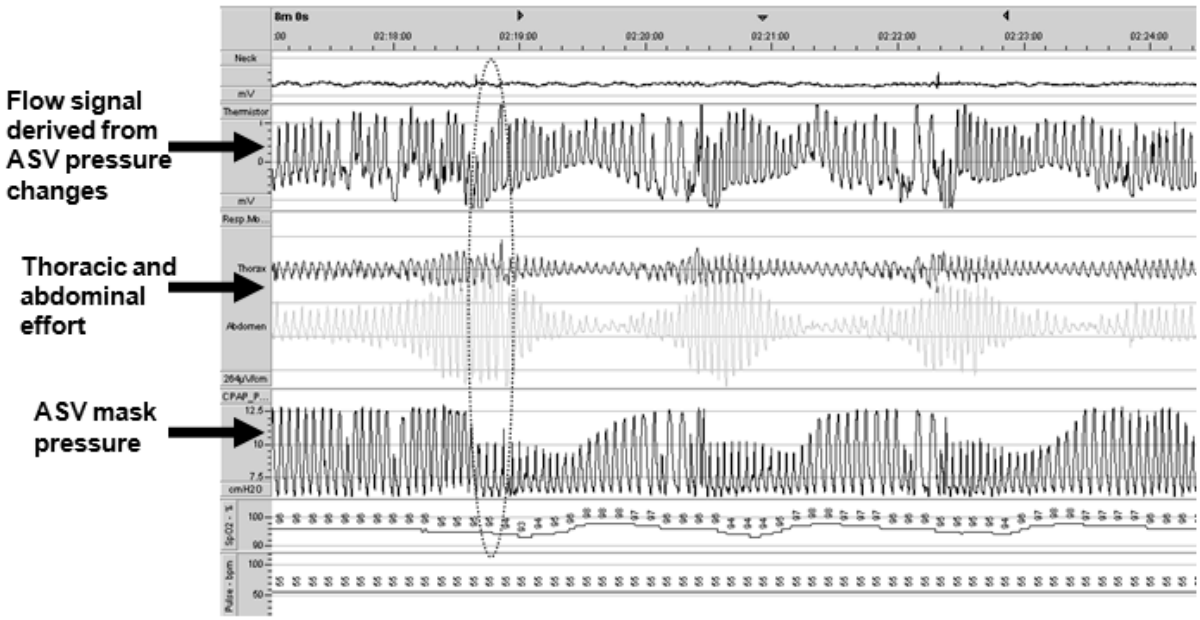


Figure 2.10: Eight minute epoch from a polygraphy study with patient wearing ASV.
Channels (from top) are snore sensor, airflow, thoracic and abdominal movement (effort), mask pressure, oxygen saturations and heart rate. The ASV device delivers a variable level of pressure support to smooth out this irregularity. The dotted oval indicates a period of hyperventilation which the device responds to reducing the pressure delivered, as evidenced by the rapid drop in mask pressure.

2.9 Activity monitoring

Actigraphy devices measure activity and can be used to discern wake from sleep as most people are more active by day, and less active by night. Historically they were used for the objective measurement of nocturnal itch (Felix and Shuster, 1975) and their use includes assessment of SDB, periodic leg movements, insomnia and the detection of circadian rhythm disturbances. The American Academy of Sleep Medicine (AASM) recognises their use as a helpful adjunct to sleep studies, particularly when availability of PSG may be limited (Morgenthaler et al., 2007a).

2.9.1 Technology

Actigraphy devices are extremely sensitive accelerometers contained within a casing the size of a conventional wrist watch. Activity is measured by a piezo-electric accelerometer which measures and records the intensity, amount and duration of movement. Movement in all directions is detected and the signal converted into a corresponding voltage which is stored as an activity count within the device. The model used in this work (Actiwatch 4; CamNtech, UK) has a sensitivity of less than 0.01g and a maximum sampling rate of 32Hz. Filters are set to 3 to 11Hz to ensure that data collected reflects movement and not artefact.

Activity is measured and recorded in counts and these units denote the amplitude of the signal from the accelerometer; the activity count is proportional to the intensity of the movement thus a higher count equals a higher intensity movement. The maximum sampling rate is 32Hz and the device samples the amplitude of the signal (32 times a second) and records the highest amplitude per second.

An epoch is selected by the user and determines the time denominator for each activity count. The actigraphy data in this thesis used a 1 minute epoch to allow a longer period of recording. The device samples the amplitude of the signal 32 times every second and the value for the epoch is the combined count from every second within that epoch. The total count for each epoch is termed the activity score. If there is no activity for the epoch the activity score will be zero. Table 2.5 gives the definitions used for some other activity terms used in this work. The Actiwatch 4 has a button which subjects press when they get into bed and when they get up in the morning.

Table 2.5: Definitions of terms used in actigraphy.

Time of day	Term	Definition
Daytime measures	**Activity score**	total activity count for an epoch
	Average duration of activity /day (hrs)	duration of time between getting up and going to bed (button presses)
	Average activity per day *	sum of daytime activity over total recording divided by number of days recorded (14 days in this work)
	Average activity per 1 min epoch *	average activity count for the period defined as wake
	Total daytime activity count over 14 days *	sum of daytime activity over total recording (14 days in this work)
Night time measures	**Time in bed (min)**	duration of time between button press when subject gets into bed and second button press when they get up
	Sleep start	requires 10 consecutive minutes of immobile data with no more than 1 epoch of movement within that time
	Sleep end	algorithm works back from last sample before "get up" button press for period of activity below the threshold for sleep (< 6 counts/epoch for 6 minutes) and classifies the last epoch in this period as sleep end
	Sleep efficiency (%)	algorithm defined sleep time as a percentage of the total duration of time spent in bed
	Sleep latency (min)	difference between bed time start (recorded by button press) and sleep start
	Immobile time (%)	number of immobile minutes (ie. only movement below threshold defined as sleep) as a percentage of total minutes in the sleep time
	Movement time (%)	number of minutes containing movement over threshold for sleep as a percentage of total minutes in the sleep time
	Total activity score (ave/night) *	total count for all epochs between sleep start and end
	Fragmentation index *	sum of percentage of minutes moving and percentage immobility; used as an indicator of restlessness.

* arbitrary units

The Actiwatch 4 uses the activity score from each epoch and those adjacent to it to determine sleep and wake, based on a validated algorithm (Oakley, 1997).

The device has a range of sensitivities, the default is medium and this was selected for the work presented in this thesis. Different sensitivities alter the number of counts/epoch required to score that epoch as wake. For example, on the medium sensitivity an activity score of 40 or more will be needed to define an epoch as wake, but only 20 for high sensitivity and 80 for low.

At the time of set up the battery in the device is placed on a reader which is attached to a computer via a serial cable. Via the specialist software (Actiwatch Activity and Sleep Analysis 5, version 5.03) the battery (lithium manganese) can checked and changed, subject ID can entered, epoch length selected and the start time (which can be delayed) selected. At the end of the recording the watch is returned and downloaded using the same reader. The time is synced between the software and the time of the computer. After set up elapsed time is measured by a crystal within the device which oscillates at a frequency of 32 Hz and it is this oscillation which the device uses to time the frequency with which it samples activity counts.

2.9.2 Instructions to subjects

The rationale of the watch was explained to all subjects in person at the start of the recording period. The watch was placed on the non-dominant wrist. Written instructions on how to use the actiwatch were provided along with instructions on how to return it and a pre-paid envelope. Subjects were asked to complete a sleep diary for all of the 14 days of the recording. These documents can be found in appendix 8 and 9. Figure 2.11 is a photograph of the device mounted on the strap. These were sterilised between each use.



Figure 2.11: Photograph of the Actiwatch 4 mounted on wrist strap. (Original figure)

2.9.3 Actograms

An actograms is a visual representation of the activity over the period of the recording and allows the difference between day and night, if there is one, to be seen. Conventionally each day is double plotted across the acrogram and this allows the interface between day and night to be seen. Figure 2.12 shows an actogram from a healthy subject who participated in the study presented in chapter 6. The horizontal bar at the top indicates the time of day and is set to start (at the left hand side) with his usual get up time of 6am. The white sections of the horizontal bar relate to daytime and the black sections relate to night time. The areas of the actograms relating to night have been enclosed with a dotted grey box. This subject attended the gym regularly and thus the very high activity levels seen every day between approximately 9.00 and 11.00 (enclosed by a white, dotted oval) correspond to his self reported gym visits (via his sleep diary). The activity here is off the scale of this actograms. Figure 2.13 shows another actogram for a healthy subject, this one a keen cyclist.

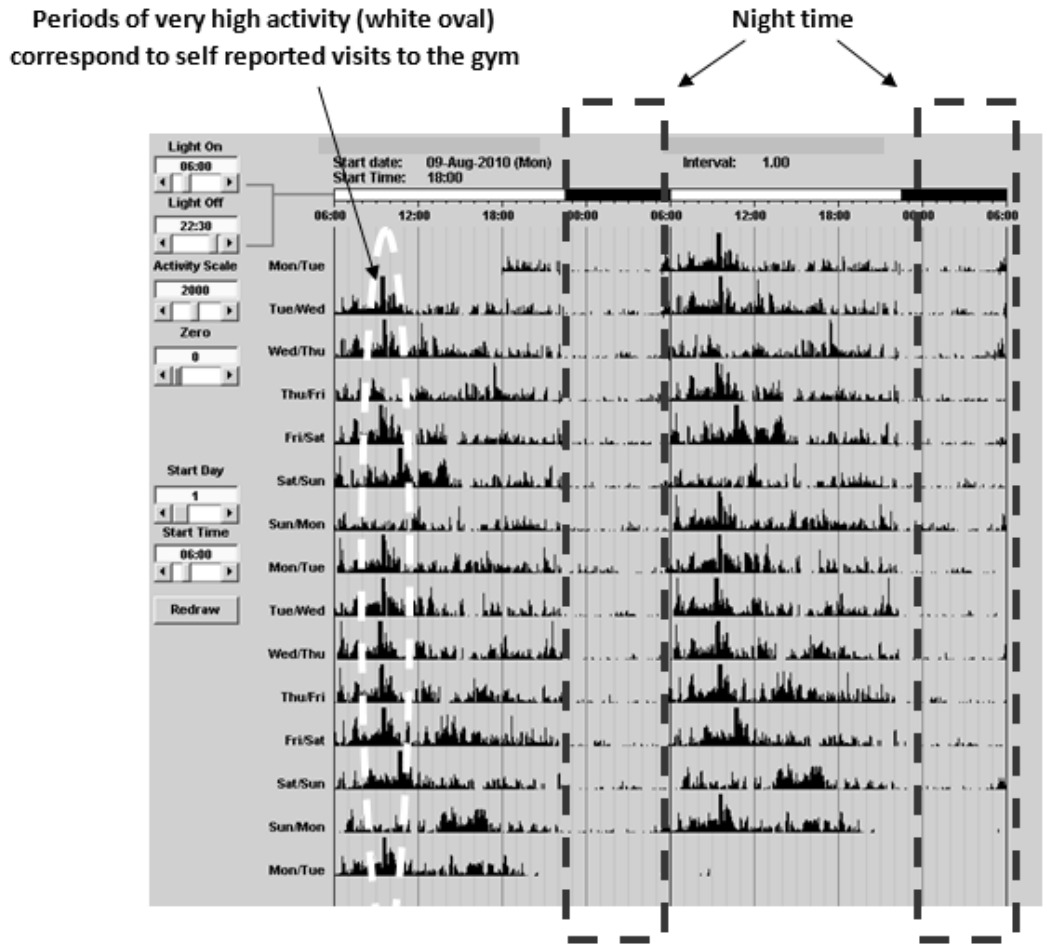


Figure 2.12: Annotated actograms for a healthy subject.

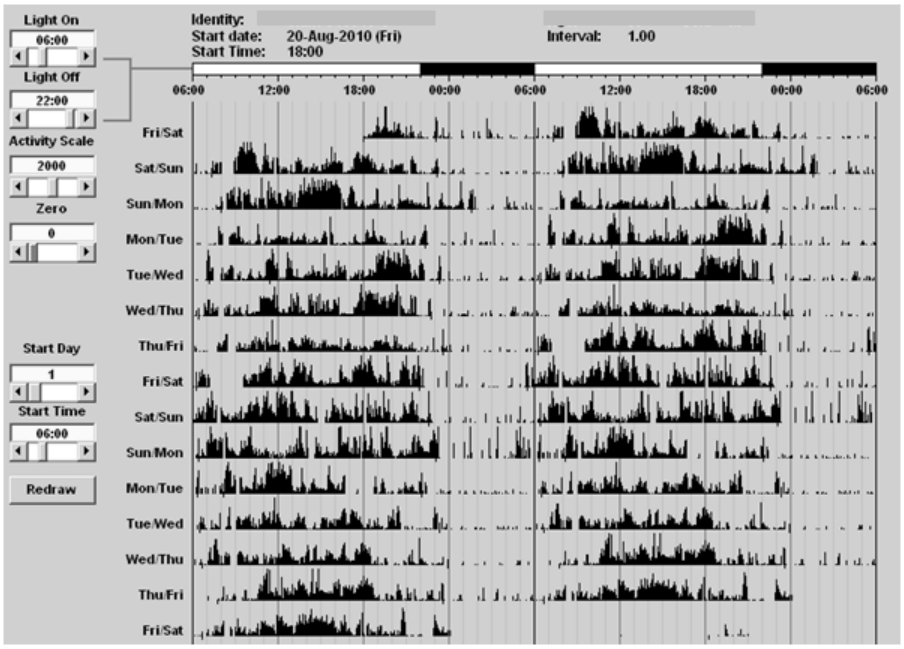


Figure 2.13: Actogram from a healthy subject.

2.9.4 Limitations of actigraphy

Subjects may forget the replace the watch after a bath or shower resulting in a variable period for which no data are available. They may forget to remove the watch before bathing which may damage the watch; the Actiwatch 4 is robust but not water resistant. Good, consistent instruction, both verbal and written, avoided this in all but 3 cases. Skin irritation may develop in response to prolonged wearing of the strap and I have customised straps for some patients to avoid this.

The actiwatch may determine the patient to be asleep if they are sitting or lying very still, but still awake. This may occur whist listening to the radio, watching television or as a passenger in a vehicle. Conversely the device may detect movement from a vehicle or a bed partner and so score an epoch as wake, when the subject is asleep. Data from patients who are tremulous or who have other abnormal movement disorders may also be inaccurate. These factors tend to result in sleep latency being lower with actigraphy than with PSG as most people lie still for a while before the onset of sleep (Blood et al., 1997). These limitations are in part countered by the subject keeping an accurate sleep log and adding information regarding their activities to it, including exercise, naps etc.

Finally, data may be affected by technical failure such as battery failure or a problem with the download process. The battery was changed before every recording to avoid this.

2.10 Data analysis

2.10.1 Scoring of sleep and respiratory events

All PSG studies were scored blinded to the identity of the patient and by the same person (AA). The AASM scoring rules (Iber et al., 2007) were used to score polysomnograms in 30 second epochs as per convention. Table 2.6 summarises the key features seen in the EEG, EMG and EOG channels for wake and each stage of sleep.

Arousals were scored according to the AASM scoring rules (Iber et al., 2007) during any sleep stage when there was an abrupt change in EEG frequency greater than 16Hz which lasted over 3 seconds and was preceeded by at least 10 seconds of stable sleep. In REM an arousal required an increase in EMG measured from the submentalis area lasting at least 1 second.

Scoring of respiratory channels was also done according to the AASM rules. An apnoea was scored when there was a cessation of flow for 10 seconds and was classified as obstructive in the event that effort was ongoing (thoracoabdominal RIP bands) and central in the event that repiratory effort ceased. A hypopnoea was scored if there was a reduction in the amplitude of the flow signal by 30% or more from its baseline for a minimum of 10 seconds in association with either a cortical arousal, as described, or a 3% reduction in oxygen saturation from baseline. A discussion relating to the scoring of hypopnoeas as either central or obstructive is given in chapter 3.

Table 2.6: Key features seen in the EEG, EMG and EOG channels for wake and each stage of sleep.

	EEG	EMG	EOG
Wake	• Alpha activity (8-13Hz) • Best seen in occipital channels (O1:A2)	• Tonic activity • High amplitude	• Blinks (0.5-2Hz) • REMs • Slow rolling movements if drowsy
Stage 1 sleep	• Theta activity (2-7Hz) • Low voltage mixed frequency • Vertex sharp waves • Alpha activity (<50% of epoch)	• Tonic activity • Slight decrease amplitude below waking levels	• Slow rolling movements at sleep onset
Stage 2 sleep	• Theta activity • Sleep spindles (>0.5sec, 12-14Hz) • K complexes (>0.5sec)	• Tonic activity • Amplitude lower than stage 1	• No eye movements • Channel activity usually reflects EEG
Stage 3 sleep	• Delta activity (<2Hz, >75µV) • 20-50% of epoch • Sleep spindles may be seen	• Tonic activity • Amplitude lower than stage 2	• No eye movements • Channel activity usually reflects EEG
Stage 4 sleep	• Delta activity (<2Hz, >75µV) • >50% of epoch • Sleep spindles may be seen	• Tonic activity • Amplitude lower than stage 3	• No eye movements • Channel activity usually reflects EEG
REM sleep	• Low voltage mixed frequency • Theta waves • no vertex waves • sleep spindles may be seen • some alpha activity	• Tonic suppression • Phasic twitches • Amplitude at lowest of recording	• REMs

EMG- electromyogram; EOG- electro-occulogram; EEG- electroencephalogram, REM- rapid eye movement.

NB; stages 3 and 4 sleep may be combined and termed slow wave sleep (SWS).

2.10.2 Statistical analysis

Statistical analyses were undertaken using the software Statistical Package for the Social Sciences (SPSS; version 19, IBM, Armonk, NY, USA). Some descriptive statistics were computed in the Microsoft Excel program (Office 2007, Microsoft, Redmond, WA, USA). Non parametric analyses were selected due to the size of the total data set or the size of the groups being compared. The Mann-Whitney U was used to compare 2 independent groups. The Kruskal-Wallis test was used to compare more than 2 independent groups and the Mann-Whitney U test was used for any subsequent between group comparisons, along with a Bonferroni correction. The Wilcoxon Signed Rank test was used to compare 2 groups before and after an intervention (such as ventilation or implantable device therapy) and where necessary the Friedman test was used when more than 2 time points were involved. Spearman Rank Order correlation was used to compare the relationships between variables.

Statistical advice was taken from statistician Mr. Winston Banya at the Royal Brompton Hospital for the sample size calculations in chapters 4 and 5. Details of the sample size calculations for each study are given within the relevant chapters.

Methought I heard a voice cry ‘Sleep no more!

Macbeth does murder sleep,’ the innocent sleep,

Sleep that knits up the ravell’d sleave of care,

The death of each day’s life, sore labour’s bath,

Balm of hurt minds, great nature’s second course,

Chief nourisher in life’s feast.

“Macbeth” (2.2.46-51)

by William Shakespeare (1564-1616)

CHAPTER THREE:

THE USE OF ADAPTIVE SERVOVENTILATION IN PATIENTS WITH HEART FAILURE AND CENTRAL SLEEP DISORDERED BREATHING - THE SERVE-HF STUDY AT THE ROYAL BROMPTON HOSPITAL

3.1 INTRODUCTION

Central SDB is prevalent in patients with HF (Javaheri, 2006b, Vazir et al., 2007, Oldenburg et al., 2007d) and is associated with nocturnal hypoxaemia, recurrent arousals from sleep and an adverse clinical outcome (Lanfranchi et al., 1999). It remains unclear, however, if treatment of this patient group with positive airways pressure is associated with a reduction in their mortality or morbidity. Nocturnal continuous positive airway pressure (CPAP) therapy has been used in a randomised control trial (the CANPAP study) (Bradley et al., 2005) and although it replicated some of the physiological benefits seen in earlier work (Naughton et al., 1995b, Mansfield et al., 2004) it failed to demonstrate a survival benefit in the CPAP group. Post hoc analyses from this study suggest that CPAP was effective in treating central SDB in some, but not all patients and that successful treatment was associated with improved survival in that subgroup (Arzt et al., 2007b). A further analysis of the CANPAP data found that CPAP treatment did not improve sleep architecture (Ruttanaumpawan et al., 2009).

As with CPAP, the use of adaptive servoventilation (ASV) has been associated with a range of physiological benefits including improved nocturnal oxygenation, left ventricular ejection fraction (LVEF) and urinary catecholamines (Pepperell et al., 2003, Hastings et al., 2008). However ASV use has also been shown to improve sleep architecture, to more effectively suppress central SDB than CPAP (Philippe et al., 2006), be preferred to CPAP by patients in the short term (Teschler et al., 2001), and to better tolerated than CPAP in the medium term (Philippe et al., 2006).

The SERVE-HF study is a multi-centre international randomised controlled trial to investigate the effect of treatment with nocturnal ASV on morbidity, mortality and health economic parameters in patients with stable chronic HF and predominantly central SDB already established on optimal medical treatment (NCT 00733343). The study rationale and design have been published in abstract form (Teschler et al., 2010). Patients are randomised to either the intervention group (ASV and standard medical treatment) or control group (standard medical treatment alone).

The study is being conducted from over 60 centres in 5 countries and is sponsored by ResMed, an Australian based manufacturer of positive pressure devices for the treatment of SDB. The study aims to test the hypothesis that the use of ASV in patients with systolic LV impairment and predominantly central SDB will be associated with a difference in time to death, transplantation or unplanned hospitalisation when compared to the control group. The SERVE-HF study started at the Royal Brompton Hospital in July 2008 and recruitment is anticipated to end in January 2013. This chapter will present data from the patients recruited at the Brompton hospital.

3.2 METHODS

Methodological issues relating both to the international study and its implementation locally at the Royal Brompton Hospital will be discussed here. A detailed description of the assessments used is available in Chapter 2, Methods.

3.2.1 Study objectives and endpoints

The SERVE-HF study is designed to compare the effects of ASV versus optimised medical treatment on the endpoints of all cause death and unplanned hospitalisation in patients with CHF and predominantly central SDB.

The primary endpoints are time to first event of;

1. All cause mortality or unplanned hospitalisation for worsening HF
2. Cardiovascular mortality or unplanned hospitalisation for worsening HF
3. All cause mortality or all cause unplanned hospitalisation

The study will test the hypothesis that the use of ASV in this patient group will be associated with a difference in time to first event compared to the control group. The null hypothesis is that there will be no difference in the time to first event between the ASV and control groups. The SERVE-HF study is an event driven study and it is anticipated that 1116 patients will need to be studied to detect a mortality difference between the groups, should one exist.

There are a range of secondary endpoints to assess several clinical and functional endpoints, including adequate shock from an implanted device, change in NYHA functional class, renal function, 6 minute walk distance and quality of life.

In addition to the main SERVE-HF study an international substudy was started in December 2010 to investigate the mechanism by which ASV may bring about clinical benefit. This study is recruiting alongside the parent study and includes measurements of left ventricular function, performance and remodelling and assessment of changes in anxiety, mood and cognition. Echocardiology is being used as well as magnetic resonance imaging (MRI) given the high proportion of patients in the parent study with an implanted device which would prohibit MRI. None of the patients enrolled at the Royal Brompton Hospital and included in the current data set were included in the international substudy during the period of my involvement in the study. A second substudy was undertaken locally, at the Royal Brompton Hospital only, and investigated the effects of central SDB in patients with HF on the control of ventilation. This study is discussed in Chapter 4.

3.2.2 Study population and enrolment

Study inclusion and exclusion criteria are shown in table 3.1. At the Royal Brompton Hospital patients were recruited from the specialist HF clinics after potential suitability for the study was identified by the clinician if the patient was interested in considering participation. The clinical research fellow would meet with the patient to discuss the study, confirm eligibility based on information available, provide a Patient Information Sheet and arrange a follow up telephone call. Most patients identified in this way did not have a known diagnosis of central SDB and so a screening sleep study was arranged; either an ApneaLink™ study (which could be set up at home by the patient and returned by post) or an in-hospital PG study. Such screening studies are done routinely at the Royal Brompton Hospital in selected chronic HF patients in whom the diagnosis of SDB is suspected.

Patients were also recruited from the general cardiology and HF clinics of 3 other hospitals in London; Ealing hospital, West Middlesex University Hospital and Chelsea and Westminster hospital. Each of these sites was visited by the research team to discuss the study with staff there. Patients met with or were contacted by the clinical research fellow or research nurse who arranged tests to confirm eligibility at the Royal Brompton Hospital. Data from ApneaLink™ studies were inspected by the Clinical Research Fellow and, where suggestive of central SDB, arrangements made for an in-patient PG study.

Patients attending for PG studies would attend the sleep laboratory at the Royal Brompton on the evening of their study. They were familiarised with the laboratory and the nature of the sleep study and the SERVE-HF study was discussed again. They were prepared for bed at their usual time and once in bed PG signals were monitored remotely by the Clinical Research Fellow from the adjoining office in case of technical failure. Patients were left to sleep until the time they usually woke and then left the department after breakfast. Sleep study results were shared with patients within 2 days and those whose PG studies met the entry criteria (See table 3.1) for the study were invited back to the hospital for randomisation, typically within a week of the in-patient PG study.

Table 3.1: Inclusion and exclusion criteria for the SERVE-HF study

Inclusion criteria	Exclusion criteria
1. Over 18 years old 2. Chronic HF; at least 12 weeks since diagnosis 3. LVEF ≤45%, documented less than 12 weeks before randomisation 4. NYHA class III or IV at the time of inclusion, or NYHA class II with at least one unplanned hospitalisation for HF in the last 24 months 5. No unplanned hospitalisation for HF for at least 4 weeks prior to inclusion 6. Optimised medical treatment, no new class of disease modifying drug, for more than 4 weeks prior to randomisation. In case of no β-blocker or ACE inhibitors/ARB the reasons must be documented. 7. SDB: AHI > 15/h with ≥50% central events and central AHI ≥10/hr 8. Patient able to fully understand study information and sign informed consent.	1. Significant COPD with FEV_1 <50% in the 4 weeks prior to randomisation 2. O_2 saturation at rest during day ≤90% at inclusion 3. Current use of positive airway pressure device therapy 4. Life expectancy <1 year for diseases unrelated to chronic HF 5. Cardiac surgery, PCI, MI or unstable angina within 6 months prior to randomisation 6. CRT or ICD implantation scheduled or within 6 months prior to randomisation 7. TIA or stroke within 3 months prior to randomisation 8. Primary haemodynamically significant uncorrected valvular heart disease expected to lead to surgery during trial 9. Acute myocarditis/pericarditis within 6 months prior to randomisation 10. Untreated or therapy refractory restless legs syndrome at the time of study entry 11. Pregnancy

HF- heart failure; LVEF- left ventricular ejection fraction;, NYHA-New York Heart Association; ACE- angiotensin converting enzyme; ARB-angiotensin II receptor blockers; SDB- sleep disordered breathing; AHI- apnoea hypopnoea index; COPD- chronic obstructive pulmonary disease; PCI- percutaneous coronary intervention; MI- myocardial infarction; CRT- cardiac resynchronisation therapy; ICD- implanted cardiac defibrillator; TIA- transient ischaemic attack.

3.2.3 Respiratory polygraphy scoring rules

Polygraphy was used in the Royal Brompton Hospital to determine the presence or absence of SDB and its predominant type and severity. In-patient PG was carried out using the Embletta™ portable diagnostic system about which more details are available in Chapter 2, section 2.6.2. Patients were asked to arrive at the laboratory no later than 20:30 and recordings were started at the patient's usual bed time, but not later than 00:00. Recordings were a minimum of 4 hours in duration. The overnight study measured breathing (by nasal pressure and oral thermistor), respiratory effort (by RIP), oxygen saturation and heart rate (by digital oximetry), snore (by vibration sensor), and body position (internal sensor). The device was worn around the patient's trunk and the various sensors secured on top of their night clothes. Signals were watched in real time via a cable from the device to a computer to a room adjacent to the patient and then remotely in the next door office in case of technical failure.

Studies were deemed technically adequate if they had an acceptable oximetry signal and 2 out of 3 respiratory signals (nasal pressure, thoracic effort band, abdominal effort band) present throughout the study. Study definitions of respiratory events are given in table 3.2.

Studies undertaken on ASV were conducted in a similar way however the measurement of breathing was done using a differential pressure device (Pneumoflow™, MAP Medizin-Technologie GmbH, Germany) and mask pressure was measured using a port on the mask connected to a pressure transducer.

Table 3.2: Definitions of respiratory events using in scoring polygraphy in the SERVE-HF study.

Polygraphy event	Study definition for scoring event
Apnoea	>90% reduction from baseline in peak amplitude of the signal from nasal cannula and oral thermistor, lasting at least 10 seconds.
Hypopnoea	30% reduction in flow and a ≥ 3% desaturation from pre-event baseline for more than 10 seconds Or 50% reduction in flow from pre-event baseline for more than 10 seconds.
Desaturation	≥3% change in saturation associated with any respiratory event; measured from the preceding stable level.
Obstructive events	Suggested by the presence of inspiratory flow limitation and/or paradoxical movement on thoracic/abdominal effort bands No mixed apnoeas scored as part of SERVE-HF; if 3 or less obstructed breaths at end of central apnoea- score as obstructive apnoea.
Central events	Suggested by the absence of features in keeping with obstructive events. Central apnoeas characterised by lack of respiratory effort on thoracic and abdominal bands. No mixed apnoeas scored as part of SERVE-HF; if 2 or less obstructed breaths at end of central apnoea- score as central apnoea.
Cheyne-Stokes respiration	At least 3 episodes of continuous cycles of waxing and waning tidal volumes with periods of hyperventilation separated by central apnoeas or hypopnoea

3.2.4 Randomisation and study schedule

Randomisation in the SERVE-HF study is done in a 1:1 ratio; ASV:control according to randomisation lists imported by the study statistician via the randomisation server of the online electronic trial management system. Randomisation is stratified by site and by the presence/absence of an implanted device.

Patients attended the sleep laboratory at the Royal Brompton Hospital for further discussion about the study and, if happy to proceed, written informed consent was obtained by the Clinical Research Fellow and randomisation undertaken. Irrespective of the outcome of randomisation patients then undertook the Baseline visit, details of which can be found in table 3.3. Further information on these assessments can be found in Chapter 2. All patients attended at 2 weeks for an electrocardiogram and assessment of adverse events. Patients subsequently attended for a 3 month and then annual visits which all had a similar format to the baseline visit. Telephone follow up took place 6 months after each visit. Those randomised to the control group had no further sleep studies, unless enrolled in a substudy. Those randomised to the ASV group had a titration (set-up) sleep study on the ASV device soon after the randomisation/baseline visit, another at 3 months and then annual studies in line with their research visits. Details of each follow up are given in table 3.3. All patients are followed up in this way until the end of the study when all randomised patients will be contacted for a final assessment by telephone.

The EQ-5D (EuroQOL) questionnaire was used at the baseline and each subsequent study visit (as described in table 3.3). This is a standardised measure of health which about which details are given in chapter 2, section 2.2.3. Briefly, it consists of questions relating to 5 dimensions; mobility, self care, usual activities, pain/discomfort and anxiety depression, as well as a visual analogue scale (EQ-VAS) which asks patients to rate their own health on a scale from “best imaginable health state” to “worst imaginable health state”. Data for the EQ-VAS only are given in the next section.

Table 3.3: Schedule for Baseline visit and subsequent annual follow up visits

	Baseline visit	3 month and annual follow up visits	Telephone follow up
All patients	• Discussion about study and time for questions • Informed consent • Randomisation • History and examination • Blood tests (haemoglobin and creatinine) • Questionnaires; MLHFQ, ESS and EQ5D • Six minute walk test • Electrocardiogram	• History and examination • Blood tests (haemoglobin and creatinine) • Questionnaires; MLHFQ, ESS and EQ5D • Six minute walk test • Electrocardiogram	• Adverse event monitoring • Arrange date for next research visit
ASV group only	• Arrangements for ASV set up (titration) study within 2 weeks. • Telephone support and troubleshooting for ASV	• In-patient sleep study on ASV	

MLHFQ- Minnesota Living with Heart Failure questionnaire; ESS- Epworth Sleepiness Score; EQ5D- EuroQol questionnaire; ASV- adaptive servoventilation.

3.2.5 Adaptive Servoventilation

Details regarding the ASV device are given in Chapter 2, section 2.8. In essence Adaptive Servoventilation (marketed as Autoset CS2™/Autoset CS™) is a novel form of positive pressure ventilation characterised by delivery of a variable level of pressure support which is the reciprocal of the patient's own effort. This variable pressure support is superimposed on a low level of EPP (analogous to CPAP) which serves to stabilise the upper airway and remove airflow limitation.

Patients randomised to the ASV group returned to the laboratory within 2 weeks of randomisation for an evening introductory session where they were familiarised with the device and how to use it, and the rationale for its use was reviewed again. After the introductory session they were fitted with a mask and spent 30 minutes wearing the device whilst relaxing. After dinner they were set up for a sleep study wearing the machine, during which signals from the device and PG equipment were

monitored from the adjoining office and pressures on the device were adjusted remotely as necessary, without disturbing the patient. In the morning the device data were downloaded and the patient returned home with the device. Telephone support was provided as necessary over the next week or so to troubleshoot any issues. The PG data were scored and the results uploaded to the online trial management system along with results of the device download.

Subsequently compliance with ASV was assessed objectively with device downloads via the serial port on a desktop computer and the software ResScan™. This download provided data on mask leak, average daily use, percentage of days the device was used for more than 3 hours, number of days the device was not used and the total hours used. The ASV device also generated data on AHI and AI based on an internal algorithm. For the purposes of the study a minimum use of 3 hours per night was deemed to indicate compliance. Download data were uploaded to the electronic trial management system, feedback given to the patient and strategies to improve device use discussed as appropriate.

3.2.6 Statistical analysis

At the time of writing an interim analysis of the international study population has not yet been published. The median and inter-quartile ranges were used to generate descriptive statistics for each group recruited at the Royal Brompton.

Statistical tests looking for differences between the 2 groups at baseline have not been undertaken as any differences between the groups have occurred by chance and the number recruited is small. The Friedman and Wilcoxon Sign Rank tests were used to compare baseline with titration, and titration with 3 month data for the ASV group, as well as comparing each group over the course of the study. The Mann-Whitney U test was used to compare those patients persisting with ASV use with those did not. A significance level of 0.05 was used. Where appropriate a Bonferroni correction was used.

3.4 RESULTS

Results for patients studied at the Royal Brompton Hospital between July 2008 and September 2011 are presented here. During these months 831 patients were randomised internationally. No interim analysis results for the total study sample were available at the time of writing. Figure 3.1 gives the number of patients screened and recruited for inclusion in the study at the Royal Brompton Hospital.

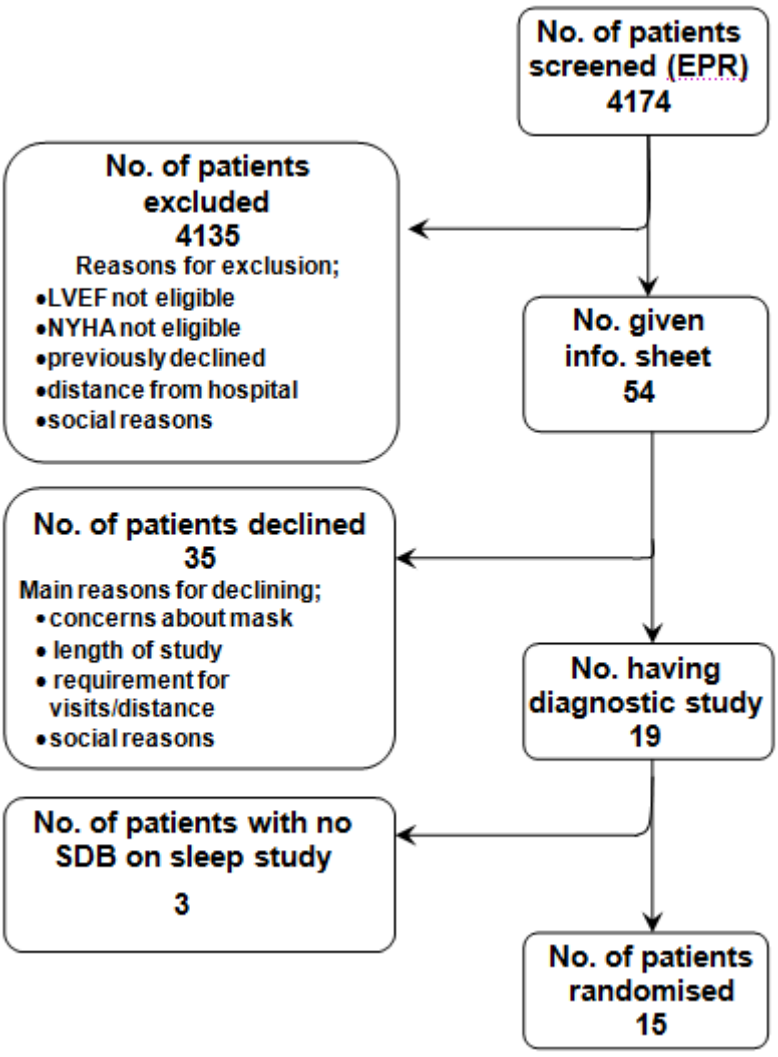


Figure 3.1: Patient screening and recruitment numbers for the first 28 months of recruitment at the Royal Brompton Hospital. *EPR- electronic patient record; LVEF- left ventricular ejection fraction; NYHA- New York Heart Association; SDB- sleep disordered breathing.*

3.4.1 Baseline characteristics and polygraphy

Nineteen patients with HF were randomised into the SERVE-HF study at the Royal Brompton Hospital between July 2008 and September 2011. The group had a median (IQR) age of 72 (70-76) years and consisted of 17 males (90%) and 2 females the majority of whom were Caucasian (79%) with the remainder being of Asian origin. At the time of randomisation only 2 (10.5%) were employed and the majority were ex-smokers (63%); there were no (self reported) current smokers. Alcohol consumption for the group was 3 (0-7) units/week and for caffeine was 4 (3-5) cups/day.

Nine patients were randomised to the control group and 10 to the treatment group. Baseline characteristics are shown in table 3.4, and HF descriptors in table 3.5. Data on inclusion (baseline) PG were available for all 19 patients and is given in table 3.6 for the control and ASV groups.

Table 3.4: Baseline characteristics for the control and ASV groups. Data are median (IQR) unless otherwise stated.

	Control group n=9	**ASV Group n=10**
Age (yrs)	**76.0** (72.5-78.5)	**70.5** (65.5-71.3)
Gender (male / female)	**9 / 0**	**8 / 2**
BMI (kg/m^2)	**24.7** (21.9-27.6)	**26.3** (22.9-31.1)
Neck circumference (cm)	**39.3** (37.0-41.4)	38.0 (34.8-45.3)
Epworth sleepiness score	**8** (5-11)	**8** (6-9)

BMI- body mass index

Table 3.5: HF characteristics for the control and treatment (ASV) groups. Data are median (IQR) unless specified.

		Control group n=9	ASV group n=10
NYHA functional class I / II / III / IV		**0 / 2 / 7 / 0**	**0 / 0 / 9 / 1**
Blood pressure (mmHg)	Systolic	**120** (100-131)	**115** (96-146)
	Diastolic	**65** (56-71)	**65** (60-73)
Heart rate (bpm)		**74** (66-80)	**71** (62-77)
Resting oxygen saturations (%)		**97** (96-98)	**97** (96-98)
Left ventricular ejection fraction (%)		**32.5** (22.5-39.5)	**23.0** (19.0-36.4)
LVEDD (cm) ‡		**5.9** (5.7-6.6)	**6.5** (6.1-7.2)
LVESD (cm) Δ ‡		**4.7** (4.6-5.1)	**5.6** (5.1-6.7)
B-type natriuretic peptide (pmol/L)		**101.0** (32.5-171.5)	**121.0** (53.8-302.0)
Aetiology of HF syndrome	Ischaemic	**6**	**6**
	DCM	**1**	**2**
	Valvular	**2**	**2**
Medications	Diuretics	**9**	**10**
	Beta blocker	**9**	**10**
	ACE inhibitor/ARB	**6**	**8**
	Digoxin	**1**	**4**
	Antidepressant	**3**	**1**
Minnesota Living with Heart Failure questionnaire score		**32** (24-44)	**47** (35-51)
EQ5D visual analogue scale for health state (0-100)		**63** (50-78)	**63** (58-75)
Average nap time after lunch (min)		**30** (0-60)	**33** (0-60)
6MWT (% predicted)		**72.4** (42.0-80.0)	**63.0** (41.7-67.6)

Δp=0.04 control vs. ASV group ‡data not available for 1 out of 19 patients.
NYHA- New York Heart Association; LVEDD- left ventricular end diastolic dimension; LVESD- left ventricular end systolic

dimension; DCM- dilated cardiomyopathy; ACE- angiotensin converting enzyme; ARB- angiotensin receptor blocker; EQ5D-EuroQol health questionnaire.

Table 3.6: Baseline polygraphy for the control and treatment (ASV) groups. Data are median (IQR) unless specified

	Control group n=9	**ASV group n=10**
Total recording time (min)	**455** (315-511)	**463** (411-543)
Apnoea hypopnea index (/hr)	**24.4** (17.1-41.1)	**30.1** (17.7-39.7)
Apnoea index (/hr)	**5.0** (0.4-27.0)	**5.3** (1.6-11.6)
Central apnoea index (/hr)	**4.0** (0.4-20.6)	**3.2** (0.3-11.6)
Obstructive apnoea index (/hr)	**0** (0-1.3)	**0** (0-1.0)
Hypopnoea index (/hr)	**17.0** (9.4-21.7)	**22.9** (14.2-26.1)
Central hypopnoea index (/hr)	**15.0** (9.4-20.5)	**21.8** (13.8-25.4)
Obstructive hypopnoea index (/hr)	**0** (0-2.0)	**0.7** (0-2.1)
Central apnoea hypopnoea index (/hr)	**24.4** (16.4-34.8)	**27.3** (17.7-37.2)
Obstructive apnoea hypopnoea index (/hr)	**0** (0-3.2)	**0.2** (0-2.6)
Cheyne-Stokes respiration (% of TRT)	**9.8** (0-58.5)	**39.5** (22.7-61.0)
Oxygen desaturation index (3% dip rate/hr)	**19.0** (15.7-42.8)	**30.0** (10.4-47.7)
Average oxygen saturation (%)	**94.3** (91.6-95.0)	**93.8** (91.8-96.0)
Time spent with O_2 sats. <90% (min)	**15.1** (1.4-79.2)	**22.5** (3.4-93.4)

TRT- total recording time.

3.4.2 ASV titration and serial polygraphy

Ten of 19 subjects included at the Royal Brompton Hospital were randomised to receive treatment with ASV. These patients were set up on ASV during a titration study which typically happened 1 week, but no later than 2 weeks after baseline. Five patients were studied again at 3 months after initiation of ASV; 3 of the remaining patients were unable to tolerate the device, 1 had an unrelated admission and the 5th patient was not due her 3 month study before the end of data collection for this thesis.

Data comparing baseline, titration and 3 month PG for this group of 10 patients are shown in table 3.7. Comparison was made statistically using the Friedman followed by Wilcoxon Signed Rank tests with a Bonferroni correction applied. From baseline to titration nights there were significant changes in respiratory data with improvements in the AHI (30.1 (17.7-39.7) vs. 3.1 (2.0-7.6) /hr, p=<0.01, r=0.62), apnoea index (5.3 (1.6-11.6) vs. 0 /hr, p=<0.01, r=0.59) and central apnoea index (3.2 (0.3-11.6) vs. 0 /hr, p=<0.01, r=0.59). The hypopnoea index (22.9 (14.2-26.1) vs. 3.0 (2.0-7.6) /hr, p=<0.01, r=0.60) and central hypopnoea index (21.8 (13.8-25.4) vs. 3.0 (1.9-7.6) /hr, p=<0.01, r=0.60) also improved. The percentage of total recording time spent in CSR also fell from the baseline to titration studies (39.5 (22.7-61.0) vs. 0 (0-7.9) %, p=<0.01, r=0.59).

The ODI improved from baseline to the titration sleep study (30.0 (10.4-47.7) vs. 7.4 (2.5-14.2) /hr, p=<0.01, r=0.60), but there was no significant difference in the average oxygen saturation (p=0.41), nor the time spent with oxygen saturations less than 90% (p=0.09). There was no difference in total recording time from the baseline to the titration study (463 (411-543) vs. 414 (256-566) min, p=0.08).

There were no significant differences between sleep study data from the titration and the 3 month study nights (n=5). Group and individual data for changes from baseline to titration and 3 month study are shown for AHI, 3% ODI and average overnight oxygen saturations are given in figure 3.2 (panels 1 to 3).

Table 3.7: Baseline, titration and 3 month polygraphy data for 10 patients randomised to ASV.
Data are median (IQR).

	Baseline polygraphy n=10	Titration Polygraphy n=10	3 month polygraphy n=5	Baseline vs. Titration*
Total recording time (min)	**463** (411-543)	**414** (256-566)	**421** (338-465)	*NS*
Apnoea hypopnea index (/hr)	**30.1** (17.7-39.7)	**3.1** (2.0-7.6)	**0.4** (0.0-2.0)	***p=<0.01, r=0.62***
Apnoea index (/hr)	**5.3** (1.6-11.6)	**0**	**0**	***p=<0.01, r=0.59***
Central apnoea index (/hr)	**3.2** (0.3-11.6)	**0**	**0**	***p=<0.01, r=0.59***
Obstructive apnoea index (/hr)	**0** (0-1.0)	**0**	**0**	*NS*
Hypopnoea index (/hr)	**22.9** (14.2-26.1)	**3.0** (2.0-7.6)	**0.4** (0-2.0)	***p=<0.01, r=0.60***
Central hypopnoea index (/hr)	**21.8** (13.8-25.4)	**3.0** (1.9-7.6)	**0** (0-1.8)	***p=<0.01, r=0.60***
Obstructive hypopnoea index (/hr)	**0.7** (0-2.1)	**0**	**0**	*NS*
Central apnoea hypopnoea index (/hr)	**27.3** (17.7-37.2)	**3** (1.9-7.6)	**0** (0-1.8)	***p=<0.01, r=0.62,***
Obstructive apnoea hypopnoea index (/hr)	**0.2** (0-2.6)	**0** (0-0.1)	**0**	*NS*
Cheyne-Stokes respiration (% of TRT)	**39.5** (22.7-61.0)	**0** (0-7.9)	**0**	***p=<0.01, r=0.59***
Oxygen desaturation index (3% dip rate/hr)	**30.0** (10.4-47.7)	**7.4** (2.5-14.2)	**1.7** (0.7-12.6)	***p=<0.01, r=0.60***
Average oxygen saturation (%)	**93.8** (91.8-96.0)	**94.4** (93.8-96.0)	**94.0** (92.0-96.2)	*NS*
Time spent with O_2 sats. <90% (min)	**22.5** (3.4-93.4)	**1.3** (0.3-5.6)	**0** (0-14.3)	*NS*

TRT- total recording time. *Wilcoxon Signed Rank Test

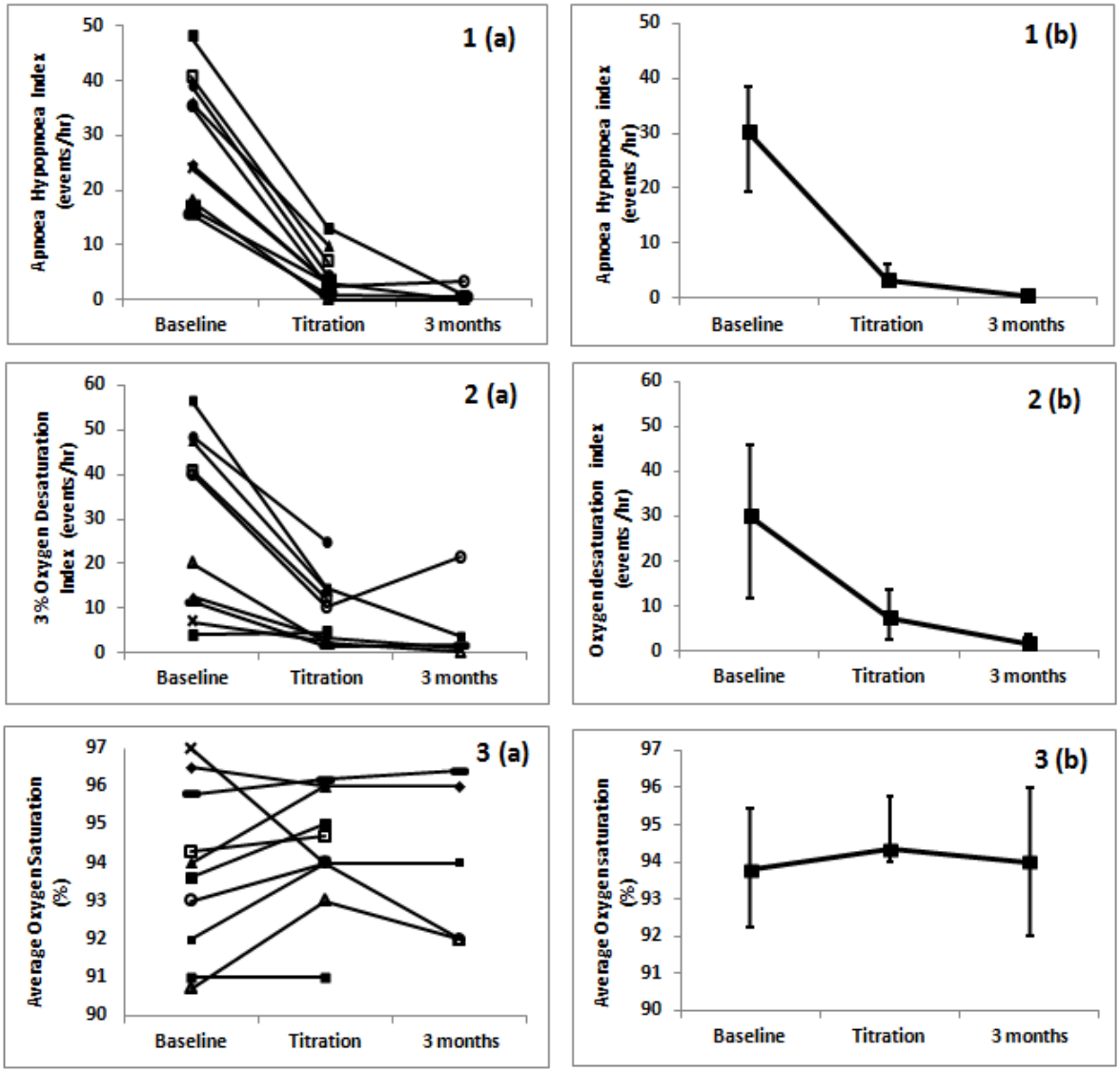


Figure 3.2: Polygraphy data to show changes from baseline to titration and 3 month study for 1) Apnoea hypopnoea index data (a) individuals and (b) group median/IQR; 2) 3 % Oxygen desaturation index data (a) individuals and (b) group median/IQR; 3) Average overnight oxygen saturation data (a) individuals and (b) group median/IQR.

3.4.3 Compliance with ASV treatment

Ten patients were randomised to receive ASV treatment and all attended for a set up session, titration study on PG, and 2 week download as part of the 2 week study visit. Not all patients randomised to ASV completed further PG studies on ASV; table 3.8 gives the numbers for whom data were available at each time point.

Table 3.8: The number of patients on ASV with data available by study visits.

Study visit	Baseline	Titration study	2 week visit	3 month study	12 month study	24 month study
Number of ASV patients attending	**10**	**10**	**10**	**6**	**3**	**2**

Of the 10 patients randomised to treatment with ASV, 4 discontinued treatment at or soon after the 2 week visit where the device was downloaded. Reasons for discontinuation were related to inability to tolerate the mask in 3 out of 4 cases. In the forth case the patient became unwell and felt unable to continue. Of these 4 patients 2 dropped out of the study completely, and 2 agreed to cross over to the control arm of the study.

Tables 3.9 and 3.10 give baseline characteristics and AHI and device download data for patients who remained on ASV (persistent users) and those who discontinued treatment (ASV drop-outs). Patients who remained on ASV had a significantly higher plasma BNP level than those who discontinued use (206.5 (109.5-409.0) vs. 52.5 (41.8-100.8) pmol/L, p=0.02). There were no differences between the groups in terms of SDB severity (as assessed by AHI) nor in device use on the titration night. However differences in device use became apparent at the time of the two week download; patients who remained on ASV therapy had significantly higher average daily use (4.4 (2.7-5.6) vs. 1.1 (0.1-2.8) hrs/night, p=0.03), spent more hours on the device in total (65.9 (40.3-90.5) vs. 3.0-37.4) hrs, p=0.03) and had a higher percentage of nights wearing the device for 3 or more hours (82.5 (62.0-95.5) vs. 13.5 (0-38.3) %, p=0.03). Figure 3.3a shows average daily use and total hours used and figure 3.3b shows the percentage of days when the device was used for 3 or more hours for the ASV user and the drop-out groups. Figure 3.4a shows the correlation between hours spent using the device on the titration study night and total hours of use at 2 weeks and figure 3.4b shows the correlation between hours spent using the device on the titration night and the percentage of days the device was used for 3 or more hours at 2 weeks.

Table 3.9: Baseline characteristics for persistent ASV users and ASV drop-outs. Data are median and IQR unless specified.

	Persistent ASV user (n=6)	**ASV drop-out (n=4)**	
Age (yrs)	**70.5** (67.8-71.5)	**69.0** (59.5-71.8)	*p=0.66*
BMI (kg/m^2)	**26.9** (22.9-31.5)	**27.3** (26.0-31.1)	*p=0.76*
Epworth sleepiness score	**7.5** (5.5-9.5)	**7.5** (4.8-8.8)	*p=0.91*
Minnesota Living with HF score	**45.5** (27.3-50.5)	**47.5** (37.5-62.0)	*p=0.48*
Systolic BP (mmHg)	**115.0** (84.5-146.0)	**115.5** (101.5-155.8)	*p=0.67*
Diastolic BP (mmHg)	**65.5** (58.0-81.3)	**64.5** (61.0-68.0)	*p=0.92*
Left ventricular ejection fraction (%)	**21.0** (19.0-27.4)	**34.3** (22.4-37.1)	*p=0.33*
B-type Natriuretic Peptide (pmol/L)	**206.5** (109.5-409.0)	**52.5** (41.8-100.8)	***p=0.02***

BMI- body mass index; BP- blood pressure.

Table 3.10: Serial AHI and ASV download data for persistent ASV users and ASV drop-outs. Data are median and IQR unless specified.

		Persistent ASV user (n=6)	**ASV drop-out (n=4)**	
Serial Apnoea Hypopnoea Index (events/hr)	**Baseline AHI**	**30.1** (17.4-39.1)	**31.7** (18.5-40.4)	*p=0.08*
	Titration AHI	**2.7** (0.6-10.6)	**3.8** (3.0-6.3)	*p=0.59*
Titration night download data	**Leak (median; L/min)**	**5.0** (2.3-17.0)	**4.0** (0.3-9.3)	*p=0.59*
	Average daily use (hrs/night)	**5.3** (3.9-6.9)	**5.0** (2.2-7.5)	*p=0.76*
	Total hours used*	**7.2** (4.9-9.4)	**6.3** (4.5-7.5)	*p=0.39*
2 week download	**Leak (median; L/min)**	**3.0** (0.8-7.0)	**6.5** (1.3-16.3)	*p=0.28*
	% days device used ≥3hrs/night	**82.5** (62.0-95.5)	**13.5** (0-38.3)	***p=0.03***
	Average daily use (hrs/night)	**4.4** (2.7-5.6)	**1.1** (0.1-2.8)	***p=0.03***
	Total hours used*	**65.9** (40.3-90.5)	**14.8** (3.0-37.4)	***p=0.03***

AHI- apnoea hypopnoea index; ASV- adaptive servoventilation.

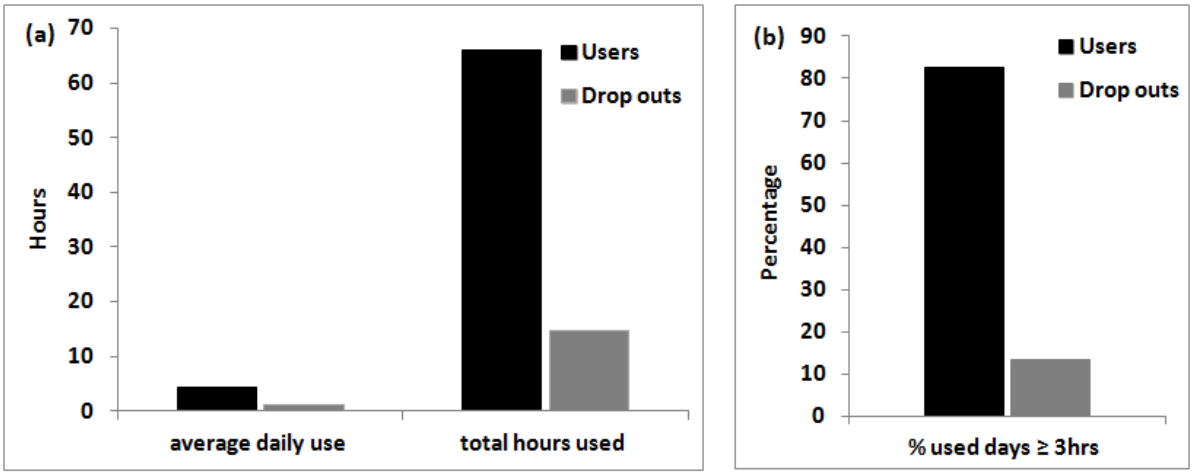


Figure 3.3: Two week download data; differences between ASV users and drop-outs in (a) average daily use, total hours used (left hand panel) and (b) percentage of days when device used for 3 or more hours per night. (right hand panel). *ASV- adaptive servoventilation.*

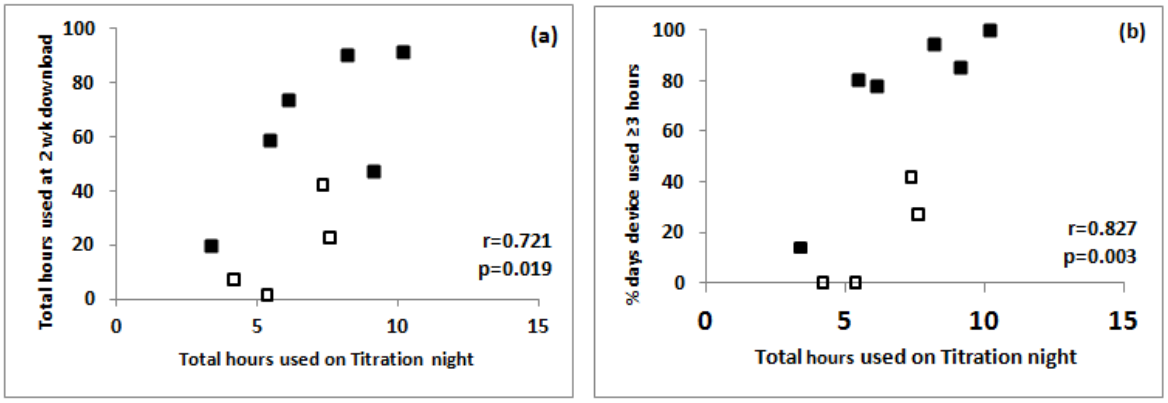


Figure 3.4: Correlations between hours ASV device used during titration study and 2 week download data in persistent users (shaded squares) and drop outs (empty squares)
(a) total hours used at 2 weeks and (b) percentage of nights device used for 3 or more hours.

ASV- adaptive servoventilation.

3.4.4 Serial data over 24 months

At each visit patients completed the ESS questionnaire and the MLHFQ, undertook a 6 minute walk test and had office blood pressure measured. Not all patients had attended for each visit at the time data collection stopped. This was due to illness, drop-out from the study or because these visits were not yet due before the time data collection stopped. Table 3.11 shows the number of patients for whom data are available for each of the study visits.

Table 3.11: Number of patients with data available by study visits.

Study visit	Baseline	3 months	12 months	24 months
Number of patients with complete data	**19**	**14**	**12**	**8**

Figure 3.5 (panels 1 to 4) illustrates scores for ESS, MLHFQ, distance walked in 6 minutes and Systolic BP for control and ASV patients at baseline, 6, 12 and 24 month visits. There were no statistically significant within group differences in these parameters in the 19 patients over 12 months (Friedman test). Twelve months was chosen for this comparison given the small numbers in each group with 24 month data (5 and 3 in the control and ASV groups respectively). Furthermore there were no significant between group differences at any time point (Mann-Whitney U test).

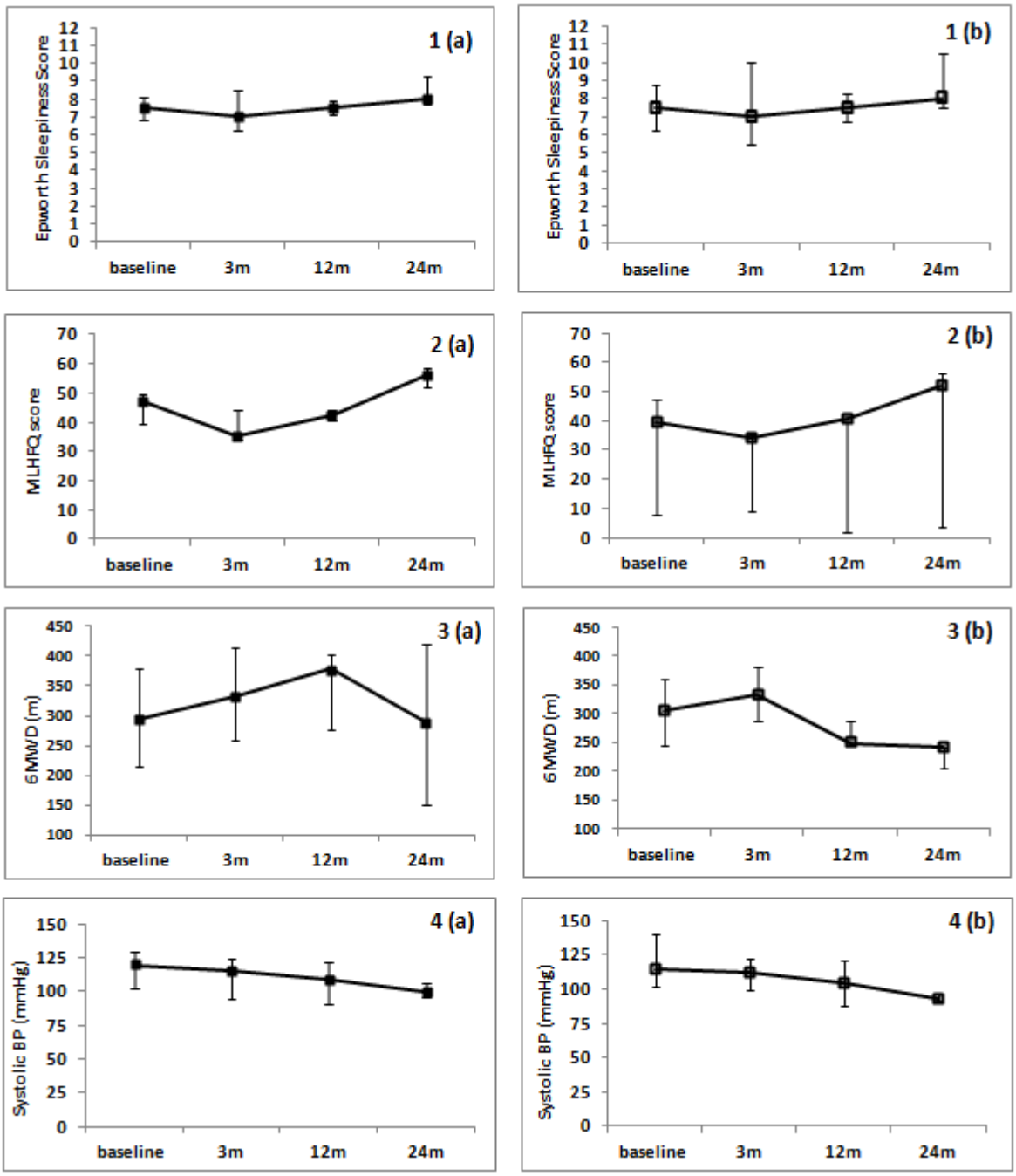


Figure 3.5: Serial data collected over 24 months (a) control subjects and (b) ASV users; panel 1) Epworth sleepiness score, panel 2) Minnesota Living with Heart Failure questionnaire score, panel 3) Six minute walk distance and panel 4) systolic blood pressure. *MLHFQ- Minnesota living with heart failure questionnaire; 6MWT- Six minute walk test; BP- blood pressure.*

3.5 DISCUSSION

Nineteen patients were randomised into the SERVE-HF study at the Royal Brompton Hospital during the period of data collection for this thesis and they form part of a larger international study population; how representative they are of that population is unknown at time of writing. In the group of 10 patients randomised to treatment with ASV its use replicated the respiratory improvements found in other work; there were significant differences in the AHI, hypopnoea index and apnoea index as well as in some measures of oxygenation; ODI and time spent with saturations less than 90%, but not average oxygen saturations. These improvements were sustained at 3 months.

Patients who continued to use the device (n=6) had higher BNP levels at baseline than those who could not tolerate it (n=4) and while there were no differences in device use on the titration night, these became apparent at the 2 week download. The number of hours the device was worn on the titration night correlated with markers of compliance at 2 weeks, in keeping with other data about the use of CPAP in non-HF patients with obstructive SDB (obstructive sleep apnoea).

There were no significant differences in subjective sleepiness, MLHFQ, BP nor the distance walked in 6 minutes between the control and intervention groups over 12 months.

3.5.1 The effects of ASV on SDB and HF

The SERVE-HF study (Teschler et al., 2010) seeks to determine if the use of ASV is associated with a reduction in mortality in patients with HF and predominantly central SDB and is the first randomised controlled trial powered for this end point. If central SDB does have a deleterious effect on survival in patients with HF it is possible that this effect is mediated via nocturnal hypoxaemia and/or sleep fragmentation and their pathophysiological sequelae.

Previous work has found the use of ASV in HF patients with predominantly central SDB to be associated with improvements in SDB and nocturnal oxygenation (Pepperell et al., 2003, Hastings et al., 2008), improvements in sleep architecture and reductions in objective sleepiness (Pepperell et al., 2003). Subjective sleepiness (assessed by Epworth) was no different after 3 months of ASV use as part of a randomised controlled trial which used sub-therapeutic ASV (Pepperell et al., 2003) whilst others found near significant changes after 6 months of device use (Philippe et al., 2006) and a study of 36 ± 18 months device use was associated with a significant improvement in subjective sleepiness (Carnevale et al., 2011). There was no difference in subjective sleepiness between the groups in the current data set; objective sleepiness was not assessed. Previous work has also found

improvements in NYHA, performance on sub-maximal exercise testing (Oldenburg et al., 2011b) nocturnal and quality of life (Hastings et al., 2008). Data from the 19 patients randomised at the Royal Brompton did not replicate these findings, but was not powered to do so. A recent meta-analysis of ASV use concluded that ASV was an effective treatment for central SDB, improving the AHI, LVEF and the distance walked in 6 minutes (Sharma et al., 2012). Other work relating to therapy with ASV is summarised in Chapter 1, section 1.7.4.

3.5.2 Recruiting and retaining patients; local and international hurdles

Proving or disproving the experimental hypothesis relies not just on its mechanistic plausibility and the study design, but also on the feasibility of the study from a practical point of view, both internationally and at a local level.

It was initially anticipated that the international recruitment rate would be approximately 70 patients per month, a figure which was revised due to a lower than expected number of eligible patients being identified, despite the reported prevalence of central SDB in HF. The new target of 30 patients per month was also too high. To counter this lower than expected recruitment rate new sites were introduced and the duration of recruitment was extended from July 2012 to January 2013. At the time of writing there are centres in 5 countries recruiting patients. The average recruitment rate internationally is approximately 25 patients per month at the time of writing and remains stable. In their 6 month randomised controlled trial of CPAP versus ASV, Phillipe *et al.* had to screen 320 patients over 32 months in order to identify 32 patients who met their study inclusion criteria (Philippe et al., 2006) which were similar to that of the SERVE-HF study. Of the 32 patients they identified only 25 then consented to inclusion in the study meaning that almost 13 patients were screened for every 1 patient recruited.

As part of the screening process for the SERVE-HF study several German and Australian sites are participating in a registry of patients with chronic HF who have been studied with the ApneaLink™ device (NCT 01500759). At the time of writing the registry includes over 10 000 patients and results from the first 3500 have been published in abstract form (Woehrle et al., 2012). The prevalence of SDB was 36% in women and 48% in men and although it is not possible to comment on the type of SDB (central vs. obstructive). However this demonstrates the lower prevalence of SDB in women.

Issues with international recruitment were echoed at a local level; recruitment was slower than anticipated at the Royal Brompton Hospital and can be seen in figure 3.6. To counter this we worked to improve the profile of the study within the hospital by giving talks to both respiratory and cardiology audiences and by putting posters up in clinic areas and the sleep laboratories which included the key inclusion and exclusion criteria as a prompt for clinicians. We also extended our screening to more clinics in the hospital. Furthermore, we extended screening to include 3 other hospitals within London; Chelsea and Westminster hospital, Ealing hospital and West Middlesex hospital. This involved visits to each hospital to discuss the study, give presentations at departmental meetings and provide support to staff for screening of patients. Finally, we used the ApneaLink™ device to increase the number of patients screened. The employment of a research nurse also helped to improve screening and the management of the additional screening sites. All of these measures helped to improve recruitment locally.

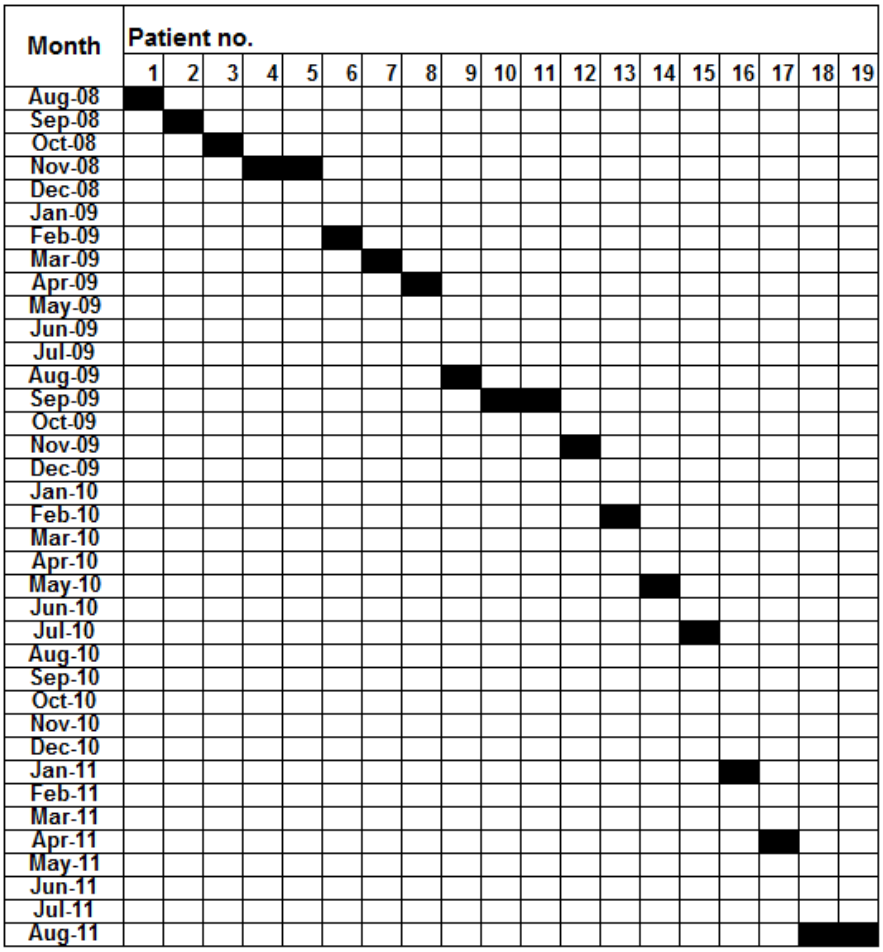


Figure 3.6: Distribution of recruitment of patients into the SERVE-HF study at the Royal Brompton Hospital.

Unlike respiratory patients those with HF tend not to be familiar with the concept of NIV, which less frequently features on a cardiology than a respiratory ward, and this had implications for explaining the nature of ASV. A minority of patients approached would not countenance the idea of a mask worn at night, despite thorough explanation. Some patients attending the HF services at the Royal Brompton attended from other regions within the UK and were unable to participate because of the distances involved. Other reasons cited for non-participation were related to the need to spend more time in the hospital (over and above clinical visits), concerns about transport to the hospital for study visits, and circumstances where the patient was also a carer for a partner or other family member at home. We aimed to keep time spent in the hospital to a minimum and arranged taxi transport for patients for whom public transport was not possible or unpalatable. Issues around compliance with ASV are discussed in the next section.

3.5.3 The issue of compliance

Compliance with the ASV device in those randomised to it is integral to the study design. This study showed that in the 10 patients randomised to ASV therapy the number of hours that the device was worn on the titration night correlated with compliance at 2 weeks. Although there are few data on compliance with positive pressure devices in patients with HF, less still for ASV, this finding is in keeping with data on compliance from non-HF populations with obstructive SDB (or obstructive sleep apnoea, OSA). In this group with OSA early compliance with CPAP predicts longer use (Budhiraja et al., 2007, Weaver et al., 1997) as does medium term compliance (McArdle et al., 1999). These findings suggest that efforts to improve compliance would best be directed at the titration study and the first 2 weeks, since these seem predictive of subsequent use.

Other studies on non-HF patients with OSA suggest that compliance with CPAP therapy is more likely if the underlying SDB is relatively more severe or associated with more marked subjective sleepiness (McArdle et al., 1999, Stepnowsky and Dimsdale, 2002). Barriers to compliance in this population include age, with older patients being more compliant (Collen et al., 2009, Poulet et al., 2009) and socioeconomic factors, with those of lower socioeconomic status and income being less receptive to CPAP (Simon-Tuval et al., 2009). Married patients have been reported to be more compliant (Platt et al., 2010) than unmarried patients. Data on gender is unclear, with some authors finding women to be more compliant (Sin et al., 2002), others men (McArdle et al., 1999) whilst still others found no difference (Budhiraja et al., 2007). Platt *et al.* found that those compliant with lipid lowering medication were more likely to be compliant with CPAP (Platt et al.,

2010). Coping skills, the ability to solve problems and self-efficacy all predict compliance in the non-HF OSA population (Stepnowsky et al., 2002, Weaver et al., 2003). Snoring is predictive of greater levels of compliance (McArdle et al., 1999) and increased nasal resistance is predictive of non-acceptance of and lower compliance with CPAP (Li et al., 2005, Sugiura et al., 2007). Where a bed partner is present and they initiate the referral for sleep assessment subsequent compliance with CPAP, if prescribed, is likely to be lower (Hoy et al., 1999).

A study of older patients with OSA found that 2 targeted pre-treatment sessions helped to improve subsequent compliance; this improvement was not seen at 1 week but was seen after 12 weeks of follow-up (Aloia et al., 2001). The use of telemonitoring and intensive support programmes over 6 months also improve compliance (Stepnowsky et al., 2007, Hoy et al., 1999). Experience of the titration study has been found to be important; an improvement in sleep efficiency from the diagnostic to the titration night is predictive of compliance (Drake et al., 2003). The use of sedatives (eszopiclone) on the titration night improved the quality of titration (Lettieri et al., 2008) and subsequent device use over 4 to 6 weeks (Lettieri et al., 2009a) while eszopiclone use over 2 weeks improved compliance over 6 months compared to placebo (Lettieri et al., 2009b).

The non-HF population with OSA differs from the HF population with central SDB in many different ways so it is unclear if the current literature on CPAP can be extrapolated to the use of ASV, a different technology, with HF patients who are demographically different from the non-HF OSA population as they tend to be older, less often obese, and critically, less often sleepy (Javaheri, 2006b, Rao et al., 2006).

Carnevale *et al.* looked at ASV use in both HF patients and non-HF patients with central SDB and found that compliance was good in both groups (70 and 78% respectively), although lower in the HF group. They also found that using 3 hours/night as a definition of compliance, the Epworth score fell significantly in those who were compliant, compared to those who were not (Carnevale et al., 2011). Work looking at the effect of ASV use on prognosis in HF patients found that there were fewer HF events in those patients who were more compliant (Koyama et al., 2011a, Takama and Kurabayashi, 2012) and a similar study of CPAP use in HF patients with obstructive SDB found that event free survival over 1 year was higher in those patients with better compliance (Kasai et al., 2008). Of course the findings of these uncontrolled studies may in part be due to the healthy user effect; those more compliant with positive pressure devices are more likely to be compliant with

other aspects of treatment which may also affect prognosis (Platt et al., 2010). Furthermore, one might speculate that those consenting to inclusion in clinical research are perhaps more likely to be compliant with treatment. In a randomised controlled trial of ASV versus sub-therapeutic (sham) ASV, Pepperell *et al.* found that ASV was well tolerated, with no withdrawals from the group whereas there were 4 withdrawals from the group using the sham device (Pepperell). In a 6 month randomised controlled trial Phillipe *et al.* found that compliance between ASV and CPAP was equal at 3 months but higher in the ASV group at 6 months (Philippe et al., 2006). The same study reported 2 and 3 patients discontinuing ASV and CPAP therapy respectively (n=15 in each group).

Both our experience of initiating ASV therapy in patients within the SERVE-HF study, and the data presented on early ASV use, has emphasised the importance of management during the titration night. An explanation of the rationale for and nature of ASV treatment must clearly be given well before the diagnostic sleep study and then again before consent and randomisation. The manner in which this is done must, like every explanation to a patient, reflect the patient's level of understanding and their background. For example, the retired engineer in our group required a different approach to the retired textiles merchant. I found that a further explanation before the day of the titration study to be useful ground work for the titration visit itself which consisted of an evening introductory session to explain the device and how to use and maintain it. The manner in which an appropriate mask was selected and fitted was also crucial, not simply because of the need to find the correct size and shape for the patient's face, but because many patients found the physical application of the mask provoked anxiety. Patients were shown different models of mask and were involved in the decision making process. They then held the mask to their faces without the straps, which were only done up later. Whilst all patients are different, with different personalities, levels of understanding and anxiety, this "gently does it" approach was crucial to acceptance and could be easily adapted. In selected patients we used a small dose of zopiclone (a non-benzodiazepine hypopnotic which does not affect chemosensitivity) for the first few nights of ASV use.

It is worth commenting that in a non-HF patient attending for CPAP set-up it is possible to definitively discuss the benefits proven in the literature and the improvements that they can expect, and explain that CPAP is the gold standard treatment for their condition. Most patients respond positively to this information. This was not possible in the context of the SERVE-HF study since the nature of the benefit derived from the device is still under investigation.

Based on this experience there are several factors which make the initiation of ASV in HF patients with central SDB quite different to that of CPAP in patients with OSA. Firstly the patients themselves are older, often frail with poor visual acuity and dexterity. This can make carrying, handling and manipulating the device difficult. This was managed by keeping instructions to a minimum, arranging transport with the driver carrying the device and providing written (large text were necessary) instructions. During the SERVE-HF study the ASV device being used (the AutosetCS2^{TM}) was superseded by the Autoset CS^{TM} which was significantly smaller, lighter and quieter than its predecessor. Secondly, the nature of the SDB experienced by these patients is different. They tend not to snore (Javaheri, 2006b) and not to be sleepy (Hastings et al., 2008); both of these factors have been associated with improved compliance in non-HF populations (McArdle et al., 1999) such that one might speculate that their absence may have an effect on device use. Careful explanation of the study rationale was helpful for patients to understand the purpose of the study. Finally there are differences in delivery of pressure by the devices; CPAP delivers a constant pressure meaning that mask fitting may be done more accurately with the patient awake and the machine turned onto the therapeutic pressure. ASV, in contrast, delivers a variable pressure such that a mask may fit well enough with the patient awake and the machine turned on, then leak during sleep when the pressure delivered increases due to the emergence of SDB in sleep. To manage this issue mask fit was a central part of the introduction session. During the titration night machine pressures and leak were watched in real time by myself from the room next to the patient and adjustments made through the night as necessary.

The use of humidification in a randomised trial of non-HF patients with OSA found it was not associated with an increase in compliance but did reduce the frequency of nasal symptoms (Ryan et al., 2009). Of those patients who persisted with ASV use (n=6) almost all were using a humidifier. Of those who were unable to tolerate the device, this was on no occasion related to nasal symptoms or dry mouth. We found that the addition of a humidifier was helpful in assisting tolerance in most patients, but, despite the relative simplicity of the equipment, some patients were unable to master the attachment, detachment and filling/emptying of the chamber with safety. One device was returned after water from the humidifier was inadvertently poured into it. Our experience suggests that while most patients would prefer a humidifier, this must be balanced against their ability to use it independently (assuming there is no family member to assist).

3.5.4 Methodological issues

The data presented in this chapter were part of an international trial and as such was not powered to find a difference between those randomised to either the control or ASV groups. For this reason statistical tests to compare the 2 groups at baseline were not done. Statistical comparisons were made to look at the effect of the ASV device, the difference between users and drop-outs and to look at serial changes over time however these are done with the caveat that the groups involved are very small.

There are several methodological issues which deserve consideration. At the time of writing it is not possible to say if the 19 patients randomised in London are representative of the total international group in terms of baseline characteristics, HF and SDB.

The classification of apnoeas as either central or obstructive is part of the AASM 2007 guidelines (Iber et al., 2007) however the classification of hypopnoeas as central or obstructive is not. Determination of the predominant type of SDB is integral to the experimental hypothesis however the use of oesophageal and /or gastric pressure probes in patients who are often frail and elderly is not realistic and so such guidelines for classification have been used in the SERVE-HF study.

The group randomly assigned to ASV therapy had more contact with the research team as they attended for a second night in the hospital (titration study), had phone calls as required to support the initiation period and also had annual sleep studies thereafter. This was very unlikely to affect the primary end point which is mortality, but could feasibly affect secondary outcomes such as quality of life.

Only 2 of 19 patients were women, which is a reflection of much of the prevalence work in this area (Woehrle et al., 2012) and is in keeping with the observation that SDB, both in (Sin et al., 1999) and outside of the HF population (Young et al., 1993), is less common in women than in men. The group was representative of the ethnicities which tend to visit the HF clinics of the Royal Brompton, but was not ethnically heterogeneous. It is not known if this factor is likely to have affected the results. None of the patients randomised had any problem with comprehension, consent nor the assessment questionnaires. Translators were not required for any patient. Most of the patients included at the Royal Brompton Hospital were NYHA class III, with only 1 patient of 19

having class IV HF and this perhaps meant that those most functionally impaired by their HF were under-represented. Twelve out of the group of 19 (63%) had an ischaemic cardiomyopathy; it is unknown if the response to ASV is different in those with different aetiologies of the HF syndrome.

The two groups had median apnoea indices of 5.0 (0.4-27.0) and 5.3 (1.6-11.6) (control and ASV respectively) and these seem low relative to other work. The total AHI was comparable to most other work; the majority of the respiratory events in this study were hypopnoeas, constituting 70% and 76% of the total AHI for the control and ASV groups respectively. The difference in time spent in CSR occurred by chance and was not significant when tested (p=0.10).

The improvements seen in respiratory parameters from baseline to titration studies in the ASV group were not further improved at 3 months. It is unclear if this is because the numbers of patients for whom 3 month data are available is very small (n=5) and so there is insufficient power to detect such a difference, or if the ASV has no additional beneficial effect once adequate initial titration has taken place. Philippe *et al.* found a change from baseline to 3 months, and baseline to 6 months, but it is unclear if there was a significant improvement from 3 to 6 months in that study (Philippe et al., 2006). The international results of the SERVE-HF study will be able to answer this question.

It is possible that further improvements from titration to 3 months may have been seen in sleep architecture, as the reduction in respiratory events allows sleep to become less disrupted and more consolidated; it is plausible that this process may take time and therefore if PSG had been done further improvement in sleep itself may have been apparent between titration and 3 months. A sub-group of the SERVE-HF patients have had PSG and so in due course this question also may be answered.

3.5.5 Summary

Data from the 19 patients randomised to the SERVE-HF study at the Royal Brompton are presented here. Data from the 10 patients randomised to receive ASV therapy confirm the findings of previous work by demonstrating that ASV effectively suppresses central SDB in patients with HF. The current data set shows, in a novel finding for ASV use in HF patients, that device use on the titration night correlates with subsequent use, a finding common with CPAP use in the non-HF OSA population. Recruitment for the SERVE-HF study will end in January 2013, and follow-up of the existing patients in the study will end in February 2015.

The woods are lovely, dark and deep.

But I have promises to keep,

And miles to go before I sleep,

And miles to go before I sleep.

"Stopping by Woods on a Snowy Evening", Robert Frost (1874-1963)

CHAPTER FOUR:

THE INFLUENCE OF SLEEP DISORDERED BREATHING ON THE HYPERCAPNIC VENTILATORY RESPONSE IN PATIENTS WITH CHRONIC HEART FAILURE

4.1 INTRODUCTION

Central SDB is prevalent in patients with HF (Javaheri, 2006b, Vazir et al., 2007). In those with severely impaired left ventricular function the severity of the SBD is associated with that of the underlying cardiac dysfunction (Oldenburg et al., 2009). The cause of central SDB in HF patients is thought to relate to the underlying pathophysiology of the HF syndrome via the instability of the negative feedback loop that controls ventilation. This feedback loop comprises controller gain (the change in ventilation in response to a change in carbon dioxide- CO_2), plant gain (the efficiency with which ventilation removes carbon dioxide from the body) and feedback gain (the interval between a change in alveolar carbon dioxide and the transmission of that change to the chemoreceptors). Heart failure may affect each component of the feedback system and contribute to ventilatory instability; this is discussed in Chapter 1, section 1.6.

Controller gain describes the chemosensitivity of the respiratory control system and may be measured as the HCVR. Previous work has shown that the HCVR is lower during sleep than wakefulness (Douglas et al., 1982b). Read found a high level of variability in HCVR during tests on 21 healthy young men and women performed during wakefulness (Read, 1967). These differences are thought to be partly due to genetic (Kawakami et al., 1984) and gender related influences (Aitken et al., 1986). Age too is known to influence the HCVR (Brischetto et al., 1984).

In a seminal paper by Javaheri (Javaheri, 1999) 10 patients with HF and central SDB, and 10 patients with HF but without SDB were studied. The HCVR (measured during wakefulness) was found to be significantly higher in the patients with HF and central SDB compared to those without, suggesting that a heightened ventilatory response to CO_2 may, at least in part, explain the presence of central SDB in the HF population. Studies of HCVR in healthy subjects show an evening to morning increase in ventilatory sensitivity to CO_2 (Cummings et al., 2007). This overnight change in HCVR has not been studied in patients with HF and central SDB but may also be mechanistically important.

The aim of this study was to confirm the mechanism of central SDB in HF patients by measuring the HCVR in HF patients with and without central SDB, and also in a group of older healthy subjects. Specifically, I tested the hypothesis that HF patients with central SDB would have an increased HCVR compared to those with HF and no SDB and secondly that there would be a difference in overnight change in HCVR between these two groups.

4.2 METHODS

4.2.1 Subjects

Patients were recruited from 2 sources; either directly from the heart failure clinics at the Royal Brompton Hospital or as part of a Control of Ventilation Substudy of the SERVE-HF study. Ethical approval for this study was granted by the South West London REC no. 1 (REC no. 09/H0708/35), documentation can be found in appendix 2. Healthy subjects were recruited from a list of participants who had volunteered for other studies in our department.

Those subjects agreeing to participate were classified into four groups on the basis of the results of their sleep study; 1) HF patients with obstructive SDB (HF-OSA), 2) HF patients with central SDB (HF-CSA), 3) HF patients with no SDB (HF-noSDB) and 4) healthy older control subjects.

Patients were included if they had a known clinical diagnosis of CHF, documented left ventricular systolic impairment and were on medical treatment for HF. Measurement of the left ventricular ejection fraction (LVEF) by echocardiogram was used as a marker of left ventricular systolic impairment although no cut off value for inclusion was used. Patients had to be clinically stable with no unplanned hospital admission (for any reason) in the preceding month and no new class of HF medication started within the same time period. Patients using PAP devices (for any reason) were excluded from the study; none of those patients involved in the control of ventilation substudy of the SERVE-HF study were established on adaptive servoventilation. Further details on the SERVE-HF study can be found in chapter 3.

Healthy subjects were considered suitable for inclusion if they were free of medical problems. All healthy subjects were asked specifically about hypertension, heart disease, diabetes or if they had any medical condition requiring regular medication or GP consultation. Subjects found to have SDB on nocturnal PSG were excluded from the study and an appropriate referral to a sleep clinic made. All subjects had to be aged 18 years or over and give informed consent. Subjects with other conditions likely to significantly disrupt sleep (ie. chronic pain syndromes) were excluded from the study. The study was approved by the South West London REC no. 1 (REC no. 09/H0708/35) and all subjects gave written informed consent (see appendix 2 for documentation).

4.2.2 Protocol

Baseline measurements

After informed consent a baseline assessment was made, including height, weight, resting oxygen saturations, non-invasive blood pressure measurement, neck circumference (measured at the level of the cricoid cartilage) and spirometry; FEV_1 and FVC. All subjects completed a measurement of subjective sleepiness (ESS) and all patients completed the MLHFQ (see appendices 5 and 6 for questionnaires and Chapter 2, section 2.2).

Hypercapnic ventilatory response

The HCVR was measured in the evening between 19.00 and 21.00 and the next morning between 6.00 and 9.00 using the Read rebreathe method (Read, 1967). Subjects were asked to refrain from drinking caffeine from at least noon on the day of the evening test until the completion of morning test the next day. A detailed description of this technique can be found in Chapter 2, section 2.5.

Nocturnal polysomnography

Overnight sleep was measured in all subjects. A detailed explanation of nocturnal PSG is given in Chapter 2, section 2.7.

4.2.3 Analysis

Physiological analysis

A detailed description of the criteria for analysis of sleep stages and breathing overnight are given in chapter 2, section 2.10.1. In brief, sleep staging was undertaken by a single scorer using standard criteria (AASM manual, 2007) and blinded to subject identity and diagnosis at the time of scoring. SDB was defined as an AHI $\geq$ 10 events per hour. The type of SDB (obstructive or central) was determined by the predominant event type. Oxygen desaturation was measured using a ≥3% dip criterion. Hypopneas were defined using a ≥ 3% dip criterion or a cortical arousal, as per the AASM guidelines (Iber et al., 2007). Resting CO_2 was measured as the average end tidal CO_2 ($ETCO_2$) for 8 breaths before commencement of the evening test.

Data obtained during the measurement of HCVR were collected using the Spike 2 data acquisition programme (version 5.04, Cambridge Electronic Design) and analysed off-line to determine the slope of the relationship between ventilation and end tidal CO_2. HCVR is expressed as a slope in units of L/min/mmHg $ETCO_2$. Further details are available in Chapter 2, section 2.5**.**

Statistical analysis

The median and inter-quartile ranges were used to generate descriptive statistics. Groups were compared using the non-parametric Mann-Whitney U test with a significance level of 0.05. Non-parametric tests were used as a more robust statistical test given the smaller group sizes, particularly with comparisons of overnight HCVR.

Taking chemosensitivity (assessed by HCVR) as the primary outcome there were no directly comparable data from which to calculate a sample size however Javaheri (Javaheri, 1999) measured the difference in HCVR between patients with and without central SDB and found this to be 3.0 (SD 2.3) L/min/mmHgCO_2 (5.1±3.1 vs. 2.1±1.0, p=<0.01). Assuming that any difference in HCVR between the groups would be of a similar magnitude I required a minimum of 10 patients in each group to detect a similar difference (α=0.05).

4.3 RESULTS

Forty nine subjects were studied; 35 HF patients (34 men) and 14 healthy older controls (11 men). Of this group 8 had predominantly obstructive SDB and one patient with predominantly central SDB was unable to tolerate the HCVR test; these patients were excluded from further analysis. Figure 4.1 illustrates the subjects studied and those included in the analysis.

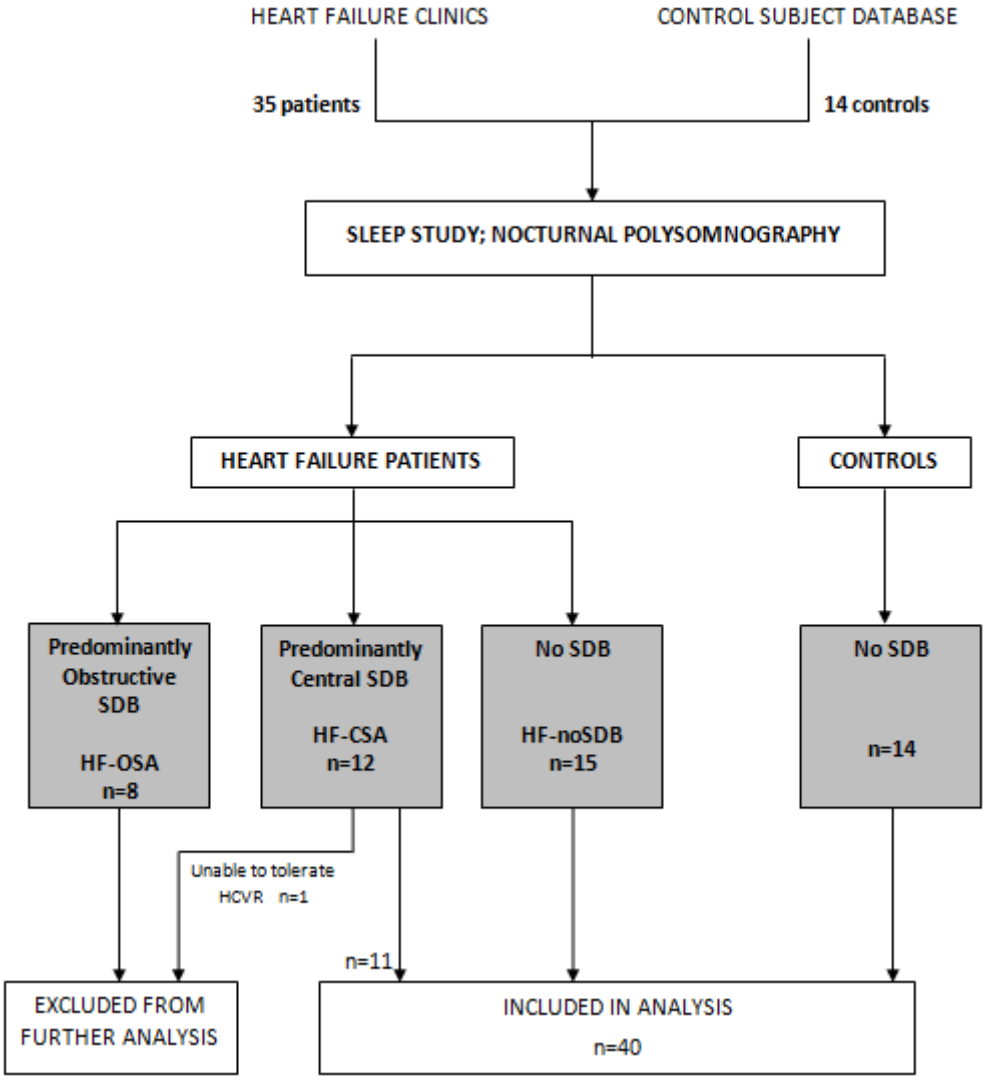


Figure 4.1: Subjects studied and included in study analysis. *SDB- sleep disordered breathing; HCVR- hypercapnic ventilatory response.*

The HF patient group had a median (IQR) age of 69 (62-78), body mass index (BMI) of 27.5 (24.6-30.6) and Epworth sleepiness score of 8 (6-10). They had an FEV_1 and FVC of 77.5 (63.8-89.5) and 84.0 (64.3-92.3) % predicted, respectively. Twenty-five of the 26 HF patients were of Caucasian origin and one was Asian. They had a median LVEF of 34 (25-43) % and BNP of 51 (28-103) pmol/L.

The majority of HF patients were established on HF therapy such as diuretics, beta blockers, ACE inhibitors and ARBs, in accordance with national guidelines (NICE, ESC and ACC/AHA). Twelve of the patients had an ischaemic cardiomyopathy and the remaining dilated cardiomyopathy (n=5), underlying valve disease (n=4) or had an unknown aetiology (n=5) for their HF syndrome.

The control group had a median age of 63 (59-67) years, a BMI of 25.6 (23.4-26.7) kg/m^2 and Epworth sleepiness score of 4 (1-6). They had an FEV_1 and FVC of 89.0 (77.3-101.3) and 89.0 (79.9-99.3)% predicted, respectively. Eleven of 14 controls were Caucasian and the remaining 3 were of Asian origin. Table 4.1 shows the baseline characteristics and of the HF patients and controls.
The HF group had a median AHI of 6.7 (4.4-14.2)/hr with apnoea and hypopnoea indices of 1.6 (0.2-6.6) and 5.8 (3.1-9.6) /hr respectively. They had an ODI of 8.4 (4.9-14.0) /hr and spent 4.6 (0.3-44.2) minutes with oxygen saturations less than 90%. Time in bed and total sleep time were 480 (435-510) and 339 (284-377) minutes respectively. Sleep efficiency and latency were 74.0 (62.1-83.8) % and 12.4 (8.0-28.7) minutes respectively.

The control group had a median AHI of 1.4 (0.5-3.6) /hr, an apnoea index of 0.9 (0-1.2) /hr and a hypopnoea index of 0.7 (0-1.4) /hr. They had an ODI of 1.6 (0.7-2.0) /hr and spent a median of 0 (0-5.7) minutes with oxygen saturations less than 90%. They spent a median time in bed of 491 (542-519) and had a total sleep time of 388 (258-421) minutes. Sleep efficiency and sleep latency were 79.2 (52.1-88.7) % and 23.2 (10.9-52.6) minutes respectively. Table 4.2 gives the PSG results for the HF patients and controls.

All 40 subjects had an evening measurement of HCVR. All 14 control subjects and 17 of the HF patients (6 out of 11 HF-CSA group and 11 out of 15 HF-noSDB group) also had a morning measurement of the HCVR as well allowing measurement of the evening to morning change in HCVR. Analysis of resting CO_2 levels was possible in 39 subjects (the 40th was prohibited by technical failure). Individual CO_2, HCVR slope and x intercept data for each subject can be found in appendix 10.

Table 4.1: Baseline demographics for HF patients and healthy controls. Data are median (IQR) unless specified.

		HF patients n=26	Controls n=14
Age (yrs)		**69** (62-78)	**63** (59-67)
Gender (M / F)		**25 / 1**	**11 / 3**
BMI (kg/m^2)		**27.5** (24.6-30.6)	**25.6** (23.4-26.7)
Neck circumference (cm)		**39** (37-43)	**38** (36-39)
Epworth sleepiness score		**8** (6-10)	**4** (1-6)
FEV$_1$ (%)		**77.5** (63.8-89.5)	**89.0** (77.3-101.3)
FVC (%)		**84.0** (64.3-92.3)	**89.0** (79.9-99.3)
NYHA functional class I / II / III / IV		**3 / 15 / 6 / 2**	
Blood pressure (mmHg)	Systolic	**121** (106-134)	
	Diastolic	**74** (64-81)	
Left ventricular ejection fraction (%)		**34** (25-43)	
B-type natriuretic peptide (pmol/L)		**51** (28-103)	
Aetiology of HF syndrome	Ischaemic	**12**	
	DCM	**5**	
	Valvular	**4**	
	Diastolic		
	Unknown	**5**	
Medications	Diuretics	**19**	
	Beta blocker	**22**	
	ACE inhibitor/ARB	**20**	
	Digoxin	**6**	
Comorbidities	Diabetes	**2**	
	Atrial fibrillation	**12 (3 with PAF)**	
Implanted devices	No device	**14**	
	PPM +/- ICD	**5**	
	CRT	**7**	
	ICD	**0**	

BMI- body mass index; FEV$_1$- forced expiratory volume in 1 second; FVC- forced vital capacity; NYHA- New York Heart Association; DCM- dilated cardiomyopathy; ACE- angiotensin converting enzyme; ARB- angiotensin receptor blocker; PPM-

permanent pacemaker; ICD-implantable cardiac defibrillator; PAF- paroxysmal atrial fibrillation; CRT- cardiac resynchronisation therapy.

NB. LVEF was missing for 1 HF patient, BNP data for 4 patients and MLHFQ data for 6 patients. BP was measured in controls before and after the HCVR protocol but was not part of the comparison between the groups.

Table 4.2: Results from nocturnal polysomnography for HF patients and healthy controls. Data are median (IQR) unless specified.

	HF patients n=26	**Controls n=14**
Apnoea hypopnoea index (events/hr)	**6.7** (4.4-14.2)	**1.4** (0.5-3.6)
Apnoea index (events/hr)	**1.6** (0.2-6.6)	**0.9** (0-1.2)
Hypopnoea index (events/hr)	**5.8** (3.1-9.6)	**0.7** (0-1.4)
Oxygen desaturation index (≥3% dip rate/hour)	**8.4** (4.9-14.0)	**1.6** (0.7-2.0)
Average oxygen saturations (%)	**93.5** (91.8-95.3)	**95.0** (94.0-96.0)
Time with O_2 saturations <90% (min)	**4.6** (0.3-44.2)	**0** (0-5.7)
Time in bed (min)	**480** (435-510)	**491** (452-519)
Total sleep time (min)	**339** (284-377)	**388** (258-421)
Sleep efficiency (%)	**74.0** (62.1-83.8)	**79.2** (52.1-88.7)
Sleep latency (min)	**12.4** (8.0-28.7)	**23.2** (10.9-52.6)
Wake after sleep onset (min)	**85.5** (50.3-155.0)	**88.0** (31.5-115.3)
Arousal index (events/hr)	**26.5** (16.7-36.4)	**29.4** (10.0-41.4)
Stage 1 (%)	**27.5** (19.2-37.3)	**14.8** (12.3-24.9)
Stage 2 (%)	**44.1** (30.8-49.1)	**39.0** (33.0-60.2)
Slow wave sleep (%)	**10.1** (5.6-14.0)	**20.2** (5.5-29.6)
REM sleep (%)	**17.6** (11.4-22.1)	**19.3** (16.6-24.5)
Periodic leg movement index (events/hr)	**8.8** (1.4-26.8)	**4.4** (0.6-12.7)
Supine position (%)	**31.5** (10.5-53.2)	**28.2** (13.1-46.7)
Left position (%)	**18.5** (2.3-32.7)	**26.8** (14.2-54.8)
Right position (%)	**34.2** (1.6-67.7)	**29.1** (15.5-38.6)

4.3.1 Differences in hypercapnic ventilatory response between HF patients with central SDB and those without SDB.

In order to test the hypothesis that the HF-CSA group would have a brisker ventilatory response to CO_2 than the HF-noSDB group I compared data from the 11 HF patients with predominantly central SDB to 15 HF patients with no SDB. Baseline characteristics for these 2 groups can be found in table 4.3. There were no significant differences between the groups in age, BMI or ESS. FEV_1 was higher in the HF-CSA group than the HF-noSDB group (83.3 (75.4-99.4) vs. 71.3 (60.8-79.3) % predicted, p=0.04), but there was no difference in FVC between the groups. The BNP was significantly higher in the HF-CSA group (97.0 (62.5-275.0) vs. 38 (26.8-61.5) pmol/L, p=0.02). There were no other differences between the groups.

Group overnight sleep and breathing data are given in table 4.4. The two groups differed in respiratory events by design. The HF-CSA group spent more time with oxygen levels less than 90% (T<90%; 18.7 (4.4-75.0) vs. 1.6 (0-7.4) minutes, p=0.04) in keeping with the presence of SDB. Similarly the HF-CSA group had a higher ODI (15.0 (11.5-23.9) vs. 5.5 (2.2-7.9)/hour, p=<0.01). There were no other significant differences in sleep between the groups.

The resting evening CO_2 for both HF groups is shown in figure 4.2 (group data). The median CO_2 level at rest was lower in the HF-CSA group compared to the HF-noSDB group (30.6 (28.6-37.3) mmHg vs. 36.2 (35.2-40.4) mmHg, p=0.02).
In the total HF group (HF-CSA and HF-noSDB) the resting CO_2 did not correlate with markers of HF severity (LVEF, BNP) but did correlate negatively with the AHI (Spearman rho=-0.41, p=0.04), as shown in figure 4.3. Resting CO_2 levels in the combined HF groups correlated positively with the body mass index (BMI; r=0.39, p=0.04, n=26) as shown in figure 4.4. In the HF-CSA alone the resting CO_2 showed a tighter correlation with BMI (r=0.66, p=0.03, n=11) and this is shown in figure 4.5.

HCVR was measured in the evening in all 26 patients. Morning data were available for 6 of 11 (55%) of the HF-CSA group and 11 of 15 (73%) of the HF-noSDB group. Contrary to the hypothesis there was no significant difference between the HF-CSA and HF-noSDB in evening HCVR (2.15 (1.70-2.74) vs. 1.99 (1.60-3.33) L/min/mmHg $ETCO_2$, p=0.53), morning HCVR (2.71 (1.43-4.88) vs. 2.20 (1.00-3.00) L/min/mmHg $ETCO_2$, p=0.23) nor in the evening to morning change in HCVR (-0.37 (-2.10 - 1.57) vs. -0.01 (-0.60 – 0.50) L/min/mmHg $ETCO_2$, p=0.69); see figure 4.6.

Table 4.3: Baseline characteristics for the HF-CSA and HF-noSDB groups. Data are median (IQR) unless specified.

		HF-CSA n=11	HF-noSDB n=15	
Age (yrs)		**68** (58-78)	**72** (67-78)	*p=0.30*
Gender (M / F)		**11 / 0**	**14 / 1**	-
BMI (kg/m^2)		**28.9** (24.3-30.4)	**26.9** (25.1-31.8)	*p=0.98*
Neck circumference (cm)		**38.7** (37.0-42.3)	**40.0** (38.0-42.8)	*p=0.45*
Epworth sleepiness score		**7** (6-9)	**8** (5-11)	*p=0.92*
FEV$_1$ (%)		**83.3** (75.4-99.4)	**71.3** (60.8-79.3)	***p=0.04***
FVC (%)		**86.0** (73.9-92.0)	**78.9** (59.7-95.5)	*p=0.72*
NYHA functional class I / II / III / IV		**1 / 5 / 3 / 2**	**2 / 10 / 3 / 0**	-
Blood pressure (mmHg)	Systolic	**115** (105-1220	**128** (111-137)	*p=0.13*
	Diastolic	**65** (58-85)	**75** (66-81)	*p=0.29*
Left ventricular ejection fraction (%)		**32** (20-40)	**40** (27-47)	*p=0.15*
B-type natriuretic peptide (pmol/L)		**97.0** (62.5-275.0)	**38** (26.8-61.5)	***p=0.02***
Aetiology of HF syndrome	Ischaemic	**7**	**5**	-
	DCM	**1**	**4**	
	Valvular	**2**	**2**	
	Diastolic	**0**	**0**	
	Unknown	**1**	**4**	
Medications	Diuretics	**8**	**11**	-
	Beta blocker	**10**	**12**	
	ACE inhibitor/ARB	**7**	**13**	
	Digoxin	**2**	**4**	
Comorbidities	Diabetes	**1**	**1**	-
	Atrial fibrillation	**5** (PAF in 1)	**7** (PAF in 2)	
Implanted devices	no device	**8**	**6**	-
	PPM +/- ICD	**0**	**5**	
	CRT	**3**	**4**	
	ICD	**0**	**0**	

BMI- body mass index; FEV$_1$- forced expiratory volume in 1 second; FVC- forced vital capacity; NYHA- New York Heart Association; DCM- dilated cardiomyopathy; ACE- angiotensin converting enzyme; ARB- angiotensin receptor blocker; PPM-

permanent pacemaker; ICD-implantable cardiac defibrillator; PAF- paroxysmal atrial fibrillation; CRT- cardiac resynchronisation therapy.

Table 4.4: Nocturnal polysomnography data for the HF-CSA and HF-noSDB groups. Data are median (IQR) unless specified.

	HF-CSA n=11	**HF-noSDB n=15**	
Apnoea hypopnoea index (events/hr)	**14.6** (12.9-37.1)	**5.0** (3.2-6.0)	
Apnoea index (events/hr)	**6.4** (2.4-10.4)	**0.2** (0-1.9)	
Hypopnoea index (events/hr)	**10.3** (8.3-18.2)	**3.6** (2.2-5.1)	
Oxygen desaturation index (≥3% dip rate/hour)	**15.0** (11.5-23.9)	**5.5** (2.2-7.9)	***p=<0.01***
Time with O_2 sats <90% (min)	**18.7** (4.4-75.0)	**1.6** (0-7.4)	***p=0.04***
Time in bed (min)	**485** (439-548)	**480** (422-494)	*p=0.24*
Total sleep time (min)	**348** (324-460)	**297** (269-368)	*p=0.23*
Sleep efficiency (%)	**74.5** (69.1-92.5)	**72.6** (52.5-83.7)	*p=0.54*
Sleep latency (min)	**11.3** (8.3-29.3)	**12.5** (6.4-28.5)	*p=0.94*
Wake after sleep onset (min)	**80** (36-149)	**108** (63-186)	*p=0.48*
Arousal index (events/hr)	**26.4** (17.1-48.2)	**24.8** (17.1-48.2)	*p=0.22*
Stage 1 (%)	**27.6** (19.8-44.8)	**25.5** (17.2-35.5)	*p=0.78*
Stage 2 (%)	**45.2** (30.8-51.0)	**43.6** (30.8-46.4)	*p=0.68*
Slow wave sleep (%)	**8.8** (4.4-12.5)	**11.3** (6.0-14.1)	*p=0.48*
REM sleep (%)	**14.5** (9.8-19.5)	**18.5** (14.4-29.4)	*p=0.14*
PLM index (events/hr)	**14.1** (5.1-49.3)	**7.5** (1.2-15.7)	*p=0.11*
Supine position (%)	**35.8** (25.3-69.3)	**22.0** (3.1-50.1)	*p=0.14*
Left position (%)	**18.2** (0-38.9)	**18.7** (12.3-32.7)	*p=0.75*
Right position (%)	**33.9** (0-70.7)	**34.5** (2.3-66.7)	*p=0.62*

REM- rapid eye movement; PLM- periodic limb movement.

NB: none of the patients in either group slept in the prone position during the sleep study therefore this data has been omitted.

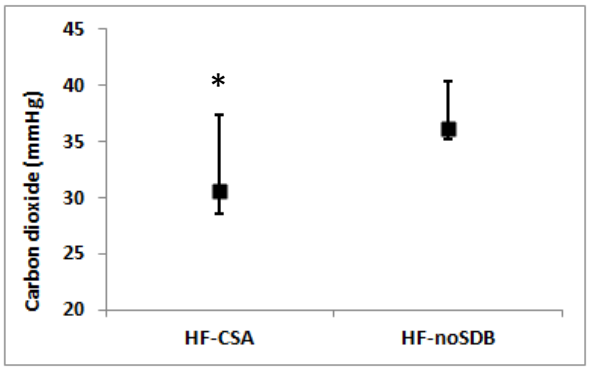


Figure 4.2: Resting carbon dioxide levels in the HF-CSA and HF-noSDB groups. (*p=0.03)

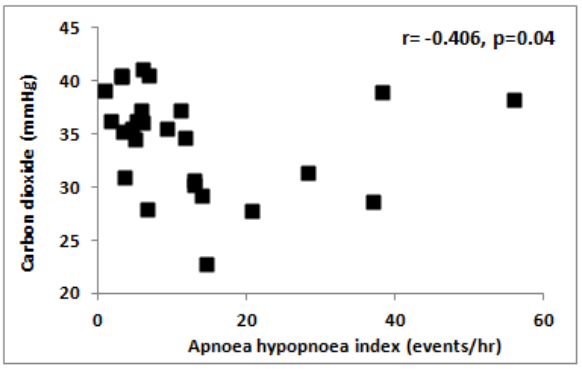


Figure 4.3: Scatter graph to show the relationship between resting CO2 levels and the apnoea hypopnoea index in the combined patient group (HF-CSA and HF-noSDB)

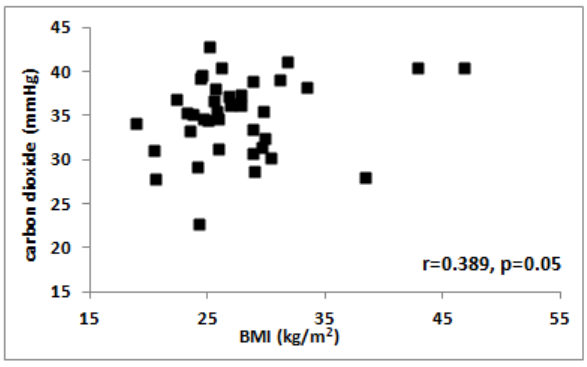


Figure 4.4: Scatter graph to show the relationship between resting CO_2 and BMI in the combined HF group (HF-CSA and HF-noSDB). *BMI; body mass index*

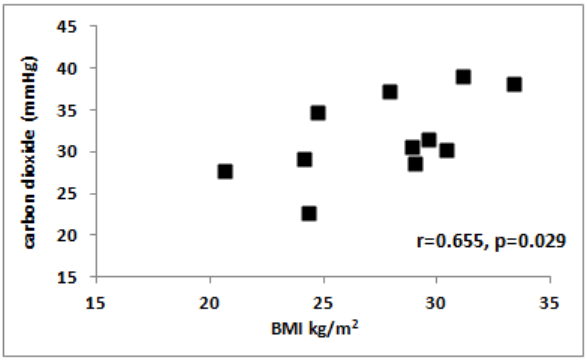


Figure 4.5: Scatter graph to show the relationship between resting CO_2 and BMI in the HF-CSA group only. *BMI; body mass index*

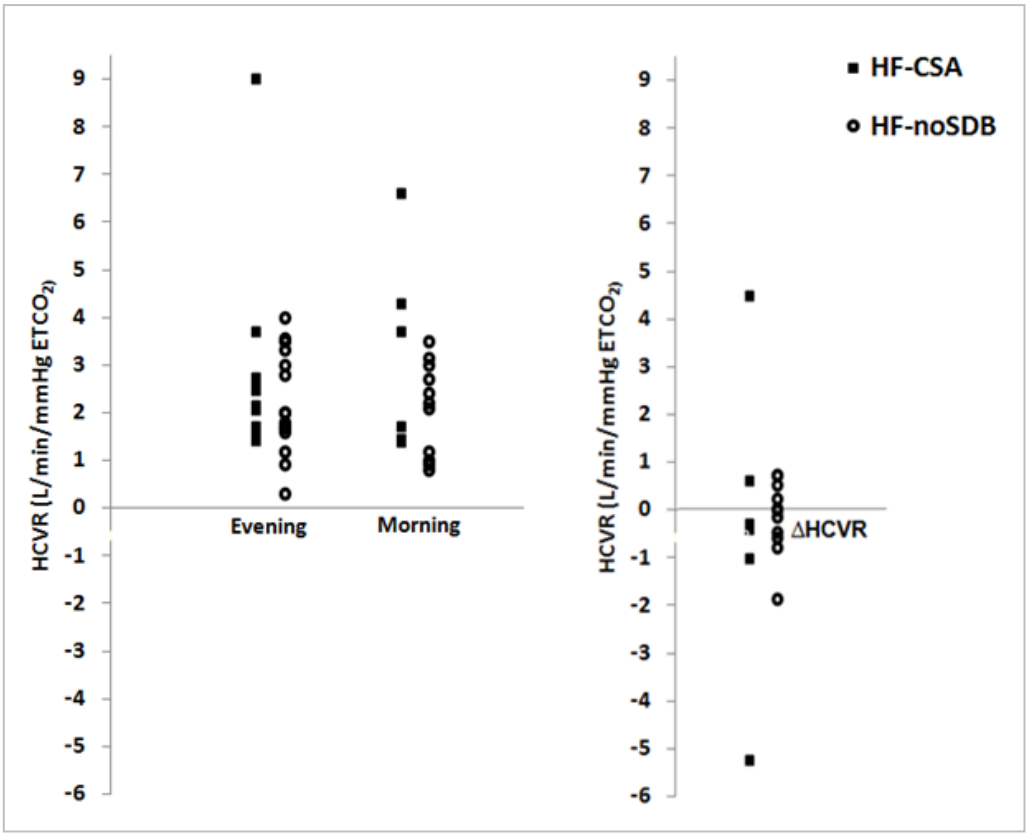


Figure 4.6: Scatter graphs showing individual HCVR for each of HF-CSA and HF-noSDB groups.
HCVR- hypercapnic ventilatory response.

4.3.2 Differences in hypercapnic ventilatory response between HF patients and healthy controls

HF patients with central SDB had a similar HCVR in the morning and evening to those with HF and no SDB. Additionally there was no difference between the groups in overnight change in HCVR. I therefore extended my hypothesis to investigate the theory that patients with HF had an increased HCVR compared to healthy older controls. Having already compared HF-CSA and HF-noSDB I compared both patient groups with the control group. Baseline characteristics can be found in table 4.5 and data from nocturnal PSG in table 4.6.

The patients with HF-noSDB were older than the control group (72 (67-78) vs. 63 (59-67) years, p=<0.01) and had higher Epworth sleepiness scores (8 (5-11) vs. 4 (1-6), p=0.01). FEV_1 was higher in the controls than the HF-noSDB group (89.0 (77.3-101.3) vs. 71.3 (60.8-79.3) % predicted, p=0.01), but there was no difference in FVC. Overnight the HF-noSDB group had a higher ODI than the controls (5.5 (2.2-7.9) vs. 1.6 (0.7-2.0) /hr, p=<0.01).

There was no difference in resting CO_2 level between the HF-CSA and control groups. Group data for all three groups are shown in figure 4.7. In the combined study population (ie. HF-noSDB, HF-CSA and the control group) there was a negative correlation between resting CO_2 and morning HCVR (r=-0.45, p=0.03, n=30) and this is shown in figure 4.8.

There was no difference between the groups in the evening (1.99 (1.60-3.33) vs. 2.04 (1.80-2.96) L/min/mmHg $ETCO_2$, p=0.62), morning (2.20 (1.00-3.00) vs. 1.76 (1.09-2.63) L/min/mmHg $ETCO_2$, p=0.71), nor evening to morning change in HCVR (-0.01 (-0.60 – 0.50) vs. -0.28 (-0.72 – 0.32) L/min/mmHg $ETCO_2$, p=0.72).

The HF-CSA group also had a higher Epworth sleepiness score than the control group (7 (6-9) vs. 4 (1-6), p=0.01) and overnight had a higher ODI during sleep (5.5 (2.2-7.9) vs. 1.6 (0.7-2.0) /hr, p=<0.01) but otherwise there were no significant differences between these 2 groups, including no difference in spirometry (FEV_1 and FVC) nor in the evening (2.15 (1.70-2.74) vs. 2.04 (1.80-2.96) L/min/mmHg $ETCO_2$, p=0.51), morning (2.71 (1.43-4.88) vs. 1.76 (1.09-2.63) L/min/mmHg $ETCO_2$, p=0.30) nor evening to morning change in HCVR (-0.37 (-2.10 - 1.57) vs. -0.28 (-0.72 – 0.32) L/min/mmHg $ETCO_2$, p=0.84). Individual and group HCVR data are shown in figures 4.9 and 4.10 respectively.

Table 4.5: Baseline characteristics of HF-CSA, HF-noSDB and control groups. *NB groups compared using Kruskall Wallis test with Bonferroni correction- Significance level 0.02*

		HF-CSA n=11	HF-noSDB n=15	Controls n=14	
Age (yrs)		**68 (58-78)**	**72 (67-78)**	**63 (59-67)**	*p=<0.01 HF-noSDB vs. control*
Gender (male %)		**100**	**93**	**79**	-
BMI (kg/m^2)		**28.9 (24.3-30.4)**	**26.9 (25.1-31.8)**	**25.6 (23.4-26.7)**	*NS*
Neck circumference (cm)		**38.7 (37.0-42.3)**	**40.0 (38.0-42.8)**	**38.1 (35.6-39.1)**	*NS*
Epworth sleepiness score		**7 (6-9)**	**8 (5-11)**	**4 (1-6)**	*p=0.01 HF-CSA vs. control p=0.02 HF-noSDB vs. control*
FEV$_1$ (%)		**83.3** (75.4-99.4)	**71.3** (60.8-79.3)	**89.0** (77.3-101.3)	*p=0.01 HF-noSDB vs. control*
FVC (%)		**86.0** (73.9-92.0)	**78.9** (59.7-95.5)	**89.0** (79.9-99.3)	*NS*
NYHA functional class I / II / III / IV		**1 / 5 / 3 / 2**	**2 / 10 / 3 / 0**	**-**	
Blood pressure (mmHg)	**Systolic**	**115 (105-1220**	**128 (111-137)**	**-**	
	Diastolic	**65 (58-85)**	**75 (66-81)**	**-**	
Left ventricular ejection fraction (%)		**32 (20-40)**	**40 (27-47)**	**-**	
B-type natriuretic peptide (pmol/L)		**97.0** (62.5-275.0)	**38.0** (26.8-61.5)	-	

Aetiology of HF syndrome	Ischaemic DCM Valvular Diastolic Unknown	**7** **1** **2** **0** **1**	**5** **4** **2** **0** **4**	-
Medications	Diuretics Beta blocker ACE inhibitor/ARB Digoxin	**8** **10** **7** **2**	**11** **12** **13** **4**	-
Comorbidities	Diabetes Atrial fibrillation	**1** **5** (PAF in 1)	**1** **7** (PAF in 2)	-
Implanted devices	no device PPM +/- ICD CRT ICD	**8** **0** **3** **0**	**6** **5** **4** **0**	-

BMI- body mass index; FEV_1- forced expiratory volume in 1 second; FVC- forced vital capacity; NYHA- New York Heart Association; DCM- dilated cardiomyopathy; ACE- angiotensin converting enzyme; ARB- angiotensin receptor blocker; PPM- permanent pacemaker; ICD-implantable cardiac defibrillator; PAF- paroxysmal atrial fibrillation; CRT- cardiac resynchronisation therapy.

Table 4.6: Nocturnal polysomnography data for the HF-CSA and HF-noSDB groups. Data are median (IQR) unless specified.

	HF-CSA n=11	HF-noSDB n=15	Controls n=14	
Apnoea hypopnoea index (events/hr)	**14.6** (12.9-37.1)	**5.0** (3.2-6.0)	**1.4** (0.5-3.6)	
Apnoea index (events/hr)	**6.4** (2.4-10.4)	**0.2** (0-1.9)	**0.9** (0-1.2)	
Hypopnoea index (events/hr)	**10.3** (8.3-18.2)	**3.6** (2.2-5.1)	**0.7** (0-1.4)	
Oxygen desaturation index (≥3% dip rate/hour)	**15.0** (11.5-23.9)	**5.5** (2.2-7.9)	**1.6** (0.7-2.0)	*p=<0.01 HF-CSA vs. control p=<0.01 HF-noSDB vs. control*
Time with O_2 sats <90% (min)	**18.7** (4.4-75.0)	**1.6** (0-7.4)	**0** (0-5.7)	*p=<0.01 HF-CSA vs. control.*
Time in bed (min)	**485** (439-548)	**480** (422-494)	**491** (452-519)	*NS*
Total sleep time (min)	**348** (324-460)	**297** (269-368)	**388** (258-421)	*NS*
Sleep efficiency (%)	**74.5** (69.1-92.5)	**72.6** (52.5-83.7)	**79.2** (52.1-88.7)	*NS*
Sleep latency (min)	**11.3** (8.3-29.3)	**12.5** (6.4-28.5)	**23.2** (10.9-52.6)	*NS*
Wake after sleep onset (min)	**80** (36-149)	**108** (63-186)	**88.0** (31.5-115.3)	*NS*
Arousal index (events/hr)	**26.4** (17.1-48.2)	**24.8** (17.1-48.2)	**29.4** (10.0-41.4)	*NS*
Stage 1 (%)	**27.6** (19.8-44.8)	**25.5** (17.2-35.5)	**14.8** (12.3-24.9)	*NS*
Stage 2 (%)	**45.2** (30.8-51.0)	**43.6** (30.8-46.4)	**39.0** (33.0-60.2)	*NS*
Slow wave sleep (%)	**8.8** (4.4-12.5)	**11.3** (6.0-14.1)	**20.2** (5.5-29.6)	*NS*

REM sleep (%)	**14.5** (9.8-19.5)	**18.5** (14.4-29.4)	**19.3** (16.6-24.4)	*NS*
PLM index (events/hr)	**14.1** (5.1-49.3)	**7.5** (1.2-15.7)	**4.4** (0.6-12.7)	*p=0.03 HF-CSA vs. control*
Supine position (%)	**35.8** (25.3-69.3)	**22.0** (3.1-50.1)	**28.2** (13.1-46.7)	*NS*
Left position (%)	**18.2** (0-38.9)	**18.7** (12.3-32.7)	**26.8** (14.2-54.8)	*NS*
Right position (%)	**33.9** (0-70.7)	**34.5** (2.3-66.7)	**29.1** (15.5-38.6)	*NS*

REM- rapid eye movement; PLM- periodic limb movement.

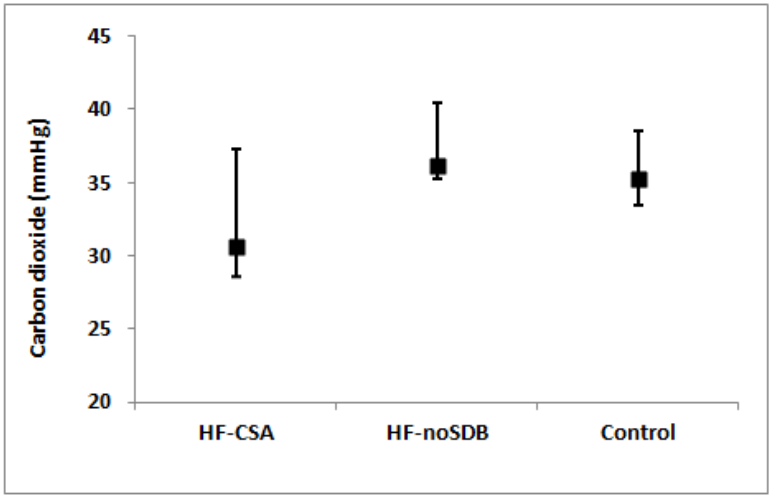


Figure 4.7: Group data for resting CO_2 levels for HF-CSA, HF-noSDB and the controls.

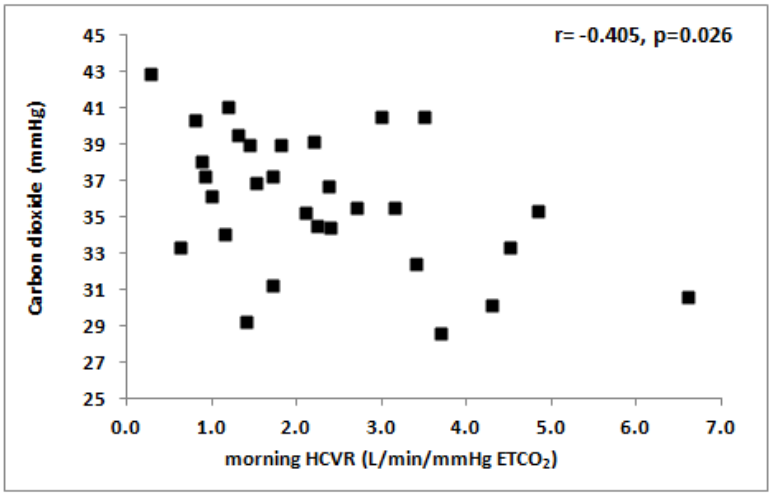


Figure 4.8: Scatter graph to show the relationship between resting CO_2 and morning HCVR in the total study population (HF-CSA, HF-noSDB and control groups combined).

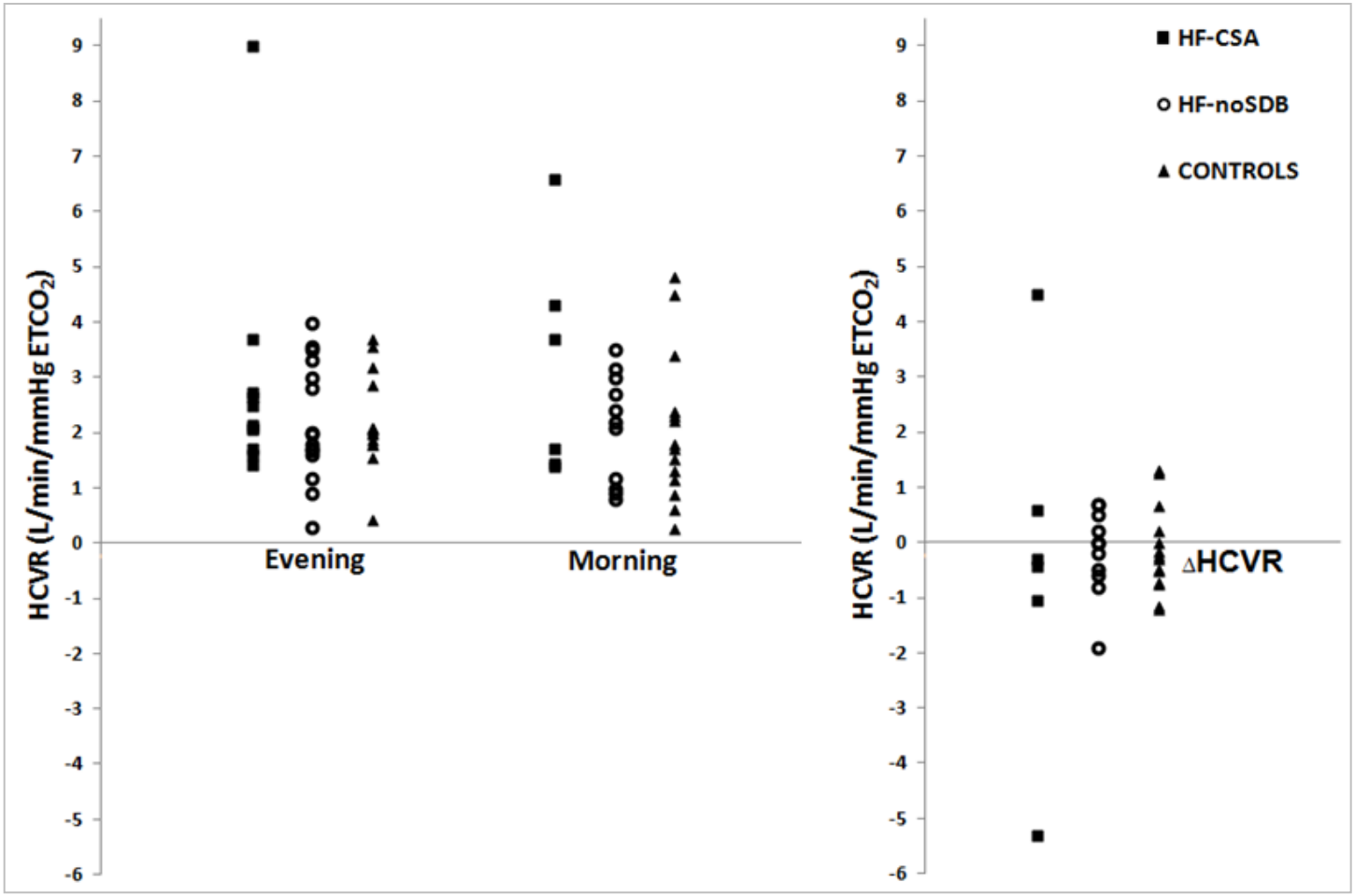


Figure 4.9: Scatter graphs to show individual evening and morning HCVR data with overnight change in HF-CSA, HF-noSDB and control groups.
HCVR- hypercapnic ventilatory response; ΔHCVR- evening to morning change in hypercapnic ventilatory response.

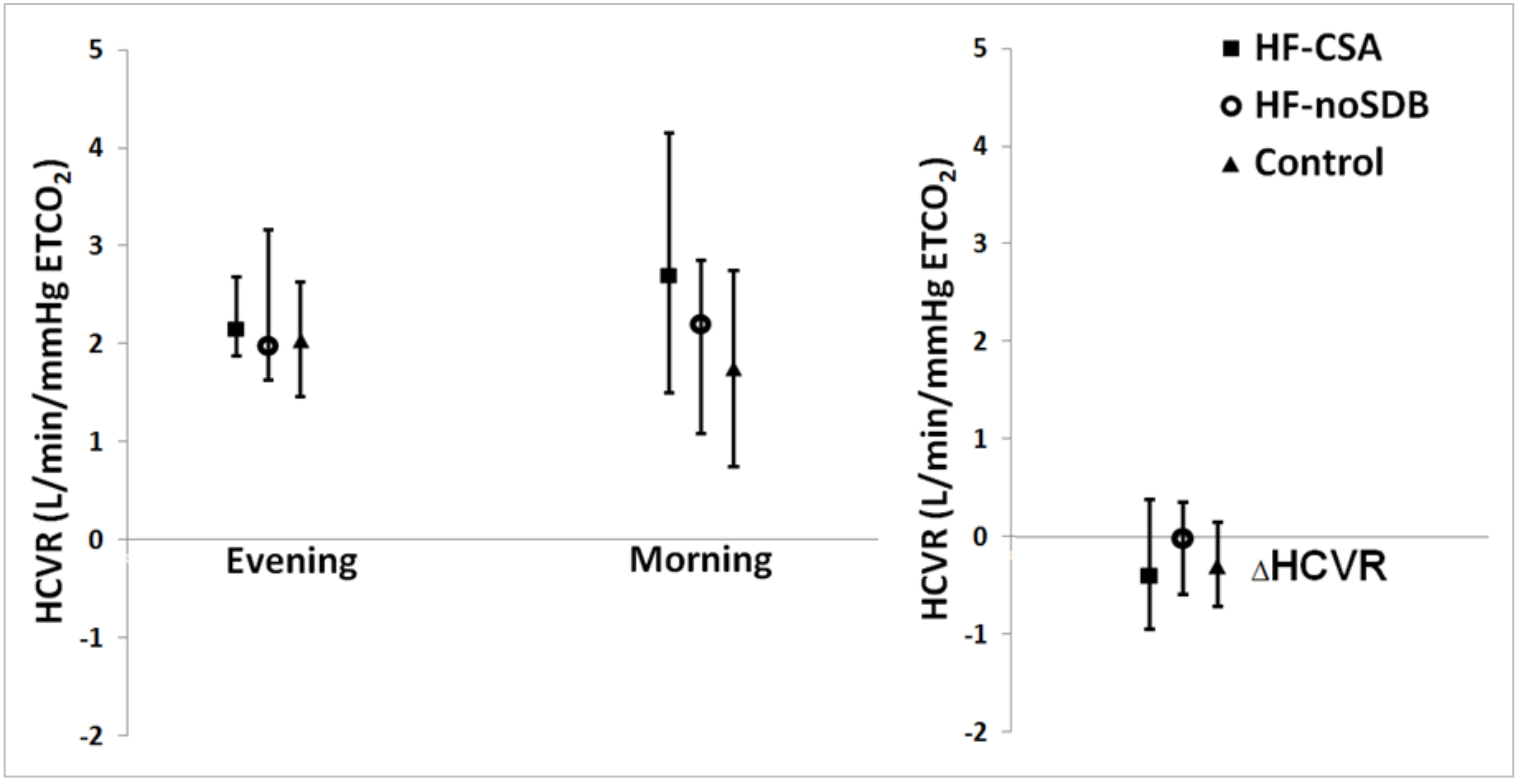


Figure 4.10: Graphs to show group data for evening and morning HCVR and overnight change in the three groups studied.
Vertical bars represent group median and IQR. *HCVR- hypercapnic ventilatory response; ΔHCVR- evening to morning change in hypercapnic ventilatory response.*

4.3.3 Factors influencing the hypercapnic ventilatory response

I found no difference in evening or morning HCVR, nor in the evening to morning change in HCVR between the 3 groups studied; however, these groups were not matched for age. I therefore sought to investigate to what extent, if at all, age might influence the HCVR in this study population. There was no correlation between age and any measure of HCVR (ie. evening, morning or overnight change). Age did correlate with LVEF in the combined HF group ($r=0.42$, $p=0.04$, $n=25$) and in the HF-CSA group ($r=0.63$, $p=0.04$, $n=11$).

Evening and morning HCVR were correlated in both the control group (Spearmans' rho $=0.736$, $p=<0.01$, $n=15$) and in the combined HF group ($r=0.74$, $p=<0.01$, $n=17$). Because the HF groups were not specifically matched for HF severity the effect of this on HCVR was investigated. There was no correlation between markers of HF severity (BNP and LVEF) and any measure of HCVR.

4.4 DISCUSSION

This study aimed to investigate the mechanism of central SDB in HF patients by measuring the ventilatory response to hypercapnia as a marker of chemosensitivity in patients with HF, both with and without central SDB, as well as a group of healthy older control subjects. In doing so the intention was to test the hypotheses that HF patients with central SDB would have an increased HCVR compared to those with HF and no SDB; secondly that there would be a difference in overnight change in HCVR between these two groups.

The data collected in 40 patients and subjects did not support the hypothesis that HF patients with central SDB had an increased HCVR compared to those with HF and no SDB. There was no difference in evening or morning HCVR, nor in the evening to morning change in HCVR between these 2 patient groups, although the highest median evening, morning, and evening to morning change in HCVR were all found in the HF-CSA group. Furthermore there was no difference in evening or morning HCVR, nor in evening to morning change in HCVR between either of the patient groups and the group of older healthy controls. Resting CO_2 levels in the group with central SDB were lower than those in the HF-noSDB group, but not significantly different to the control group. Furthermore, resting CO_2 in the HF-CSA group showed negative correlations with both AHI and BMI. In the total study population (patients and controls), resting CO_2 levels correlated with morning, but not evening, HCVR.

Previous work has shown an increase in evening to morning HCVR in healthy controls (Cummings et al., 2007). However, the group data for the control subjects (n=14) demonstrated a net reduction in HCVR overnight, as did both patient groups. To my knowledge evening to morning changes in HCVR have not been studied in HF patients previously. As with previous work (Javaheri, 1999) there was a high level of within group variability and between group overlap in HCVR in each of the 3 groups studied. Although the groups were not matched for age, which is known to affect the HCVR (Brischetto et al., 1984, Browne et al., 2003), age did not correlate with any aspect of the HCVR data. In addition to age several other factors are known to affect the HCVR and these will be considered below in the context of the current study.

4.4.1 The effect of heart failure on the hypercapnic ventilatory response

As discussed in Chapter 1, section 1.5, breathing during sleep is vulnerable to instability in health, for several reasons, including changes in chemosensitivity. HF patients with central SDB tend to have a resting hypocapnia (Sin et al., 1999) and do not have the same rise in CO_2 at sleep onset (Xie et al., 2002) meaning that their sleeping levels are closer to the apnoeic threshold. In addition, several studies have shown brisker hypercapnic (Javaheri, 1999, Topor et al., 2001, Solin et al., 2000) ventilatory response further contributing to an increased controller gain, and so instability. Low cardiac output, pulmonary congestion and reduced lung volumes all contribute to an increased plant gain; furthermore a prolonged circulation time causes an increase in feedback gain, although this is not thought to be a major cause of ventilatory instability. To summarise; the potential for ventilatory instability seen in healthy subjects is magnified in the presence of HF, which may explain the prevalence of central SDB in patients with HF, as outside of the HF population it is rare (DeBacker et al., 1995).

The results of this study found no difference in chemosensitivity, as assessed by measurement of the HCVR, between HF patients with and without central SDB, nor between HF patients and older healthy controls, as might be anticipated (the reasons for this are discussed below). There were, however, differences in resting CO_2 levels between the HF groups which, although not a cause of ventilatory instability, is often associated with it (Sin et al., 1999, Javaheri, 2006b), probably because, as discussed, these patients fail to increase CO_2 levels at sleep onset such that sleeping CO_2 is closer to the apnoeic threshold than in those with HF without central SDB (Xie et al., 2002). Taking this finding as a marker of ventilatory instability (even in the absence of between group differences in HCVR) one can interpret the negative correlation of CO_2 and AHI as indicative of the mechanism underlying the SDB. That is, ventilatory instability is both associated with hypocapnia and a likely cause of SDB in this population.

4.4.2 Factors affecting the hypercapnic ventilatory response and how these might explain differences between this and previous work

Increasing age has been associated with a reduction in the HCVR (Kronenberg and Drage, 1973, Brischetto et al., 1984) which is contrary to what might be expected given the higher prevalence of SDB seen in older subjects (Bixler et al., 1998). Although the HCVR falls with age, the sleep related reduction in HCVR described before (Douglas et al., 1982b) is unchanged by age (Browne et al., 2003), contrary to early studies which found no decrease and proposed this as an explanation for the higher prevalence of SDB in older populations (Naifeh et al., 1989). Similarly, the cerebrovascular response to CO_2 falls with age in women, but not in men (Kastrup et al., 1998). This study compared HF patients with and without central SDB, with older healthy controls. Median (IQR) age was 68 (58-78), 72 (67-78) and 63 (59-67) years, respectively (p=0.30 HF-CSA vs. HF-noSDB; p=0.37 HF-CSA vs. control and p=<0.01 HF-noSDB vs. controls). Given the difference in age between the HF-noSDB and control groups it is possible that age affected the HCVR of each group differently and so may have obscured any true effect attributable to the difference between the groups related to the presence/absence of SDB/HF. Notably however, there was no difference in HCVR between the HF-CSA and HF-noSDB, who were the basis of the primary hypothesis.

Gender too is known to affect the HCVR; men have more brisk ventilatory responses than women in most (Aitken et al., 1986, Patrick and Howard, 1972, White et al., 1983a, Kunitomo et al., 1988), but not all (Kunitomo et al., 1988) previous work. Menstrual phase (luteal vs. follicular phases) does not affect HCVR (Macnutt et al., 2011, Itoh et al., 2007) despite progesterone being a respiratory stimulant. The use of hormone replacement therapy in older women has been associated with an increase in the cerebrovascular hypercapnic response (Kastrup et al., 1998) and so may affect the HCVR. Of 40 subjects in this study only 4 were female (1 patient and 3 controls); all were post menopausal and but none was taking hormone replacement therapy.

Obesity has been associated with an enhancement of the HCVR in women, but not in men (Kunitomo et al., 1988, Buyse et al., 2003) although again, not in all studies (Miyamura et al., 1985). There was no significant difference in BMI between the 3 groups studied in this work, however all 3 group medians were within the overweight range. This study found that, in the total HF group but particularly in the HF-CSA group, resting CO_2 levels were associated with BMI. This novel finding may be explained in 1 of 2 ways. Firstly it is possible that a lower BMI is a signal for HF severity, which is known to be worse in those with HF and central SDB (BNP levels were higher in the HF-CSA group), hence the relationship. Secondly it is possible that a higher BMI affects ventilation such that resting

CO_2 levels are higher. Obesity is known to affect lung volumes causing a reduction in FVC (Perez de Llano et al., 2005), which would be exacerbated in the sleeping state when muscle tone falls, and this may have caused a compensatory increase in respiratory rate and a reduction in CO_2 levels.

The protocol employed in the current study involved measurement of the HCVR with patients in the supine position. A few patients were not able to tolerate this, either because of dyspnoea or because of musculoskeletal discomfort. In his study of HCVR in HF patients Javaheri used a protocol involving measurement in a sitting position. Measurement of the HCVR in the supine and sitting positions has been found to yield the same results (Rigg et al., 1974) and studies looking at the effect of tilting subjects from supine to a head up position for between 10 and 20 minutes found no significant effect on HCVR (Anthonisen et al., 1964, Yoshizaki et al., 1998), although more prolonged tilt (19 days of head down bed rest) was shown to significantly decrease HCVR in a small group of men (Katayama et al., 2004).

Genetic factors (Kawakami et al., 1984) are known to influence the HCVR and are thought to explain the high level of variability found in healthy controls. It must be assumed that such factors affected all 3 groups in this work equally. None of the subjects studied were related.

As discussed before, while early studies suggested that sleep deprivation may attenuate chemosensitivity (White et al., 1983b), later controlled studies on sleep deprivation (Spengler and Shea, 2000) and fragmentation (Espinoza et al., 1991) have not found any effect on HCVR. Patients and subjects participating in this study were asked not to modify their sleep pattern prior to their visit to the laboratory, and shift workers were not enrolled. The HCVR may also be affected by sustained physical training (Bradley and Unger, 1981, Kelley et al., 1984); while several participants engaged in regular exercise (swimming, cycling), only 1 control subject regularly visited the gymnasium (daily). Studies also suggest that the HCVR may vary with season (Hiruta et al., 1990). Figure 4.11 shows the distribution of HCVR measurement by season for each group (Winter; December to February, Spring; March to May, Summer; June to August and Autumn; September to November). There were no control subject tests in the spring; otherwise testing was evenly spread between the seasons.

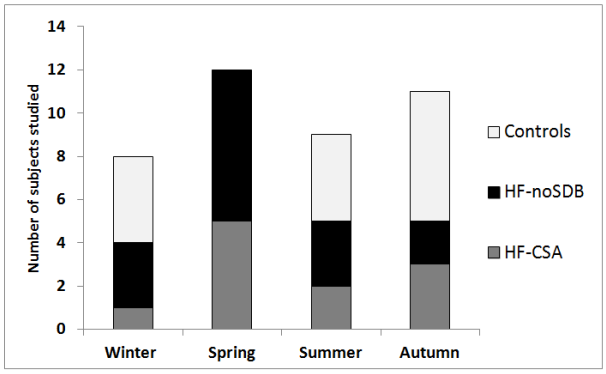


Figure 4.11: Distribution of HCVR tests according to season.

HCVR exhibits a circadian rhythm (Spengler et al., 2000) with an increase from evening to morning reported in healthy subjects (Spengler et al., 2000, Cummings et al., 2007). In order to account for this the protocol used involved measurement of the HCVR during fixed times in the evening and morning. The control group in this study did not have the same evening to morning rise in HCVR reported by Cummings et al. and Spengler et al. and the reasons for this are unclear but may relate to the subjects in both of these studies being significantly younger (mean (SD) age 25 (4) and 37.7 (3.9) yrs respectively) than the controls in the current work (median (IQR) 63 (59-67) years). The effect of age on the evening to morning change in HCVR in older subjects has not previously been studied.

HCVR seems to be amenable to manipulation by both voluntary and hypnotic suggestion (Sato et al., 1986) and furthermore is affected by some aspects of personality (in women, but not men) (Saunders et al., 1972). These curious observations emphasise the impact of the behavioural / volitional control of breathing and the importance of clear instructions to the subjects prior to the measurement of HCVR. Unless fully briefed about the nature of the test and the importance of not voluntarily controlling (particularly, slowing down) their breathing, I found that subjects would instinctively do this. My protocol involved explanation at several points, including immediately before the test.

The results of this study differ from that of previous work, most notably that of Javaheri. He made measurements of the HCVR in the morning (exact time unknown) which, as discussed, may have had an effect on the results obtained. It is feasible that had he made measurements in the evening he may not have found a difference between his groups as I did not with my evening measurements, although this seems unlikely given that in my own work I have found evening and morning measurements to be similar. Only some of my subjects had morning measurements made and while this work was adequately powered for the primary hypothesis (a difference in evening HCVR) it may have lacked power for the comparison of morning and evening to morning changes in HCVR.

The difference in resting CO_2 levels between the HF-CSA and HF-noSDB groups confirms the work of others (Sin et al., 1999, Javaheri, 2006b, Xie et al., 2002) and demonstrates that the HF-CSA group were similar to those in previous work, at least in terms of their resting hypocapnia. The correlation between resting CO_2 and morning HCVR perhaps suggests that it is morning HCVR which is significantly brisker in those with central SDB (compared to no SDB); ie. that morning HCVR is a better indicator of ventilatory instability and that significant differences in HCVR are present only in the morning and not in the evening. This is mechanistically plausible given that overnight the patient experiences considerable pathophysiological stressors in the form of apnoeas, hypopnoeas, recurrent desaturations and adrenergic surges, as well as the stress placed on heart by sleep (discussed in chapter 1, section 1.4.3). My findings may differ from those of Javaheri because his HCVR were in the morning, and it is likely that in my work the size of the groups undergoing measurement of HCVR in the morning were too small to detect such a difference, if one did exist.

The aetiology of the HF syndrome in the 20 patients studied by Javaheri is not given in the publication. The current study predominantly included patients with ischaemic cardiomyopathy (7 HF-CSA and 5 HF-noSDB) and dilated cardiomyopathy (1 and 4 respectively). If HF aetiology does influence the HCVR then, given that 50% of the HF patients studied had an ischaemic cardiomyopathy, it is possible this may have influenced the result. This is unlikely given that Solin et al. (Solin et al., 2000) made similar conclusions to Javaheri in a study including a similar proportion of patients with ischaemic cardiomyopathy.

It is notable that none of the patients in the Javaheri study (published in 1999) were on beta blocking medications, now considered an integral part of the management of HF. There are no data which suggest that beta blockers might affect the HCVR, although a prevalence study of SDB in HF patients concluded that rates remain relatively unchanged despite the evolution of pharmacological treatment (MacDonald et al., 2008). However a study looking at the use of a beta blocker (carvedilol) in HF patients with central SDB was associated with a reduction in the central apnoea index after 6 months of treatment (Tamura et al., 2007) suggesting that beta blocker use may manipulate the HCVR.

Finally, 19 out of 20 patients in the Javaheri study were taking digoxin compared with just 6 in the current study (2 in HF-CSA and 4 in HF-noSDB groups), a difference which reflects the evolution of HF management. Interestingly, digoxin use has been associated with an increase in peripheral chemosensitivity in normal subjects (Janssen et al., 2009) although its effects on central chemosensitivity have not been assessed specifically. It is possible that this increased the HCVR in the Javaheri study, but does not account for the difference between his groups, and the lack of

difference between the groups in this work. Information on medication use is not given in the publications by Solin et al. (Solin et al., 2000) or Topor et al. (Topor et al., 2001).

4.4.3 Methodological considerations

This was an observational study investigating chemosensitivity in HF patients with and without central SDB, and age matched controls. Whilst it was adequately powered to answer the primary hypothesis it had a number of limitations.

The 3 groups studied were not matched fully for age, HF severity (assessed by BNP) or levels of subjective sleepiness. Notably they were matched for BMI which is known to affect the HCVR, as discussed. These differences between the groups may have affected the results, although it is difficult to predict what the net direction of any such effect might be. I did not adjust for the same factors as Javaheri did, namely oxygen consumption, CO_2 production, maximal voluntary ventilation and FVC, which are likely to have affected HCVR.

The Read rebreathe method (Read, 1967) was chosen for this study as it is relatively quick test of the HCVR and is generally well tolerated by patients. One patient was excluded because he was unable to tolerate the test which resulted in inadequate hypercapnia and so an invalid test. Several patients had trouble tolerating the increase in respiratory effort and rate, and it is possible this affected the results of the study by excluding patients with higher hypercapnic ventilatory responses. To try and counter any potential discomfort the test was fully explained prior to its start so that patients knew what to expect. I also carefully explained the need for a good seal around the mouthpiece, and took every effort to make patients comfortable during the test, particularly with reference to the nose clip which some found uncomfortable. In all but two cases (both in the HF-noSDB group) only 1 attempt was made to measure the HCVR due to patient tolerance. Repetition of the HCVR test during the same session, using the Read rebreathe method, has been shown to yield results which do not vary significantly apart from in a subgroup of subjects with brisker responses in whom there is reduction from first to subsequent measurements, suggesting incomplete recovery (Miyamura et al., 1980). One of the 2 HF-noSDB patients in whom the test was repeated had a HCVR in the highest quartile of his group (3.55 L/min/mmHg $ETCO_2$) and so in this single patient the result obtained may have been an underestimate.

There was no upper (or lower) limit for LVEF specified for patients to be included in this study. The majority of patients had systolic dysfunction, as evidenced by a reduction in LVEF at the time of randomisation. However there were 4 patients who had relatively preserved LVEF (>50%), 1 in the

HF-CSA group and the remainder in the HF-noSDB group. Although previous work has shown a similar prevalence of SDB in HF patients with preserved ejection fractions (HFNEF; see chapter 1, section 1.1.2), chemosensitivity in this group has not been studied and it is possible that this may have affected the results. In the study by Javaheri the group with central SDB had a mean (SD) LVEF of 21 ±6, and those without SDB 25 ±7 %.

It is possible that some of the medications taken by the patients (such as beta blockers, ACE inhibitors etc) may have effects on chemosensitivity, however stopping such medications (with prognostic implications) in the context of an observational study was not possible.

Although this study was adequately powered to answer the primary hypothesis (the difference in evening HCVR between HF-CSA and HF-noSDB groups), using data from the Javaheri study it is likely that the numbers of subjects with morning data were not adequate to demonstrate any difference in HCVR between the groups, if there was a difference to detect in this population.

4.4.4 Summary

In summary this study, which aimed to investigate the mechanism underlying central SDB in HF patients, has found no difference in evening or morning HCVR, nor evening to morning change in HCVR between HF patients with and without central SDB, nor between these groups and a group of older healthy controls. It found that resting CO_2 in the total patient population correlated inversely with the AHI. The investigation of evening and morning HCVR in a HF population alongside a group of healthy controls has, to my knowledge, not previously been undertaken. Previous work has found differences in HCVR between HF patients with and without central SDB. The difference between that work and the current study may relate to differences in age between the groups studied or medications, particularly the use of digoxin in the majority of patients in previous work.

When are you are old and grey and full of sleep,

And nodding by the fire, take down this book,

And slowly read, and dream of the soft look

Your eyes had once, and of their shadows deep.

“When you are old”, William Butler Yeats (1865-1939)

CHAPTER FIVE:

THE EFFECT OF CARDIAC RESYNCHRONISATION THERAPY

ON SLEEP IN PATIENTS WITH CHRONIC HEART FAILURE

5.1 INTRODUCTION

Cardiac resynchronisation therapy (CRT) is now an established part of the management of the HF syndrome and its use is associated with a range of benefits including a reduction in mortality, unplanned hospitalisation (Bristow et al., 2004, Cleland et al., 2005), improvements in quality of life and exercise capacity (Abraham et al., 2002, Cleland et al., 2005). A recent meta-analysis concluded that CRT reduces the severity of SDB in patients with HF, particularly in patients with central SDB (Lamba et al., 2011). CRT implantation improves atrio-ventricular, inter-ventricular and intra-ventricular coordination and so improves cardiac output (Skobel et al., 2005, Stanchina et al., 2007, Luthje et al., 2009, Czarnecka et al., 2010) and it is thought this might be the mechanism by which CRT improves central SDB (Oldenburg et al., 2007a).

Previous work has shown that patients with chronic HF and central SDB have a brisker ventilatory response to CO_2 (chemosensitivity) than those with CHF alone (Javaheri, 1999, Topor et al., 2001), although this was not the finding of my previous study (chapter 4). This heightened chemosensitivity contributes to ventilatory instability and is thought to play a key pathophysiological role in central SDB (see chapter 1, section 1.6.1). Other treatments for central SDB, such as nocturnal oxygen therapy and adaptive servoventilation (chapter 3), have been found to reduce chemosensitivity in patients with HF (Andreas et al., 1998, Oldenburg et al., 2011b) as well as improve left ventricular ejection fraction (Sasayama et al., 2009, Hastings et al., 2008). It is unclear if the improvement in cardiac function might be linked to the reduction in ventilatory response to CO_2.

Although the effect of CRT on central SDB and LVEF is established, it's effect on chemosensitivity and sleep is unknown. It is possible that, like nocturnal oxygen therapy and adaptive servoventilation, CRT could reduce central SDB by a reduction in chemosensitivity via its effects on myocardial contractility and ventilatory stability. I therefore aimed to test the hypothesis that CRT implantation improves SDB and sleep quality in patients from baseline (pre-implantation) to 3 months post implantation. Furthermore, that this is associated with a reduction in chemosensitivity as assessed by the HCVR to CO_2 at 3 months post implantation.

5.2 METHODS

5.2.1 Subjects

Patients with chronic HF due for CRT implantation for clinical reasons were recruited from the HF clinics at the Royal Brompton Hospital. They were included in the study if they fulfilled the current guidance (NICE HTA, 2007) for the implantation of a CRT device (see table 5.1), were clinically stable with no unplanned hospital admission (for any reason) in the preceding 4 weeks and no new class of HF medication started in the same time period. In addition they had to be aged 18 years or over and be able to read and understand the information sheet and to give informed consent. Patients with other conditions likely to significantly disrupt sleep (ie. chronic pain syndromes) and those using nocturnal positive pressure devices were excluded from the study. The study was approved by the West London REC number 3 (REC no. 10/H0706/5) and all subjects gave written informed consent (see appendix 3 for documentation). Data from the baseline studies of all 8 patients was included in the study presented in chapter 4.

Table 5.1: Clinical criteria for implantation of Cardiac resynchronisation. (NICE HTA, 2007)

Criteria for CRT Implantation (NICE HTA, 2007)
• Established on optimal medical treatment for heart failure • Broad QRS complex on electrocardiogram with or without evidence of cardiac dyssynchrony as appropriate • LVEF $\leq$35%, • Functional impairment as defined by an NYHA class of III-IV)

CRT- cardiac resynchronisation therapy; LVEF-left ventricular ejection fraction; NYHA- New York Heart Association.

5.2.2 Protocol

A flow chart illustrating the study design is given in figure 5.1.

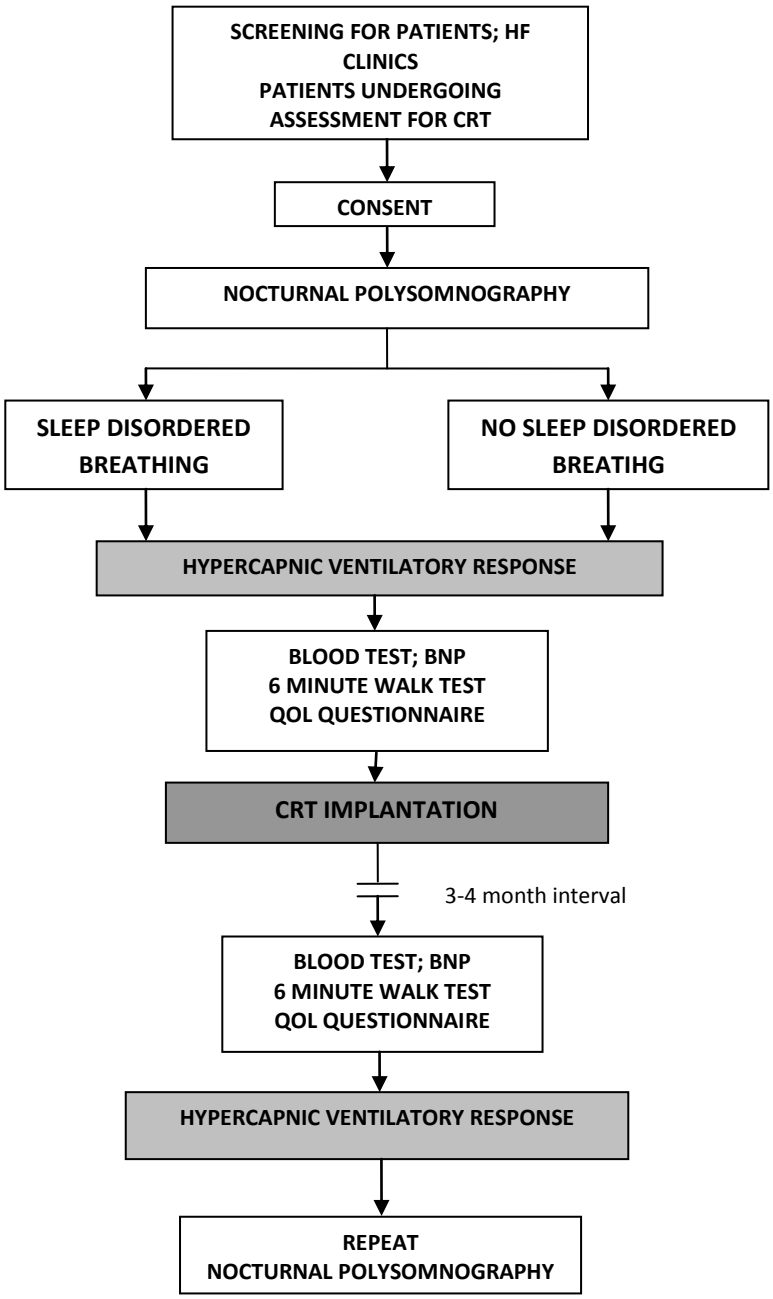


Figure 5.1: CRT study flow chart.

CRT- cardiac resynchronisation therapy; BNP- B-type natriuretic peptide; QOL- quality of life.

Baseline measurements

After informed consent a baseline assessment was made, including height, weight, resting oxygen saturation, non-invasive blood pressure measurement and neck circumference (measured at the level of the cricoid cartilage). All patients completed a measurement of subjective sleepiness (ESS), the MLHFQ and the 6MWT (see appendices 5 and 6 for questionnaires and Chapter 2, section 2.3**).** At the time of clinical assessment for CRT implantation patients had blood taken for routine testing and BNP and had an echocardiogram assessing, amongst other things LVEF and left ventricular diastolic and systolic dimensions (LVEDD and left ventricular end systolic diameter; LVESD).

Hypercapnic ventilatory response

The HCVR was measured in the evening between 19.00 and 21.00 using the Read rebreathe method (Read, 1967) at the baseline and follow-up visits. Patients were asked to refrain from drinking caffeine from at least noon on the day of the evening test. A detailed description of this technique can be found in Chapter 2, section 2.5. Resting CO_2 was measured by calculating the average end tidal CO_2 ($ETCO_2$) from 8 breaths before the start of the test.

Nocturnal polysomnography

Overnight sleep was measured in all subjects. A detailed explanation of nocturnal PSG is given in Chapter 2, section 2.7.

Follow-up measurements

Patients returned 3 (but no later than 4) months after CRT implantation, where this was successful. The schedule of follow-up assessments was identical to that in the baseline visit.

5.2.3 Analysis

Physiological analysis

A detailed description of the criteria for analysis of sleep stages and overnight breathing are given in chapter 2, section 2.10.

Data obtained during the measurement of HCVR was collected using the Spike data acquisition programme (version 5.04, Cambridge Electronic Design) and analysed off-line to determine the slope of the relationship between ventilation and end tidal CO_2. HCVR is expressed as a slope in units of L/min/mmHg $ETCO_2$. From this slope the x intercept can be calculated; this is the theoretical level of CO_2 at which ventilation would cease (see chapter 1, section 1.5.5). Further details on the measurement of HCVR are available in Chapter 2, section 2.5**.**

Statistical analysis

The median and inter-quartile ranges were used to generate descriptive statistics. Taking chemosensitivity (assessed by HCVR) as the primary outcome there were no directly comparable data from which to calculate a sample size however Andreas *et al.* measured HCVR before and after nocturnal oxygen in 20 patients with CHF and SDB (Andreas et al., 1998). They found a mean (SD) difference of 0.33 (0.23) between the before and after measurements. Using these data and assuming an alpha error level of 5% (corresponding to a 95% confidence interval) and a beta error level or statistical power [1 - Beta] of 80%; in order to detect a change in HCVR of the same magnitude 7 patients would need to be studied before and after CRT implantation. Although 8 patients were subsequently recruited the data collected was incomplete and so the numbers of subjects prohibited valid analysis beyond descriptive statistics. Furthermore, the sample size calculation did not account for only half of patients having SDB before CRT implantation nor for the response rate to CRT being less than 100%; both of these factors will have influenced the required sample size.

5.3 RESULTS

5.3.1 Baseline characteristics

Eight HF patients participated in the study; one patient was unable to tolerate the HCVR measurement and also suffered intra-operative complications during attempted CRT implantation (ventricular tachycardia). Two other HF patients declined to return for follow-up research visits after CRT was successfully implanted. Of the 5 patients who had successful CRT implantation and who returned for follow-up 1 was unable to manage the HCVR protocol on 2 attempts. In total there was baseline HCVR data on 6 out of 8 patients and follow up HCVR data on 5 out of 8 patients (see Table 5.2).

All patients were male, 5 out of 8 were Caucasian, 2 were Asian and 1 was Afro-Caribbean. The median (IQR) age was 71.5 (62.8-81.8) years, Epworth sleepiness score was 8 (7-11), BMI was 25.6 (21.1-29.5) kg/m^2 and neck circumference was 39.5 (36.5-41.3) cm. Two out of 8 patients were in paid employment at the time of enrolment. Individual characteristics for all subjects are shown in table 5.2.

Table 5.2: Characteristics of individual patients at baseline. Data are median (IQR) unless specified.

	Individual Patients								Group median (IQR)
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	
Age (yrs)	84	58	75	68	86	73	70	61	**71.5** (62.8-81.8)
Systolic BP (mmHg)	137	95	119	134	178	133	143	100	**133.5** (104.8-141.5)
Diastolic BP (mmHg)	69	55	60	95	77	66	81	65	**67.5** (61.3-80.0)
Aetiology of HF	DCM	Ischaemic	DCM	not known	DCM	not known	Valvular	Ischaemic	
Atrial fibrillation	no	no	no	yes	no	yes	yes	no	
Diabetes Mellitus	no	no	yes	no	no	no	no	yes	
Pre-existing device	yes	no	no	yes	no	yes	yes	no	
Data available	baseline only, no HCVR	baseline only	baseline and FU but no HCVR	all data	all data	baseline only	all data	all data	

BP-blood pressure; DCM- dilated cardiomyopathy.

Note that shaded columns above indicate patients who returned for the follow-up visit and for whom HCVR data is available.

5.3.2 The effect of CRT on heart failure

Eight HF patients were studied before CRT implantation and 5 afterwards. Table 5.3 shows the effect of CRT on HF characteristics for the group (n=8), and for those with data at both baseline and follow-up (n=5). Table 5.4 shows individual patient data at baseline and follow-up, after CRT implantation. Seven out of 8 patients had left bundle branch block, patient no. 8 had right bundle branch block but was selected for CRT based on the level of dyssynchrony.

Table 5.3: Group patient characteristics at baseline and follow-up visits. Data are median (IQR) unless specified.

	BASELINE (n= 8)	**Patients attending for both visits**	
		BASELINE (n= 5)	**FOLLOW-UP (n=5)**
NYHA I / II / III / IV	**1 / 3 / 4 / 0**	**0 / 3 / 2 / 0**	**0 / 3 / 2 / 0**
BMI (kg/m^2)	**25.6** (21.1-29.5)	**27.2** (26.9-30.3)	**28.2** (24.6-34.3)
NC (cm)	**39.5** (36.5-41.3)	**40.5** (40.0-41.5)	**40.0** (39.0-47.3)
ESS	**8** (7-11)	**8** (8-11)	**9** (7.5-12.5)
MLHFQ	**34** (21-42)	**38** (18-46)	**28** (15-47)
LVEF (%)	**27.0** (21.0-30.0)	**30** (29.3-32.8)	**30.0** (27.5-50.2)
BNP (pmol/L)	**83** (42-280)	**54** (42-73)	**44** (38-71)
6MWT (m)	**360** (306-407)	**363** (322-396)	**360** (306-406)

NYHA- New York Heart Association; BMI- body mass index; NC- neck circumference; ESS- Epworth sleepiness score; MLHFQ- Minnesota Living with HF questionnaire; LVEF- left ventricular ejection fraction; BNP- B-type natriuretic peptide; 6MWT- Six minute walk distance.

Table 5.4: Individual patient characteristics at Baseline and follow up. Data are median (IQR) unless specified.

	Baseline HF characteristics of individual patients							
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**
NYHA class	3	3	2	3	3	1	2	2
BMI (kg/m^2)	20.3	24.3	22.9	38.4	27.2	20.5	26.9	30.3
NC (cm)	36	39	40	50	38	35	42	41
ESS	11	7	8	8	16	2	11	7
MLHFQ	36	32	18	51	43	30	16	38
LVEF (%)	21	20	30	30	41	27	-	27
BNP (pmol/L)	105	804	63	44	37	-	103	-
6MWT (m)	300	357	411	222	396	423	363	322

	Follow-up HF characteristics of individual patients							
NYHA class			2	3	3		2	2
BMI (kg/m^2)			22.6	39.2	26.5		28.2	29.3
NC (cm)			40	52	38		43	40
ESS			9	6	13		9	12
MLHFQ			17	29	28		12	64
LVEF (%)			27	49	28		51	30
BNP (pmol/L)			79	37	42		46	-
6MWT (m)			425	283	360		330	386

NYHA- New York Heart Association; BMI- body mass index; NC- neck circumference; ESS- Epworth sleepiness score; MLHFQ- Minnesota Living with HF questionnaire; LVEF- left ventricular ejection fraction; BNP- B-type natriuretic peptide; 6MWT- Six minute walk test.

5.3.3 The effect of CRT on sleep

All patients had nocturnal PSG at baseline, and 5 patients at follow-up, after CRT implantation. Table 5.5 shows the group PSG data for both time points, table 5.6 shows the individual data at baseline and follow-up. Figure 5.2 shows the PLMi from baseline to follow-up in (a) individual patients and (b) group data.

Table 5.5: Results of in laboratory nocturnal polysomnography in HF patients before and after CRT implantation; group data. Data are median (IQR) unless specified.

	BASELINE (n=8)	Patients attending for both visits	
		BASELINE (n=5)	FOLLOW-UP (n=5)
Apnoea hypopnoea index (/hr)	**8.5** (4.0-14.6)	**6.5** (5.1-10.4)	**9.2** (4.9-27.6)
Apnoea index (/hr)	**1.4** (0-7.2)	**0.6** (0-2.2)	**0.4** (0.3-12.8)
Hypopnoea index (/hr)	**6.1** (4.0-8.9)	**6.5** (5.1-8.2)	**8.9** (4.5-14.9)
Oxygen desaturation index (/hr)	**8.2** (1.1-10.1)	**8.9** (2.2-10.3)	**14.2** (1.9-29.9)
Time with sats. <90% (min)	**1.0** (0-10.6)	**1.4** (0-12.6)	**0** (0-86.5)
Total sleep time (min)	**270** (206-372)	**271** (269-278)	**336** (275-352)
Sleep efficiency (%)	**59** (46-82)	**62** (55-69)	**69** (58-80)
Wake after sleep onset (min)	**137** (60-191)	**130** (114-143)	**132** (67-173)
Arousal Index (/hr)	**20.0** (13.8-25.6)	**20.2** (19.7-27.3)	**36.9** (15.1-53.5)
Stage 1 (%)	**34** (25-45)	**26** (25-33)	**25** (20-54)
Stage 2 (%)	**44** (29-50)	**45** (44-52)	**49** (32-59)
Slow wave sleep (%)	**13** (8-22)	**12** (10-14)	**10** (3-14)
REM sleep (%)	**9** (8-16)	**26** (25-33)	**14** (2-17)
Periodic leg movement index (/hr)	**7.6** (1.8-27.7)	**9.4** (2.8-18.3)	**1.3** (0.4-46.3)

Table 5.6: Results of in laboratory nocturnal polysomnography in HF patients before and after CRT implantation; group data. Data are median (IQR) unless specified.

	Baseline PSG results for individual patients							
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**
AHI (/hr)	**14.6**	**14.6**	**24.4**	**6.5**	**1.7**	**3.6**	**5.1**	**10.4**
AI (/hr)	5.5	8.9	7.8	0	0.6	0	0	2.2
HI (/hr)	9.1	5.7	16.7	6.5	1.1	3.6	5.1	8.2
ODI (/hr)	7.5	9.5	17.7	8.9	2.2	0.7	0.6	10.3
T<90% (min)	0	4.4	12.6	123.0	0	0.5	0	1.4
TST (min)	261	475	271	269	278	167	187	403
SE (%)	44	94	62	69	55	39	52	86
WASO (min)	283	25	130	114	186	192	143	42
ArI (/hr)	18.2	12.3	20.2	34.0	7.4	20.5	27.3	19.7
S 1 (%)	49	35	43	33	23	45	26	25
S 2 (%)	10	45	25	44	52	41	45	60
SWS (%)	32	3	24	14	10	14	12	7
REM (%)	9	16	9	10	14	0	19	8
PLMi (/hr)	5.7	104.2	30.8	9.4	2.8	1.4	18.3	0

	Follow-up PSG results for individual patients							
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**
AHI (/hr)			**43.8**	**11.3**	**0.8**		**9.2**	**9.0**
AI (/hr)			25.0	0.4	0.2		0.3	0.6
HI (/hr)			18.8	10.9	0.6		8.9	8.4
ODI (/hr)			44.5	15.3	0.9		2.8	14.2
T<90% (min)			0	146.0	0		0	27.0
TST (min)			360	334	336		216	344
SE (%)			61	83	69		54	77
WASO (min)			190	62	132		155	71
ArI (/hr)			53.8	36.9	16.3		13.9	53.1
S 1 (%)			78	18	22		25	29
S 2 (%)			18	52	45		49	66
SWS (%)			2	10	18		10	3
REM (%)			2	19	14		15	2
PLMi (/hr)			16.5	1.3	0.2		76.0	0.5

AHI- apnoea hypopnoea index; AI- apnoea index; HI- hypopnoea index; ODI- oxygen desaturation index; T<90%- time spent with oxygen saturations below 90%; TST- total sleep time; WASO- wake after sleep onset; ArI- arousal index; S1/2- stage 1 and 2 sleep respectively; REM- rapid eye movement; PLMi- periodic limb movement index.

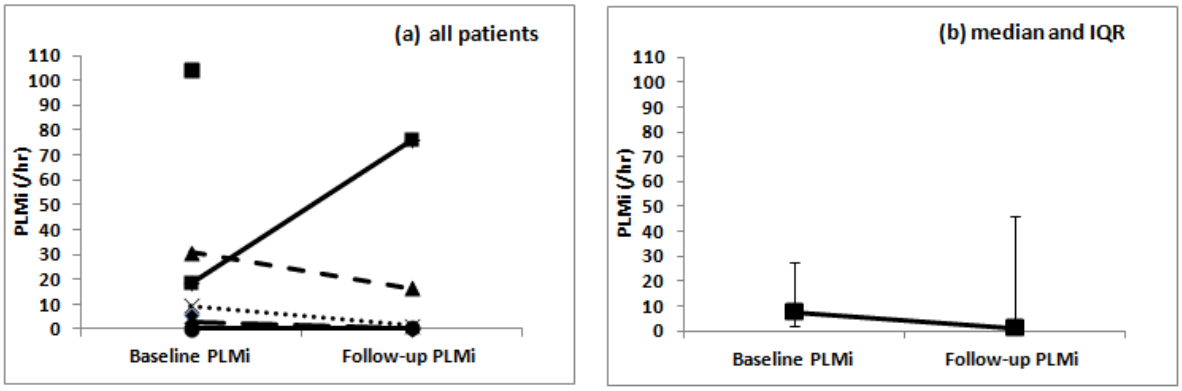


Figure 5.2: Periodic limb index from baseline to follow-up in HF patients. (a) all patients, (b) group change. Baseline data available for 8 patients, follow up data for 5 patients. *PLMi- periodic limb movement index.*

5.3.4 The effect of CRT on chemosensitivity

Chemosensitivity was assessed by measurement of the HCVR. Although 8 patients attended for baseline visits, data for evening HCVR were available for only 6 patients (1 patient was unable to tolerate the test and another unable to manage the protocol). Five patients attended for a follow-up visit, however data for evening HCVR were available for only 4 patients at follow-up (1 patient was unable to manage the protocol). Therefore baseline HCVR was available in 6 patients, follow-up HCVR was available in 4 patients. Individual and group patient data for resting CO_2 and the slope and intercept of the HCVR are shown in table 5.7. The slope represents the relationship between the CO_2 and ventilation and the x intercept is the theoretical CO_2 level at which ventilation would cease (an approximation of the apnoeic threshold), as discussed in the Introduction, section 1.5.5. Figure 5.3 illustrates the HCVR slope for each of the 6 patients able to complete the protocol; patient numbers in this figure refer to those used in tables 5.2, 5.4, 5.6 and 5.7. Notably there was a reduction in HCVR in patient number 8, who had right bundle branch block. Figure 5.4 shows changes in both HCVR and CO_2 in the 4 patients for whom there is baseline and follow-up data.

5.3.5 Changes in sleep and chemosensitivity

Four patients who successfully underwent CRT implantation attended at both baseline and follow-up. Figure 5.5 shows changes in HCVR/CO_2 (from figure 5.4) from baseline to follow-up alongside concomitant changes in the AHI, total sleep time and sleep efficiency.

Table 5.7: Resting CO_2 levels, x intercept and HCVR data in HF patients at baseline and follow-up; group data. Data are median (IQR) unless specified.

	BASELINE PATIENT DATA								GROUP DATA
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	
Resting CO_2 (mmHg)	-	22.7	-	22.9	36.3	31.0	36.2	32.6	**31.78** (24.98-35.28)
x intercept (mmHg)	-	22.14	-	23.21	44.34	31.08	36.30	41.99	**33.69** (25.17-40.57)
HCVR (L/min/mmHg $ETCO_2$)	-	1.406	-	1.782	3.550	1.180	1.988	3.174	**1.885** (1.50-2.88)

	FOLLOW-UP PATIENT DATA								GROUP DATA
Resting CO_2 (mmHg)			-	27.4	35.9		33.8	34.0	**33.90** (32.20-34.47)
Intercept			-	29.94	43.69		38.37	39.51	**38.94** (36.26-40.56)
HCVR (L/min/mmHg $ETCO_2$)			-	2.40	2.94		2.55	2.38	**2.48** (2.40-2.65)

HCVR- hypercapnic ventilatory response.

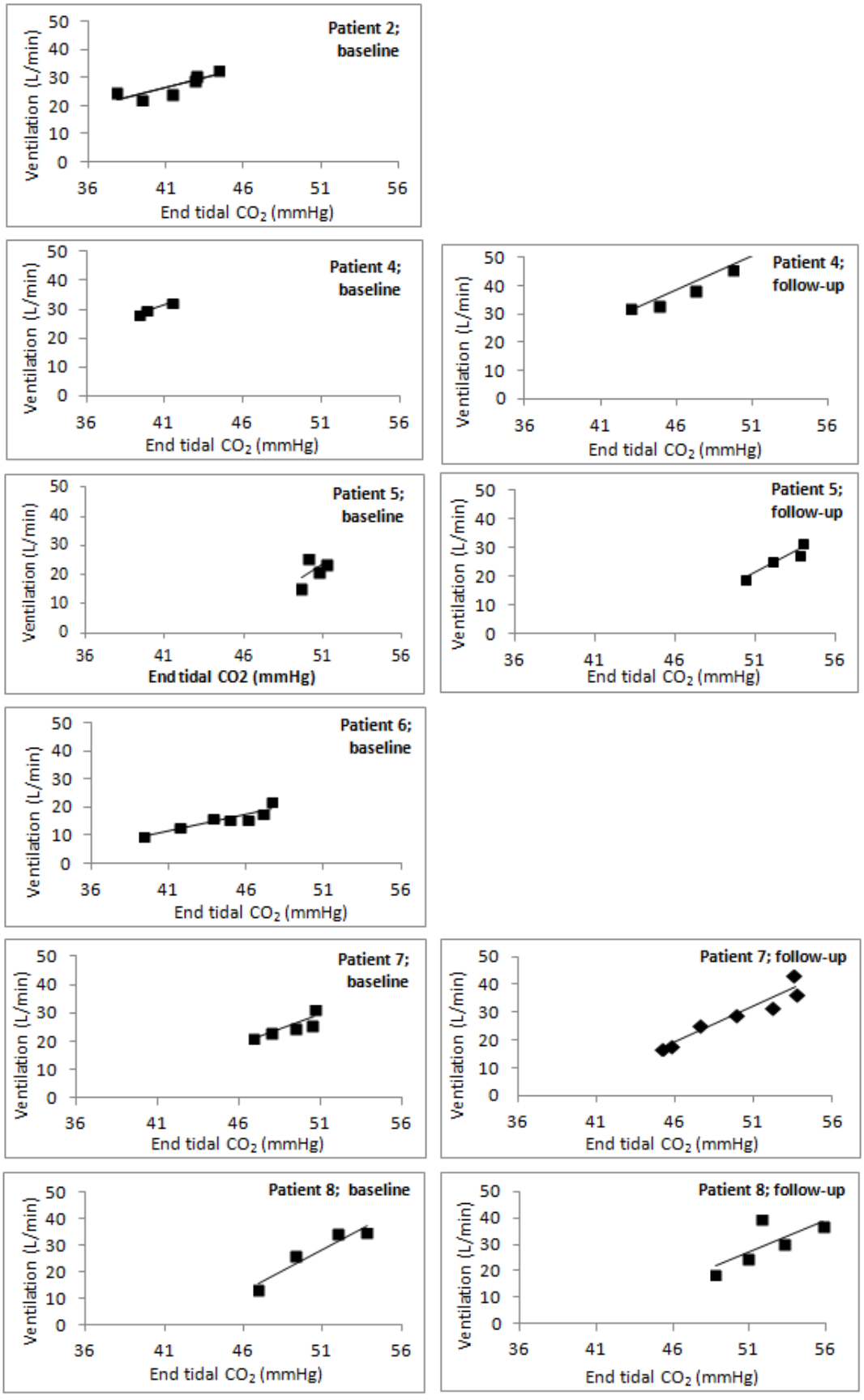


Figure 5.3: HCVR slopes for each patient able to complete the protocol. Patient numbers refer to those used in tables 5.2, 5.4, 5.6 and 5.7.

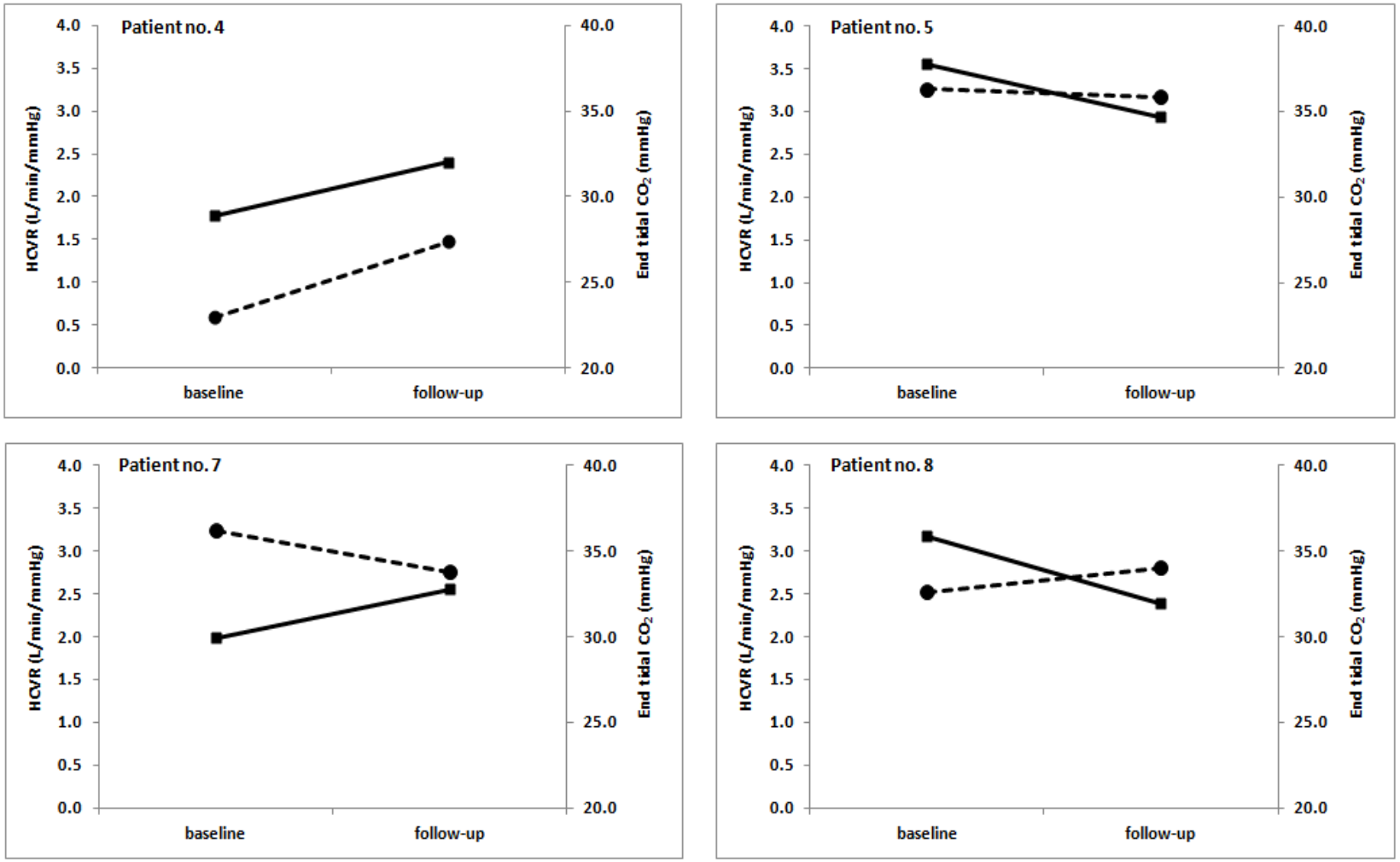


Figure 5.4: Changes in HCVR (solid line) and resting CO_2 (dotted line) at baseline and follow up. *HCVR- hypercapnic ventilatory response; CO_2- carbon dioxide.*

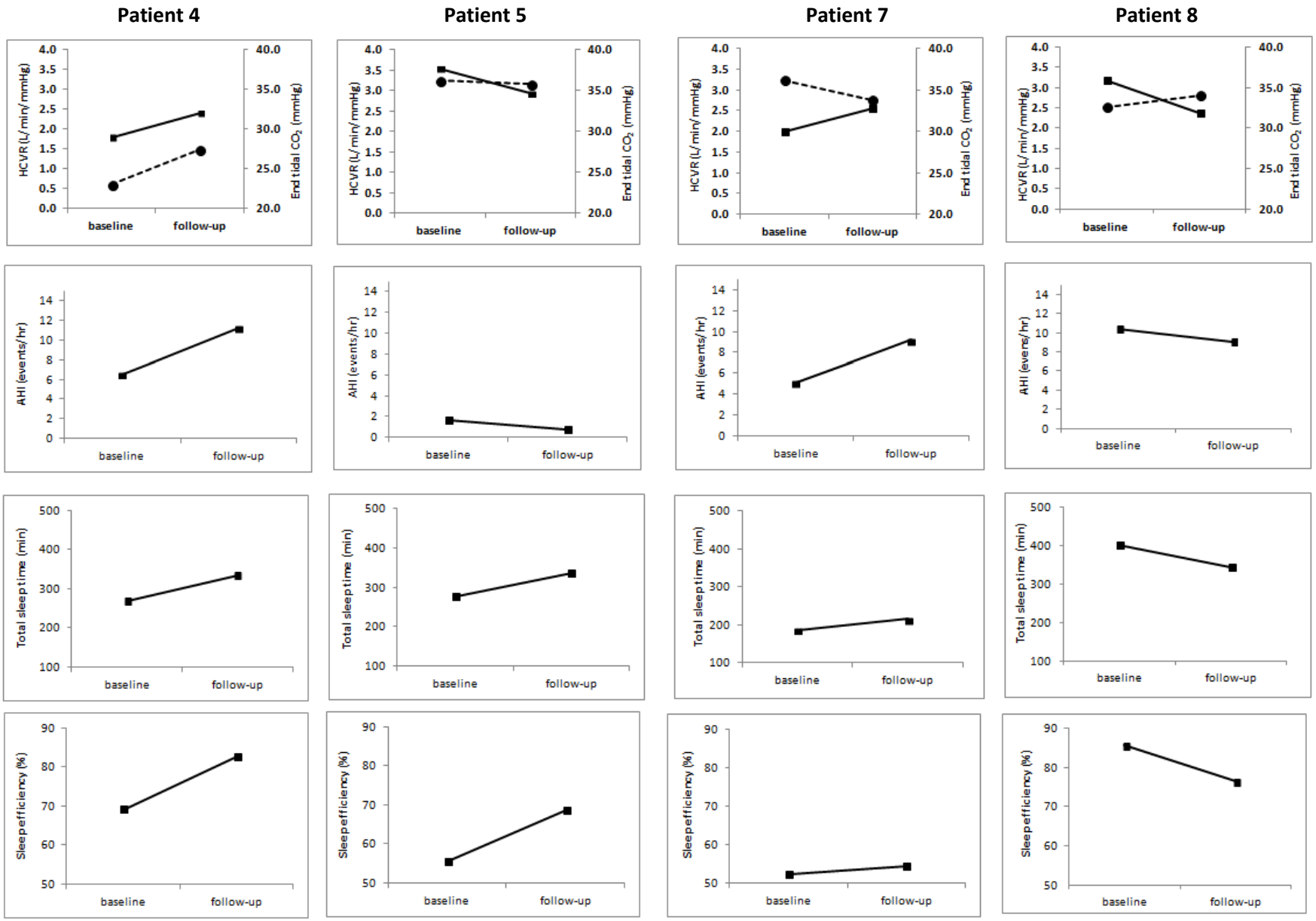


Figure 5.5: Changes in HCVR (solid line) and carbon dioxide (dotted line) alongside changes in SDB and sleep. *HCVR- hypercapnic ventilatory response; AHI- apnoea hypopnoea index.*

5.4 DISCUSSION

This study was designed to test the hypothesis that CRT implantation would improve SDB (where present) and improve sleep quality, and that this would be associated with a reduction in the HCVR to CO_2 from baseline to 3 months post implantation. In a limited number of patients I found that CRT had a variable effect on SDB and HCVR. Interestingly, in the 2 patients (patients 7 and 8) with a reduction in apnoea-hypopnoea index from baseline to follow-up there was also a reduction in HCVR, similarly in those with an increase in apnoea-hypopnoea index from baseline to follow-up there was an increase in HCVR.

Resting CO_2, a marker of ventilatory instability, (although not itself directly causal), also changed after CRT implantation. In 2 patients the CO_2 change reflected the HCVR as would be expected; CO_2 fell when the HCVR increased after CRT implantation (patient 7), and CO_2 increased when HCVR fell after CRT (patient 8). Three out of 4 patients had an improvement in total sleep time and sleep efficiency, although there was no clear trend between these and changes in HCVR.

Patient 4 had an increase in both HCVR and CO_2 after CRT implantation, contrary to the hypothesis. Furthermore the same patient had improvements in total sleep time and sleep efficiency, along with an increase in AHI. Notably this patient had a clear response to CRT implantation in terms of cardiac function (a fall in BNP and a clinically significant increase in LVEF of 19%) and functional status (an increase in the 6MWT of 61 meters). It is hard to explain this apparent mismatch between a cardiac response and a worsening of HCVR but an increase in CO_2; they may simply reflect the complexity of the factors involved. A possible explanation, although simplistic, is that the device improved heart function such that sleep was less disturbed (for the reasons discussed in 1.4.2 and 1.4.3), hence the improvements in total sleep time and sleep efficiency. However while the duration of sleep increased this occurred while SDB persisted, hence a higher AHI. Patient 4 also had a reduction in periodic leg movement index (PLM; from 9.4 to 1.3), which is further evidence for improved sleep, and is discussed below. It is also possible that a longer interval of follow up may have captured a change in chemosensitivity and ventilatory stability, which perhaps lags behind the cardiac changes, although evidence for this speculation is lacking.

5.4.1 The effect of CRT on chemosensitivity

Previous work has found HF patients with central SDB to have heightened HCVR (Javaheri, 1999, Solin et al., 2000, Topor et al., 2001), although this was not the finding of my study presented in chapter 4. The effect, if any, of CRT on HCVR has not previously been investigated. Although this study had a small sample size it is interesting to note that the 2 patients who had a reduction in AHI from baseline to follow-up also had a reduction in HCVR (slope and intercept), and the 2 patients who had an increase in AHI also had an increase in HCVR (slope and intercept). Also that CO_2 changes in patients 7 and 8 were in keeping with changes in both HCVR and AHI. Previous work on CRT has found resting, awake CO_2 to increase after CRT implantation (Gabor et al., 2005, Oldenburg et al., 2007a).

My hypothesis was that CRT implantation would result in a reduction in HCVR in patients with CHF. This effect might be anticipated for a number of reasons. Firstly, CRT is known to improve cardiac function and impaired cardiac function may contribute to ventilatory instability due to effects on plant and feedback gain (see chapter 1; section 1.6.2). The effect of cardiac impairment on controller gain (ie. HCVR) is not clear but it is noteworthy that interventions such as nocturnal oxygen and adaptive servoventilation both improve LVEF as well as reduce HCVR. Secondly previous studies have found that CRT therapy, in those with central SDB, corrects hypocapnia (Gabor et al., 2005, Oldenburg et al., 2007a) and this would be expected to have a stabilising effect on ventilation (Naughton et al., 1993).

Oxygen therapy has been found to both correct central SDB (Andreas et al., 1998, Hanly et al., 1989, Staniforth et al., 1998, Javaheri et al., 1999) and to reduce the HCVR in this group of patients (Andreas et al., 1998). A change in the HCVR irrespective of the presence or absence of SDB at baseline might be anticipated because a clinical and haemodynamic response to CRT implantation is not dependant on the presence of central SDB (Oldenburg et al., 2007a). Whilst it is unlikely that CRT mediates its effects solely via a change in HCVR, it is possible that if interventions which improve cardiac function also improve chemosensitivity, then a change in HCVR after CRT implantation may be another indication of a physiological response.

5.4.2 The effect of CRT on sleep

In the present study 4 patients had SDB prior to CRT implantation; of these 2 returned for their follow-up visit after CRT implantation, SDB improved in one and worsened in the other. Where SDB worsened there were concomitant falls in SWS. Where SDB improved there was an increase in SWS in one patient, and a slight fall in the other.

It is notable that from baseline to follow-up there are increases in both total sleep time and sleep efficiency. Possible explanations include better sleep quality due to being more familiar with the laboratory environment thus sleeping better- although the arousal index increases from baseline to follow-up. The PLM index also falls and this may have affected sleep quality on the follow-up night. The PLM index is known to increase with increasing age (Pennestri et al., 2006) and to be high in those with HF (Hanly and Zuberi-Khokhar, 1996, Skomro et al., 2009, Yumino et al., 2011). Improvement of the restless legs syndrome and reduction in PLM index after CRT implantation has been suggested in a case report but never formally investigated (Shalaby et al., 2005), as well as after cardiac transplantation (Hanly and Zuberi, 1992). Taken together these data suggest a link between cardiac function and the presence and severity of PLM overnight. There was no concomitant increase in LVEF, although numbers were small.

In this study the MLHFQ score improved after CRT implantation and there was a modest reduction in BNP. There was no change in the distance walked over 6 minutes. An improvement in cardiac function, irrespective of the presence or absence of SDB, may also theoretically improve sleep quality by reducing paroxysmal nocturnal dyspnoea and CRT is well established as improving LVEF (Abraham 2002), reducing PCWP (Blanc et al., 1997, Leclercq et al., 1998) and improving cardiac dynamics by reverse remodelling (Cleland et al., 2005) and these may also play a role in the effect of CRT on sleep (see below).

5.4.3 Methodological considerations

This was a physiological observational study designed to test a novel hypothesis; however it was not adequately powered for the reasons given above. Therefore is it not possible to draw definitive conclusions from these data, although this work has generated hypotheses which merit further investigation (eg. the potential effect of CRT implantation on periodic leg movements and sleep quality). Of 8 patients 2 declined to return citing the HCVR test as the reason in 1 case, and no reason given in the other. One of the 8 patients suffered ventricular tachycardia during the

implantation which was abandoned however implantation was successful in all other patients; a success rate similar to that in larger studies (Abraham et al., 2002, Bristow et al., 2004).

Of those 5 patients returning to the laboratory analysable data was obtained in only 4 who were able to tolerate the HCVR test; in 1 case this was not possible despite 2 attempts and coaching. My impression, from this study, and that presented in chapter 4 is that patients who are more frail or who have a brisk ventilatory response to carbon dioxide tend to struggle with the laboratory measurement of HCVR (although this was true in only 1 of the 2 patients who declined to return). This observation would suggest that patients with a higher HCVR may be less likely to tolerate and therefore complete the test; in fact this was not the case. Patients 2 and 6 who did not complete follow-up HCVR measurements had lower HCVR than the other patients suggesting that other factors, perhaps pulmonary manifestations of HF such as alveolar oedema or orthopnoea, or claustrophobia played a role. However it remains possible that any patient with a brisk ventilatory response to carbon dioxide may find the test more difficult and this does have implications for future work as those with the most brisk HCVR may be excluded for this reason (although this was not the case in the current study). Different methods of measuring HCVR may be better tolerated and so more appropriate in this population e.g. Fenn and Craig technique (Fenn and Craig, 1963, Morrell et al., 2007).

Repeated PSG testing raises the issue of the effect of season. The sleep laboratory was fitted with black out curtains however it is possible that there may have been some seasonal effect on sleep structure or duration on one of the visits (Anderson et al., 1994).

In this work patients were invited to return for a follow-up visit 3 months after CRT. It is unclear what the optimal duration for reassessment of sleep, or indeed HCVR, is after CRT implantation. It is possible that the 3 month interval used in this study was not long enough, although other authors have found changes in sleep and other parameters after 3 months (Luthje et al., 2009, Czarnecka et al., 2010).

5.4.4 Summary

A variable response to CRT in terms of SDB and HCVR was found in a small number of HF patients. Notably, in keeping with the hypothesis, those patients who had SDB which improved after CRT also had a reduction in HCVR, whereas the patient in whom CRT did not reverse the SDB had an increase in HCVR. In addition the group data showed a reduction in periodic leg movement index and an improvement in sleep efficiency and total sleep time after CRT implantation. These data suggest that an adequately powered study may be of value in HF patients undergoing resynchronisation therapy to establish if there is indeed an improvement in chemosensitivity after CRT implantation. Furthermore, an adequately powered study may demonstrate if such an improvement correlates with an improvement in cardiac function and so help to elucidate the underlying mechanism by which CRT improves central SDB.

O sleep! O gentle sleep!

Nature's soft nurse, how have I frighted thee,

That thou no more wilt weigh my eyelids down

And steep my senses in forgetfulness?

Why rather, sleep, liest thou in smoky cribs,

Upon uneasy pallets stretching thee,

And hush'd with buzzing night-flies to thy slumber,

Than in the perfum'd chambers of the great,

Under the canopies of costly state,

And lull'd with sound of sweetest melody?

Henry IV (3.1.7-16)

by William Shakespeare (1564-1616)

CHAPTER SIX:

SUBJECTIVE SLEEPINESS AND ACTIVITY LEVELS IN HEART FAILURE PATIENTS WITH AND WITHOUT SLEEP DISORDERED BREATHING

6.1 INTRODUCTION

Sleep disordered breathing disrupts sleep and often causes daytime sleepiness (Baldwin et al., 2001). However in HF patients SDB produces minimal symptoms of sleepiness (Hastings et al., 2006, Kaneko et al., 2003, Rao et al., 2006). Indeed, HF patients with obstructive SDB are less sleepy than those with obstructive sleep apnoea (OSA) but no HF, despite having a shorter total sleep time, longer sleep latency and spending more time awake after the initial onset of sleep (wake after sleep onset) (Arzt et al., 2006). It is possible that the reduced symptoms of daytime sleepiness in HF patients with SDB are due to differences in the amount of daytime activity, with HF patients taking more daytime naps. Hastings et al. (Hastings et al., 2006) studied activity levels in patients with HF and found that there was no difference in the subjective sleepiness of HF patients with and without SDB, but that HF patients with SDB had a shorter duration of daytime activity compared to HF patients without SDB. They also spent more time in bed and had more disrupted sleep with a significantly longer sleep latency, and lower sleep efficiency. Sleep diaries showed no differences in the naps taken by the two groups.

An alternative explanation for the lack of sleepiness symptoms in HF patients with SDB is that increased SNA, related to the HF itself (Mansfield et al., 2003) may reduce the propensity to feel sleepy (Montemurro et al., 2012). This may have the greatest impact in those with central SDB/central sleep apnoea (CSA) in whom HF tends to be more severe (Oldenburg et al., 2009) and in whom sympathetic nerve activity is higher than those with HF and obstructive SDB, and HF alone (Solin et al., 2003). It is noteworthy that in the study by Hastings *et al.*, many of the HF patients with SDB had obstructive SDB (12 of 22 patients). Thus previous studies have established that patients with obstructive SDB and HF are less sleepy compared to a community cohort with obstructive SDB (Arzt et al., 2006) but the effect of central SDB in HF on subjective sleepiness and the role of physical activity is less clear.

The aim of the current study was to expand the findings of Hastings by studying HF patients with central SDB. A secondary aim was to investigate the effect of HF itself on sleepiness and activity levels by comparing a group of HF patients without SDB with a group of age matched healthy controls. Specifically, I tested the hypothesis that HF patients with central SDB would not be subjectively sleepy compared to those with HF and no SDB. The secondary hypothesis was that HF patients without SDB would also not be sleepy compared to healthy controls.

6.2 METHODS

6.2.1 Subjects

Patients were recruited from the HF clinics at the Royal Brompton and Ealing hospitals in London and those agreeing to participate were classified into four groups on the basis of their sleep study; 1) HF patients with obstructive SDB (HF-OSA), 2) HF patients with central SDB (HF-CSA), 3) HF patients with no SDB (HF-noSDB) and 4) older healthy controls. Healthy subjects were recruited from a list of participants who had volunteered for other studies in our department.

Patients were included in the study if they had a known clinical diagnosis of chronic HF, documented left ventricular systolic impairment and were on medical treatment for HF. Measurement of the left ventricular ejection fraction (LVEF) by echocardiogram was used as a marker of left ventricular systolic function and there was no cut off value for inclusion. Patients had to be clinically stable with no unplanned hospital admission (for any reason) in the preceding 4 weeks and no new class of HF medication started in the same time period. Patients using PAP devices (for any reason) were excluded from the study.

Healthy subjects were considered suitable for inclusion if they were free of medical problems. All healthy subjects were asked specifically about hypertension, heart disease, diabetes or if they had any medical condition requiring regular medication or GP consultation. Subjects found to have SDB on nocturnal PSG were excluded from the study and an appropriate referral to a sleep clinic made. All subjects had to be aged 18 years or over and give informed consent. Subjects with other conditions likely to significantly disrupt sleep (ie. chronic pain syndromes) were excluded from the study. The study was approved by South West London REC no. 1 (REC no. 09/H0708/35) and all subjects gave written informed consent (see appendix 4 for documentation).

6.2.2 Protocol

Baseline measurements

After informed consent a baseline assessment was made, including height, weight, resting oxygen saturations, non-invasive blood pressure measurement and neck circumference (measured at the level of the cricoid cartilage). All subjects completed a measurement of subjective sleepiness (ESS, see appendix 6) and all HF patients also completed the Minnesota Living with Heart Failure Questionnaire (MLHFQ, see appendix 5).

Nocturnal polysomnography

Overnight sleep was measured in all subjects. A detailed explanation of nocturnal PSG is given in Chapter 2, section 2.7. In short this study involved measuring 3 electroencephalograms, electromyograms and electrooculograms to enable accurate sleep staging. Respiratory measurements were also undertaken with digital pulse oximetry, nasal pressure, oronasal thermistor and RIP. Sleep position was measured using a sensor integrated into the amplifier box worn by the patient and was classified as prone, supine or lateral. All electrodes were attached before the subject retired at their usual bed time.

Actigraphy

Activity levels were measured in all subjects using actigraphy which involves the use of a watch-like accelerometer (Actiwatch 4, CamNtech, UK), worn on the non-dominant wrist for 14 consecutive days and nights. Subsequent device download provides several measures of physical activity (duration, average activity per hour and per 1 minute epoch) and some derived data (such as sleep efficiency and latency) predominantly relating to presumed sleep. A detailed explanation of actigraphy is given in Chapter 2, section 2.9**.** Subjects were also asked to complete a sleep and nap diary for each day the watch was worn.

6.2.3 Analysis

Physiological analysis

A detailed description of the analysis of the sleep stages, breathing and activity levels are given in chapter 2, sections 2.9 and 2.10.1. In brief, sleep staging was undertaken by a single scorer (AA) using standard AASM criteria (Iber et al., 2007) and blinded to the identity of the subject (and their diagnosis) at the time of scoring. SDB was defined as an AHI $\geq$ 10 events per hour. The type of SDB (obstructive or central) was determined by the predominant event type. Oxygen desaturation was

measured using a ≥3% dip criterion. Hypopneas were defined using a ≥ 3% dip criterion or a cortical arousal (Iber et al., 2007).

For the activity measurements, days when the watch was not worn for more than 4 consecutive hours were excluded from analysis. Day time activity was measured in arbitrary units and expressed as the average count per day and per 1 minute epoch. The mean duration of daytime activity over the 14 day recording was also calculated.

Statistical analysis

Hastings *et al*., 2006 investigated 2 groups of HF patients (with and without SDB) and found a significant difference in the duration of daytime activity (15.2 ±1.2 hrs SDB group vs. 16.3 ± 1.0 hrs no SDB group, p=<0.01). The current study was designed to detect a similar difference in daytime activity between HF patients with central SDB and HF patients with no SDB. Assuming a similar magnitude of difference a sample size of 17 would be required in the 2 groups (in this case, HF-CSA and HF-noSDB) being compared to achieve 80% power (α=0.05).

The median and inter-quartile ranges were used to generate descriptive statistics. Groups were compared using the non-parametric Mann-Whitney U test with a significance level of 0.05. Data from the combined groups of HF-OSA and HF-CSA, were compared with the HF-noSDB group to verify the findings of Hastings *et al.*

6.3 RESULTS

A total of 68 subjects were studied; 54 HF patients and 14 healthy age matched controls. Eleven of the HF patients had previously participated in the study by Hastings *et al.* Two control subjects were found to have abnormal sleep or SDB and were excluded from further analysis (see appendix 6 for the characteristics of the control subjects included vs. those excluded). Twenty-two of the patients and 7 healthy controls in this study participated in the study presented in chapter 4.

The median age of the HF patients was 68 (IQR; 59-73) years, with a BMI of 28.6 (25.8-30.6) kg/m^2. Nine of the 54 HF patients were of Asian origin, 3 of Afro-Caribbean origin, 1 was Middle Eastern and the remainder were Caucasian. The median LVEF was 34 (24-40) %, BNP 50 (31-93) pmol/L and MLHFQ score 33 (18-44). The majority of patients were established on diuretics, beta blockers and ACE inhibitors or angiotensin receptor antagonists (ARB), in accordance with national guidelines (NICE, ESC and ACC/AHA). The median age of the control group was 67 (65-69) years, with a BMI of 25.0 (23.2-26.2) kg/m^2. Three of 11 control subjects were of Asian origin and the remainder were Caucasian. None of the participants regularly used night sedation. Table 6.1 gives the patient characteristics for the HF patients classified by presence (HF-SDB) and absence (HF-noSDB) of SDB. Baseline characteristics of the control subjects are found in table 6.7, section 6.3.3.

6.3.1 The effect of SDB on subjective sleepiness, sleep and physical activity in HF patients

To investigate the effect of SDB *per se* on subjective sleepiness, as in previous work (Hastings et al., 2006), HF patients with SDB (HF-SDB, n=32) were compared with HF patients with no SDB (HF-noSDB, n=22). The HF-SDB group were older than the HF-noSDB group (70 (63.8-74.8) vs. 62 (53.5-69.8) yrs; p=0.01) and also had higher levels of BNP (66.5 (37.3-126.8) vs. 37.0 (27.0-56.5) pmol/L; p=0.03). There were no other significant differences between any of the baseline demographics and notably no difference in subjective sleepiness between the groups.

Overnight sleep and breathing patterns (from nocturnal PSG) are shown in Table 6.2. The HF-SDB and HF-noSDB groups differed in respiratory events by design. The HF-SDB group had a significantly higher ODI (15.2 (7.6-33.4) vs. 4.2 (1.0-8.1) events/hr; p=<0.01) and spent more time with oxygen saturations less than 90% (T<90%; 16.0 (5.0-33.0) vs. 2.0 (0-5.0) minutes; p=<0.01) than the HF-noSDB group. Sleep was impaired in the HF-SDB group who spent significantly more time in bed (493 (463-547) vs. 460 (402-488) minutes; p=<0.01) although once they had initially fallen asleep they spent more time awake (wake after sleep onset; 104 (80-149) vs. 37 (0-91) minutes; p=<0.01) and therefore there was no significant difference between the groups in the total sleep time (352 (311-

391) vs. 355 (295-383) minutes; p=0.97) nor any difference in sleep efficiency. The HF-SDB group spent more time in light stage 1 (28.6 (21.2-49.6) vs. 20.5 (9.6-31.2) %; p=0.01) but less time in stage 2 sleep (37.1 (27.2-51.1) vs. 44.5 (38.4-52.1) %; p=0.03) than the HF-noSDB group. The HF-SDB group also spent less time in REM sleep than the HF-noSDB group (12.9 (9.4-17.9) vs. 18.4 (13.5-22.0) %; p=0.01). Notably, there was no difference in arousal index between the 2 groups (31.5 (22.4-52.4) vs. 31.8 (14.2-41.8) /hr; p=0.20).

The HF-SDB group spent a greater percentage of time asleep in the supine position than those in the HF-noSDB group (47.4 (33.3-80.1) vs. 23.0 (0-42.2) %; p=<0.01). There was no difference in time spent in the prone or lateral positions, nor in the frequency of periodic leg movements (PLM index) between the groups.

Activity data were available for all 66 participants. On two occasions watches, which are not waterproof, were worn in the bath or shower. In both cases the watch was returned and a new watch given to the participant. Two subjects were regular swimmers (one control and one patient) and so had to remove the watch for their exercise. The actigraphy recording was typically started the morning after nocturnal PSG; the median (IQR) duration between sleep study and starting the activity measurements was 9 (1 -39) days. Typical actograms are shown in figure 6.1. Median daytime activity data for both groups are shown in Table 6.3. Night time data derived from the actiwatch are shown in appendix 11. There were no significant differences in daytime or night time activity between the 2 groups.

Table 6.1: Patient characteristics of all HF patients with and without SDB. Data are median (IQR) unless specified.

		HF-SDB n=32	HF-No SDB n=22	
Age (yrs)		**70** (63.8-74.8)	**62** (53.5-69.8)	***p=0.01***
Gender (male/female)		**31 / 1**	**19 / 3**	-
BMI (kg/m^2)		**28.7** (25.9-30.9)	**27.9** (25.3-31.1)	*p=0.97*
Neck circumference (cm)		**41** (37-43)	**40** (39-42)	*p=0.87*
Alcohol (units/week)		**1** (0-7)	**2** (0-7)	*p=0.61*
Epworth sleepiness score		**8** (5-10)	**8** (6-12)	*p=0.32*
NYHA functional class I / II / III / IV		2 / 14 / 14 / 2	12 / 1 / 7 /2	-
Blood pressure (mmHg)*	Systolic	**119** (112-135)	**118** (100-126)	*p=0.23*
	Diastolic	**72** (63-80)	**72** (63-78)	*p=0.99*
Left ventricular ejection fraction (%)		**34** (20-40)	**35** (28-42)	*p=0.32*
B-type natriuretic peptide (pmol/L)*		**66.5** (37.3-126.8)	**37.0** (27.0-56.5)	***p=0.03***
Aetiology of HF syndrome*	Ischaemic	**19**	**12**	-
	DCM	**6**	**7**	
	Valvular	**5**	**2**	
	Unknown	**2**	**1**	
Medications*	Diuretics	**25**	**17**	-
	Beta blocker	**27**	**17**	
	ACE inhibitor/ARB	**22**	**21**	
	Digoxin	**6**	**5**	
Comorbidities*	Diabetes	**9**	**3**	-
	Atrial fibrillation	**9** (1 with PAF)	**6** (2 with PAF)	
Implanted devices*	no device	**16**	**12**	-
	PPM +/- ICD	**3**	**1**	
	CRT	**11**	**7**	
	ICD	**0**	**2**	
Minnesota Living with Heart Failure questionnaire score		**26** (14-42)	**38** (19-58)	*p=0.24*
Nocturia (no of episodes over 14d)		**20** (9-28)	**11** (9-19)	*p=0.38*

BMI- body mass index; SDB- sleep disordered breathing; NYHA- New York Heart Association; DCM- dilated cardiomyopathy; ACE- angiotensin converting enzyme; ARB- angiotensin receptor blocker; PPM- permanent pacemaker; ICD-implantable cardiac defibrillator; PAF- paroxysmal atrial fibrillation; CRT- cardiac resynchronisation therapy.

*data not available for all patients; BP data missing for 6/53 patients, BNP data missing for 19/53 patients, LVEF data missing for 2/53 patients, information missing on aetiology (1 patient), comorbidities (2 patients) and implanted devices (2 patients)

Table 6.2: Nocturnal polysomnographic data for the HF-SDB and HF-noSDB groups. Data are median (IQR).

	HF-SDB n=32	**HF-No SDB n=22**	
Apnoea hypopnoea index (events/hr)	**19.5** (12.8-38.1)	**3.7** (2.5-5.9)	
Apnoea index (events/hr)	**7.2** (1.3-15.6)	**0.2** (0-0.8)	
Hypopnoea index (events/hr)	**11.5** (8.7-18.7)	**3.0** (1.4-5)	
Oxygen desaturation index (≥3% dip rate/hour)	**15.2** (7.6-33.4)	**4.2** (1.0-8.1)	***p=<0.01***
Time with O_2 saturations <90% (min)	**16.0** (5.0-33.0)	**2.0** (0-5.0)	***p=<0.01***
Time in bed (min)	**493** (463-547)	**460** (402-488)	***p=<0.01***
Total sleep time (min)	**352** (311-391)	**355** (295-383)	*p=0.97*
Sleep efficiency (%)	**74.0** (67.2-77.9)	**78.5** (70.1-84.1)	*p=0.07*
Sleep latency (min)	**19.5** (10.5-28.8)	**14.6** (10.9-29.0)	*p=0.75*
Wake after sleep onset (min)	**104** (80-149)	**37** (0-91)	***p=<0.01***
Arousal index (events/hr)	**31.5** (22.4-52.4)	**31.8** (14.2-41.8)	*p=0.20*
Stage 1 (%)	**28.6** (21.2-49.6)	**20.5** (9.6-31.2)	***p=<0.01***
Stage 2 (%)	**37.1** (27.2-51.1)	**44.5** (38.4-52.1)	***p=0.03***
Stage 3 (%)	**44.5** (38.4-52.1)	**8.1** (6.2-12.6)	*p=0.55*
Stage 4 (%)	**0.4** (0-7.6)	**1.6** (0.2-6.5)	*p=0.31*
REM sleep (%)	**12.9** (9.4-17.9)	**18.4** (13.5-22.0)	***p=0.01***
PLM index (events/hr)	**12.5** (1.3-35.4)	**4.6** (0.3-11.4)	*p=0.07*
Supine (%)	**47.4** (33.3-80.1)	**23.0** (0-42.2)	***p=<0.01***

AHI- apnoea hypopnoea index; AI- apnoea index; HI- hypopnoea index; ODI- oxygen desaturation index; T<90%- time spent with oxygen saturations below 90%; TIB- time in bed; TST- total sleep time; WASO- wake after sleep onset; REM- rapid eye movement; PLM- periodic limb movement.

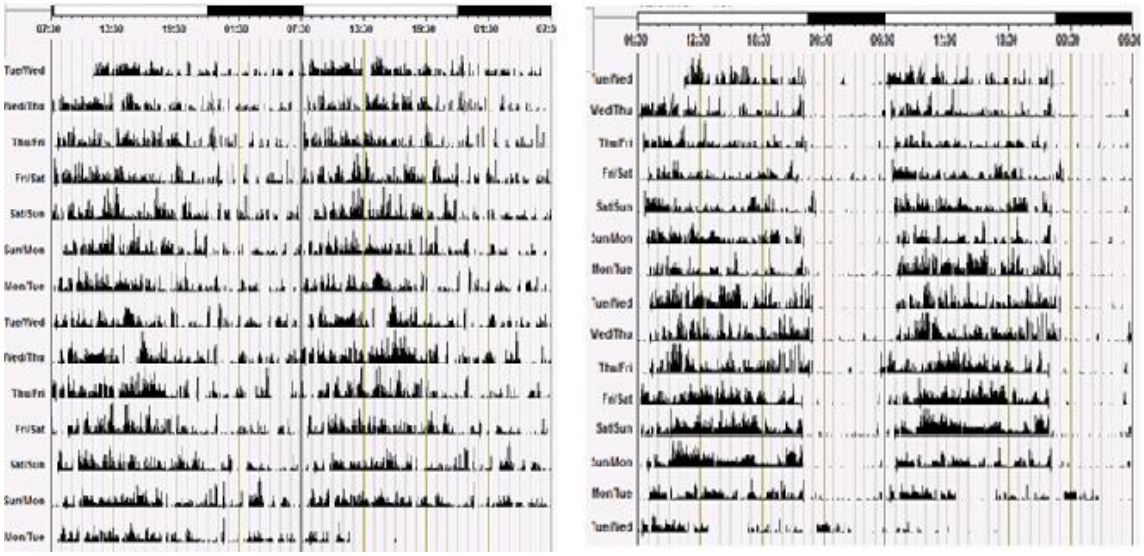


Figure 6.1: Actograms from each group over 14 days- left, HF-SDB and right, HF-noSDB. See General Methods (Chapter 2, section 2.9.3) for a full explanation of the actogram – in brief each day is plotted twice. The horizontal bar at the top indicates time (day is white, night is black).

Table 6.3: Daytime activity in HF patients with and without SDB. Results are median (IQR).

	HF-SDB n=32	**HF-No SDB n=22**	
Average duration of activity /day (hrs)	**14.5** (14.1-15.3)	**15.1** (14.4-15.3)	*p=0.15*
Average activity per day (arbitrary units)	**198777** (128952-273756)	**217926** (196900-275933)	*p=0.23*
Average activity per 1 min epoch (arbitrary units)	**220.0** (149.7-301.1)	**231.1** (210.6-305.0)	*p=0.30*
Total daytime activity count over 14 days (arbitrary units)	**2,903,915** (1,901,140-3,833,354)	**3068856** (2,834,952-4,019,950)	*p=0.29*

6.3.2 The effect of central SDB on subjective sleepiness, sleep and physical activity in HF patients

Having confirmed that HF patients with SDB were not more sleepy than those without SDB I addressed my central hypothesis by comparing the HF patients with central SDB (HF-CSA) to those with no SDB (HF-noSDB). Characteristics of these 2 patient groups are given in Table 6.4. There were no significant differences in subjective sleepiness between the groups. However, the HF-CSA group were older (70 (66.0-77.0) vs. 62 (53.5-69.8) years, p=<0.01) and had higher BNP levels (81.5 (50.0-132.5) vs. 37.0 (27.0-56.5) pmol/L, p=<0.01) than the HF-noSDB group. The groups were comparable in all other characteristics with no significant differences between them.

Overnight sleep and breathing patterns (from nocturnal PSG) are shown in Table 6.5. The HF-CSA group spent more time in bed (500 (465-548) vs. 460 (402-488) minutes; p=<0.01) but had less efficient sleep (sleep efficiency; 73.4 (61.2-76.5) vs. 78.5 (70.1-84.1) %; p=0.04), spending more time in lighter stage 1 sleep (27.6 (21.0-49.1) vs. 20.5 (9.6-31.2)%; p=0.03) and more time awake after initial sleep onset (100.0 (80.0-149.0) vs. 36.7 (0-90.5) minutes; p=<0.01) than those in the HF-noSDB group. Furthermore, there was a higher PLM index in the HF-CSA group (14.0 (5.7-37.1) vs. 4.6 (0.3-11.4) /hr; p=0.03) who also had worse overnight oxygen parameters (higher ODI, p=<0.01 and longer time spent with oxygen saturations less than 90%, p=0.01). The HF-CSA group spent a significantly greater proportion of total sleep time in the supine position (45.9 (33.3-80.1) vs. 23.0 (0-42.2) %; p=<0.01).

Daytime activity data for both groups are shown in table 6.6. There was no difference in daytime activity duration or activity levels between the HF-CSA and HF-noSDB groups. Furthermore there were no differences in nocturnal activity levels or other markers of sleep derived from the actiwatch between the two groups; this data is shown in appendix 11.

Table 6.4: Patient characteristics of the HF-CSA and HF-noSDB groups. Results are median (IQR) unless specified.

		HF-CSA n=23	HF-No SDB n=22	
Age (yrs)		**70** (66.0-77.0)	**62** (53.5-69.8)	***p=<0.01***
Gender (male/female)		**22 / 1**	**19 / 3**	-
BMI (kg/m^2)		**28.6** (24.1-29.8)	**27.9** (25.3-31.1)	*p=0.57*
Neck circumference (cm)		**40** (37-42)	**40** (39-43)	*p=0.47*
Alcohol (units/week)		**1** (0-6)	**2** (0-7)	*p=0.58*
Epworth sleepiness score		**8** (4-10)	**8** (6-12)	*p=0.49*
NYHA functional class I / II / III / IV		10 / 2 / 11 / 0	12 / 1 / 7 /2	-
Blood pressure (mmHg)*	Systolic	**120** (107-134)	**118** (100-126)	*p=0.32*
	Diastolic	**72** (62-81)	**72** (63-78)	*p=0.95*
Left ventricular ejection fraction (%)*		**29** (19-38)	**35** (28-42)	*p=0.09*
B-type natriuretic peptide (pmol/L)*		**81.5** (50.0-132.5)	**37.0** (27.0-56.5)	***p=<0.01***
Aetiology of HF syndrome*	Ischaemic	**14**	**12**	-
	DCM	**3**	**7**	
	Valvular	**5**	**2**	
	Unknown	**1**	**1**	
Medications	Diuretics	**20**	**17**	-
	Beta blocker	**22**	**17**	
	ACE inhibitor/ARB	**16**	**21**	
	Digoxin	**5**	**5**	
Comorbidities*	Diabetes	**4**	**3**	-
	Atrial fibrillation	**9** (1 with PAF)	**6** (2 with PAF)	
Implanted devices*	no device	**10**	**12**	-
	PPM +/- ICD	**2**	**1**	
	CRT	**11**	**7**	
	ICD	**0**	**2**	
Minnesota Living with Heart Failure questionnaire score		**25** (17-45)	**38** (19-58)	*p=0.33*
Nocturia (no of episodes over 14d)		**20** (12-28)	**11** (9-19)	*p=0.26*

BMI- body mass index; SDB- sleep disordered breathing; NYHA- New York Heart Association; DCM- dilated cardiomyopathy; ACE- angiotensin converting enzyme; ARB- angiotensin receptor blocker; PPM- permanent pacemaker; ICD-implantable cardiac defibrillator; CRT- cardiac resynchronisation therapy.

*Data not available for all patients; BP data missing for 1/22 HF-noSDB group, BNP data missing in 19 patients, LVEF data missing for 2 patients and information not available on aetiology (1 patient), comorbidities (2 patients) and implanted device (2 patients).

Table 6.5: Nocturnal polysomnographic data for the HF-CSA and HF-noSDB groups. Data are median (IQR).

	HF-CSA n=23	**HF-No SDB n=22**	
Apnoea hypopnoea index (events/hr)	**20.6** (12.9-40.2)	**3.7** (2.5-5.9)	
Apnoea index (events/hr)	**8.0** (2.4-16.6)	**0.2** (0-0.8)	
Hypopnoea index (events/hr)	**11.7** (9.1-18.8)	**3.0** (1.4-5)	
Oxygen desaturation index (≥3% dip rate/hour)	**16.5** (8.6-38.7)	**4.2** (1.0-8.1)	***p=<0.01***
Time with O_2 saturations <90% (min) *	**18.7** (5-35.2)	**2.0** (0-5.0)	***p=<0.01***
Time in bed (min)	**500** (465-548)	**460** (402-488)	***p=<0.01***
Total sleep time (min)	**348** (303-383)	**355** (295-383)	*p=0.75*
Sleep efficiency (%)	**73.4** (61.2-76.5)	**78.5** (70.1-84.1)	***p=0.04***
Sleep latency (min)	**20.3** (11.3-29.3)	**14.6** (10.9-29.0)	*p=0.40*
Wake after sleep onset (min) *	**100.0** (80.0-149.0)	**36.7** (0-90.5)	***p=<0.01***
Arousal index (events/hr)	**28.3** (21.3-47.7)	**31.8** (14.2-41.8)	*p=0.53*
Stage 1 (%)	**27.6** (21.0-49.1)	**20.5** (9.6-31.2)	***p=0.03***
Stage 2 (%)	**39.4** (29.1-51.3)	**44.5** (38.4-52.1)	*p=0.14*
Stage 3 (%)	**8.2** (3.6-10.5)	**8.1** (6.2-12.6)	*p=0.26*
Stage 4 (%)	**0.2** (0-5.0)	**1.6** (0.2-6.5)	*p=0.26*
REM sleep (%)	**14.1** (9.0-18.9)	**18.4** (13.5-22.0)	***p=0.04***
PLM index (events/hr)	**14.0** (5.7-37.1)	**4.6** (0.3-11.4)	***p=0.02***
Supine (%)*	**45.9** (33.3-80.1)	**23.0** (0-42.2)	***p=<0.01***

REM- rapid eye movement; PLM- periodic limb movement.

*Data not available for all patients; T<90%, WASO and data on sleeping position (ie. supine, right, left etc) not available for 6 of 45 patients (all HF-noSDB group).

Table 6.6: Daytime activity in HF patients with and without central SDB. Results are median (IQR).

	HF-CSA n=32	HF-No SDB n=22	
Average duration of activity /day (hrs)	**14.5** (14.1-15.2)	**15.1** (14.4-15.3)	*p=0.10*
Average activity per day (arbitrary units)	**193594** (135582-255557)	**217926** (196900-275933)	*p=0.10*
Average activity per 1 minute epoch (arbitrary units)	**215.3** (160.3-296.6)	**231.1** (210.6-305.0)	*p=0.15*
Total daytime activity count over 14d (arbitrary units)	**2,903,915** (2,033,728-3,833,354)	**3,068,856** (2834952-4,019,950)	*p=0.38*

SDB- sleep disordered breathing.

6.3.3 The effect of heart failure on subjective sleepiness, sleep and physical activity

To investigate the effect of HF itself on subjective sleepiness and daytime activity I compared the group of HF patients with no SDB (HF-noSDB) with a group of age matched healthy controls. Subject characteristics for these 2 groups are shown in Table 6.7. The HF-noSDB group had a higher BMI (27.9 (25.3-31.1) vs. 25.0 (22.7-26.5) kg/m^2; p=0.01) and a larger neck circumference (40.3 (38.7-42.5) vs. 38.5 (34.5-39.4) cm; p=0.04) and were significantly more sleepy than the healthy controls (ESS; 8 (6-12) vs. 4 (3-9); p=0.01), although both groups were below the score of 11 (out of 24) indicative of excessive daytime sleepiness. There were no other significant differences between the groups; specifically we took care to age match the groups.

Overnight sleep and breathing patterns (measured during nocturnal PSG) are shown in Table 6.8. The HF-noSDB group spent more time with saturations less than 90% (2 (0-5.0) vs. 0 minutes; p=0.02) despite the absence of SDB. There were also differences in sleep architecture; HF-noSDB patients had more light stage 1 sleep (20.5 (9.6-31.2) vs. 13.5 (8.3-15.9) %; p=0.02) and less deep stage 4 sleep (1.6 (0.2-6.5) vs. 14.4 (7.2-20.4) %; p=<0.01) than the healthy control subjects.

Table 6.7: Characteristics of HF patients without SDB and age matched healthy controls. Results are median (IQR) unless stated.

	HF-No SDB n=22	**Controls n=12**	
Age (yrs)	**62** (53.5-69.8)	**67** (64-70)	*p=0.09*
Gender (male/female)	**19 / 3**	**9 / 3**	-
BMI (kg/m^2)	**27.9** (25.3-31.1)	**25.0** (22.7-26.5)	***p=0.01***
Neck circumference (cm)	**40.3** (38.7-42.5)	**38.5** (34.5-39.4)	***p=0.04***
Alcohol (units/week)	**2** (0-7)	**3** (0-13)	*p=0.87*
Epworth sleepiness score	**8** (6-12)	**4** (3-9)	***p=0.01***
Nocturia (no of episodes over 14d)	**10.5** (8.8-18.5)	**8.0** (3.8-15.0)	*p=0.18*

BMI- body mass index; SDB- sleep disordered breathing;

Table 6.8: Nocturnal polysomnographic data for the HF-noSDB and control groups. Data are median (IQR).

	HF-No SDB n=22	Controls n=12	
Apnoea hypopnoea index (events/hr)	**3.7** (2.5-5.9)	**2.8** (1.7-4.8)	*p=0.44*
Apnoea index (events/hr)	**0.2** (0-0.8)	**1.0** (0.3-1.8)	***p=0.04***
Hypopnoea index (events/hr)	**3.0** (1.4-5)	**1.1** (0.5-3.2)	*p=0.09*
Oxygen desaturation index (≥3% dip rate/hour)	**4.2** (1.0-8.1)	**2.0** (0.8-4.2)	*p=0.17*
Time with O_2 saturations <90% (min) *****	**2** (0-5.0)	**0**	***p=0.02***
Time in bed (min)	**460** (402-488)	**475** (433-512)	*p=0.21*
Total sleep time (min)	**355** (295-383)	**411** (344-437)	*p=0.13*
Sleep efficiency (%)	**78.5** (70.1-84.1)	**85.1** (79.0-88.9)	*p=0.10*
Sleep latency (min)	**14.6** (10.9-29.0)	**16.0** (8.3-29.6)	*p=0.91*
Wake after sleep onset (min**)***	**36.7** (0-90.5)	**47.5** (27.8-94.0)	*p=0.29*
Arousal index (events/hr)	**31.8** (14.2-41.8)	**27.5** (8.5-49.1)	*p=0.84*
Stage 1 (%)	**20.5** (9.6-31.2)	**13.5** (8.3-15.9)	***p=0.02***
Stage 2 (%)	**44.5** (38.4-52.1)	**40.0** (33.0-54.1)	*p=0.47*
Stage 3 (%)	**8.1** (6.2-12.6)	**9.2** (6.8-10.2)	*p=0.84*
Stage 4 (%)	**1.6** (0.2-6.5)	**14.4** (7.2-20.4)	***p=<0.01***
REM sleep (%)	**18.4** (13.5-22.0)	**21.3** (19.3-23.2)	*p=0.11*
PLM index (events/hr)	**4.6** (0.3-11.4)	**5.5** (0.4-18.1)	*p=0.79*

REM- rapid eye movement; PLM- periodic limb movement.

*Data not available for all patients- data on T<90% and WASO missing for 6/22 from the HF-noSDB group.

Daytime activity data are given in Table 6.9. As with the previous analyses there was no difference in daytime activity duration or levels between the HF-noSDB and control groups. Results for night time actigraphy data are shown in appendix 11. Unlike the previous comparisons between HF groups which showed no differences, the night time data from the actiwatch showed longer sleep latency (14.0 (10.3-18.8) vs. 6.5 (3.8-9.0) minutes; p=<0.01) and more fragmented sleep (47.5 (39.0-62.4) vs. 31.7 (20.4-45.5) no units; p=<0.01), less efficient sleep (78.4 (71.0-82.8) vs. 85.3 (79.8-90.0) %,

p=<0.01) compared to the control group. The HF-noSDB group also reported a longer total nap time (125.0 (41.3-341.4) vs. 2.0 (0-8.0) minutes; p=<0.01).

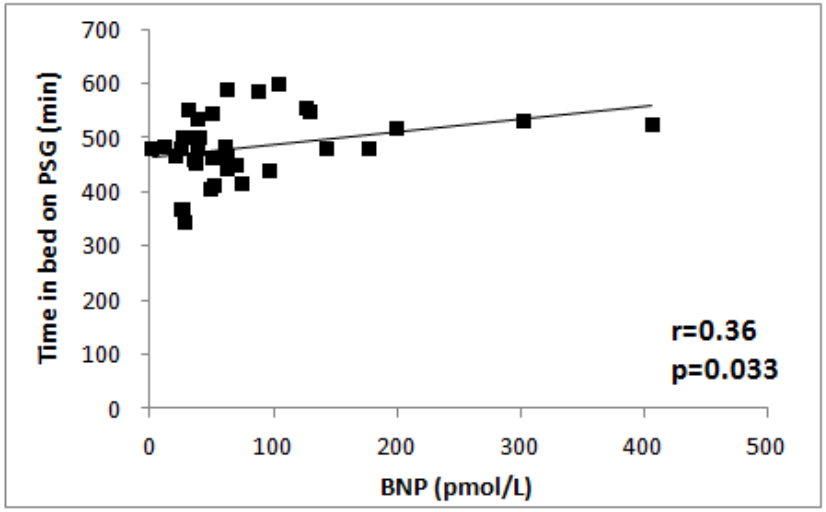
Table 6.9: Daytime activity in HF patients without SDB and healthy control subjects. Results are median (IQR) unless stated.

	HF-No SDB n=22	**Controls n=12**	
Average duration of activity /day (hrs)	**15.1** (14.4-15.3)	**14.5** (12.7-15.6)	*p=0.27*
Average activity per day (arbitrary units)	**217926** (196900-275933)	**217751** (172699-304318)	*p=0.86*
Average activity per 1 minute epoch (arbitrary units)	**231.1** (210.6-305.0)	**230.7** (171.3-311.5)	*p=0.72*
Total daytime activity count over 14d (arbitrary units)	**3,068,856** (2,834,952-4019950)	**3,106,372** (2,287,621-3,849,165)	*p=0.85*

SDB- sleep disordered breathing.

In order to investigate the potential role of BMI in this comparison the 7 patients whose BMI was ≥30kg/m^2 were removed from the HF-noSDB group and the remaining group of 15 patients compared with the group of 12 controls. With those subjects excluded there was no significant difference in either BMI (HF-noSDB: 26.2 (24.4-27.9) vs. controls: 25.0 (22.7-26.5) kg/m^2, p=0.15) or neck circumference (HF-noSDB: 40.0 (38.7-41.5) vs. controls: 38.5 (34.5-39.4) cm, p=0.06) between the groups as before but the findings changed little in other respects. The patient group had a higher ESS (8 (5-12) vs. 4 (3-9), p=0.04) and the same pattern of sleep disturbance as measured by actigraphy. Sleep efficiency assessed by nocturnal PSG was significantly worse in the new patient group (75.6 (66.1-83.7) vs. 85.1 (78.9-88.9) %, p=0.04) but other differences in sleep architecture were unchanged. The data for this comparison can be found in appendix 12.

In the complete HF group (n=55) both BNP and LVEF had weak correlations with aspects of sleep, but showed no correlation with any measure of activity, naps or nocturia. BNP correlated with TIB measured by both PSG and actigraphy (Spearman's rho 0.36 and 0.34 respectively, p=<0.05; figure 6.2). LVEF correlated negatively with stage 1 sleep and positively with stage 2 sleep (Spearman's rho -0.30 and 0.38 respectively, p=<0.05; figure 6.3). Scores from the MLHFQ did not correlate with any measure of sleep, activity, naps or nocturia.



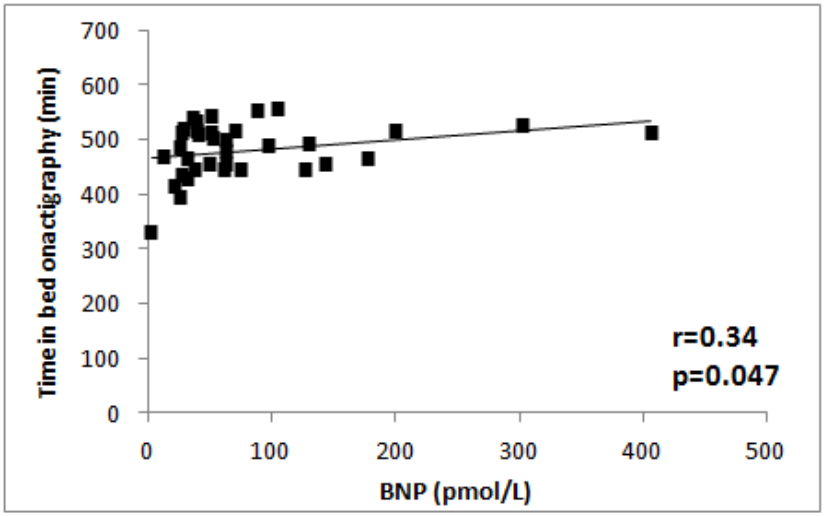
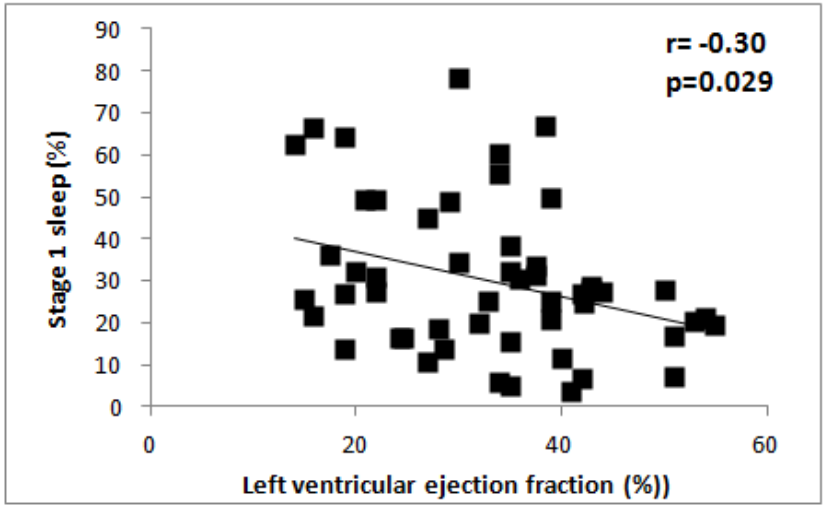


Figure 6.2: Relationships between BNP and time in bed assessed by polysomnography (top panel) and actigraphy (bottom panel). *BNP: B-type natriuretic peptide.*



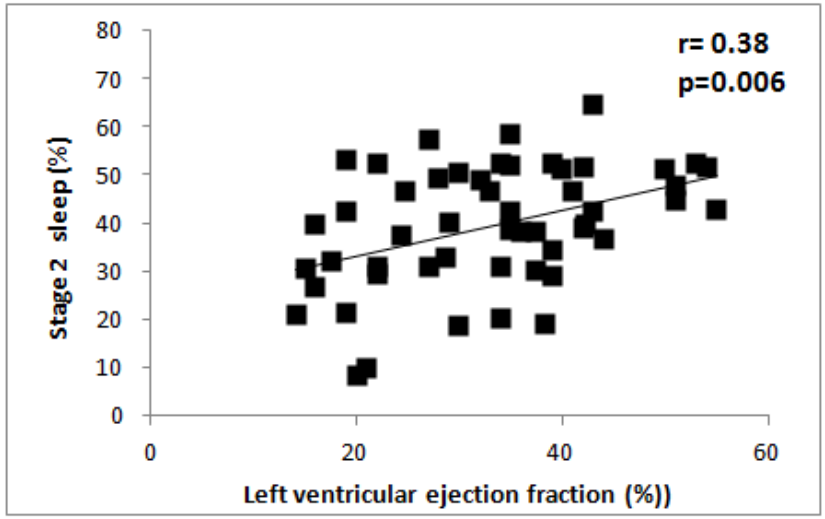


Figure 6.3: Relationships between left ventricular ejection fraction and stage 1 (top panel) and stage 2 (bottom panel) sleep expressed as a percentage of total sleep time.

6.4 DISCUSSION

The findings of this study have confirmed previous work from our laboratory showed that SDB in patients with HF is not associated with symptoms of subjective sleepiness, compared to those with HF and no SDB. This study also extends the understanding of the impact of SDB in HF patients by showing that central SDB is not associated with subjective sleepiness in HF patients. Furthermore, this is unlikely to be explained by a reduction in daytime activity levels since there was no difference in daytime physical activity levels between the HF-CSA and HF-noSDB groups. Additionally, this study also found that in patients with HF alone (ie. no SDB) symptoms of sleepiness are greater than in a group of older healthy controls, and that sleep is disrupted in HF despite the absence of SDB. Taken together, these data suggest that HF itself disrupts sleep to a greater extent than SDB does, or that other factors attenuate the sleep disrupting effect of SDB, but not HF itself, in these patients.

The findings of this study have clinical relevance since conventional screening questionnaires for sleep apnoea in this population are likely to be of limited value given the absence of subjective sleepiness. This raises the necessity of a screening sleep study in HF patients in whom a diagnosis of SDB is sought. The wider issue of universal screening for SDB in patients with cardiovascular disease is by no means clear; some authors advocate it (Oldenburg et al., 2007e) whilst others argue that without robust evidence of a mortality benefit of treatment screening is not justified (Franklin, 2007) and furthermore may not fulfil the requirements of a screening test (Wilson and Jungner, 1968).

From a mechanistic point of view these data demonstrate that the lack of subjective sleepiness in this population occurs by a mechanism other than a reduction in physical activity. Other potential mechanisms are discussed below.

6.4.1 The effect of heart failure on activity levels, subjective sleepiness and sleep

Previous work has shown that HF patients with SDB are no more sleepy than those with HF alone (Hastings et al., 2006) and that HF patients with obstructive SDB are *less* sleepy than subjects with obstructive SDB but without HF (Arzt et al., 2006). This latter study by Arzt *et al.* found that patients with HF were significantly less sleepy than those without HF, even when the AHI was <5 (ie. no SDB) and the groups were matched for the severity of SDB. This group can be considered analogous to the HF-noSDB group in the current study.

Sleep disruption is common in patients with HF and may be due to medications, comorbidities, effects of the HF syndrome itself or due to SDB (see chapter 1, section 1.3). The current study found that sleep was disrupted in all groups with HF, with and without SDB. The HF-noSDB group had longer sleep latency and more fragmented less efficient sleep on 14 days of actigraphy compared to the controls and this may explain complaints of poor sleep and insomnia in this group. The HF-CSA group had a higher PLM index than the HF-noSDB. Although these can disrupt sleep there was no difference in the arousal index between the 2 groups. Interestingly, the presence of periodic leg movements in a group of patients with HF has been associated with objective (Hanly and Zuberi-Khokhar, 1996) but not subjective (Skomro et al., 2009) sleepiness, as seen with central SDB in HF patients. This raises the possibility that PLM, which are common in patients with HF (Yumino et al., 2011), may also increase sympathetic nerve activity and so attenuate subjective sleepiness.

A study of 24 hour activity levels found they were lower in those with HF compared to age matched controls, although no assessment of breathing during sleep was made (Davies et al., 1992). I found no difference in *daytime* activity between the HF-noSDB and control groups using 14 days of actigraphy, although I did find differences in *night time* activity between the groups including greater movement time per night in the HF-noSDB group, although total activity scores overnight were not different between the groups. Unlike Davies *et al.* I did not directly compare 24 hour physical activity, and the technology in each study was different (movement sensor vs. actigraphy).

It is well established that markers of left ventricular function do not correlate with measures of physical function (Volterrani et al., 1994) although the reasons for this are not fully understood. This is in keeping with the results of this study which found no correlation between LVEF and any measure of activity (neither absolute counts nor duration of activity).

Previous work investigating self reported sleep dysfunction in patients with HF has found that it is not significantly determined by SDB (Riegel et al., 2011a) and this is in keeping with the objective findings of Artz *et al.* and Hastings *et al.* as well as the results of the current study. I found no difference in sleep assessed by nocturnal PSG, nor day and night time activity over 14 days between the HF-SDB and HF-noSDB groups; sleep was disrupted in both of these groups, but to a similar extent. This, along with the third comparison of HF-noSDB and control groups suggests that HF disrupts sleep more than SDB, and also the disruptive effects of SDB and HF are not additive. This may in part explain the lack of difference in subjective sleepiness between the groups.

The current study, in which the majority (72%) of patients with SDB had predominantly central events, found the HF-CSA group spent more time in the supine position than the HF-noSDB group; there were no differences in time spent in either lateral position. This finding is in keeping with that of Szollosi *et al.* who found that the severity of central SDB is attenuated during sleep in the lateral (rather than supine) position (Szollosi et al., 2006b). The mechanism for this is unclear but may relate to the role of plant gain (see chapter 1, section 1.5.5). The left lateral position has long been recognised as poorly tolerated by HF patients. Wood attributed this preference for other sleeping positions to the uncomfortable sensation of the heart within the thorax under the effect of gravity; "trepopnea" (Wood, 1959, Wood, 1937). Subsequent work investigating the levels of SNA in the supine and lateral positions suggests that HF patients avoid the left lateral position (Leung et al., 2003) and that SNA is lower in the right lateral position (Miyamoto et al., 2001). The relative effect of the supine position, however, on SNA is unclear, as is the apparent preference for this position over either lateral position by the HF-CSA group. It is possible that the presence of SDB in the HF-CSA is a result of their preference for the supine position and therefore that sleeping in the lateral position may have attenuated or perhaps completely suppressed their central SDB, a concept more readily applied to the patient with obstructive SDB (Cartwright, 1984, Oksenberg et al., 2000).

Redeker *et al.* used 3 days of actigraphy and domicillary PSG in 170 patients with HF and found worse self reported physical function in the most severe quartile of SDB (classified by AHI) (Redeker et al., 2010). They found that neither LVEF nor NYHA were associated with SDB severity. Interestingly, they found differences in the duration of daily mobility with those with central SDB (n=16) spending less time active than those without SDB. It is not clear what the denominator used to calculate the percentage of mobile time was (24 hours or presumed/self reported wake time) and this may explain the difference between their results and the current study, which, although included twice as many patients with central SDB, did not control for the same variables (age, gender, co-morbidities and BMI).

Witham *et al.* found that age and NYHA, as well as psychological and attitudinal factors played a role in explaining distance covered in the 6MWT (Witham et al., 2006). Brostrom *et al.* (Brostrom et al., 2001) interviewed 20 patients with HF and found that worries about heart failure, problems in daily life and cardiac symptoms all disturb sleep in HF patients. The emotional sequelae of HF are assessed by the MLHFQ (appendix 5) of which 5 of 21 facets relate to psychological distress. I found no difference in MLHFQ scores between the HF groups.

6.4.2 Differences between the current study and previous work

Hastings *et al.* (Hastings et al., 2006) found that patients with both HF and SDB were less active by day than those without SDB, suggesting a behavioural compensatory mechanism. However these findings were not replicated by the current study; I found no difference in activity levels between the HF-SDB and HF-noSDB groups. Possible explanations for this include differences in the HF patient populations, SDB type, methodological and sample size differences and changes in the way that HF is managed.

The HF populations in the current work and that by Hastings compare well in terms of age, BMI, NYHA functional class and LVEF. There are no data in the Hastings paper about implanted devices, BNP levels nor the MLHF questionnaire so it is not possible to comment on these. The current study had more patients with an ischaemic aetiology of HF, whereas the Hastings study had more idiopathic DCM, although the majority still had ischaemic cardiomyopathy. That said, HF aetiology is not known to have an effect on physical activity, sleepiness or sleep. None of the 38 patients in the Hastings study were employed, 12 of 54 patients in the current work (22%) were employed although the majority of these were low intensity/part time jobs (eg. desk worker). There were no significant methodological differences between the studies by design.

It seems likely that differences in SDB type between the studies may explain the difference in results with regards to daytime activity levels. Hastings *et al.* studied a group of 38 HF patients, of whom 12 had central and 10 had obstructive SDB. The current study included 53 patients, of whom 23 had central and 8 had obstructive SDB, and was designed to answer a hypothesis relating exclusively to HF-CSA patients and how they compared to HF-noSDB patients. Patients with HF-OSA were studied but this was not the primary purpose of the study and the numbers of HF-OSA patients would prohibit robust analysis if that had been the intention (reference data on all subject groups can be found in appendix 13). That said; the Hastings study of a predominantly (55%) obstructive group found a higher arousal index in the HF-SDB group. Taking the current data set in its entirety there were more arousals in the HF-OSA (n=9) group suggesting that obstructive SDB in HF causes more cortical arousals from sleep than central SDB, although this has not been universally found (Sin et al., 1999). The idea that cortical arousals may be more frequent in obstructive SDB is plausible in that an obstructive event relates to a narrowing or closure of the upper airway, rendered hypotonic by sleep. A return of patency therefore requires a wakening from sleep in the majority (but not all) cases (Younes, 2004). The finding of a reduction in the duration of physical activity in the Hastings study may be a signal from the patients with HF-OSA who, with more cortical arousals at night, may

therefore have been less active by day. A study of a larger number of HF-OSA patients would be needed to test this idea.

Levels of subjective sleepiness may in part be related to the degree to which sleep architecture is preserved or disrupted. Hastings *et al.* observed that despite respiratory events the proportion of slow wave sleep (SWS) was the same, and relatively preserved, in both groups (SWS 11±7 (median ±SD) in both groups, p=0.86). Similarly this study found no significant difference in SWS between the HF-SDB and HF-noSDB groups, nor between the HF-CSA and HF-noSDB groups. However the control group had significantly more stage 4 sleep, and therefore more SWS overall than the HF-noSDB group (p=<0.01 and 0.02 respectively) supporting the theory that HF itself disrupts sleep. Levels of SWS in the current study for each group are given in figure 6.4 (expressed as median and inter-quartile range) and figure 6.5 for the Hastings study (expressed as mean ± SD).

It is interesting that only stage 4 sleep seems to be affected in the HF groups, and also that deep sleep is equally affected in each of these patient groups irrespective of the presence or absence of SDB. This observation again suggests that, as before with subjective sleepiness, the presence of SDB as well as HF has no additional effect on deep sleep. The difference in SWS between the HF-noSDB and control groups, and the lack of such a difference between the HF-SDB/HF-CSA and HF-noSDB groups, may explain at least in part the findings concerning subjective sleepiness. This study found no difference in subjective sleepiness between any of the patient groups, but did find that those with HF alone were more subjectively sleepy than healthy controls. This study did not compare patients with HF-SDB/HF-CSA with control subjects.

This study found no significant difference in arousal index between the groups studied however it is noteworthy that despite respiratory events the HF-CSA group had an arousal index similar to the control group (median 28.3 and 27.5/hr, respectively) and both groups had an arousal index lower than that in the HF-noSDB group (31.8/hr). This apparent mismatch between respiratory events and arousals may in part explain the lack of sleepiness seen in HF patients with central SDB. Overall sleep architecture was not different between the HF-CSA and HF-noSDB groups, a finding in keeping with that of Solin *et al.* (Solin et al., 2003) who compared healthy controls with patients with obstructive SDB without HF, and obstructive SDB with HF.

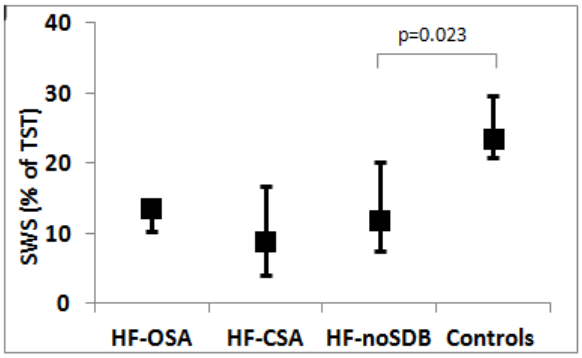


Figure 6.4: Proportion of total sleep time spent in slow wave sleep for each group in the current study. Results are median and inter-quartile range.

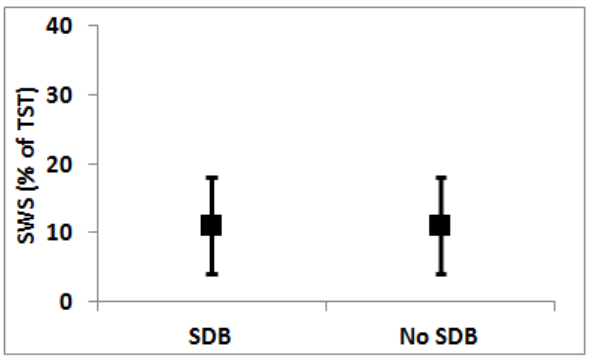


Figure 6.5: Proportion of total sleep time spent in slow wave sleep for both groups in the Hastings study. Results are mean and standard deviation.

Maurer *et al.* (Maurer et al., 2009) investigated the syndrome of anergia (lack of energy) in 61 patients with HF in a study which included the use of actigraphy, but which did not evaluate sleep or SDB. They found that those patients with anergia spent less time undertaking moderate physical activity and had lower peak activity counts for 6 minute and 30 minute periods per day compared to those without anergia. Their published data does not include complete 3 month actigraphy data, nor comparable actigraphy parameters to the current study which did not include assessment of peak counts but rather total counts and duration of activity. The use of peak activity counts (total counts during the most active 6 and 30 minutes of the day) are more recent metrics which the same group compared to conventional measures of functional capacity in a later study in older adults with HF (Howell et al., 2010). They found a significant ($p=<0.05$) correlation between the maximum 6 minutes of daily activity, the six minute walk test ($r=0.70$) and peak VO_2 ($r=0.61$) on cardiopulmonary exercise testing. Furthermore they found the maximum 6 minutes of daily activity was significantly associated with later adverse clinical events (HR 2.728, 95% CI 1.10-6.77). The data from Maurer *et al.* raise the possibility that although the total amount and duration of activity were not reduced in the group studied, there may have been changes in the pattern or intensity of activity through the day not captured with the measures used. The current study was designed to extend the work of Hastings *et al.* and as such a similar methodology, using conventional average and total counts for the day was chosen.

Data from the Hastings study was collected approximately 5 years before that in the current study. The management of HF continues to evolve with a greater emphasis on self management plans, higher priority given to disease modifying medications (such as ACE inhibitors and angiotensin II receptor blockers), new medications (such as eplerenone and ivabradine) and new technologies,

notably the increasing use of telemonitoring and CRT. The global effect of this evolution in management is likely to play some part in explaining differences between this and earlier work.

6.4.3 Subjective and objective sleepiness

The results of the work by Hastings *et al.* suggest a mismatch between objective and subjective sleepiness; those with SDB were no more subjectively sleepy (using the Epworth score) than those without SDB, but they were more objectively sleepy (using the Oxford Sleep Resistance Test) (Hastings et al., 2006, Pepperell et al., 2003). Other work has reported a shorter sleep latency in patients with HF and central SDB compared to HF patients without SDB and a group of control subjects (Hanly and Zuberi-Khokhar, 1995).

The current study did not include an objective measurement of sleepiness but it has been measured by other authors as part of a randomised controlled trial of adaptive servoventilation (ASV) in a group of patients with HF and central SDB (Pepperell et al., 2003). Those authors found a reduction in objective sleepiness in association with the successful treatment of SDB by ASV. They also reported, like the current study, a mean ESS of less than 11. It seems that SDB in patients with central SDB is not associated with subjective sleepiness, but is associated with objective sleepiness which responds to treatment of SDB. This raises the possibility that objective sleepiness relates more to the presence of SDB and that subjective sleepiness relates more to the effect of the HF syndrome. This would explain the lack of difference in subjective sleepiness between those HF with and without SDB. Heightened sympathetic activity has been suggested as an explanation for the lack of subjective sleepiness but this does not fully explain the disparity between objective and subjective sleepiness.

Subjective sleepiness relates strongly to the perception of sleepiness and it could be expected that HF patients, who tend to be older (median age 68 in this study) and retired may be able to compensate for objective sleepiness by lifestyle and other changes. The lack of subjective sleepiness in this group suggests that the ESS (Johns, 1991), discussed in chapter 2, section 2.2.1, may be an insensitive measure of sleepiness in the HF population. Data from this study do not support the theory that any such behavioural or lifestyle modifications involve a reduction in physical activity (neither duration or amount of activity). Of 54 patients in this study 12 (22%) were employed, although the majority of these were part time, low intensity jobs (desk based work, voluntary part time work).

6.4.4 Methodological considerations

This was an observational study investigating subjective sleepiness and activity levels in HF patients with and without SDB, and age matched controls. Whilst it was adequately powered to answer the hypothesis posed it had a number of limitations.

The actiwatches used were not water proof and so subjects were asked to remove them before bathing and put them on again afterwards; on 2 occasions watches were worn in the bath or shower and had to be checked and re-set. In terms of data acquisition this meant that subjects for whom swimming, or other similar activities constituted their main exercise, the actiwatch failed to capture all of their activity. This was relevant to one control and one patient only. Similarly, one patient removed his watch briefly several times every day for bathing before prayers. Actiwatches only capture movement of one arm, in this case the non-dominant arm, which is a surrogate of total body movement. Furthermore, actigraphy tends to underestimate sleep latency (as found in the current data; night time activity data are found in appendix 11) and this is due to the period of relative immobility before sleep onset (Blood et al., 1997) which the actigraphy algorithm scores as sleep. Finally, compliance with the devices was critical to data collection; failure to remember to wear the watch would mean loss of opportunity to collect the data. This was rarely a problem in practice as my protocol included clear verbal and written instructions with at least 2 and up to 3 telephone calls (or emails) to subjects during the 14 days the watch was worn.

One night, in laboratory, PSG was used and may have affected sleep due to the subject sleeping in a foreign environment, rather than at home. There is also a significant equipment burden and this may also disrupt sleep. Since all 66 subjects underwent in laboratory PSG it can be assumed that these effects broadly affected all groups equally. Several of the participants had taken part in previous research and so the sleep laboratory environment and equipment were familiar to them. These effects are mitigated in part by the 14 days and nights of actigraphy, which is validated against PSG for confirming sleep (Oakley, 1997), collected from each subject, giving a more medium term picture of activity and sleep.

Other factors may affect sleep and activity levels. Socioeconomic factors have a deleterious effect on sleep with income found to be independently associated with sleep latency and efficiency (Lauderdale et al., 2006) in a study using actigraphy. Ethnicity also affects sleep architecture with those from ethnic minorities spending more time in stages 1 and 2 sleep, and less time in stage 3 and 4 sleep (Redline et al., 2004, Lauderdale et al., 2006, Jean-Louis et al., 2000, Tomfohr et al.,

2012). One study of African Americans found a relationship between perceived discrimination and changes in sleep architecture (Tomfohr et al., 2012). These findings are drawn from studies of populations from the United States which were more ethnically heterogeneous than the current study and included subjects described as white, black, American Indian, Hispanic and American Asian. The current study did not exclude subjects on the basis of ethnicity and of 66 subjects comprised 80% Caucasians, 15% Asians with the remaining 5% from the Caribbean and the Middle East. The available literature does not include these ethnic minorities and so it is not possible to comment on how this may have affected the results. Those subjects of a non-Caucasian origin were distributed throughout the groups and so any effect of ethnicity is likely to have been small and was not controlled for in the analyses.

The time of year is also likely to affect sleep and activity patterns (Anderson et al., 1994) particularly in the group of HF patients in whom cold weather may precipitate symptoms on exertion.
The use of night sedation to assist with sleep may also have affected my results and while such patients were not excluded none were regular users of night sedation. No patient used night sedation on the night of the laboratory PSG. Redeker and Hilkert found that such medication use was negatively associated with daytime activity, 6MWT and physical function as assessed by the SF-36 questionnaire (Redeker and Hilkert, 2005).

6.4.5 Summary

In summary this study has shown that patients with HF and central SDB are not sleepy compared to those patients with HF and no SDB. In a second novel finding this study found that this lack of sleepiness cannot be explained by a reduction in physical activity levels; there was no difference in physical activity measured by actigraphy between HF patients with central SDB and those with HF alone. Furthermore, although there was no difference in subjective sleepiness between HF patients with and without central SDB, the group without SDB were more subjectively sleepy than a group of older healthy controls.

HF itself disrupts sleep, having a marked effect on those with HF alone compared to the control group, with the HF-noSDB group having longer sleep latency, more fragmented and less efficient sleep which explains the high prevalence of sleep complaints in this population. The amount of stage 4 sleep was comparable across the 3 patient groups, irrespective of the presence or absence of SDB, and this may in part explain the lack of sleepiness seen in the HF-CSA group.

There was no difference in the number of cortical arousals from sleep between the HF-CSA group and the healthy older controls and this lack of difference, despite the presence of SDB in one group but not the other, may also explain the lack of sleepiness between them. How this explains the previously found objective sleepiness in these patients warrants further investigation. These findings support the need for sleep studies in cases where there is a need to exclude SDB in a HF patient since patients do not complain of subjective sleepiness.

Sleep, baby mine. The failing light is low,
The witch-elms toss their branches to and fro;
And howling winds sing baby's lullaby.
Move, shadows move, and grey frost-clouds go by,
My baby sleeps, whatever winds may blow.

Sleep, baby mine; while he, who loves us so,
Is daring all the bitter, drifting snow
Across the moorlands where the great winds cry.
Sleep, baby mine!

Within--The crackling wide-fire's ruddy glow
Warms each wee hand, and curlèd roseleaf toe.
Without--The blinding, biting storm mounts high,
And barbèd snowflakes scatter down the sky.
God send thy father ere the darkness grow!
Sleep, baby mine!

“Sleep, Baby Mine”, William Wilsey Martin (1833-1913)

CHAPTER SEVEN:

GENERAL DISCUSSION

7.1 Summary of the main findings of this thesis

Central SDB in patients with HF is increasingly recognised as an important clinical problem and one which may hold opportunity for life lengthening treatments to emerge, be they PAP devices or otherwise.

Central SDB in patients with HF allows us an insight into the way that ventilation is controlled and how its stability might be compromised. Considering both HF and central SDB as separate entities we can see in each physiological mechanisms which have some capacity to compensate for disturbances but which are overwhelmed in the face of disease. In health the ventilatory system has the capacity to dampen out disturbances such that there is a return to stable breathing. However in central SDB the system is sensitive and "over-reacts" to disturbances such that breathing becomes unstable and periodic. The heart has enormous capacity to adapt to an increase in demand, such as that seen in exercise. However in the HF syndrome these compensatory mechanisms are also overwhelmed and so cardiac output is insufficient to meet the demands of the body, with all of the downstream consequences that this has.

This thesis aimed to investigate the mechanisms underlying central SDB in patients with HF (particularly that of ventilatory instability), to elucidate their consequences, both by day (on physical activity and subjective sleepiness) and night (on sleep architecture and SDB) and to address the ways in which various treatment modalities may modify these pathophysiological mechanisms.

The main findings and conclusions from each chapter are summarised below.

Chapter 3: The SERVE-HF Study. The data presented within this chapter consisted of patients from The Royal Brompton Hospital recruited to an international randomised controlled trial of adaptive servoventilation (ASV) in patients with central SDB and HF. As such, no hypothesis testing was done.

Nineteen patients were randomised at the Royal Brompton Hospital, 10 to receive treatment with the ASV device. These patients experienced an improvement in their SDB and nocturnal hypoxaemia after a titration night with ASV. From the titration night to a 3 month repeat study on the device there was no further improvement in these parameters, although the number of patients still using the device at 3 months (n=5) may have affected the chances of finding such an improvement if it did exist. Of this group of 10 patients, 6 were identified as persistent ASV users and 4 as ASV drop-outs. The former group had significantly higher BNP levels. A difference in the pattern of compliance between these two groups emerged as early as the 2 week device download when the persistent users had a significantly higher average daily use, longer number of total hours used and a greater proportion of nights wearing the device for 3 or more hours, compared to the group who later

dropped out. Markers of compliance at 2 weeks correlated with the number of hours the device was worn on the titration night.

Chapter 4: The influence of SDB on the hypercapnic ventilatory response in patients with chronic HF. The aim of this study was to confirm the mechanism of central SDB in HF patients by measuring the HCVR in HF patients with and without central SDB, and also in a group of older healthy subjects. It investigated sleep and chemosensitivity (by measuring the HCVR) in 3 groups; patients with HF and central SDB (HF-CSA), patients with HF but without SDB (HF-noSDB) and older healthy controls. Measurements were made in the evening and morning.

This study found no difference in evening, morning or evening to morning change in HCVR between the 3 groups. However it did find that the median carbon dioxide (CO_2) level at rest was lower in the HF-CSA group compared to the HF-noSDB group, as previously found. There was no difference in CO_2 level between the HF-CSA and control groups.

In the total study population (ie. HF-noSDB, HF-CSA and the control group) there was a negative correlation between resting CO_2 and morning HCVR, but not evening HCVR. In the combined HF population (ie. HF-CSA and HF-noSDB) there was a weak correlation between resting CO_2 and body mass index (BMI), and a medium negative correlation between CO_2 and the AHI. In the HF-CSA group alone there was a large correlation between resting CO_2 and body mass index.

It is surprising that, unlike previous work, this study found no difference in HCVR between those with and without central SDB. This might be explained if only the morning, rather than the evening, HCVR is higher in those with central SDB compared to those without and it is noteworthy that Javaheri (Javaheri, 1999) measured HCVR in the morning in his seminal work. This theory is supported by the correlation between resting CO_2 and morning HCVR in the total study population. Morning HCVR may better reflect the ventilatory instability of the preceding night and this may be why Javaheri found that the HCVR was correlated with the AHI in those with HF and central SDB. Notable too is the finding in this work that resting CO_2 correlated negatively with the AHI in the group with central SDB. The finding that resting CO_2 correlated negatively with BMI in both HF groups, but particularly in those with central SDB, suggests that obesity may influence ventilatory instability, probably via its effects on lung volumes; an effect magnified whilst asleep and supine.

Chapter 5: The effect of cardiac resynchronisation therapy on sleep in patients with chronic HF. The aim of this study was to investigate the effect of CRT implantation on SDB, sleep quality and chemosensitivity (assessed by the HCVR) on patients with chronic HF. Specifically, I tested the hypothesis that CRT implantation would improve SDB and sleep quality from baseline (pre-

implantation) to 3 months post implantation as well as the hypothesis that this would be associated with a reduction in HCVR at 3 months post implantation. Eight patients were recruited to this study. Four patients attended for both baseline and follow-up (post CRT) assessment of sleep and chemosensitivity.

This study found that CRT had a variable effect on SDB, sleep quality and HCVR. One of the 4 patients had a clear improvement in cardiac function and sub-maximal exercise capacity but an increase in both SDB and HCVR. Other patients had either small or no discernable improvement in cardiac or functional status at the time of follow-up, yet 2 had a reduction in HCVR from baseline to follow up. Interestingly, in the 2 patients where there was an increase in SDB, there was also an increase in HCVR, with the reverse being true in the other patients. Furthermore, 2 of the patients had a change in resting CO_2 levels which were the opposite of those seen in HCVR, which is what one might expect as hypocapnia is a marker of ventilatory instability.

Interpreting these findings is difficult as sample size is highly likely to have played a part. Certainly, in the one patient with a clear improvement in cardiac function the increase in SDB may have reflected a decrease in sleep disruption and so an increase in total sleep time which was associated with persistent SDB, hence the increase in the AHI. It is possible that a study of more patients, before and after implantation, and with a longer interval of follow up (such as 6 months) may detect a change in SDB such as been found in other work. Although this study found no consistent change in HCVR from baseline to follow up, neither can it be concluded that no such change can exist based on the results obtained.

Chapter 6: Subjective sleepiness and activity levels in HF patients with and without SDB. The aim of this study was to expand the findings of previous work by investigating the effect of central SDB on subjective sleepiness and physical activity levels in patients with chronic HF. A secondary aim was to investigate the effect of HF itself on sleepiness and activity levels by comparing a group of HF patients without SDB with a group of age matched healthy controls.

This study found that patients with HF and central SDB are not sleepy compared to those with HF and no SDB, as has previously been found for HF patients with obstructive SDB. Furthermore, this study found that this lack of sleepiness cannot be explained by a reduction in physical activity levels as there was no difference in actigraphy measured daytime activity levels between the 2 groups. In fact, there was no difference in the duration or level of daytime activity between any of the 3 groups. HF patients with central SDB were not more subjectively sleepy than the group of older controls, despite the presence of SDB. Conversely, despite the absence of SDB, the HF group without SDB were more subjectively sleepy than the group of controls.

These data suggest that something attenuates the effect of SDB such that its presence is not associated with an increase in subjective sleepiness compared to those with HF and no SDB. Notably those with HF alone were more subjectively sleepy than healthy controls whereas there was no difference in subjective sleepiness between the group with central SDB and the older controls. It is interesting that the number of cortical arousals in the HF groups was similar and this raises the possibility that those with HF and central SDB simply do not wake up in response to respiratory events overnight. However, previous work has shown this group to be more objectively, if not subjectively, sleepy compared to those with HF alone making a lack of cortical arousals unlikely to be the entire story. The proposed role of SNA is intriguing but does not explain the mismatch between subjective and objective sleepiness in those with HF and central SDB.

7.2 Potential direction of future work

There are several areas relating to this thesis and the results presented in it that merit further exploration and they are summarised below.

7.2.1 Explaining the absence of central SDB in some HF patients; the potential role of pre-morbid ventilatory stability.

The significant prevalence of SDB in HF is well established and the mechanisms underlying both obstructive and central SDB are increasingly understood. Perhaps less well understood however are the reasons why some HF patients *do not* develop SDB, particularly central SDB, in spite of impaired left ventricular function, increased circulation time, increased pulmonary congestion, amongst other factors- all exerting what might be considered a "physiological pressure" for the emergence of SDB. Studying ventilatory stability (chemosensitivity, waking and sleeping CO_2 and the apnoeic threshold) in this patient group, who are seemingly resistant to the development of central SDB, may answer further questions about its pathophysiology. I speculate that part of the explanation may lie in the wide range of HCVR seen in normal subjects. It is possible that one of the factors which determines the likelihood of a HF patient developing central SDB, alongside the severity of their cardiac failure, might be their pre-existing level of ventilatory stability. In this way an aspect of pre-morbid physiology, which is of limited or no consequence in health, determines an aspect of the response to the HF syndrome.

During the course of studying healthy controls I noticed that REM sleep is often the time when flow limitation and/or snoring would emerge in some subjects (because of the atonia associated with

REM). Some physicians feel that it is this group of patients who, under certain conditions (such as weight gain or sedation), would be at risk of developing obstructive SDB. Similarly, I noticed that in others, periodicity of ventilation would emerge in REM sleep. I speculate that this may be evidence of ventilatory instability that, under certain conditions (such as heart failure), may develop into central SDB. Studying the relationship between markers of ventilatory instability in control subjects and their tendency to periodic breathing in REM may provide useful insights into explaining why some patients with HF don't develop central SDB.

7.2.2 Objective and subjective sleepiness in HF patients

Patients with HF and SDB are not subjectively sleepy and the study in chapter 6 demonstrated that this is true of a group of HF patients with central SDB compared to both a group of HF patients without SDB and also a group of older healthy controls. Interestingly, the group with HF but without SDB *were* more subjectively sleepy than the group of older healthy controls. This suggests that something about HF itself contributes to subjective sleepiness, but that something about central SDB attenuates this effect. Sympathetic nerve activity has been postulated as a possible explanation but it is unclear how might explain the finding that HF patients with SDB (both obstructive and central) are more *objectively* sleepy, despite their lack of subjective sleepiness.

Previous work has found a similar mismatch to be associated with the presence of PLM in patients with HF, in whom they are common and associated with a worse prognosis (Yumino et al., 2011),. Patients with HF and an PLM index of over 10 are more objectively sleepy than healthy controls, although there was no significant difference in subjective sleepiness (Hanly and Zuberi-Khokhar, 1996). I speculate that PLM in patients with HF may, like the presence of SDB, contribute to an increase in SNA which may attenuate the effect of sleep disturbance. A study of sleep (with measurement of the PLM index) in a group of HF patients with measurement of urinary and/or plasma catecholamines and measurement of objective and subjective sleepiness would explore this theory.

7.2.3 The relationship between ventilatory instability and cardiac function

The links between central SDB and cardiac function are established; SDB is more prevalent and more severe in those with more severely impaired cardiac function (Oldenburg et al., 2009). Javaheri found that the HCVR in a group of 10 men with central SDB correlated with the AHI (Javaheri, 1999) and so the link between chemosensitivity (HCVR) and SDB is secure. Less clear is the relationship, if there is one, between cardiac function and chemosensitivity. It is interesting that several

interventions shown to treat central SDB, such as oxygen and adaptive servoventilation, have both improved cardiac function (LVEF and BNP) as well as reduced HCVR (Andreas et al., 1998, Oldenburg et al., 2011b). The model of loop gain suggests that cardiac output will influence feedback gain (circulation time) and plant gain (pulmonary congestion) but the part it might play, if any, in altering controller gain warrants further investigation. Given the importance of the cerebral circulation in mediating the response of the central (medullary) chemoreceptor and the fact that hypercapnic cerebrovascular responses are impaired in chronic HF (Xie et al., 2005, Georgiadis et al., 2000), I would speculate that an abnormality of cerebral perfusion is involved.

7.2.4 The effect of age on the evening to morning change in hypercapnic ventilatory response

Previous work in young healthy controls found an evening to morning increase in the HCVR (Cummings et al., 2007, Spengler et al., 2000). The work presented in chapter 4 found a reduction in the HCVR from evening to morning in the group of healthy controls who were older (median (IQR) 63 (59-67) years) than those in the previous studies. It is known that increasing age does not affect the sleep related decrease seen in the HCVR (Browne et al., 2003) which is discussed in chapter 1, section 1.5.5. However, the effect of age on the evening to morning change in HCVR has not previously been investigated although the results presented in chapter 4 suggest this may differ from that seen in younger subjects. Given the wide range of normal variability in HCVR a larger group of older healthy subjects would need to be studied during the evening before and the morning after a sleep study, with measurement of FEV_1 and FVC taken as well as these may affect HCVR (Jones et al., 1993).

Night grows uneasy near the dawn

Till even I sleep light; but who

Has tired of his own company?

What one of Maeve's nine brawling sons

Sick of his grave has wakened me?

But let him keep his grave for once

That I may find the sleep I have lost.

“The Hour Before Dawn”, William Butler Yeats,(1865-1939)

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Lay your sleeping head, my love,

Human on my faithless arm;

Time and fevers burn away

Individual beauty from

Thoughtful children, and the grave

Proves the child ephemeral:

But in my arms till break of day

Let the living creature lie,

Mortal, guilty, but to me

The entirely beautiful.

"Lullaby ", W.H. Auden (1907-1973)

APPENDICES

APPENDIX ONE

Ethical approvals for the SERVE-HF study

NHS

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Leeds (West) Research Ethics Committee

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Telephone: 0113 3923181
Facsimile: 0113 3922863

20 May 2008

Prof Martin Cowie
Professor of Cardiology
Imperial College, London
NHLI
Dovehouse Street
London
SW3 6LY

Dear Professor Cowie

Full title of study: **Treatment of sleep-disordered breathing with predominant central sleep apnoea by adaptive servo ventilation in patients with heart failure**

REC reference number: **08/H1307/41**

The Research Ethics Committee reviewed the above application at the meeting held on 9 May 2008. Thank you for attending to discuss the study.

Ethical opinion

Members agreed that their previous concerns had been addressed in the revised application, in particular, the use of CPAP, the model of the device to be used and the Data Monitoring Committee.

Members were happy with the proposed mechanism for checking that patients had not died before re-contacting them.

The members of the Committee present gave a favourable ethical opinion of the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below.

Ethical review of research sites

The Committee has not yet been notified of the outcome of any site-specific assessment (SSA) for the research site(s) taking part in this study. The favourable opinion does not therefore apply to any site at present. I will write to you again as soon as one Research Ethics Committee has notified the outcome of a SSA. In the meantime no study procedures should be initiated at sites requiring SSA.

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission at NHS sites ("R&D approval") should be obtained from the relevant care organisation(s) in accordance with NHS research governance arrangements. Guidance on applying for NHS permission is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

Notice of no objection must be obtained from the Medicines and Healthcare products Regulatory Agency (MHRA).

The sponsor is asked to provide the Committee with a copy of the notice from the MHRA, either confirming no objection or giving grounds for objection, as soon as this is available.

Approved documents

The documents reviewed and approved at the meeting were:

Document	*Version*	*Date*
Application		29 February 2008
Investigator CV	Professor Martin Richard Cowie	29 February 2008
Protocol	V1	10 October 2007
Covering Letter		29 February 2008
Letter from Sponsor	RESMED	26 February 2008
Questionnaire: MLWHF		
Questionnaire: ESS		
Questionnaire: EQ-5D		
GP/Consultant Information Sheets	V1	20 December 2007
Participant Information Sheet	V2	22 February 2008
Participant Consent Form	V1	20 December 2007
Liability and Insurance		14 December 2007
Clinical Training Manual		07 January 2004
Declaration of Conformity		21 February 2007
Flow Diagram	V1	10 October 2007
Leeds West Unfavourable Opinion Letter		13 February 2008

Membership of the Committee

The members of the Ethics Committee who were present at the meeting are listed on the attached sheet.

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.

After ethical review

Now that you have completed the application process please visit the National Research Ethics Website > After Review

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

The attached document "After ethical review – guidance for researchers" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

We would also like to inform you that we consult regularly with stakeholders to improve our service. If you would like to join our Reference Group please email referencegroup@nres.npsa.nhs.uk.

08/H1307/41	**Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project

Yours sincerely

Ann Prothero

Mr Jon Silcock
Chair

Email: ann.prothero@leedsth.nhs.uk

Enclosures: List of names and professions of members who were present at the meeting and those who submitted written comments
"After ethical review – guidance for researchers"

Site approval form (SF1)

Copy to: Mr Michael Loveridge
Research & Development Office
Royal Brompton Hospital
Sydney Street
London SW3 6NP

NHS

National Research Ethics Service

Leeds (West) Research Ethics Committee
A/B Floor, Old Site
Leeds General Infirmary
Great George Street
Leeds
LS1 3EX

Telephone: 0113 392 6788
Facsimile: 0113 392 2853

04 June 2008

Professor Martin Cowie
Professor of Cardiology
Imperial College, London
NHLI
Dovehouse Street
London
SW3 6LY

Dear Professor Cowie

Full title of study: **Treatment of sleep-disordered breathing with predominant central sleep apnoea by adaptive servo ventilation in patients with heart failure**

REC reference number: **08/H1307/41**

The REC gave a favourable ethical opinion to this study on 09 May 2008.

Further notification(s) have been received from local site assessor(s) following site-specific assessment. On behalf of the Committee, I am pleased to confirm the extension of the favourable opinion to the new site(s). I attach an updated version of the site approval form, listing all sites with a favourable ethical opinion to conduct the research.

R&D approval

The Chief Investigator or sponsor should inform the local Principal Investigator at each site of the favourable opinion by sending a copy of this letter and the attached form. The research should not commence at any NHS site until approval from the R&D office for the relevant NHS care organisation has been confirmed.

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.

08/H1307/41	**Please quote this number on all correspondence**

Yours sincerely



Miss Anna Fawlk
Assistant Administrator

Email: anna.fawlk@leedsth.nhs.uk

Enclosure: *Site approval form*

Copy to: Mr Michael Loveridge
Research & Development Office
Royal Brompton Hospital
Sydney Street
London SW3 6NP

Research and Development office approval

Royal Brompton & Harefield NHS
NHS Trust

Professor Martin Cowie
Chelsea Wing
Royal Brompton Hospital
Sydney Street

10 July, 2008

Dear *Martin,*

Project Title: *SERVE-HF*
Project Reference: 2008EP001B

Thank you for registering your Research Project with the R&D office. The project details have been entered on our Research Management Database. Please ensure you keep the R&D office informed of the following:

- changes to the status of the project e.g. abandoned, completed etc
- changes to the funding arrangements
- changes to the original application e.g. change in personnel or amendments requiring ethical review

RESEARCH GOVERNANCE

Royal Brompton & Harefield NHS Trust manages all research in accordance with the requirements of the research governance framework. Whilst working as an employee of the Royal Brompton and Harefield NHS Trust, or holding an Honorary Contract to do research which involves NHS staff or patients, their organs tissue or data, you must comply with all reporting requirements, systems, and duties of action put in place by the Trust to deliver research governance. As such if you are acting as either Chief/Principal Investigator your responsibilities under this framework include:

- ensuring compliance with protocol and advising of any changes to the protocol
- reporting any adverse events whether related to research or not to clinical governance/ethics/R&D
- taking appropriate urgent safety measures
- ensuring adherence to the principles of ICH GCP
- ensuring researchers have necessary expertise
- ensuring compliance with the Data Protection Act
- ensure adequate monitoring arrangements are in place
- ensure compliance with the Human Tissue Act

The Trust routinely audits a minimum of 10% of its research activity. This is to ensure that research is progressing satisfactorily and to guard against research fraud. You are requested to maintain and retain appropriate records of your research, and assist the Trust as and when required should any such audit take place in your area.

CLINICAL TRIALS REGISTRATION

The majority of research journals will now only publish research that has been registered at a publicly accessible database before the enrolment of the first patient. Where research projects are sponsored by either the Trust or Imperial College it is recommended that the project is registered at www.ClinicalTrials.gov which is free of charge. For Trust sponsored projects please contact 020 7351 8575 and an account will be set-up for you to register your project. Similarly, please contact clinical.researchoffice@imperial.ac.uk for an account to register Imperial College sponsored projects.

In receiving this letter you are agreeing to abide by the terms as outlined above. Please accept this letter as the Trust's authorisation to commence your research.

Yours sincerely

Wendy Butcher
Head of Research & Development

APPENDIX TWO

Ethical approval for the Control of Ventilation study (chapter 4)

Brompton, Harefield & NHLI Research Ethics Committee
Room W4/11, 4th Floor West
Charing Cross Hospital
Fulham Palace Road
London
W6 8RF

Telephone: 0208 846 7287
Facsimile: 0208 846 7280

19 June 2009

Dr Mary Morrell
Reader in Respiratory Physiology
Imperial College
Sleep and Ventilation Unit
Royal Brompton Hospital
Sydney Street, London
SW3 6NP

Dear Dr Morrell

Study Title: **Mechanisms of action of Adaptive Servoventilation: Ventilatory Control in Heart Failure patients with Central Sleep Apnoea.**
REC reference number: **09/H0708/35**

Thank you for your letter of 01 June 2009, 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 subject to the conditions specified below.

Ethical review of research sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

The favourable opinion applies to the following research site(s):

Research Site	Principal Investigator / Local Collaborator
Royal Brompton and Harefield NHS Trust	Dr Mary Morrell

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

For NHS research sites only, management permission for research ("R&D approval") should be obtained from the relevant care organisation(s) in accordance with NHS research governance arrangements. Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk. *Where the only involvement of the NHS organisation is as a Participant Identification Centre, management permission for research is not required but the R&D office should be notified of the study. Guidance should be sought from the R&D office where necessary.*

Sponsors are not required to notify the Committee of approvals from host organisations.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Covering Letter		07 April 2009
Application	8555/33155/1/534	07 April 2009
Angela Atalla		04 February 2009
Investigator CV		21 January 2009
Assessors' Report of Research Plan: Dr Stuart D. Rosen		26 October 2008
Assessors' Report of Research Plan:Prof Michael Polkey		
Insurance documents for another study (08/H1307/41) linked to this study		04 December 2008
Current application for insurance documents		29 January 2009
Response to Request for Further Information		01 June 2009
Participant Consent Form	2	27 May 2009
Participant Information Sheet	2	27 May 2009
Protocol	2	27 May 2009

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.

After ethical review

Now that you have completed the application process please visit the National Research Ethics Service website > After Review

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

The attached document *"After ethical review – guidance for researchers"* gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

We would also like to inform you that we consult regularly with stakeholders to improve our service. If you would like to join our Reference Group please email referencegroup@nres.npsa.nhs.uk.

09/H0708/35	Please quote this number on all correspondence

Yours sincerely

Dr Derek Gibson
Chairman

Email: adriana.fanigliulo@imperial.nhs.uk

Enclosures: "After ethical review – guidance for researchers"

Copy to: Dr. Emma Braithwaite, Ventilation and Cardiology Business Manager, ResMed (UK) Ltd, 96 Milton Park, Abingdon, Oxforshire OX14 4RY
R&D office for Royal Brompton & Harefield NHS Trust

Consent forms

Imperial College London

Royal Brompton & Harefield NHS
NHS Trust

CONSENT FORM FOR HEALTHY SUBJECTS

MECHANISMS OF ACTION OF ADAPTIVE SERVOVENTILATION

Subject Name **Subject ID**

Name of Researcher:

		Please Initial
1.	I confirm that I have read and understand the **information sheet for healthy subjects (version 1.0, 25/3/10)** for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	.....
2.	I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.	.....
3.	I understand that data collected during the study may be looked at by responsible individuals from regulatory authorities or from the NHS Trust where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. I understand that my name will never be disclosed outside of the hospital.	.....
4.	**I agree to my blood being taken for nitric oxide levels.** I understand this blood sample will not be used for any other tests. No testing will be done for any serious communicable diseases (such as HIV or Hepatitis B). After analysis it will be discarded safely.	.....
5.	I understand that should I withdraw from the study my anonymous data will be included in the analysis unless I request that it be removed.	.....
6.	I agree to take part in the **Hypercapnic Ventilatory Response (HCVR)** and **Transcranial Doppler (TCD)** protocols at the start of the study and 3 months later.	.....
7.	**I agree to take part in the activity monitoring protocol** at the start of the study and 3 months later.	.....
8.	**I agree to have a sleep study (nocturnal polysomnogram)** at the start of the study and 3 months later.	.....

_____ _____ _____

Name of Subject Date Signature

Imperial College London

Royal Brompton & Harefield NHS
NHS Trust

CONSENT FORM FOR PATIENTS

MECHANISMS OF ACTION OF ADAPTIVE SERVOVENTILATION

Patient Name **Patient ID**

Name of Researcher:

		Please Initial
1.	I confirm that I have read and understand the information sheet for patients **(version 3.0, 25/3/10)** for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	.....
2.	I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.	.....
3.	I understand that relevant sections of any of my medical notes and data collected during the study may be looked at by responsible individuals from regulatory authorities or from the NHS Trust where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.	.....
4.	I agree to my blood being taken for nitric oxide levels. **I understand this blood sample will not be used for any other tests.** No testing will be done for any serious communicable diseases (such as HIV or Hepatitis B). **After analysis it will be discarded safely.**	.....
5.	I agree to my GP being informed of my participation in the study.	.....
6.	I understand that should I withdraw from the study my anonymous data will be included in the analysis unless I request that it be removed.	.....
7.	I agree to take part in the Hypercapnic Ventilatory Response (HCVR) and Transcranial Doppler (TCD) protocols which are the main parts of this study.	.....
8.	**I agree to have activity monitoring at the start of the study and 3 months later.**	.....
9.	**I agree to have a sleep study (nocturnal polysomnogram) at the start of the study and 3 months later.**	.....

_____ _____ _____

Name of Patient Date Signature

Patient information sheet

PATIENT INFORMATION SHEET

MECHANISMS OF ACTION OF ADAPTIVE SERVOVENTILATION

You have been invited to take part in this study alongside the SERVE-HF study which is investigating the treatment of sleep disordered breathing in heart failure patients. You should have a separate information sheet regarding the SERVE-HF study, please read that before this information sheet. Thank you for your interest in our work.

Patients who are proven to have sleep disordered breathing on an overnight test and are invited into the SERVE-HF study are having this study discussed with them as well. **It is not a separate study to SERVE-HF but rather an additional piece of work which is optional.** You do not need to pick one of the studies, please consider all the information and if you would like to be considered for SERVE-HF then consider if you would be interested in this additional study as well in which case you will be entered into both studies at the same time.

It is not possible to be involved in this study if you are not in the SERVE-HF study.

Please take time to read the following information carefully.

- **Part One** tells you the purpose of this study and what will happen to you if you take part.
- **Part Two** gives you more detailed information about the conduct of the study.

PART ONE

1. What do we wish to find out in this study?

We know that around half of patients with heart failure will have **sleep disordered breathing** and that very often this has not been diagnosed. In patients with heart failure the most common form of sleep disordered breathing means that at times patients breathe too much, at times too little and at times they may briefly stop breathing altogether. We call this problem **Central Sleep Apnoea (or Cheyne Stokes breathing)** and the SERVE-HF study is being carried out to find out the best way of treating this problem.

We also know that central sleep apnoea is an important problem for patients with heart failure, not just because it seems to be common but because patients who have heart failure **and** central sleep apnoea do not do as well as those who have heart failure alone. We think that central sleep apnoea may place an extra strain on the heart, although this is difficult to prove.

In central sleep apnoea the main problem is that breathing is **unstable**. This instability is due to a problem with the way in which breathing is controlled during sleep. Patients in the SERVE-HF study are randomly allocated to EITHER continue with their usual treatment OR to receive treatment with

a machine to support the breathing at night in addition to their usual treatment. No-one has ever done such a large study to investigate this issue. The machine is called adaptive servoventilation (ASV- more details can be found in the SERVE-HF patient information sheet).

We want to understand how the ASV machine improves the breathing instability by investigating some of the factors which influence breathing. We hope that this will help us to improve the way that sleep disordered breathing is treated with the overall aim of keeping heart failure patients better for longer.

It is well known that sleep disordered breathing has an effect on the **quality of sleep** that people have. It does this by fragmenting sleep which means that people who have sleep disordered breathing don't get a good night's sleep as the breathing problem they have wakes them from deep sleep to lighter sleep and makes it hard for them to stay asleep. Often people with this problem don't remember waking in the night and that is because these wakenings are often very brief but despite this they can leave people very tired in the morning.

We also know that people with heart failure and sleep disordered breathing are **less active** than those with heart failure but without sleep disordered breathing.

We are interested in looking at **sleep quality** and **activity levels** because we want to know if the ventilator we are testing is able to improve these things for heart failure patients.

2. Why have I been chosen?

We are discussing this study with all patients who may be suitable for the SERVE-HF study. This study is an additional study and being included in it is an option available to patients who take part in the SERVE-HF study. Your involvement is absolutely voluntary.

3. If I take part, what will you need from me?

Please ensure you have read the SERVE-HF Patient information sheet already.

As part of the SERVE-HF study you will be asked to visit the hospital at the start of the study, at 2 weeks, 3 months, and 12 months; and then yearly thereafter until the end of the study. We also talk to you on the phone to carry out telephone assessments in between your visits.

For this additional study you need not make extra visits into the hospital but you may need to spend some extra nights in the hospital. If you are in the ASV group in the SERVE-HF study then you will simply have some additional tests done before and after the sleep studies you would have had anyway at the start and at 3 months. If you are in the group randomly allocated **not** to have the ASV machine then this additional study will mean we would ask you to have additional sleep studies at the start and at 3 months. We would then do some additional tests before and after these sleep studies as above.

4. Do I have to do anything different?

Part of the tests involves wearing an activity monitor on your wrist for a 2 week period. Whilst wearing this there is no need to change your usual lifestyle and treatment. Apart from this there is no need for you to do anything different.

5. What about my travelling costs?

Any travel fees you incur as part of travelling to the hospital for this study will be reimbursed. In some circumstances we will arrange transport for you.

6. What are the possible benefits in taking part?

Although you will not benefit directly by taking part in this additional study we hope that it will improve the care of heart failure patients in the future, specifically to keep them better for longer. We hope that by doing this study we will understand the instability in breathing that we see in heart failure patients with central sleep apnoea (or Cheyne Stokes breathing). We also hope that it will improve the care of heart failure patients in the future by helping us to understand their sleep and helping them to be more active.

PART TWO

7. What do these tests involve?

This additional study involves tests which will be incorporated into the visits to the hospital that are necessary for SERVE-HF (ie. we will do the additional tests at the initial hospital visit for SERVE-HF, then at 3 months). We will ask you to do some blowing tests (spirometry) at the start to measure how well your lungs are working. **The other tests are done on the evening before, and the morning after a sleep study.** Note some blood samples will be taken. After both of these sets of tests you will be sent home with an activity monitor. Details of the additional tests are given below.

How the brain changes the breathing pattern in response to breathing safe levels of carbon dioxide (also called Chemosensitivity)

This test takes about an hour in total and involves us measuring your breathing in response to having your carbon dioxide levels increased slightly, which we do by asking you to breathe through some special tubing. Carbon dioxide is a gas that is made naturally by our bodies. It is transported in the blood to the lungs and we breathe it out.

On the day of the test we will ask that you do not have any caffeinated drinks (eg tea, coffee or cola). We will make sure you are sitting comfortably on a bed and we will attach some monitoring equipment to you, explaining everything as we go. We will monitor your oxygen levels (using a probe on your finger); your heart rhythm and heart beat (using 3 sticky sensors attached to the chest- an ECG); the amount of carbon dioxide that you breathe out and your blood pressure (using a special cuff that you wear on your finger).

We will then ask you to breathe normally through a nose mask (like an oxygen mask) which will increase your carbon dioxide levels. We will give you some time to get used to this. The nasal mask will be attached to a machine to measure how much you are breathing. There will be a break in between the tests and we will then repeat the test as this will make our results more accurate. We

will continue to monitor you for another 10-15 minutes afterwards and then the test will be finished. A member of the research team will be with you throughout the test. This is a very safe test that we have a lot of experience with in many different groups of patients. Very rarely people may feel breathless or develop a headache during the test. If this happened we would stop the test. This test will be done in the evening before, and the morning after, a sleep study.

How the blood vessels in the brain change in response to breathing safe levels of carbon dioxide (also called Cerebral Vascular Reactivity)

We will monitor you in exactly the same way and have you breathe through the same equipment as described in the section above. We will take a blood sample (from a vein) before this test, which is usually taken from the inside of the elbow and will be about 10mls of blood (about 2 teaspoons). This will be analysed for nitric oxide levels which we believe may be important in the control of breathing. We will measure the effect of breathing through the equipment on the blood vessels in your brain by measuring them using an ultrasound device. This involves a small ultrasound probe attached in front of your ears on either side using a headset. The ultrasound probe is about 2cm long and the shape of a pen. The headset (like a sweat band) will be carefully adjusted so that it is tight but not uncomfortable. We can then measure the blood flow to the brain in a specific artery that runs under the temple. The test will be done in conjunction with the first test, so in total both should take an hour. A member of the research team will be with you throughout the test. Like the first test this will be done in the evening before and the morning after a sleep study.

The blood samples will be collected by a doctor experienced in taking these samples. They can occasionally be uncomfortable and sometimes people are left with a bruise. See question 9 for more details.

The sleep study that we will do overnight in between these tests involves a night in the hospital which we will arrange at a time that is convenient to you. Before you go to bed at your usual time we set up non-invasive equipment that allows us to monitor your brain waves (using wires that we can attach to your head) and your breathing (using bands that are worn around your chest and abdomen). We also measure your oxygen levels, heart beat and if you are snoring. This is a routine test that is frequently done when patients are sleepy and we need to look in detail at the quality of their sleep. In the morning all of the equipment is removed before you go home.

The activity monitoring involves wearing a small wrist watch-like device on the wrist of your non-dominant hand. We will explain how to wear this device and then ask you to take it away with you and wear it continuously for two weeks during your normal routine. During this time we'll ask you to keep an activity diary so we know when you get up in the morning, what time you go to bed and something about your level of activity. At the end of two weeks we'll ask you to send the device back to us by a pre-arranged means that we will pay for. We'll also phone you at least twice during the two weeks to ensure that everything is going smoothly.

At the end of this information sheet there is a table to show which tests are done and when.

8. Will you do any extra tests on my blood samples?

The blood sample will be used to measure levels of nitric oxide which we think may be important in the control of breathing. **This sample will not be used for any other tests. Specifically we will not perform the sort of genetic tests that would need to be declared on insurance forms. No testing**

will be done for any serious communicable diseases (such as HIV or Hepatitis B). We will anonymise the samples and then store them in a special laboratory freezer to which only researchers have access, without the use of your personal information. We will use a study code for identification purposes. **We will keep the blood in the freezer until it has all been tested and the study analysis is complete then safely dispose of it.** We will not store the blood indefinitely. If you agree to take part in this study you will be giving permission for the testing and subsequent temporary storage of your blood in the way described here.

9. What happens if something goes wrong?

It is extremely unlikely that you will come to any harm by participating in this study. Very occasionally people feel a little light headed when breathing through the breathing equipment. However, in the unlikely event that something does go wrong, compensation for any injury will be in accordance with the cover provided by ResMed who are the sponsors of this study and the SERVE-HF study.

10. How will you protect my personal information?

Any information that is collected about you during the course of the research will be kept strictly confidential. Information stored on computers will have your name and address removed from it and it will be identified by a study code. The details of your code and your personal information will be kept securely with only the research team having access to it. Your GP will however be informed, by letter, that you are participating in the study and it will be recorded in your medical notes. We will also let your hospital consultant know that you are involved in our research.

11. What will happen to my data if I withdraw from the study?

The information that we collect from you (data) will be stored securely without the use of your name and address. If you decided to withdraw from the study we would usually keep your anonymised data in our results. If you withdraw from the study and would like us to withdraw your data from our results we will do this on your request.

12. What happens to the results of the study and will I find out what they are?

We will write to you and your GP with the results of your tests at the end of the study. Once all the data has been collected and analysed, it will be written up as a scientific paper and made available to the scientific community. If you wish, you can obtain a copy of the published results by contacting us.

13. Who has reviewed the study?

This study has been given a favourable opinion by the Brompton, Harefield and NHLI's Research Ethics Committee (REC) as well as several doctors and scientists who are experienced in designing, setting up and running research projects. An independent Steering Committee made up of senior doctors involved in the SERVE-HF study at an international level has also reviewed the study design.

14. What happens when the study stops?

The final tests will be done at one year from the start of this study. When the analysis of the results is complete we will write to you and your GP to explain the results. Because all patients who participate in this study will be part of the SERVE-HF study they will continue to be followed up as part of that study which continues after this study has finished.

15. What if new information becomes available during the study?

During the time that we do this study new information may become available about the area that is being studied. If this happens, and it is relevant to you we will tell you about it and discuss with you whether you want to continue in the study. If you decide to continue in the study you may be asked to sign an updated consent form. Also, on receiving new information we may think it's in your best interests to withdraw from the study. If this were to happen we would write to you and explain everything, as well as ensuring you had time to ask any questions.

16. How can I get more information?

If you would like more information, or to ask questions or arrange to meet to discuss this further please contact us using the details which follow.

Dr Angela Atalla

Clinical Research Fellow

Departments of Cardiology and Sleep and Ventilation

c/o secretary to Dr. A. K. Simonds

Royal Brompton Hospital

Sydney Street, London SW3 6NP

On the next page there is a summary of what this study involves at each stage. For details of the SERVE-HF study please refer to the relevant Patient Information Sheet.

We are extremely grateful for your interest in our work. If you do not wish to participate in this study it 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.

Dr. Angela Atalla

Clinical Research Fellow, Royal Brompton Hospital and Imperial College

May 2009

BASELINE VISIT

Lung tests (spirometry)

Evening tests

- Blood sample (from vein)
- Chemosensitivity tests
- Cerebral vascular reactivity tests

Overnight sleep study

This may be the "set-up" night for the ASV machine if you have been randomly allocated to that as part of the SERVE-HF study. If you are randomly allocated to the other group (control group) you will have a sleep study without the ASV machine

Morning tests

- Blood sample (from vein)
- Chemosensitivity tests
- Cerebral vascular reactivity tests

Activity monitoring; wearing the wrist watch-like device for 2 weeks

3 MONTH VISIT

Evening tests

- Blood sample (from vein)
- Chemosensitivity tests
- Cerebral vascular reactivity tests

Overnight sleep study

This would be done with you wearing the ASV machine if you have been randomly allocated to that as part of the SERVE-HF study. If you are randomly allocated to the other group (control group) you will have a sleep study without the ASV machine

Morning tests

- Blood sample (from vein)
- Chemosensitivity tests
- Cerebral vascular reactivity tests

Activity monitoring; wearing the wrist watch-like device for 2 weeks

Healthy subject information sheet

SUBJECT INFORMATION SHEET

MECHANISMS OF ACTION OF ADAPTIVE SERVOVENTILATION

You are invited to take part in this study which is investigating the treatment of sleep disordered breathing in heart failure patients. You are invited to be a healthy subject in this work which will allow us to compare our results in heart failure patients with healthy controls.
Thank you for your interest in our work.

Please take time to read the following information carefully.

- **Part One** tells you the purpose of this study and what will happen to you if you take part.
- **Part Two** gives you more detailed information about the conduct of the study.

PART ONE

17. What do we wish to find out in this study?

We know that around half of patients with heart failure will have **sleep disordered breathing** and that very often this has not been diagnosed. In patients with heart failure the most common form of sleep disordered breathing means that at times patients breathe too much, at times too little and at times they may briefly stop breathing altogether. We call this problem **Central Sleep Apnoea (or Cheyne Stokes breathing)** and the SERVE-HF study is being carried out to find out the best way of treating this problem.

We also know that central sleep apnoea is an important problem for patients with heart failure, not just because it seems to be common but because patients who have heart failure **and** central sleep apnoea do not do as well as those who have heart failure alone. We think that central sleep apnoea may place an extra strain on the heart, although this is difficult to prove.

In central sleep apnoea the main problem is that breathing is **unstable**. This instability is due to a problem with the way in which breathing is controlled during sleep. Patients in the SERVE-HF study are randomly allocated to EITHER continue with their usual treatment OR to receive treatment with a machine to support the breathing at night in addition to their usual treatment. No-one has ever done such a large study to investigate this issue. The machine is called adaptive servoventilation (ASV).

We want to understand how the ASV machine improves the breathing instability by investigating some of the factors which influence breathing. We hope that this will help us to improve the way that sleep disordered breathing is treated with the overall aim of keeping heart failure patients better for longer.

It is well known that sleep disordered breathing has an effect on the **quality of sleep** that people have. It does this by <u>fragmenting</u> sleep which means that people who have sleep disordered breathing don't get a good night's sleep as the breathing problem they have wakes them from deep sleep to lighter sleep and makes it harder for them to stay asleep. Often people with this problem

don't remember waking in the night and that is because these wakenings are often very brief but despite this they can leave people very tired in the morning.

We also know that people with heart failure and sleep disordered breathing are **less active** than those with heart failure but without sleep disordered breathing.

We are interested in looking at **sleep quality** and **activity levels** because we want to know if the ventilator we are testing is able to improve these things for heart failure patients.

18. Why have I been chosen?

We are looking for healthy people of a similar age to the patients in our study so that we can make a scientific comparison of the results from the patients in our study and people who are healthy. Your involvement is absolutely voluntary.

If I take part, what will you need from me?

You will need to attend the hospital on two occasions that we will arrange at a time that is convenient for you. One will be at the start of the study, and the second occasion will be three months later. Both visits will involve some evening laboratory tests, an overnight sleep study, and then further laboratory tests in the morning. We will ask you to take home an activity monitor which is a small wrist watch-like device which we will ask you to wear for 2 weeks before sending it back to us. The laboratory tests involve a blood test. More details are given below.

19. Do I have to do anything different?

Part of the tests involves wearing an activity monitor on your wrist for a 2 week period. Whilst wearing this there is no need to change your usual lifestyle. Apart from this there is no need for you to do anything different.

20. What about my travelling costs?

To cover the inconvenience of attending the hospital as well as any fees incurred as part of travelling to the hospital we will offer £100 for taking part in the tests detailed in this information sheet.

21. What are the possible benefits in taking part?

Although you will not benefit directly by taking part in this additional study we hope that it will improve the care of heart failure patients in the future, specifically to keep them better for longer. We hope that by doing this study we will understand the instability in breathing that we see in heart failure patients with central sleep apnoea (or Cheyne Stokes breathing). We also hope that it will improve the care of heart failure patients in the future by helping us to understand their sleep and enabling them to become more active.

PART TWO

22. What do these tests involve?

These tests will involve you attending the hospital on two separate occasions, three months apart. At each visit we will ask you to do some blowing tests (spirometry) at the start to measure how well your lungs are working. **The other tests are done on the evening before, and the morning after a sleep study.** Note some blood samples will be taken. After both of these sets of tests you will be sent home with an activity monitor. Details of the additional tests are given below.

How the brain changes the breathing pattern in response to breathing safe levels of carbon dioxide (also called Chemosensitivity)

This test takes about an hour in total and involves us measuring your breathing in response to having your carbon dioxide levels increased slightly, which we do by asking you to breathe through some special tubing. Carbon dioxide is a gas that is made naturally by our bodies. It is transported in the blood to the lungs and we breathe it out.

On the day of the test we will ask that you do not have any caffeinated drinks (eg tea, coffee or cola). We will make sure you are sitting comfortably on a bed and we will attach some monitoring equipment to you, explaining everything as we go. We will monitor your oxygen levels (using a probe on your finger); your heart rhythm and heart beat (using 3 sticky sensors attached to the chest- an ECG); the amount of carbon dioxide that you breathe out and your blood pressure (using a special cuff that you wear on your finger).

We will then ask you to breathe normally through a mouth piece (like an oxygen mask) which will increase your carbon dioxide levels. We will give you some time to get used to this. The mouth piece will be attached to a machine to measure how much you are breathing. We will continue to monitor you for another 10-15 minutes afterwards and then the test will be finished. A member of the research team will be with you throughout the test. This is a very safe test that we have a lot of experience with in many different groups of patients. Very rarely people may feel breathless or develop a headache during the test. If this happened we would stop the test. This test will be done in the evening before, and the morning after, a sleep study.

How the blood vessels in the brain change in response to breathing safe levels of carbon dioxide (also called Cerebral Vascular Reactivity)

We will monitor you in exactly the same way and have you breathe through the same equipment as described in the section above. We will take a blood sample (from a vein) before this test, which is usually taken from the inside of the elbow and will be about 10mls of blood (about 2 teaspoons). This will be analysed for nitric oxide levels which we believe may be important in the control of breathing. We will measure the effect of breathing through the equipment on the blood vessels in your brain by measuring them using an ultrasound device. This involves a small ultrasound probe attached in front of your ears on either side using a headset. The ultrasound probe is about 2cm long and the shape of a pen. The headset (like a sweat band) will be carefully adjusted so that it is tight but not uncomfortable. We can then measure the blood flow to the brain in a specific artery that runs under the temple. The test will be done in conjunction with the first test, so in total both should take an hour. A member of the research team will be with you throughout the test. Like the first test this will be done in the evening before and the morning after a sleep study.

The blood samples will be collected by a doctor experienced in taking these samples. They can occasionally be uncomfortable and sometimes people are left with a bruise. See question 8 for more details.

The sleep study that we will do overnight in between these tests involves a night in the hospital which we will arrange at a time that is convenient to you. Before you go to bed at your usual time we set up non-invasive equipment that allows us to monitor your brain waves (using wires that we can attach to your head) and your breathing (using bands that are worn around your chest and abdomen). We also measure your oxygen levels, heart beat and if you are snoring. This is a routine test that is frequently done when patients are sleepy and we need to look in detail at the quality of their sleep. In the morning all of the equipment is removed before you go home.

The activity monitoring involves wearing a small wrist watch-like device on the wrist of your non-dominant hand. We will explain how to wear this device and then ask you to take it away with you and wear it continuously for two weeks during your normal routine. During this time we'll ask you to keep an activity diary so we know when you get up in the morning, what time you go to bed and something about your level of activity. At the end of two weeks we'll ask you to send the device back to us by a pre-arranged means that we will pay for. We'll also phone you at least twice during the two weeks to ensure that everything is going smoothly.

At the end of this information sheet there is a table to show which tests are done and when.

23. Will you do any extra tests on my blood samples?

The blood sample will be used to measure levels of nitric oxide which we think may be important in the control of breathing. **This sample will not be used for any other tests. Specifically we will not perform the sort of genetic tests that would need to be declared on insurance forms. No testing will be done for any serious communicable diseases (such as HIV or Hepatitis B).** We will anonymise the samples and then store them in a special laboratory freezer to which only researchers have access, without the use of your personal information. We will use a study code for identification purposes. **We will keep the blood in the freezer until it has all been tested and the study analysis is complete then safely dispose of it.** We will not store the blood indefinitely. If you agree to take part in this study you will be giving permission for the testing and subsequent temporary storage of your blood in the way described here.

24. What happens if something goes wrong?

It is extremely unlikely that you will come to any harm by participating in this study. Very occasionally people feel a little light headed when breathing through the breathing equipment. However, in the unlikely event that something does go wrong, compensation for any injury will be in accordance with the cover provided by ResMed who are the sponsors of this study and the SERVE-HF study.

25. How will you protect my personal information?

Any information that is collected about you during the course of the research will be kept strictly confidential. Information stored on computers will have your name and address removed from it and it will be identified by a study code. The details of your code and your personal information will be kept securely with only the research team having access to it. Your GP will not be routinely

involved of your involvement in this work and should this become necessary this will only be done with your express permission.

26. What will happen to my data if I withdraw from the study?

The information that we collect from you (data) will be stored securely without the use of your name and address. If you decided to withdraw from the study we would usually keep your anonymised data in our results. If you withdraw from the study and would like us to withdraw your data from our results we will do this on your request.

27. What happens to the results of the study and will I find out what they are?

Once all the data has been collected and analysed, it will be written up as a scientific paper and made available to the scientific community. If you wish, you can obtain a copy of the published results by contacting us.

28. Who has reviewed the study?

This study has been given a favourable opinion by the Brompton, Harefield and NHLI's Research Ethics Committee (REC) as well as several doctors and scientists who are experienced in designing, setting up and running research projects. An independent Steering Committee made up of senior doctors involved in the SERVE-HF study at an international level has also reviewed the study design.

29. What happens when the study stops?

The final tests will be done at three months from the start of this study and data will be analysed in the months that follow.

30. How can I get more information?

If you would like more information, or to ask questions or arrange to meet to discuss this further please contact us using the details which follow.

Dr Angela Atalla
Clinical Research Fellow
Departments of Cardiology and Sleep & Ventilation
c/o secretary to Dr. A. K. Simonds
Royal Brompton Hospital
Sydney Street, London SW3 6NP
a.atalla@imperial.ac.uk
tel 0207 352 8121 extension 4606

Many thanks for your interest in our work.

Dr. Angela Atalla

Clinical Research Fellow, Royal Brompton Hospital and Imperial College

May 2009

BASELINE VISIT

Lung tests (spirometry)

Evening tests

- Blood sample (from vein)
- Chemosensitivity tests
- Cerebral vascular reactivity tests

Overnight sleep study

Morning tests

- Blood sample (from vein)
- Chemosensitivity tests
- Cerebral vascular reactivity tests

Activity monitoring; wearing the wrist watch-like device for 2 weeks

3 MONTH VISIT

Evening tests

- Blood sample (from vein)
- Chemosensitivity tests
- Cerebral vascular reactivity tests

Overnight sleep study

Morning tests

- Blood sample (from vein)
- Chemosensitivity tests
- Cerebral vascular reactivity tests

Activity monitoring; wearing the wrist watch-like device for 2 weeks

APPENDIX THREE

Ethical approval for the Cardiac Resynchronisation Study (chapter 5)

NHS
National Research Ethics Service
West London REC 3
Room 4W12, 4th Floor West
Charing Cross Hospital
Fulham Palace Road
London W6 8RF
Telephone: 020 3311 7282
Facsimile: 020 3311 7280

Professor Martin Cowie
Chair in Cardiology (Health Services Research)
Imperial College and Royal Brompton Hospital
Chelsea Wing
Royal Brompton Hospital
Sydney Street, London
SW3 6NP

RECEIVED
27 SEP 2010

17 September 2010

Dear Professor Cowie

Study Title: **A study of the effect of CRT on chemosensitivity in patients with chronic heart failure with and without sleep disordered breathing.**

REC reference number: **10/H0706/50**

Thank you for your letter of 25 August 2010, 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 Chair

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, subject to the conditions specified below.

Ethical review of research sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

For NHS research sites only, management permission for research ("R&D approval") should be obtained from the relevant care organisation(s) in accordance with NHS research governance arrangements. Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

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

Where the only involvement of the NHS organisation is as a Participant Identification Centre (PIC), management permission for research is not required but the R&D office should be notified of the study and agree to the organisation's involvement. Guidance on procedures for PICs is available in IRAS. Further advice should be sought from the R&D office where necessary.

Sponsors are not required to notify the Committee of approvals from host organisations.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	Version	Date
Investigator CV	Atalla	01 July 2010
Investigator CV	Cowie	05 February 2009
Protocol	2	25 August 2010
Letter to GP	1.0	01 July 2010
Letter Re: Peer Review		07 July 2010
REC application	57105/13228 5/1/83	01 July 2010
Covering Letter		01 July 2010
Letter from Sponsor		28 June 2010
Participant Information Sheet	2	25 August 2010
Response to Request for Further Information		25 August 2010
Participant Consent Form	1.0	01 July 2010

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.

After ethical review

Now that you have completed the application process please visit the National Research Ethics Service website > After Review

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

The attached document *"After ethical review – guidance for researchers"* gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of

changes in reporting requirements or procedures.

We would also like to inform you that we consult regularly with stakeholders to improve our service. If you would like to join our Reference Group please email referencegroup@nres.npsa.nhs.uk.

10/H0706/50	**Please quote this number on all correspondence**

Yours sincerely



Dr Sabita Uthaya
Chair

Email: louise.moran2@imperial.nhs.uk

Enclosures: "After ethical review – guidance for researchers"

Copy to: *Ms Lucy Parker*

Research and Development office approval

Royal Brompton & Harefield NHS
NHS Foundation Trust

Professor Martin Cowie
Professor of Cardiology and Honorary Consultant Cardiologist
Royal Brompton Hospital
Sydney Street
London SW3 6NP

Wednesday 13th October 2010

Dear Prof Cowie, Hadi

The effect of CRT on chemosensitivity in patients with chronic heart failure, with and without sleep disordered breathing

Project Reference:	**2010CS005B**
R&D Form Submission Code:	**57105/132289/14/331**
SSIF Submission Code:	**57105/133380/6/975/61523/182385**

Thank you for registering your Research Project with the R&D office. The project details have been entered on our Research Management Database. Please ensure you keep the R&D office informed of the following:

- changes to the status of the project e.g. abandoned, completed etc
- changes to the funding arrangements
- changes to the original application e.g. change in personnel or amendments requiring ethical review

RESEARCH GOVERNANCE
Royal Brompton & Harefield NHS Foundation Trust manages all research in accordance with the requirements of the research governance framework. Whilst working as an employee of the Royal Brompton and Harefield NHS Foundation Trust, or holding an Honorary Contract to do research which involves NHS staff or patients, their organs tissue or data, you must comply with all reporting requirements, systems, and duties of action put in place by the Trust to deliver research governance. As such if you are acting as either Chief/Principal Investigator your responsibilities under this framework include:

- ensuring compliance with protocol and advising of any changes to the protocol
- reporting any adverse events whether related to research or not to clinical governance/ethics/R&D
- taking appropriate urgent safety measures
- ensuring adherence to the principles of ICH GCP
- ensuring researchers have necessary expertise
- ensuring compliance with the Data Protection Act
- ensure adequate monitoring arrangements are in place
- ensure compliance with the Human Tissue Act

The Trust routinely audits a minimum of 10% of its research activity. This is to ensure that research is progressing satisfactorily and to guard against research fraud. You are requested to maintain and retain appropriate records of your research, and assist the Trust as and when required should any such audit take place in your area.

CLINICAL TRIALS REGISTRATION
The majority of research journals will now only publish research that has been registered at a publicly accessible database before the enrolment of the first patient. Where research projects are sponsored by either the Trust or Imperial College it is recommended that the project is registered at www.ClinicalTrials.gov which is free of charge. For Trust sponsored projects please contact 020 7351 8736 and an account will be set-up for you to register your project. Similarly, please contact clinical.researchoffice@imperial.ac.uk for an account to register Imperial College sponsored projects.

In receiving this letter you are agreeing to abide by the terms as outlined above. Please accept this letter as the Trust's authorisation to commence your research.

Yours sincerely

Wendy Butcher
Head of Research Governance and Performance

Consent form

Imperial College London

Royal Brompton & Harefield NHS
NHS Foundation Trust

CONSENT FORM FOR PATIENTS

THE CARDIAC RESYNCHRONISATION THERAPY STUDY

A study of the effect of CRT on chemosensitivity in patients with chronic heart failure with and without sleep disordered breathing.

Patient Name **Patient ID**

Name of Researcher:

		Please Initial
1.	I confirm that I have read and understand the information sheet for patients (version 1; date 1/7/10) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	.....
2.	I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.	.....
3.	I understand that relevant sections of any of my medical notes and data collected during the study may be looked at by responsible individuals from regulatory authorities, the NHS Trust or from Imperial College where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.	.....
4.	I agree to my GP being informed of my participation in the study.	.....
5.	I understand that should I withdraw from the study my anonymous data will be included in the analysis unless I request that it be removed.	.....
6.	I agree to take part in the breathing test (chemosensitivity), walking test, questionnaires and overnight sleep study before and after my pacemaker.	.....

_____	_____	_____
Name of Patient	Date	Signature
_____	_____	_____
Researcher	Date	Signature

Patient information sheet

PATIENT INFORMATION SHEET

THE CARDIAC RESYNCHRONISATION THERAPY STUDY

A study of the effect of the CRT pacemaker on breathing at night in patients with chronic heart failure

You have been invited to take part in this research study which is about the effect of the CRT pacemaker on your breathing at night. We are extremely grateful for your interest in our work.

Please take time to read the following information carefully.

- **Part One** tells you the purpose of this study and what will happen to you if you take part.
- **Part Two** gives you more detailed information about the conduct of the study.

PART ONE

31. What do we wish to find out in this study?

We know that around half of patients with heart failure will have **sleep apnoea** and that very often this has not been diagnosed as people are not aware that they have it. Sleep apnoea means that breathing overnight either briefly stops, or is too shallow/slow. The reason why so many patients with heart failure have this problem at night is not fully understood.

Sleep apnoea can be classified as either **obstructive sleep apnoea** or **central sleep apnoea.** Obstructive sleep apnoea is due to the top part of the airway flopping shut overnight and is more common in people who snore. In central sleep apnoea the main problem is that breathing is unstable. This instability is due to a problem with the way in which breathing is controlled during sleep. Often patients with heart failure have both kinds of sleep apnoea with one or the other being the main type. It is thought that sleep apnoea in heart failure places an extra strain on the heart, although this has not yet been definitely proven.

In this study we want to find out what the effect of the CRT pacemaker is on people with heart failure and their breathing at night. We know that the pacemaker can help to improve breathing at night in people with heart failure but we don't know how it does this. We would like to understand this better so we can help more people with heart failure, both with and without sleep apnoea.

32. Why have I been chosen?

We are discussing this work with patients who are due to have a CRT pacemaker or who might be having one in the near future. You are under no obligation to take part and your involvement is absolutely voluntary.

33. If I take part, what will you need from me?

For this study you need to visit the hospital twice for some additional tests, once before the pacemaker is put in, and once afterwards. The first visit will be one month before your pacemaker, and the second about 3 months afterwards. At least one of these visits will require an overnight stay.

34. Do I have to do anything different?

Apart from attending for the additional tests there is no need to change your usual lifestyle and treatment. This study does not involve any changes to your medications.

35. What about my travelling costs?

Any travel costs you incur as part of travelling to the hospital for this study will be reimbursed. In some circumstances we will arrange transport for you.

36. What are the possible benefits in taking part?

Although you will not benefit directly by taking part in this study we hope that it will improve the care of heart failure patients in the future.

PART TWO

37. What do these tests involve?

At each of the two visits we will do some tests. On the first visit (before the pacemaker) you will have a breathing test done, complete some questionnaires and a short walking test and then will have a sleep study. In the morning you will go home. On the second visit (after the pacemaker) we do exactly the same but some patients won't need to stay overnight for the sleep study; this will depend on the results of their initial sleep study. You will only need to stay for a sleep study on the second visit if you had irregular breathing on the first sleep study. Details of the tests are given below.

BREATHING TEST: How the brain changes the breathing pattern in response to breathing safe levels of carbon dioxide (also called Chemosensitivity)

This test takes about an hour in total and involves us measuring your breathing in response to having your carbon dioxide levels increased slightly, which we do by asking you to breathe through some special tubing. Carbon dioxide is a gas that is made naturally by our bodies. It is transported in the blood to the lungs and we breathe it out.

On the day of the test we will ask that you do not have any caffeinated drinks (eg. tea, coffee or cola). We will make sure you are lying comfortably on a bed and we will attach some monitoring equipment to you, explaining everything as we go. We will monitor your oxygen levels (using a probe on your finger); your heart rhythm and heart beat (using 3 sticky sensors attached to the chest- an ECG); the amount of carbon dioxide that you breathe out and your blood pressure (using a special cuff that you wear on your finger).

We will then ask you to breathe normally through a mouth piece which will increase your carbon dioxide levels. We will give you some time to get used to this. The mouth piece will be attached to a machine to measure how much you are breathing. We will continue to monitor you for another 10-15 minutes afterwards and then the test will be finished. A member of the research team will be with you throughout the test. This is a very safe test that we have a lot of experience with this in

many different groups of patients. Very rarely people may develop a headache during the test. If this happened we would stop the test.

WALKING TEST; This is a measure of your normal walking speed and how far you can walk in six minutes. During the test you are allowed to stop and rest if you need to and the test can be stopped at any time if you want. We will measure your heart rate and blood pressure just before and after the test.

QUESTIONNAIRES; We will ask you to complete some questions about how your symptoms affect you, how sleepy you feel (if at all) and how you feel your heart failure affects your life.

SLEEP STUDY; The sleep study that we will do overnight after the breathing tests involves a night in the hospital. Before you go to bed at your usual time we set up non-invasive equipment that allows us to monitor your brain waves (using wires that we can attach to your head) and your breathing (using bands that are worn around your chest and abdomen). We also measure your oxygen levels, heart beat and if you are snoring. This is a routine test that is frequently done when patients are sleepy and we need to look in detail at the quality of their sleep. In the morning all of the equipment is removed before you go home.

At the end of this information sheet there is a summary to show which tests are done and when.

38. Will you take any blood samples?

We will look at some of the results taken by the clinical team that normally looks after you before and after your pacemaker is put in. This study **does not** require us to take any additional blood samples.

39. What happens if something goes wrong?

Imperial College London holds insurance policies which apply to this study. If you experience serious and enduring harm or injury as a result of taking part in this study, you may 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 (Dr. Angela Atalla on 0207 352 8121 ext 4606). The normal National Health Service complaint complaints mechanisms are also available to you. If you are still not satisfied with the response, you may contact the Imperial AHSC Joint Research Office.

40. How will you protect my personal information?

Any information that is collected about you during the course of the research will be kept strictly confidential. Information stored on computers will have your name and address removed from it and it will be identified by a study code. The details of your code and your personal information will be kept securely with only the research team having access to it. Your GP will however be informed, by letter, that you are participating in the study and it will be recorded in your medical notes. We will also let your hospital consultant know that you are involved in our research.

41. What will happen to my data if I withdraw from the study?

The information that we collect from you (data) will be stored securely without the use of your name and address. If you decided to withdraw from the study we would usually keep your anonymised data in our results. If you withdraw from the study and would like us to withdraw your data from our results we will do this on your request.

42. What happens to the results of the study and will I find out what they are?

We will write to you and your GP with the results of your tests at the end of the study. Once all the data have been collected and analysed, it will be written up as a scientific paper and made available to the scientific community. If you wish, you can obtain a copy of the published results by contacting us.

43. Who has reviewed the study?

This study has been given a favourable opinion by a Research Ethics Committee after being designed by several doctors and scientists who are experienced in setting up and running research projects.

44. What happens when the study stops?

The final tests will be done approximately three months after you have had the pacemaker and then your involvement in the study will be over. When the analysis of the results is complete we will write to you and your GP to explain the results.

45. What if new information becomes available during the study?

During the time that we do this study new information may become available about the area that is being studied. If this happens, and it is relevant to you, we will tell you about it and discuss with you whether you want to continue in the study. If you decide to continue in the study you may be asked to sign an updated consent form. Also, on receiving new information we may think it's in your best interests to withdraw from the study. If this were to happen we would write to you and explain everything as well as ensuring you had time to ask any questions.

46. How can I get more information?

If you would like more information or to ask further questions or arrange to meet to discuss this please contact us using the details which follow.

Dr. Angela Atalla,

Clinical Research Fellow

Departments of Cardiology and Sleep & Ventilation

Royal Brompton Hospital, Sydney Street, London SW3 6NP

a.atalla@imperial.ac.uk **tel 0207 352 8121 extension 4606**

Below there is a summary of what this study involves at each stage.

We are extremely grateful for your interest in our work. If you do not wish to participate in this study it 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.

Dr. Angela Atalla

Clinical Research Fellow, Royal Brompton Hospital and Imperial College

June 2010

BASELINE VISIT- 1 MONTH BEFORE THE PACEMAKER

Evening tests

- breathing test (chemosensitivity)
- walking test
- questionnaires

Overnight sleep study- in all patients

FOLLOW UP VISIT- 3 MONTHS AFTER THE PACEMAKER

Evening tests

- breathing test (chemosensitivity)
- walking test
- questionnaires

Overnight sleep study- in some but not all patients. You will only need to stay for a sleep study on the second visit if you had irregular breathing on the first sleep study.

APPENDIX FOUR

Ethical approval for the Activity Study (chapter 6)

NHS
National Research Ethics Service
South West London REC 1
Room 4W12, 4th Floor West
Charing Cross Hospital
Fulham Palace Road
London
W6 8RF

Tel: 020 331 17251
Fax: 020 331 17280

17 November 2010

Dr Mary Morrell
Reader in Respiratory Physiology
Imperial College
Reader in Respiratory Physiology
Sleep and Ventilation Unit
Royal Brompton Hospital
Sydney Street, London
SW3 6NP

Dear Dr Morrell

Study title:	**Mechanisms of action of Adaptive Servoventilation: Ventilatory Control in Heart Failure patients with Central Sleep Apnoea.**
REC reference:	**09/H0708/35**
Amendment number:	**Amendment TWO**
Amendment date:	**08 November 2010**

The above amendment was reviewed at the meeting of the Sub-Committee held on 15 November 2010

Ethical opinion

The members of the Committee taking part in the review gave a **favourable ethical opinion** of the amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents
The documents reviewed and approved at the meeting were:

Document	Version	Date
GP/Consultant Information Sheets	1	08 November 2010
Participant Consent Form: for patients not in the Serve-HF study	1	08 November 2010
Participant Information Sheet: for patients not in the Serve-HF study	1	08 November 2010
Notice of Substantial Amendment (non-CTIMPs)	Amendment TWO	08 November 2010
Covering Letter		09 November 2010
Protocol	4.0	08 November 2010

NHS
National Patient Safety Agency

National Research Ethics Service

NOTICE OF SUBSTANTIAL AMENDMENT

For use in the case of all research other than clinical trials of investigational medicinal products (CTIMPs). For substantial amendments to CTIMPs, please use the EU-approved notice of amendment form (Annex 2 to ENTR/CT1) at http://eudract.emea.eu.int/document.html#guidance.

To be completed in typescript by the Chief Investigator in language comprehensible to a lay person and submitted to the Research Ethics Committee that gave a favourable opinion of the research ("the main REC"). In the case of multi-site studies, there is no need to send copies to other RECs unless specifically required by the main REC.

Further guidance is available at http://www.nres.npsa.nhs.uk/applicants/review/after/amendments.htm.

Details of Chief Investigator:

Name:	Dr. Mary Morrell Reader in Respiratory Physiology, Imperial College
Address:	Clinical and Academic Unit of Sleep and Ventilation Royal Brompton Hospital Sydney Street, London SW3 6NP
Telephone:	020 7352 8121
Email:	m.morrell@imperial.ac.uk
Fax:	0207 351 8911

Full title of study:	**Mechanisms of action of Adaptive Servoventilation: Ventilatory Control in Heart Failure patients with Central Sleep Apnoea.**
Name of main REC:	Brompton, Harefield & NHLI Research Ethics Committee
REC reference number:	09/H0708/35
Date study commenced:	3rd September 2009
Protocol reference *(if applicable)*, current version and date:	Protocol v 2.0, 27/5/09
Amendment number and date:	Amendment TWO, 8/11/10

APPENDIX FIVE

Minnesota Living with Heart Failure questionnaire

MINNESOTA LIVING WITH HEART FAILURE® QUESTIONNAIRE

The following questions ask how much your heart failure (heart condition) affected your life during the past month (4 weeks). After each question, circle the 0, 1, 2, 3, 4 or 5 to show how much your life was affected. If a question does not apply to you, circle the 0 after that question.

Did your heart failure prevent you from living as you wanted during the past month (4 weeks) by -	**No**	**Very Little**				**Very Much**
1. causing swelling in your ankles or legs?	0	1	2	3	4	5
2. making you sit or lie down to rest during the day?	0	1	2	3	4	5
3. making your walking about or climbing stairs difficult?	0	1	2	3	4	5
4. making your working around the house or yard difficult?	0	1	2	3	4	5
5. making your going places away from home difficult?	0	1	2	3	4	5
6. making your sleeping well at night difficult?	0	1	2	3	4	5
7. making your relating to or doing things with your friends or family difficult?	0	1	2	3	4	5
8. making your working to earn a living difficult?	0	1	2	3	4	5
9. making your recreational pastimes, sports or hobbies difficult?	0	1	2	3	4	5
10. making your sexual activities difficult?	0	1	2	3	4	5
11. making you eat less of the foods you like?	0	1	2	3	4	5
12. making you short of breath?	0	1	2	3	4	5
13. making you tired, fatigued, or low on energy?	0	1	2	3	4	5
14. making you stay in a hospital?	0	1	2	3	4	5
15. costing you money for medical care?	0	1	2	3	4	5
16. giving you side effects from treatments?	0	1	2	3	4	5
17. making you feel you are a burden to your family or friends?	0	1	2	3	4	5
18. making you feel a loss of self-control in your life?	0	1	2	3	4	5
19. making you worry?	0	1	2	3	4	5
20. making it difficult for you to concentrate or remember things?	0	1	2	3	4	5
21. making you feel depressed?	0	1	2	3	4	5

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11/10/04

APPENDIX SIX

Epworth Sleepiness Scale

Epworth Sleepiness Scale

Name: _____ Today's date: _____

Your age (Yrs): _____ Your sex (Male = M, Female = F): _____

How likely are you to doze off or fall asleep in the following situations, in contrast to feeling just tired?

This refers to your usual way of life in recent times.

Even if you haven't done some of these things recently try to work out how they would have affected you.

Use the following scale to choose the **most appropriate number** for each situation:

0 = would **never** doze
1 = **slight chance** of dozing
2 = **moderate chance** of dozing
3 = **high chance** of dozing

It is important that you answer each question as best you can.

Situation	**Chance of Dozing (0-3)**
Sitting and reading	
Watching TV	
Sitting, inactive in a public place (e.g. a theatre or a meeting)	
As a passenger in a car for an hour without a break	
Lying down to rest in the afternoon when circumstances permit	
Sitting and talking to someone	
Sitting quietly after a lunch without alcohol	
In a car, while stopped for a few minutes in the traffic	

THANK YOU FOR YOUR COOPERATION

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APPENDIX SEVEN

EQ5D questionnaire





Health Questionnaire

(English version for the UK)
(validated for use in Eire)

Patient-ID: _____

© EuroQoL Group 1990

Patient-ID _____

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about	❑
I have some problems in walking about	❑
I am confined to bed	❑

Self-Care

I have no problems with self-care	❑
I have some problems washing or dressing myself	❑
I am unable to wash or dress myself	❑

Usual Activities (*e.g. work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities	❑
I have some problems with performing my usual activities	❑
I am unable to perform my usual activities	❑

Pain/Discomfort

I have no pain or discomfort	❑
I have moderate pain or discomfort	❑
I have extreme pain or discomfort	❑

Anxiety/Depression

I am not anxious or depressed	❑
I am moderately anxious or depressed	❑
I am extremely anxious or depressed	❑

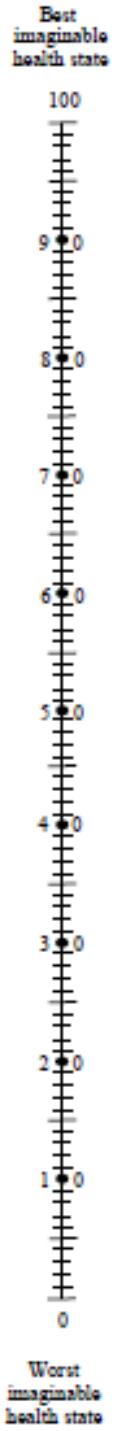
© EuroQoL Group 1990

Patient-ID _____

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today



Date: _____ **Patient Signature**_____

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APPENDIX EIGHT

Actiwatch instructions given to subjects

The Sleep Architecture Study

Actiwatch Instructions

for Patients and Subjects

Please keep this by your bedside to remind you!

The actiwatch you have been given is a device that monitors activity, both day and night. You should wear it like a watch continuously for the next 2 weeks. It should only be removed if you are taking a bath or shower. Please wear it on your non-dominant hand (i.e. the hand you don't write with.)

It will be "active" for the whole time and **cannot be accidentally switched off**. It is very important that you start wearing it as soon as you receive it. The device has no lights and makes no sounds; there is no way for you to tell that it is working.

Press the EVENT MARKER BUTTON when you are just about to go to sleep, and when you wake up in the morning. It doesn't matter if you press it twice by accident.

EVENT MARKER BUTTON



While you wear the watch please complete the sleep diary every day**. This is really important, without this information we cannot interpret the data from the device.** Please record whenever you remove the watch on the sleep diary.

Your START DATE &TIME; **Your END DATE & TIME**:

After the 2 weeks you need to return the watch to me as indicated below;

☐ **Return in person; I am due to see you again on**_____

☐ **Please post the watch back to me using the envelope provided .**

I will contact you *at least twice* as a matter of routine during this 2 week period to ensure everything is running smoothly. Please don't hesitate to contact me if you have any questions or concerns.

Dr. Angela Atalla, Clinical Research Fellow
Tel 0207 352 8121 ext 4606 (answer machine) a.atalla@imperial.ac.uk

The Sleep Architecture Study

Instructions for Returning the Actiwatch

for Patients and Subjects who have been given a pre-paid envelope

Please keep these instructions with your sleep diary until you need them at the end of the two weeks.

You have been given a pre-paid envelope so you can return the actiwatch to us without incurring any costs yourself. You will need to take the envelope to the Post Office.

This envelope will be tracked by Royal Mail and should reach me the day after you take it to the Post Office.

I have already made a record of the number on the envelope.

Please follow these instructions;

1. At the end of your 14 days of wearing the actiwatch take the watch off. You don't need to remove the strap. You will find the dates on your diary.
2. Carefully wrap the watch and strap, **as well as your sleep diary**, in the packaging I've given you.
3. Complete the "sender" box on the envelope with your name and address.
4. Seal the envelope and take it to your nearest post office where they will know what to do with it. They are likely to give you a receipt for the envelope. Keep this somewhere safe in case the envelope goes astray.
5. It doesn't matter if there are a few days delay before you take the envelope to the post office.

Please don't hesitate to contact me if you have any questions or concerns.

Dr. Angela Atalla, Clinical Research Fellow
Tel 0207 352 8121 ext 4606 (answer machine) a.atalla@imperial.ac.uk

APPENDIX NINE

Sleep diary used with Actiwatch

Sleep Diary Record for use with Actiwatch

for Patients and Subjects Please keep this by your bedside to remind you!

WEEK ONE:

	Naps: The times and duration of naps during the day	Times watch removed	Time of lights out	No. of times you get up in the night i.e. to urinate	Time of lights on	Overall sleep quality: Poor = 1 Average = 2 Good = 3
Example Date (d/m/y)	*2.00pm for 45mins* *6.30pm for 30mins*	*9am for shower*	*10pm*	*3*	*7am*	*2*

Dr. Angela Atalla, Clinical Research Fellow
Tel 0207 352 8121 ext 4606 (answer machine) a.atalla@imperial.ac.uk

APPENDIX TEN

Individual patient HCVR results, x intercepts and resting carbon dioxide levels (chapter 4)

For the study investigating chemosensitivity in HF patients with (HF-CSA) and without (HF-noSDB) central sleep disordered and in older healthy controls (chapter 4)

Table A.1: HF-CSA group (n=14)

Subject no.	Resting CO_2 (mmHg)	Evening data		Morning data		Overnight change in HCVR*
		HCVR*	x intercept (mmHg)	HCVR*	x intercept (mmHg)	
1	38.97	2.48	47.16	1.44	42.32	-1.04
2	34.66	1.59	41.64	-	-	-
3	28.63	9.00	46.95	3.70	41.42	-5.30
4	29.22	1.70	32.16	1.40	28.2	-0.30
5	27.76	2.64	40.25	-	-	-
6	30.64	2.10	33.74	6.60	42.10	+4.50
7	38.21	2.74	38.45	-	-	-
8	30.18	3.70	42.05	4.30	41.57	+0.60
9	31.41	2.05	40.69	-	-	-
10	37.30	2.15	38.54	1.71	34.48	-0.44
11	22.7	1.41	22.15	-	-	-

HCVR- hypercapnic ventilatory response.

Note that the x intercept refers to the theoretical CO_2 at which ventilation will cease. See chapter 1 section 1.5.5.

* units are L/min/mmHg $ETCO_2$

Table A.2: HF-noSDB group (n=15)

Subject no.	Resting CO_2 (mmHg)	Evening data		Morning data		Overnight change in HCVR*
		HCVR*	x intercept (mmHg)	HCVR*	x intercept (mmHg)	
1	40.48	2.80	44.51	3.50	45.32	+0.70
2	36.13	1.60	41.15	1.00	35.57	-0.60
3	39.17	2.00	43.55	2.20	43.52	+0.20
4	40.49	3.00	48.39	3.00	46.39	0
5	40.36	0.30	-	0.80	27.97	+0.50
6	35.21	4.00	43.48	2.10	40.46	-1.90
7	34.46	1.70	37.90	2.40	39.35	+0.70
8	35.47	3.50	37.10	2.70	38.10	-0.80
9	41.06	1.68	-	1.19	-	-0.49
10	37.21	0.92	-	0.91	-	-0.01
11	35.52	3.33	45.24	3.15	40.05	-0.18
12	27.97	1.78	23.20	-	-	-
13	36.30	3.55	44.34	-	-	-
14	36.18	1.99	36.30	-	-	-
15	31.00	1.18	31.08	-	-	-

HCVR- hypercapnic ventilatory response.

Table A.3: Control group (n=14)

Subject no.	Resting CO_2 (mmHg)	Evening data		Morning data		Overnight change in HCVR*
		HCVR*	x intercept (mmHg)	HCVR*	x intercept (mmHg)	
1	34.55	1.56	33.78	2.23	36.2	+0.67
2	36.90	2.00	41.90	1.52	40.12	-0.48
3	36.69	2.88	41.11	2.37	42.23	-0.51
4	39.49	2.07	40.50	1.31	29.45	-0.76
5	33.33	1.79	29.59	0.62	7.69	-1.17
6	34.05	1.87	39.83	1.16	42.57	-0.71
7	-	2.10	-	2.30	-	+0.20
8	31.20	1.97	38.30	1.71	39.53	-0.26
9	38.01	2.09	41.43	0.87	26.99	-1.22
10	35.29	3.57	39.85	4.83	42.84	+1.26
11	42.88	0.43	31.36	0.27	10.76	-0.16
12	33.36	3.20	33.89	4.50	37.07	+1.30
13	32.45	3.70	41.17	3.40	41.93	-0.30
14	38.93	1.80	44.23	1.80	40.83	0

HCVR- hypercapnic ventilatory response.

APPENDIX ELEVEN

Night time actigraphy data for 3 comparisons (chapter 6)

Table A.4: Comparison of HF-SDB and HF-noSDB groups

	HF-SDB (n=27)	**HF-noSDB (n=16)**	
Time in bed (min)	**498** (453-531)	**465** (444-508)	*p=0.13*
Sleep efficiency (%)	**81.8** (72.3-85.4)	**78.4** (71.0-82.9)	*p=0.18*
Sleep latency (min)	**11.0** (7.0-22.0)	**14.0** (10.3-18.8)	*p=0.44*
Immobile time (%)	**79.0** (72.0-85.7)	**76.0** (70.6-82.8)	*p=0.41*
Movement time (%)	**21.0** (14.3-28.0)	**24.0** (17.2-29.4)	*p=0.41*
Total activity score (ave/night)	**8393** (5318-14466)	**7307** (5709-13266)	*p=1.0*
Fragmentation index	**48.3** (33.9-59.6)	**47.5** (39.0-62.4)	*p=0.69*

Note; night time data were only available for 16 out of 32 patients in the HF-noSDB group and 27 out of 32 patients in the HF-SDB group.

Table A.5: Comparison of HF-CSA and HF-noSDB groups

	HF-CSA (n=23)	**HF-noSDB (n=16)**	
Time in bed (min)	**507** (453-531)	**465** (444-508)	*p=0.06*
Sleep efficiency (%)	**81.8** (72.3-85.4)	**78.4** (71.0-82.9)	*p=0.24*
Sleep latency (min)	**11.0** (7.0-19.0)	**14.0** (10.3-18.8)	*p=0.24*
Immobile time (%)	**78.1** (72.0-85.7)	**76.0** (70.6-82.8)	*p=0.36*
Movement time (%)	**21.9** (14.3-28.0)	**24.0** (17.2-29.4)	*p=0.36*
Total activity score (ave/night)	**8372** (5318-14931)	**7307** (5709-13266)	*p=0.95*
Fragmentation index	**46.7** (32.8-59.6)	**47.5** (39.0-62.4)	*p=0.58*

Table A.6: Comparison of HF-noSDB and control groups

	HF-noSDB (n=16)	Controls n=12	
Time in bed (min)	**465** (444-508)	**469** (419-482)	*p=0.49*
Sleep efficiency (%)	**78.4** (71.0-82.9)	**85.3** (79.8-90.0)	***p=<0.01***
Sleep latency (min)	**14.0** (10.3-18.8)	**6.5** (3.8-9.0)	***p=<0.01***
Immobile time (%)	**76.0** (70.6-82.8)	**84.8** (78.6-90.4)	***p=<0.01***
Movement time (%)	**24.0** (17.2-29.4)	**15.2** (9.6-21.4)	***p=<0.01***
Total activity score (ave/night)	**7307** (5709-13266)	**5314** (2867-11677)	*p=0.15*
Fragmentation index	**47.5** (39.0-62.4)	**31.7** (20.4-45.5)	***p=<0.01***

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APPENDIX TWELVE

Additional analysis for the Activity study (chapter 6)

These data are for the analysis removing those patients from the HF-noSDB group with a BMI over 30 kg/m^2.

Table A.7: Characteristics of HF patients without SDB (BMI <30kg/m^2) and age matched healthy controls. Results are median (IQR) unless stated.

	HF-No SDB n=15	**Controls n=12**	
Age (yrs)	**68.0** (56-73)	**67** (64-70)	*p=0.66*
Gender (male /female)	**1 / 14**	**9 /12**	-
BMI (kg/m^2)	**26.2** (24.4-27.9)	**25.0** (22.7-26.5)	*p=0.15*
Neck circumference (cm)	**40.0** (38.7-41.5)	**38.5** (34.5-39.4)	*p=0.07*
Alcohol (units/week)	**3** (2-11)	**3** (0-13)	*p=0.62*
Epworth sleepiness score	**8** (5-12)	**4** (3-9)	***p=0.04***
Nocturia (no of episodes over 14d)	**11** (8-41)	**8** (4-15)	*p=0.18*

BMI- body mass index; SDB- sleep disordered breathing;

Table A.8: Nocturnal polysomnographic data for the HF-noSDB (BMI <30kg/m^2) and control groups. Data are median (IQR).

	HF-No SDB n=15	Controls n=12	
Apnoea hypopnoea index (events/hr)	**3.9** (1.2-5.9)	**2.8** (1.7-4.8)	*p*=0.83
Apnoea index (events/hr)	**0.2** (0-0.9)	**1.0** (0.3-1.8)	*p*=0.10
Hypopnoea index (events/hr)	**3.1** (0.6-4.9)	**1.1** (0.5-3.2)	*p*=0.26
Oxygen desaturation index (≥3% dip rate/hour)	**4.2** (1.0-8.0)	**2.0** (0.8-4.2)	*p=0.20*
Time spent with saturations <90% (min)	**1.0** (0-3.0)	**0**	*p=0.11*
Time in bed (min)	**452** (367-482)	**475** (433-512)	*p=0.15*
Total sleep time (min)	**324** (288-377)	**411** (344-437)	*p=0.06*
Sleep efficiency (%)	**75.6** (66.1-83.7)	**85.1** (79.0-88.9)	***p=0.04***
Sleep latency (%)	**12.5** (11.4-24.1)	**16.0** (8.3-29.6)	*p=0.96*
Wake after sleep onset (min)	**89.0** (42.2-114.0)	**47.5** (27.8-94.0)	*p=0.31*
Arousal index (events/hr)	**34.4** (28.1-43.7)	**27.5** (8.5-49.1)	*p=0.56*
Stage 1 (%)	**24.8** (10.6-34.4)	**13.5** (8.3-15.9)	***p=0.02***
Stage 2 (%)	**42.1** (38.5-52.1)	**40.0** (33.0-54.1)	*p=0.50*
Stage 3 (%)	**7.3** (5.7-14.1)	**9.2** (6.8-10.2)	*p=1.0*
Stage 4 (%)	**1.5** (0-5.9)	**14.4** (7.2-20.4)	***p=<0.01***
REM sleep (%)	**17.1** (11.6-20.5)	**21.3** (19.3-23.2)	***p=0.04***
PLM index (events/hr)	**4.9** (0.2-13.6)	**5.5** (0.4-18.1)	*p=0.87*

PLM- periodic limb movement; SDB- sleep disordered breathing; REM- rapid eye movement. .

Table A.9: Daytime actigraphy data from HF patients without SDB (BMI <30kg/m^2) and healthy control subjects. Results are median (IQR) unless stated.

	HF-No SDB n=15	Controls n=12	
Average duration of activity /day (hrs)	**15.2** (14.3-15.4)	**14.5** (12.7-15.6)	*p=0.33*
Average activity per day (arbitrary units)	**206428** (187391-277195)	**217751** (172699-304318)	*p=0.66*
Average activity per 1 minute epoch (arbitrary units)	**217.7** (196.6-297.3)	**230.7** (171.3-311.5)	*p=0.85*
Total daytime activity count over 14d (arbitrary units)	**2,968,933** (2,780,279-3,901,549)	**3,106,372** (2,287,621-3,849,165)	*p=0.58*

SDB- sleep disordered breathing.

Table A.10: Night time actigraphy data from HF patients without SDB (BMI <30kg.m2) and healthy control subjects. Results are median (IQR) unless stated.

	HF-No SDB n=11	Controls n=12	
Time in bed (min)	**454** (434-510)	**469** (419-482)	*p=0.88*
Sleep efficiency (%)	**78.8** (72.8-83.7)	**85.3** (79.8-90.0)	***p=0.03***
Sleep latency (min)	**13.0** (10.0-19.0)	**6.5** (3.8-9.0)	***p=<0.01***
Immobile time (%)	**79.1** (70.4-82.2)	**84.8** (78.6-90.4)	***p=0.02***
Movement time (%)	**20.9** (17.8-29.6)	**15.2** (9.6-21.4)	***p=0.02***
Total activity score (ave/night)	**7057** (6197-11130)	**5314** (2867-11677)	*p=0.27*
Fragmentation index	**44.9** (38.6-61.8)	**31.7** (20.4-45.5)	***p=0.01***

Note; night time actigraphy data were only available for 11 out of 15 of this subgroup (and for 16 out of 22 of the original HF-noSDB group).

APPENDIX THIRTEEN

Data for all 4 patient groups in the Activity study (chapter 6)

Table A.11: Baseline Characteristics

		HF-OSA n=9	HF-CSA n=23	HF-No SDB n=22	Control n=12
Age (yrs)		**70** (54-71)	**70** (66-77)	**62** (54-70)	**67** (64-70)
Gender (male / female)		**9 / 0**	**22 / 1**	**19 / 3**	**9 / 3**
BMI (kg/m^2)		**29.0** (26.7-37.1)	**28.6** (24.1-29.8)	**27.9** (25.3-31.1)	**25.0** (22.7-26.5)
Neck circumference (cm)		**41.5** (39.0-47.5)	**40.0** (37.0-42.3)	**40.3** (38.7-42.5)	**38.5** (34.5-39.4)
Alcohol (units/week)		**2** (0-8)	**1** (0-6)	**2** (0-7)	**3** (0-13)
Epworth sleepiness score		**7** (5-10)	**8** (4-10)	**8** (6-12)	**4** (3-9)
NYHA functional class I / II / III / IV		1 / 5 / 3 / 0	10 / 2 / 11 / 0	12 / 1 / 7 /2	
Blood pressure (mmHg)	**Systolic**	**117** (116-143)	**120** (107-134)	**118** (100-126)	
	Diastolic	**70** (66-76)	**72** (62-81)	**72** (63-78)	
Left ventricular ejection fraction (%)		**38** (31-47)	**29** (19-38)	**35** (28-42)	
B-type Natriuretic Peptide (pmol/L)		**28.5** (8.0-34.0)	**81.5** (50.0-132.5)	**37.0** (27.0-56.5)	
Aetiology of HF syndrome	Ischaemic	**5**	**14**	**12**	
	DCM	**3**	**3**	**7**	
	Valvular	**0**	**5**	**2**	
	Unknown	**1**	**1**	**1**	
Medications	Diuretics	**5**	**20**	**17**	
	Beta blocker	**5**	**22**	**5**	
	ACE inhibitor/ARB	**6**	**16**	**21**	
	Digoxin	**1**	**5**	**5**	
Comorbidities	Diabetes	**1**	**4**	**3**	
	Atrial fibrillation	**1**	**9** (1 with PAF)	**6** (2 with PAF)	
Implanted devices	no device	**0**	**10**	**12**	
	PPM +/- ICD	**1**	**2**	**1**	
	CRT	**0**	**11**	**7**	
	ICD	**0**	**0**	**2**	
Minnesota Living with Heart Failure questionnaire score		**29** (7-41)	**25** (17-45)	**38** (19-58)	

BMI-body mass index; DCM- dilated cardiomyopathy; ACE- angiotensin converting enzyme; PPM- permanent pacemaker; ICD- implantable cardioverter defibrillator; CRT- cardiac resynchronisation therapy.

Table A.12: Polysomnography

	HF-OSA n=9	HF-CSA n=23	HF-No SDB n=22	Controls n=12
AHI (events/hr)	**18.4** (12.5-34.2)	**20.6** (12.9-40.2)	**3.7** (2.5-5.9)	**2.8** (1.7-4.8)
AI (events/hr)	**1.9** (0.3-14.8)	**8.0** (2.4-16.6)	**0.2** (0-0.8)	**1.0** (0.3-1.8)
HI (events/hr)	**10.9** (3.4-17.0)	**11.7** (9.1-18.8)	**3.0** (1.4-5)	**1.1** (0.5-3.2)
ODI (4% dip rate/hour)	**8.0** (4.8-18.8)	**16.5** (8.6-38.7)	**4.2** (1.0-8.1)	**2.0** (0.8-4.2)
T<90% (min)	**10.2** (5.3-24.0)	**18.7** (5-35.2)	**2.0** (0-5.0)	**0**
TIB (min)	**478** (437-534)	**500** (465-548)	**460** (402-488)	**475** (433-512)
TST (min)	**360** (325-416)	**348** (303-383)	**355** (295-383)	**411** (344-437)
Sleep efficiency %	**77.4** (68.1-83.5)	**73.4** (61.2-76.5)	**78.5** (70.1-84.1)	**85.1** (79.0-88.9)
Sleep latency (min)	**13.5** (7.1-25.3)	**20.3** (11.3-29.3)	**14.6** (10.9-29.0)	**16.0** (8.3-29.6)
WASO (min)	**116.0** (26.0-152.0)	**100.0** (80.0-149)	**36.7** (0-90.5)	**47.5** (27.8-94.0)
Arousal index (events/hr)	**45.5** (23.5-62.7)	**28.3** (21.3-47.7)	**31.8** (14.2-41.8)	**27.5** (8.5-49.1)
Stage 1 (%)	**31.8** (21.9-58.8)	**27.6** (21.0-49.1)	**20.5** (9.6-31.2)	**13.5** (8.3-15.9)
Stage 2 (%)	**32.6** (20.3-43.3)	**39.4** (29.1-51.3)	**44.5** (38.4-52.1)	**40.0** (33.0-54.1)
Stage 3 (%)	**10.3** (6.8-14.4)	**8.2** (3.6-10.5)	**8.1** (6.2-12.6)	**9.2** (6.8-10.2)

Stage 4 (%)	**1.5** (0-10.1)	**0.2** (0-5.0)	**1.6** (0.2-6.5)	**14.4** (7.2-20.4)
REM sleep (%)	**11.0** (9.9-13.9)	**14.1** (9.0-18.9)	**18.4** (13.5-22.0)	**21.3** (19.3-23.2)
PLM index	**2.1** (0.7-31.0)	**14.0** (5.7-37.1)	**4.6** (0.3-11.4)	**5.5** (0.4-18.1)
Supine	**53.3** (11.9-79.3)	**45.9** (33.3-80.1)	**23.0** (0-42.2)	**44.8** (11.1-30.7)

AHI- apnoea hypopnoea index; AI- apnoea index; HI- hypopnoea index; ODI- oxygen desaturation index; T<90%- time spent with oxygen saturations below 90%; TST- total sleep time; WASO- wake after sleep onset; S1/2- stage 1 and 2 sleep respectively; REM- rapid eye movement; PLMi- periodic limb movement index.

Table A.13: Actigraphy- Daytime activity

	HF-OSA n=9	**HF-CSA n=23**	**HF-No SDB n=22**	**Controls n=12**
Average duration of activity /day (hrs)	**14.8** (4.0-16.6)	**14.5** (14.1-15.2)	**15.1** (14.4-15.3)	**14.5** (12.7-15.6)
Average activity per day*	**251274** (110866-325794)	**193594** (135582-255557)	**217926** (196900-275933)	**217751** (172699-304318)
Average activity per 1 minute epoch*	**254.2** (138.0-321.2)	**215.3** (160.3-296.6)	**231.1** (210.6-305.0)	**230.7** (171.3-311.5)
Total daytime activity count over 14d*	**2458738** (1090625-3743920)	**2903915** (2033728-3833354)	**3068856** (2834952-4019950)	**3106372** (2287621-3849165)

**arbitrary units*

Table A.14: Actigraphy- Night time activity

	HF-OSA n=9	HF-CSA n=23	HF-noSDB n=16	Controls n=12
Time in bed (min)	**456** (353-525)	**507** (453-531)	**465** (444-508)	**469** (419-482)
Sleep efficiency (%)	**82.6** (67.7-88.8)	**81.8** (72.3-85.4)	**78.4** (71.0-82.9)	**85.3** (79.8-90.0)
Sleep latency (min)	**24.0** (9.3-70.0	**11.0** (7.0-19.0)	**14.0** (10.3-18.8)	**6.5** (3.8-9.0)
Immobile time (%)	**79.4** (63.7-83.3)	**78.1** (72.0-85.7)	**76.0** (70.6-82.8)	**84.8** (78.6-90.4)
Movement time (%)	**20.7** (16.7-36.3)	**21.9** (14.3-28.0)	**24.0** (17.2-29.4)	**15.2** (9.6-21.4)
Total activity score (ave/night)	**9660** (4831-11703)	**8372** (5318-14931)	**7307** (5709-13266)	**5314** (2867-11677)
Fragmentation index	**49.0** (42.1-69.10	**46.7** (32.8-59.6)	**47.5** (39.0-62.4)	**31.7** (20.4-45.5)

Table A.15: Nocturia data (from sleep diary)

Average/night over 14 nights (data are median and IQR)

HF-OSA n=9	HF-CSA n=23	HF-No SDB n=22	Controls n=12
1.04 (0.34-1.82)	**1.43** (0.82-1.96)	**0.75** (0.63-1.32)	**0.57** (0.27-1.07)

APPENDIX FOURTEEN

Instructions given to patients using the ApneaLink™ device

Patient Instructions for using the Apnoea Link

How to set up your Overnight Sleep Test

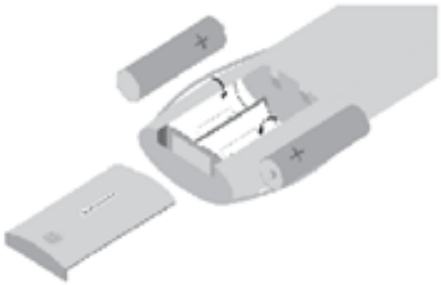
This test will measure your breathing, oxygen levels and how fast your heart beats overnight while you sleep. It uses a very simple piece of equipment to measure this. In order to look at the information that is gathered overnight the equipment needs to go back to the doctors and nurses at the hospital and they will look at the results on a computer.
You will find everything you need in the blue pouch you have been given or sent.

Before you go to bed take everything out of the blue pouch you have been given. You will find the following;

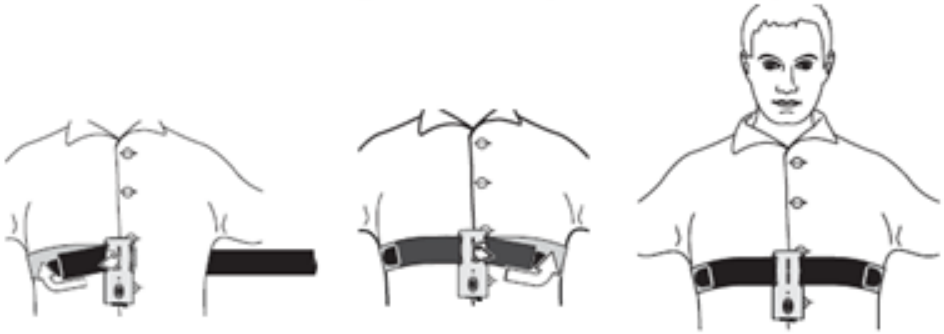
- New pair of batteries
- One unopened set of nasal tubes
- One oxygen sensor sticker
- Blue machine to record your sleep study overnight; this will have a Velcro band looped through it and a long oxygen sensor attached.
- A roll of tape

Follow these instructions to set up the machine for your study before you go to bed. This will take less than 10 minutes.

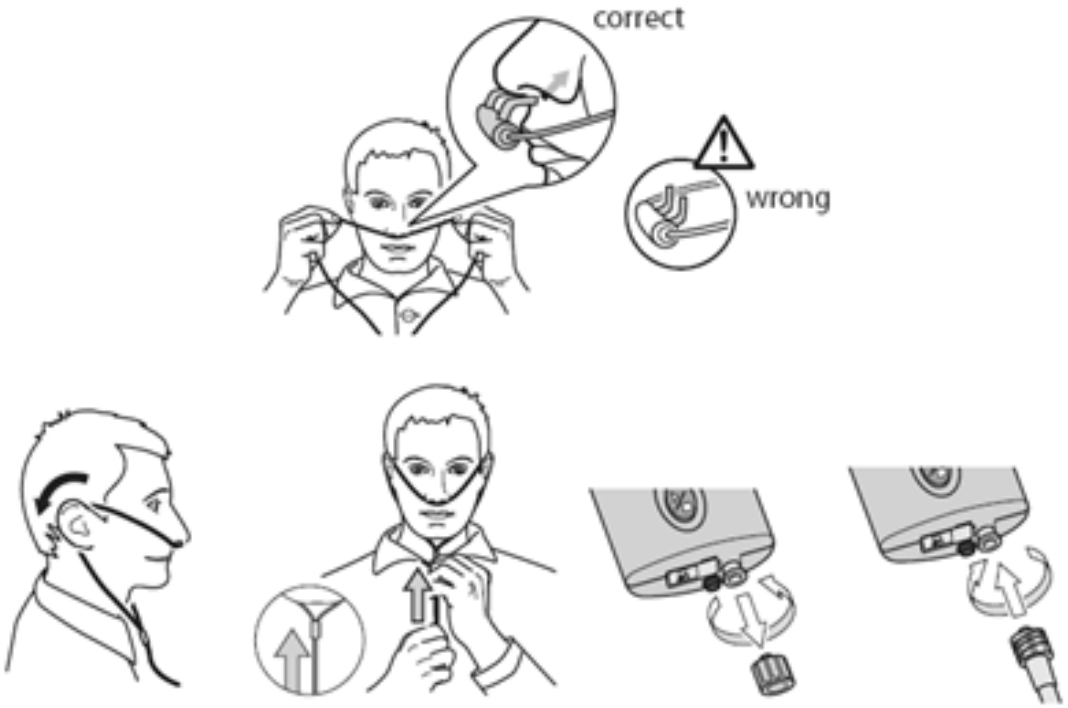
1. **Remove the back of the blue machine and insert the batteries as shown**



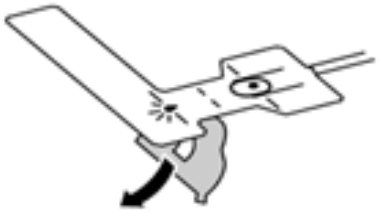
2. **Fit the blue machine using the Velcro strap as shown in the 3 pictures below**



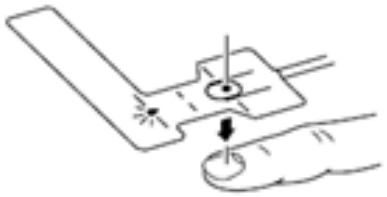
3. **Next unwrap the nasal tubes. Fit them carefully as shown below. You need to remove the protective cap from the machine (put it somewhere safe, you will need it in the morning) and screw the nasal tubes in to the bottom of the machine. Adjust the tubes to ensure they are fitted snugly, but not too tight, as in the bottom picture below.**



4. **Now you need to attach the oxygen sensor. This will already be attached to the blue machine. The oxygen sensor is held on your finger overnight using a sticker. Take the sticker you have in the blue pouch and carefully follow the pictures below.** If you are wearing nail varnish you will need to remove it from your index finger, otherwise the oxygen sensor won't work.
    a. **Peel the backing paper off the sticker and place the sensor on the sticky side as shown**



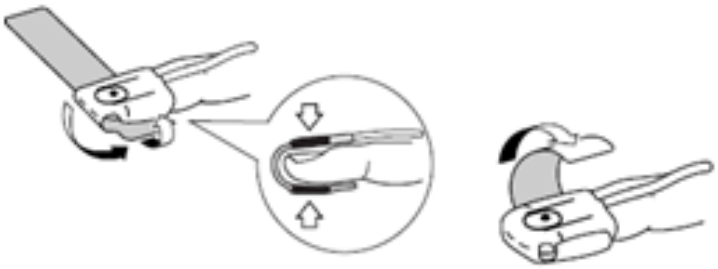
b. Next lower this onto your finger so the sensor is stuck to your nail. If you are RIGHT handed its best to put the sensor on your LEFT index finger.



c. Now wrap the sides of the sticker around the side of your index finger.



d. Now wrap the rest of the sticker around your finger like this; you should have part of the sensor on top and the bottom of your index finger.



e. You should finish with the sticker like this



f. Because the wire for the oxygen sensor is very long you can clip it to the band around your chest like in the picture so it doesn't get in the way overnight. You can also use a small bit of the tape to secure the wire to the top of your wrist (where your watch would sit) to keep it out of the way.



5. **Now you are ready to start the machine. Hold down the START/STOP button FIRMLY until the light on the machine shows green. Then let go of the button.** The machine is working properly if the green light goes on and off as you breathe. This light will dim slightly after a couple of minutes, this is normal. The oxygen sensor on your finger will glow red and this is also normal.

6. If the light on the machine is RED then check that the oxygen tubes are properly screwed into the bottom of the machine. The light will also go red if you breathe through your mouth as the nasal tubes are unable to detect this.

7. **Make a note here of the time and date you started the machine. This helps us to interpret the results;**

Date of study: _____
Time I pressed the START/STOP button at night before the study: _____

In the morning follow these instructions; this will take less than 5 minutes.

1. **Press the START/STOP button *THREE TIMES IN A ROW* until the light on the machine goes out. This stops the recording.**

2. **Make a note of the time you stop the study here**

Time I pressed the START/STOP button in the morning after the study: _____

3. **Carefully take off the oxygen sensor and throw away the sticker.**

4. **Take off the nasal tubes, unscrew them from the bottom of the machine, and throw them away.** Replace the cap that you removed the night before.

5. **Put everything (including this page) back into the blue pouch and send it back to the doctors and nurses who gave it to you. If you had any problems please write them down in the space below.**

O soft embalmer of the still midnight,

Shutting, with careful fingers and benign,

Our gloom-pleas'd eyes, embower'd from the light,

Enshaded in forgetfulness divine:

O soothest Sleep! if so it please thee, close

In midst of this thine hymn my willing eyes,

Or wait the "Amen," ere thy poppy throws

Around my bed its lulling charities.

Then save me, or the passed day will shine

Upon my pillow, breeding many woes,—

Save me from curious Conscience, that still lords

Its strength for darkness, burrowing like a mole;

Turn the key deftly in the oiled wards,

And seal the hushed Casket of my Soul.

“To Sleep”, by John Keats (1795–1821)