EARLY DETECTION OF DECOMPENSATION OF CHRONIC HEART FAILURE USING A NON-CONTACT MONITOR OF NOCTURNAL RESPIRATORY PATTERNS

By

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Statement of Originality

I, Henry Oluwasefunmi Savage, hereby declare that this work is completely original and no part of this manuscript has been submitted in application for a higher degree. Publication in the form of abstract presentations arising from this work is listed on Page 7. Information derived from the work of others is referenced in text and listed in the bibliography.

I am the main investigator of all the works presented in this thesis and was directly involved in the design, execution and analysis with guidance from my supervisors Professor Martin Cowie and Professor Anita Simonds. I performed and scored all the overnight Polysomnography (PSG) studies, as described in methods, except in the group of patients who participated from Essen, Germany in Chapter 3 where I received additional support from Mr Peter Bateman and Mr Darrel Wicks.

I acknowledge the invaluable contribution of the applied research team of engineers whom I worked with at ResMed Ltd, Sydney Australia, led by Professor Klaus Schindhelm and Dr Steven Farrugia in signal analysis and developing the various SleepMinder™ algorithms used in this study. The analysis of plasma samples for renal function, Full Blood Counts and Plasma B-type Natriuretic Peptide were by the biochemist at the Royal Brompton Hospital London Laboratory. I also received statistical support from Mr Winston Banya of the Royal Brompton Hospital London Research and Development department.
Abstract

Heart failure affects 1-2% of the adult population in the United Kingdom and accounts for the majority of hospitalisations in patients with cardiovascular disease. The financial implications are enormous as it consumes 1-2% of the national health care budget with 70% of these costs relating to hospitalisation expenses.

Prevention of these admissions may be possible by detecting early signs of decompensation in patients with chronic heart failure (CHF) and instituting interventions that may steer the course of disease back to stability without the need for a hospital inpatient stay.

Further, Sleep Disordered Breathing (SDB) and in particular Central Sleep Apnoea (CSA) is found in patients with CHF and at any symptomatic stage of the condition. This may be associated with Cheyne-Stokes Respiration (CSR), which has been shown to be an independent predictor of mortality.

In the first study of this thesis, I investigated the accuracy of the SleepMinder™ (SM) device; which is a non-contact monitor of nocturnal respiratory patterns; in diagnosing SDB by deriving measures of the Apnoea Hypopnea Index (AHI) and percentage overnight CSR from the SM signals. I found that SM was good in terms of diagnostic accuracy with an area under receiver operator characteristic curve (ROC) of 0.82 (p=0.02) for an AHI threshold >15, but only moderately so for % overnight CSR>0, with an area under ROC curve of 0.72 (p=0.06).

In the second study, I examined the changes that occur in SM derived respiratory parameters over a long period of monitoring and found that the AHI, quantity of CSR, Total Sleep Time (TST) and Respiratory Rate (RR) were highly variable with Intra-Class Correlation (ICC) measures of 0.32, 0.39, 0.25, 0.36 respectively over a period of 12 months. Relying on data from a year rather than a single night resulted in misclassification of patients into a different severity group of SDB during 35% of the follow up period and placed patients into a different treatment group during 21% of this period. I also observed that a high proportion (59%) of patients studied had a mean AHI that was consistently above the accepted threshold for treatment (AHI>15). This was consistent even over a shorter follow up period of 2 weeks suggesting that a single night measure of the AHI may not be a sufficient risk assessment of SDB in heart failure patients.
In the final study, I have investigated the predictive value of the SleepMinder™ for acute decompensation of heart failure (ADHF) using algorithms derived from its signals. I found that the SM was not accurate for this purpose, performing with a sensitivity and specificity of 0.38 and 0.71, respectively.

In summary this study has demonstrated that the SleepMinder™ device provides a novel screening method, which is convenient for the detection of sleep disordered breathing in patients with CHF. It performs with a good diagnostic accuracy and is acceptable to these patients due to its non-contact operation. Algorithms derived from its signals however cannot be used to predict acute decompensation of chronic heart failure. Further, longitudinal analyses of nocturnal respiratory patterns in these patients have demonstrated that the Apnoea Hypopnea Index (AHI) is highly variable over a prolonged period of monitoring and a mean value rather that a single night measurement may be a more appropriate risk assessment tool for SDB. This requires confirmation.
Publications Arising From This Thesis

Published Abstracts


Savage HO, Khushaba R, Cowie MR et al A Novel Non-Contact Device that identifies and categorises Sleep Disordered Breathing in Patients with Chronic Heart Failure. Heart 2013;99:A15-A16 doi:10.1136/heartjnl-2013-304019.18

Awards

Winner Young Investigator Award for Clinical Research — Savage HO Cheyne Stokes respiration in patients with heart failure detected by a novel non-contact monitor of nocturnal respiration presented at the Heart Failure Association of the European Society of Cardiology, Congress May 2013 Lisbon

Other Publications Whilst Registered For This Degree

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Other Abstracts Whilst Registered For This Degree

Guha K, Morley-Smith A, **Savage HO**, T McDonagh, R Sharma The impact of upgrading dual chamber ICD to biventricular ICD upon ventricular arrhythmia burden Eur J Heart Fail (2013) 12 (suppl 1): S73-S325 doi:10.1093/eurjhf/hst009


**Book Chapters/Reviews/E-learning**

**Savage HO** Book Review for British Journal Of Cardiology; The Oxford Textbook of Heart Failure Edited by T McDonagh, R Gardner, AL Clark, HJ Dargie. August 2012; Volume 19, Issue 3  Br J Cardiol 2012; 19:144

Gibbs S, **Savage HO** et al Pulmonary Hypertension, e-learning programme and handbook, a continuing educational programme for health care professionals. Edited by Rachel Arthur, [http://bjcardio.co.uk/category/pulmonary-arterial-hypertension-learning/](http://bjcardio.co.uk/category/pulmonary-arterial-hypertension-learning/) 2013

Clark A, **Savage HO** et al Heart Failure e-learning programme. "Heart failure e-learning programme" at BJC Learning [http://bjcardio.co.uk/category/heart-failure-learning/](http://bjcardio.co.uk/category/heart-failure-learning/) 2014


**Letters**

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Abbreviations

AASM – American Association of Sleep Medicine
ACE – Angiotensin Converting Enzyme
ADHF – Acute Decompensated Heart Failure
AHI – Apnoea Hypopnea Index
ARB – Angiotensin Receptor Blocker
ASV – Adaptive Servo Ventilation
AUC – Area Under Curve
BB – Beta Blocker
BMI – Body Mass Index
BNP – B-Type Natriuretic peptide
CHF – Chronic Heart Failure
CO2 – Carbon Dioxide
COPD – Chronic Obstructive Pulmonary Disease
CoV – Coefficient of Variation
CPAP – Continuous Positive Airway Pressure
CRT – Cardiac Resynchronisation Therapy
CSA – Central Sleep Apnoea
CSR – Cheyne-Stokes’ Respiration
DM – Diabetes Mellitus
ECG – Electrocardiogram
EEG – Electroencephalogram
EMG – Electromyogram
EOG – Electrooculogram
ESS – Epworth Sleepiness Scale
HFNEF – Heart Failure with Normal Ejection Fraction
HFPEF – Heart Failure with Preserved Ejection Fraction
HRV – Heart Rate Variability
HTN – Systemic Hypertension
ICC – Intra-class Correlation Co-efficient
ICD – Implantable Cardiac Defibrillator
IMP – Impedance
IQR – Interquartile Range
LoV – Limits of Variation
LVEF – Left Ventricular Ejection Fraction
MDT – Multidisciplinary Team Meeting
MRA – Mineralocorticoid Receptor Antagonist
NYHA – New York Heart Association
ODI – Oxygen Desaturation Index
OSA – Obstructive Sleep Apnoea
PCWP – Pulmonary Capillary Wedge Pressure
PLM – Periodic Leg Movement
PSG – Polysomnography
RDI – Respiratory Disturbance Index
REM – Rapid Eye Movement
RIP – Respiratory Inductance Plethysmography
ROC – Receiver Operator Characteristic Curve
SDB – Sleep Disordered Breathing
SM – SleepMinder™
SMApA – SleepMinder™ ADHF Predictor Algorithm
TST – Total Sleep Time
TTE – Transthoracic Echocardiography
CHAPTER 1 – INTRODUCTION
Background

About 900,000 people suffer from Chronic Heart Failure (CHF) in the United Kingdom and 5% of all emergency medical admissions to hospital are related to this, accounting for 2% of all NHS inpatient bed days (1). 1-2% of the national health care budget is consumed by this burden, with 70% of these costs relating to hospitalisation expenses (2)

Preventing these admissions may be possible by detecting early signs of Acute Decompensation of Chronic Heart Failure (ADHF) and instituting interventions that may steer the course of disease back to stability without the need for a hospital inpatient stay.

Meta-analysis of multidisciplinary team (MDT) approaches to the management of patients (3) with heart failure suggests that there is potential mortality benefit from this strategy and as a result this has now been included in international guidelines (4). Unfortunately this is sometimes not accessible to all patients, and even when available, some patients frequently have periods of instability of their heart failure.

It therefore seems prudent to identify other management strategies that may be of benefit in the early identification of patients who may be deteriorating.

Furthermore, varying and inconsistent results have been obtained from studies that have investigated various physiological parameters; monitored directly or from implanted devices; that may be predictive of patients who are likely to decompensate (5).

It therefore becomes necessary to identify other variables that could give potential signals of heart failure instability, which could be targeted to prevent hospital admissions, to the benefit of the patients and cost saving to health funders.

Sleep Disordered Breathing (SDB) is found in patients with CHF and at any symptomatic stage of the condition (6-8). This may present as Obstructive Sleep Apnoea (OSA) or Central Sleep Apnoea (CSA) associated with Cheyne-Stokes’ Respiration (CSR). The latter has been shown to be an independent predictor of mortality and the need for urgent cardiac transplantation, (9) while the former is associated with the development and progression of cardiovascular disease including systemic hypertension and heart failure (10).
The majority of patients with CHF have mild symptoms of disease (11); however the presence of SDB may accelerate progression of disease. For this reason, early identification of this problem is desirable.

In the first section of this chapter, I will discuss the epidemiology, pathophysiology, diagnosis and current treatment of CHF. In the following section, I will discuss the burden of Acute Decompensated Heart Failure (ADHF) and review the literature regarding variables currently used in clinical practice. Furthermore, I will highlight the role monitoring of respiratory patterns may have in predicting ADHF.

In the third section I will review Sleep Disordered Breathing in Heart Failure, the impact these group of breathing disorders have on heart failure, and the potential utility of some of the measures of SDB in predicting deterioration. In the penultimate section, I discuss digital signal processing in medicine, as this was a key process used for developing the algorithms used in this thesis.

In the final section, I will introduce the clinical evaluations I have performed with the SleepMinder™ device (ResMed Ltd. Australia), which is a novel, non-contact monitor of breathing patterns during sleep.
SECTION ONE: Definition, Epidemiology, Diagnosis, Pathophysiology and Treatment of Chronic Heart Failure
1.1. Definitions

There is no universal definition for heart failure and attempts at describing this condition dates as far back as 1500BC when the ancient Egyptians described it as ‘….an inundation of the heart, where saliva is in excess and therefore the body is weak’]. A widely referenced description is one from Hippocrates who described this condition in 460-370BC as ‘…one where the flesh is consumed and becomes water…the abdomen fills with water; the feet and legs swell; the shoulders, clavicles, chest, and thigh melt away.’ (12).

A modern definition describes heart failure as a clinical syndrome with a constellation of symptoms and signs caused by an abnormality of the heart resulting in a characteristic pattern of hemodynamic, renal, neural and hormonal responses (13). This definition encompasses both clinical criteria sometimes used solely to define heart failure and other definitions that isolate specific physiological features to explain this condition.

1.2. Epidemiology of Chronic Heart Failure

The prevalence of heart failure is predicted to continue to rise as we develop new strategies that improve survival from coronary artery disease, congenital heart disease and sudden cardiac death. It is estimated that an average hospital trust in the United Kingdom would see approximately 1500 cases who present with symptoms of heart failure in a year, with at least 400 of them been incident cases (14).

Community and population-based studies have demonstrated that the prevalence of heart failure is higher in older patients (>75 years) and in men (15;16). The Rotterdam heart study examined 5540 participants over the age of 55 years and found an overall prevalence rate of heart failure of 3.7%. In the sub-group of these patients who had trans-thoracic echocardiographic examination, 2.2% had asymptomatic left ventricular systolic dysfunction (LVSD) suggesting that a significant number of patients with organic disease may not exhibit clinical symptoms or signs. It is possible therefore that prevalence rates might be higher in populations where cardiac ultrasound was not employed to aid diagnosis (17).
Those findings mirrored that of the North Glasgow Multinational Monitoring of trends and determinants in cardiovascular disease (MONICA) study that reported an estimated prevalence of heart failure of 2.9% based on the presence of LVSD with half of these patients being asymptomatic (15).

More recent data show that on average, the diagnosis of heart failure is made in men 5 years earlier than women and significantly more men than women have evidence of Left Ventricular Systolic Dysfunction (LVSD) (Figure 1). It has also been observed that people of a lower socioeconomic background are more likely to develop this syndrome at an earlier age. These patients are less likely to seek or have access to clinical care and may therefore have a delay in diagnosis. As a consequence the potential for such patients to decompensate would be higher until they are appropriately managed on prognostically relevant treatment (18).

![Figure 1: Age and Sex Distribution in Chronic Heart Failure Based on The National Heart Failure Audit 2012](image)

There are fewer studies on incidence of heart failure. In the Hillingdon study, it was ascertained in a west London district; (population 151,000); that the incidence of heart failure was 0.02/1000 per year in the 25-34 year age group rising to 11.6/1000 per year in those aged over 85 years showing that this was a disease predominantly of the elderly with a median age at presentation of 76 years (16).
Data from the United States, suggest incidence rates of 19.3/1000 person years in a 5.5 year follow up period (19), and this is similar to a much larger study using a General Practice based cohort of patients in the United Kingdom where the overall incidence rose to 20.2/1000 person years if patients with a classification for ‘probable diagnosis’ of heart failure were included (20).

Mortality rates up to 62% in Men and 42% in women at 5 years from incident diagnosis have previously been reported (21). Over the past decades however, it is clear that advances in pharmacological and device therapy for heart failure have had a positive impact on survival outcomes. This is demonstrated by a fall in all-cause mortality over a 6 month follow-up period from 25% to 14% from a recent comparison of secular trends in survival for the same geographic population (22).

Overall the incidence of heart failure has not increased over the last 40 years of the Framingham study, and in fact may have declined. The trend however is towards an upward increase in prevalence rates as we improve our diagnostic abilities for this syndrome and halt the progression of previously fatal cardiovascular diseases as a result of improved treatment and with a rapidly ageing population.

It is important to note that majority of these epidemiological studies have utilised patients with LVSD to define heart failure however the clinical syndrome of CHF also occurs in a cohort of patients who have a preserved ejection fraction. Up to half of patients with HF may have Heart failure with preserved ejection fraction (HFPEF), and this may skew prevalence rates of CHF higher if these figures were considered in prior studies that have excluded this patient group (23).
1.3. Clinical Course

Heart Failure runs a highly variable and sometimes unpredictable course. Two patterns are described.

1.3.1. Acute Heart Failure

1.3.1.1. De novo Acute Heart Failure (De novo AHF)

This is usually the presenting state of heart failure at diagnosis following insult or injury to an undamaged heart. The most likely precipitant particularly when symptoms develop abruptly is an acute coronary syndrome. The patient may present to the emergency room in pulmonary oedema or in cardiogenic shock. Once this acute phase resolves the patient may over time develop a stable CHF syndrome if there was significant persisting myocardial injury.

1.3.1.2. Acute Decompensated Heart Failure (ADHF)

While there is no consensus definition for ADHF, it is generally agreed that a patient has arrived at a state of decompensated heart failure when they have developed signs and symptoms of fluid overload to the extent that they require a hospital admission for intravenous administration of diuretics to ‘offload’.

A patient with stable CHF may periodically deteriorate and this may happen acutely, with acute coronary ischaemia and arrhythmias been the main precipitants leading to a hospital admission, or it may occur sub-acute, over days or weeks, with the usual precipitants in this case including non-compliance with medication or dietary restrictions, uncontrolled hypertension, and infections. Other known causes include, anaemia, renal dysfunction and side effects of medication such as non-steroidal anti-inflammatory drugs (NSAIDS) and calcium channel blockers (24;24).

If the patient succumbs to any one of these triggers, compensatory mechanisms and medication become insufficient to maintain a euvolaemic status, and fluid overload ensues. At this point, the patient is said to have entered a state of acute decompensated heart failure (ADHF). This process may occur over days or weeks (25) (See Figure 2).
Figure 2: Number of days from onset of worsening of selected symptoms of heart failure to hospital admission in 83 patients admitted with heart failure. Most symptoms were present 1 week before admission, which suggests that earlier outpatient intervention might reduce hospitalisations (26).

Generally, the clinical course of heart failure may see a patient have repeated periods of ADHF leading to potential hospitalisation for treatment followed by a recovery period leading back to stability. Importantly, each episode of ADHF and subsequent hospitalisation reduces the chances for complete recovery of the myocardium back to baseline and there is often progression of ventricular dysfunction (27). The trajectory that follows therefore is often one of longer ADHF episodes and shorter stable periods, which ultimately leads to worse outcomes (Figure 3).
1.3.2. **Chronic Heart Failure**

This is the clinical state in which majority of heart failure patients are found, and at various levels of symptomatology, according to their New York Heart Association (NYHA) classification (Table 1). Patients in NYHA class I have no symptoms attributable to heart disease; those in NYHA classes II, III or IV are sometimes said to have mild, moderate or severe symptoms, respectively. Most patients with CHF usually have some symptoms but cope with this by minimising activity.

In clinical practice, a patient is considered to be in a ‘stable state’ of CHF if following drug and/or device therapy, there are minimal restrictions to activities of daily living from heart failure symptoms and they have a reasonable quality of life regardless of NYHA class. These treated patients may have symptoms and signs that have been unchanged for at least a month (4). Important markers of stability include freedom from clinical congestion, usually defined as the absence of orthopnoea or Paroxysmal Nocturnal Dyspnoea (PND), peripheral oedema, a recent increase in weight or diuretic doses and a raised JVP (28). These patients may continue in this state for months or years following initial diagnosis and especially if the patient was on optimum medical management.
The usual outcomes from this position is that the patient may remain in this situation for prolonged spells and in some cases completely recover myocardial function, depending on the cause; for example a viral cardiomyopathy; or alternatively develop periodic states of acute decompensation of heart failure (ADHF) leading to hospitalisation for treatment. There is also a group of CHF patients who would progressively decline; in a less punctuated and more relentless way towards death or transplantation even when on the appropriate drug or device treatment (29).

Regardless of the course taken, the patient with CHF is always at risk of sudden death; usually from arrhythmias and these patients may have related symptoms such as palpitations and presyncope.

Table 1: New York Heart Association Functional Classification of Heart Failure

1.4. Pathophysiology of Chronic Heart Failure

CHF results from a complex inter-play of structural, neurohormonal, vascular and hemodynamic mechanisms. A variety of causes are well documented but in some cases the exact trigger cannot be identified (30). Irrespective of the cause however, what is critical in this vicious circle is that the patient arrives at a critical point where there is an inability of the myocardium to maintain a sufficient cardiac output to meet what is required for normal organ function. It is this shortage in supply against the body’s usual demands; which goes up during exercise, which results in majority of the symptoms that accompanies this syndrome.

The failing heart responds to this by activating mechanism that try to restore cardiac output and ensure that organ tissue perfusion is maintained at a near normal level. These mechanisms
include structural changes to the heart muscle, as well as hormonal and neural processes. The long-term effects of these changes are deleterious but in the short term they augment cardiac function to a reasonable degree.

1.4.1. Frank-Starling Mechanism

The Frank-Starling mechanism is one of the most important physiological principles for regulation of myocardial contractile performance. It is intrinsic to cardiac muscle and this principle describes the ability of the heart to change its force of contraction and therefore stroke volume in response to changes in venous return – the end diastolic volume (EDV) – when all other factors remain constant.

This mechanism is particularly important in Acute Heart Failure following abrupt insult to the myocardium and is evident within minutes of cardiac injury. As left ventricular filling pressures rises following the sudden fall in stroke volume, this mechanism ensures that an adequate cardiac output is delivered by matching this with the increased venous return. It does this by increasing myocardial sarcomere length, which up to a point increases myocyte tension, in response to the increased EDV and thereby increasing stroke volume.

The exact mechanism relates to the stretch or length of myocardial fibres, which is determined by the resting force, myocardial compliance, and the degree of filling from the left atrium. This distending force is the preload of the muscle and ventricular performance is enhanced with increasing sarcomere length, which results in an improved cardiac output.

In Chronic heart failure, this mechanism is attenuated (31) but is still present, even though significant alterations of diastolic myocardial distensibility may be evident. In this situation, the body utilises the Frank-Starling mechanism by increasing sodium and water retention as well as venoconstriction in an attempt to increase left ventricular filling pressures and preload. The consequence of this haemodynamic change is an increasing venous return to the heart; preload; which stretches the ventricular wall increasing EDV and causing cardiac muscle to contract more forcefully. This initial increased stroke volume is beneficial to maintain a normal cardiac output.

However in patients with CHF there are little changes in cardiac output even with increasing stretch or left ventricular end diastolic volume (See Figure 4). This is because sarcomere-length
reserve becomes rapidly exhausted, and there is inadequate sarcomere extension due to impaired relaxation or reduced distensibility of the damaged ventricular wall (32).

This mechanism therefore becomes inadequate to continue to maintain normal haemodynamics. Further, abnormally increased left atrial pressures leads to increase pulmonary capillary pressures, which contribute to increased symptoms of shortness of breath experienced by patients with chronic heart failure. In addition sodium and water retention in the vascular wall causes arterial stiffening and constriction leading to an increased afterload that causes the heart to fail further.

Figure 4: Graphical Representation of Frank-Starling Curve. In the normal heart, as Preload (End-Diastolic Volume/Pressure) increases, there is an increase in the stroke volume. In Heart failure this response is attenuated and a plateau of response is reached early.

1.4.2. Ventricular Remodelling

The healthy human heart is estimated to contain 3 billion cardiomyocytes in the ventricular myocardium, which are arranged in a complex three-dimensional pattern within myocardial tissue. In a diseased state, these cells may elongate, increase in size or may undergo cell death by
necrosis or apoptosis. Three distinct macroscopic patterns may occur in myocytes of the failing myocardium in the context of chronic heart failure. These include dilatation, hypertrophy and the formation of scar tissue. These changes are grouped under the heading ‘remodelling’ which is the term commonly used to describe the changes in size, shape and function of the left ventricle that may occur following myocardial injury. These changes may be the consequence of the primary insult to the myocardium and can occur within hours to days, or may be part of a much longer pathophysiological process over months.

1.4.2.1. Dilatation

Dilatation results in an enlargement of the cardiac chambers with the initial effect being an augmentation of cardiac output as a result of greater stroke volume. The latter effects include functional valvular regurgitation, arrhythmias from micro re-entry and mechanical dysynchrony as the heart loses its geometry and consequently its efficiency leading to a worsening of heart function. Dilatation occurs when there is volume overload of the ventricle but may also be from de-novo cardiomyopathies, primary valvular disease or myocardial infarction.

1.4.2.2. Hypertrophy

The cardiac myocytes may hypertrophy in response to an excessive afterload such as in hypertension, so as to maintain a normal stroke volume. Other stimuli for this process include oxidative stress, inflammation and neurohormonal driven signalling pathways. Hypertrophy results in a non-compliant ventricle that does not relax appropriately, the resultant effect been an increase in left atrial pressures from impaired filling of the ventricles, which is transmitted back into the pulmonary vasculature leading to congestion. Initially systolic function of the ventricles may be preserved but as the process carries on, there may be dilatation and thinning of the ventricular walls leading to a decline in function (33).

1.4.2.3. Myocardial Cell Death

Focal myocardial injury may lead to scar tissue formation and a reduction in the amount of myocytes that can contribute effectively to the cardiac output. The aetiology is usually coronary ischaemia leading to myocardial infarction and if a large area of the myocardium is affected, there may also be associated changes of hypertrophy or dilation in adjacent myocytes. Cell death
in this case is a result of acute cell necrosis but programmed cell death or apoptosis is also known to occur. Apoptosis is rare in the healthy heart but the rates are significantly increased in the chronically failing heart irrespective of aetiology (34). It is an energy consuming process via protein and chromatin fragmentation that does not trigger an immune response. In contrast, necrosis is characterised by cell swelling, membrane lysis and release of intracellular contents into the interstitial space resulting in inflammation and secondary injury. Both processes may lead to scar tissue formation as the body works to replace infarcted myocardium. Scar tissue is dynamic tissue, which is cellular, vascularised and metabolically active, it however remains functionally dormant in its contributions to cardiac output (35).

In summary the architectural changes in the hearts structure following damage are in the first instance compensatory, aimed at preservation of cardiac function, but eventually the changes results in inefficiencies ultimately leading to a worsened situation.

1.4.3. Neurohormonal Activation

These processes primarily refer to activation of the sympathetic system and the renin angiotensin aldosterone system which are well developed response systems in place designed to respond to altered cardiac function by maintaining blood pressure and critical organ perfusion in the short term but becoming maladaptive when chronically stimulated.

1.4.3.1. Sympathetic Nervous System (SNS)

When cardiac output and blood pressure falls, afferent signals are carried from baroreceptors mainly in the carotids and aortic arch, to the sympathetic chain and adrenal medulla leading to an increase in central sympathetic flow. There is an attendant increase in the amount of circulating catecholamines, noradrenaline and adrenaline, which act rapidly but for a short period to increase the myocardial contractility by catecholine-mediated intracellular signal transduction pathways which improve the efficiency of myocardial excitation-coupling function. There is also a decreased re-uptake of these neurohormones, which prolongs their presence in peripheral circulation.

The immediate effect is an increase in cardiac output from a direct increase in myocardial contractility, vasoconstriction and an increase in heart rate which immediately supports the failing circulation by improving perfusion pressures to the vital organs.
In the long term however this process is damaging to the heart from direct toxic damage to the myocytes from these catecholamines, which promote apoptosis, calcium overload and ventricular remodelling from hypertrophy (36). Furthermore there is an eventual down regulation of β1-adrenoceptors as well as a maximising of intracellular signalling pathway effector mechanisms, which further limits the ability of the heart to respond to this catecholamine surge (37).

1.4.3.2. Renin Aldosterone Angiotensin System (RAAS)

The RAAS plays an instrumental role as a systemic response to the failing heart. Renin is released from the juxtaglomerular apparatus in the Bowman’s capsule of the nephron in response to β-adrenoceptor stimulation and a fall in renal blood flow. Its actions on circulating angiotensinogen leads to the production on angiotensin I, which is converted by the angiotensin converting enzyme (ACE) to angiotensin II which is the main effector hormone of RAAS.

Its main actions are to increase blood pressure by potent vasoconstriction and salt and water retention, a direct effect of aldosterone release from the renal cortex. It also stimulates the release of other hormones including vasopressin, endothelin and catecholamines from stimulation of the SNS. Angiotensin II mediates this effects via two main receptors type I (AT₁) and II (AT₂), the former mainly accounting for most of the deleterious effects of this hormone.

1.4.3.3. Inflammatory Responses

Several inflammatory markers are known to have elevated plasma concentrations in patients with heart failure and potentially play an important role in its pathophysiology by activation of the immune system (38). C-reactive protein (CRP) may be raised as part of a non-specific generalised inflammation in heart failure and is also known to be associated with a worse outcome particularly in severe heart failure (39). Tumour necrosis factor (TNFα) is predominantly released from macrophages and studies have shown that an increased level along with its soluble receptors suggest an increase in severity of heart failure (40). Interleukins 1 (IL1) and 6 (IL-6) are other cytokines that have been widely studied and are an independent predictor of prognosis in HF (41), exerting their effects via negative haemodynamic and pro-inflammatory toxic effects on the myocardium contributing to apoptosis, myocyte hypertrophy and progressive adverse ventricular re-modelling (42).
1.4.3.4. The Role of Natriuretic Peptides

These hormones are released in response to increase myocardial wall stress as well as stimulus from other circulating neurohormones, aldosterone, angiotensin II, endothelin, vasopressin and noradrenaline. There are two main types, the Atrial Natriuretic Peptide (ANP) released from both atria and ventricles and the B-type natriuretic peptide (BNP) released from cardiac ventricles.

In HF, natriuretic peptides represent a weak counter-regulatory system, which attempts to maintain cardiovascular homeostasis by increasing natriuresis, diuresis and vasodilation of peripheral vasculature. In essence they directly antagonise the actions of angiotensin II, catecholamines and aldosterone but the effects are ultimately insufficient to prevent the progression of HF (43).

1.5. Diagnosis of Chronic Heart Failure

There are no pathognomonic symptoms or signs of heart failure and so a diagnosis based on clinical features alone is difficult to achieve (44;45).

Patients may complain of symptoms that include dyspnoea, fatigue and a reduced exercise tolerance. Signs that may be identified include a raised jugular venous pressure, peripheral oedema and basal lung crepitation. These features are not specific to the heart failure syndrome and may be difficult to detect in early disease and also in certain individuals (obese patients or those with chronic obstructive airway disease). They are also not always reproducible (46).

In addition to clinical features therefore, current guidelines recommend early diagnosis of suspected heart failure using imaging, in particular transthoracic echocardiography, to assess left ventricular systolic function and valvular disease (47). Radionuclide angiography and cardiac magnetic resonance imaging are other modalities that can be employed for this assessment where necessary. Where there is a history of previous myocardial infarction, an echocardiogram should be performed within 2 weeks. Alternatively, if measured plasma levels of natriuretic peptides are high, imaging should be performed within 6 weeks.

NICE has recommended that a specialist, usually a cardiologist with an interest in heart failure is recommended to lead a multidisciplinary team tasked to manage these patients. Figure 5 shows the current NICE recommended pathway to diagnosis of heart failure.
Figure 5: NICE recommended pathway for diagnosing Heart Failure. (47)
1.6. Treatment of Chronic Heart Failure (due to LVSD)

1.6.1. Goals of Treatment

The main objectives of treating patients with heart failure are to reduce symptoms, prevent hospitalisations and to reduce mortality. These targets are achieved using a variety of strategies that are complimentary.

1.6.2. Contemporary Pharmacological Treatment

A good body of evidence that demonstrate mortality benefit supports drug treatment of heart failure (48-50). Provided that there are no contra-indications, all patients should be offered disease modifying drug therapy that includes an ACE-inhibitor or Angiotensin II receptor blocker (AIIRB), a beta-blocker and a mineralocorticoid receptor antagonist (MRA). Other drug treatments include the use Hydralazine where intolerant of ACEi or AIIRBs and the use of Ivabradine for heart rate reduction where a patient has failed to achieve optimal control on maximally tolerated beta blockade (51). In addition, diuretics are usually prescribed for symptom control and to maintain euvolaemia. (See Figure 6)

1.6.3. Non-Surgical Device Therapy

Heart failure patients who are currently experiencing or have recently experienced NYHA class III–IV symptoms, with a broad QRS complex on ECG (>120ms) and on optimal drug therapy are usually recommended to have treatment with Cardiac Resynchronisation therapy. This has been shown to improve symptoms and reduce mortality (52;53). Where these patients fulfil risk criteria for sudden cardiac death, an Implanted Cardioverter Defibrillator (ICD) is also recommended as part of their therapy (4;47) (54).

1.6.4. Treatment of Co-Morbidities

Aggressive treatment of co-morbidities including Hypertension, Diabetes, Obesity, Anaemia and Sleep disordered breathing improves outcomes in these patients and as such they should be aggressively managed (55-58)
1.6.5. Non Pharmacological Therapy

1.6.5.1. Lifestyle Modification

Smoking cessation and the reduction of alcohol intake (10-20g per day) is a general recommendation as part of lifestyle changes in these patients. Regular exercise and a balanced nutrition with low salt intake (not exceeding 2-3g per day) are also recommended to reduce risk (4) (47).

Oxygen therapy is advisable for patients with New York Heart Association (NYHA) class III or IV symptoms that embark on air travel (59). Patients who are this symptomatic are usually disqualified from driving low or heavy goods vehicles (60).

1.6.5.2. Multidisciplinary Management and Palliative Care

An integrated approach for managing heart failure patients involving primary and secondary care is usually recommended and end-of-life care should be in place for those with advanced forms of the syndrome.

A summary of recommended treatment pathway for heart failure due to left ventricular systolic dysfunction is shown in Figure 6.
Figure 6: Treatment options for patients with chronic symptomatic systolic heart failure (NYHA functional class II–IV). (4)
SECTION TWO: Acute Decompensation of Chronic Heart Failure
1.7. The Burden of Acute Decompensated Heart Failure

Acute Decompensation of Heart Failure (ADHF) is associated with increased morbidity and mortality and around 4-7% of patients who suffer a decompensation do not survive to hospital discharge (27;61). This rises to up to 45% in patients who were admitted initially in cardiogenic shock (61). Even in those patients who survive, there is still a high risk of subsequent re-admission. In one study up to 30% of patients who were discharged following an admission with ADHF were re-admitted within 3 months and this included up to 9% who also died during this period (62). In the United Kingdom about 12% of patients who are admitted in a decompensated state of heart failure will die (63). It is therefore desirable to keep patients with CHF as stable as possible, which may prevent progression of disease and a hospital admission for decompensation.

Deterioration of heart failure is also expensive and this mainly relates to the costs of admitting patients into hospital and consequent number of inpatient days required to achieve stability. It is estimated that up to 2% of the NHS budget is spent on patients with chronic heart failure and 70% of these costs relate to inpatient stay for treatment of ADHF (2).

1.8. Definition

There is no consensus definition for acute decompensated heart failure (ADHF); however it is generally agreed that a patient has arrived at a decompensated state when they have developed symptoms and signs of fluid overload usually to the extent that they require a hospital admission for intravenous administration of diuretics to ‘offload’.

Acute decompensation of heart failure (ADHF) is associated with a rapid onset of, or change in, symptoms and signs of HF. It is usually life-threatening and requires immediate medical attention, which usually leads to urgent admission to hospital. Diagnosis and treatment are usually carried out in parallel, especially in patients who are particularly unwell, and management must be initiated promptly.
In some cases, expert patients who are experienced in managing their disease may avert a hospital admission by increasing the dose of their oral diuretics at the first sign of change of symptoms and this may be sufficient to restore stability.

1.9. Classification

Acute heart failure has previously been classified according to various clinical presentations by the European Society of Cardiology (ESC) (64) see Table 2.

<table>
<thead>
<tr>
<th>Classification</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute decompensated heart failure (de novo or as decompensation of chronic heart failure)</td>
<td></td>
</tr>
<tr>
<td>Hypertensive AHF- relatively preserved LVEF</td>
<td></td>
</tr>
<tr>
<td>Pulmonary oedema (verified by chest X-ray)</td>
<td></td>
</tr>
<tr>
<td>Cardiogenic shock – characterised by tissue hypoperfusion</td>
<td></td>
</tr>
<tr>
<td>High output Failure- for example in Thyrotoxicosis, Anaemia, and Pregnancy</td>
<td></td>
</tr>
<tr>
<td>Right heart Failure</td>
<td></td>
</tr>
</tbody>
</table>

Table 2: Clinical classification of acute heart failure syndrome. (64)

Other classifications that have been used include the Killip and Forrester classifications system but these have only been validated in a population presenting with acute myocardial infarction. The Killip classification was designed to provide a clinical estimate of the severity of myocardial derangement in the treatment of AMI(65) while the Forrester classification describes four groups of heart failure patients, according to clinical and haemodynamic status (66) .

In the clinical setting, because there is a lot of overlap of these presentations which do not necessarily affect the management goals of the patient, this method of classification is not included in current guidelines (4).

1.10. Risk Factors For Decompensation of Heart Failure

Patients with a more severe form of the heart failure syndrome (higher NYHA status) have a higher risk of decompensation. In addition a previous history of hospitalisation in the last year and a higher resting heart rate attributes a higher risk of clinical destabilisation in these patients (27;67).
Opasich and colleagues, using The Italian Network on Congestive Heart Failure (IN-CHF), which was a registry of 2,701 outpatients followed by 133 cardiology centres examined variables that were independent predictors of short term (an average of 2 months from index outpatient visit) worsening of heart failure. They found that a previous hospitalization for HF, long duration of symptoms, faster heart rate, atrial fibrillation, high functional class, ischemic aetiology, and low systolic blood pressure resulted as independently associated with clinical destabilization (30). See Figure 7.

![Figure 7: Independent predictors of short-term destabilization. CHD-coronary heart disease; EF-ejection fraction; Na - natraemia; SBP- systolic blood pressure. From the IN-CHF Registry (30)](image)

1.11. Precipitants

It is important to establish aetiology for any decompensation episode as this provides vital information for the index treatment but may also identify preventable causes. However, up to 50% of ADHF episodes have no readily identifiable cause (30).

The Randomised Evaluation of Strategies for Left Ventricular Dysfunction Pilot Study (RESOLVD), was a crossover study where 768 patients with an EF of less than 40% were randomly assigned to receive an ACEi or AIIRB or both for 17 weeks and then randomly assigned to placebo or beta blockers for 26 weeks. During a 7-month period, there were 323 episodes of worsening heart failure and 143 patients required hospitalisation. The factors implicated in these episodes
included, non-compliance with salt and water restriction, pulmonary infective processes (20%), study medication (15%), use of anti-arrhythmic drugs in the last 48 hours (15%), arrhythmias (13%), calcium channel blockers (13%) and inappropriate reductions in CHF therapy (10%) (68).

In the European Heart Failure Surveys EHFS II, decompensation of CHF was the commonest clinical presentation of acute heart failure and almost 25% of these patients presented as a consequence of acute coronary ischaemia. 37% of patients did not have a prior diagnosis of heart failure and in these patients the commonest cause for acute heart failure was also related to acute coronary ischaemia, which occurred in 42% of these patients (69).

The issue of compliance with drug therapy was identified as causative of decompensation in a third of this cohort.

Other causative factors, some of which are preventable that have been identified as possible triggers fore ADHF are listed in Table 3 (24). These have also been identified in other studies and include arrhythmia (particularly atrial fibrillation) and concurrent sepsis (70;71).

<table>
<thead>
<tr>
<th>Factor</th>
<th>No. of Patients</th>
<th>Adjusted Length of Stay Ratio</th>
<th>P Value</th>
<th>Adjusted Odds Ratio (95% Confidence Interval)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemia/acute coronary syndrome</td>
<td>7155</td>
<td>0.99</td>
<td>.22</td>
<td>1.20 (1.03-1.40)</td>
<td>.02</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>6552</td>
<td>1.04</td>
<td>&lt;.001</td>
<td>0.85 (0.71-1.01)</td>
<td>.07</td>
</tr>
<tr>
<td>Nonadherence to diet</td>
<td>2504</td>
<td>0.96</td>
<td>.01</td>
<td>0.69 (0.48-1.00)</td>
<td>.05</td>
</tr>
<tr>
<td>Uncontrolled hypertension</td>
<td>5220</td>
<td>0.96</td>
<td>&lt;.001</td>
<td>0.74 (0.55-0.99)</td>
<td>.04</td>
</tr>
<tr>
<td>Nonadherence to medications</td>
<td>4309</td>
<td>0.96</td>
<td>&lt;.001</td>
<td>0.88 (0.67-1.17)</td>
<td>.39</td>
</tr>
<tr>
<td>Pneumonia/respiratory process</td>
<td>7425</td>
<td>1.08</td>
<td>&lt;.001</td>
<td>1.63 (1.36-1.95)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Worsening renal function</td>
<td>3304</td>
<td>1.09</td>
<td>&lt;.001</td>
<td>1.46 (1.23-1.79)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Other</td>
<td>8171</td>
<td>0.99</td>
<td>.26</td>
<td>1.15 (0.97-1.36)</td>
<td>.10</td>
</tr>
</tbody>
</table>

Table 3: Factors Identified as Precipitating Hospital Admissions for Heart Failure and Clinical Outcomes: findings From OPTIMIZE-HF. (24)

### 1.12. Pathophysiology

Most patients who decompensate have usually been in a stable state of CHF with appropriate fluid balance management and taking disease modifying drug therapy. There is however a precipitant that causes a failure of the compensatory mechanisms that for the most of the time have played an important role in maintaining cardiac stability. In a number of patients, no precipitants are found and their decompensation is part of a progressive heart failure syndrome, which is ultimately terminal.
The clinical presentation of ADHF is characterised by an accumulation of fluid within the periphery (predominantly leg oedema) and within the lung’s interstitial spaces and alveolar spaces as a result of elevated left ventricular filling pressures. Depending on the aetiology of decompensation, this process may happen over hours and in some cases days or weeks before the patient is symptomatic.

1.12.1. Haemodynamic Response

At the start of a decompensation, there is a failure of the Frank-Starlings mechanism to maintain an adequate stroke volume. As end diastolic pressure representing preload of the left ventricle increases, left atrial pressures and eventually pulmonary venous and capillary pressures increase which results in dysfunction at the level of the alveolar basement membrane and overload of the pulmonary lymphatics. This leads to protein-poor fluid transudation from the vessel wall into the alveolar spaces and this occurs in the absence of a primary change in the permeability or integrity of the endothelial and epithelial layers of the pulmonary capillaries. The consequence is accumulation of fluid in the pulmonary interstitium, then alveoli and ultimately airways (72). In addition continued sodium and water retention as the body attempts to increase venous return to the heart leads to further fluid overload.

1.12.2. Neurohormonal Response

Pulmonary congestion increases the work of breathing and reduces gas exchange leading to tissue hypoxia. The body responds to this by increasing its compensatory sympathetic drive and activating of the renin-angiotensin aldosterone system. These promote further sodium and water retention, which in conjunction with increased pulmonary venous capillary pressures and reduced plasma oncotic pressure, results in fluid extravasation and peripheral oedema.

Further, an enhanced sympathetic tone results in tachycardia which shortens diastolic filling time and further impairs left ventricular filling, while peripheral vasoconstriction raises the afterload against which the failing heart now has to work, further worsening the situation. These processes all lead to a further increase in left ventricular end-diastolic pressure and more oedema formation as a vicious cycle ensues.

At the peak of a decompensation episode, the patient experiences worsening of their symptoms and may be unable to perform usual activities of daily living. In addition, the patient’s usual oral
drug therapy becomes insufficient to curb further deterioration. As a result, restoration to stability usually involves a hospital admission with the administration of intravenous diuretics and in some cases inotropes.

1.13. Clinical Features

Unfortunately signs and symptoms of CHF are neither sensitive nor specific (73;74). Similarly in a decompensated state, it has been reported that between 10-20% of patients who are admitted via the emergency department may have initial treatment for an alternative diagnosis for example chronic obstructive airway disease (75).

The predominant feature in ADHF is fluid overload. This may present as symptoms of worsening dyspnoea as a result of pulmonary congestion or as leg oedema and ascites.

It is important to note that while increasing dyspnoea at rest is expected to be a common symptom at presentation, as little as 32% of patients may complain of this at an admission with decompensation. (62)

The pathophysiological processes leading up to ADHF may occur over a period of days to weeks and most patients may have accumulated litres of extracellular fluid before they become symptomatic.

Consequently the clinical features that one would find depend largely on the aetiology and time course of the decompensation. Pulmonary signs for instance may not be so apparent if there has been sufficient time for compensatory mechanisms to be established, such as lymphatic hypertrophy, which may increase the capacity of the heart to deal with high pulmonary artery wedge pressures (PAWP). Some common signs and symptoms of ADHF are listed in Table 4.
 ✓ Dyspnoea
 ✓ Paroxysmal Nocturnal Dyspnoea
 ✓ Increasing Fatigue
 ✓ Increased leg and abdominal swellings
 ✓ Raised JVP
 ✓ Lung crepitation (Bibasal)
 ✓ Leg and Sacral oedema

Table 4: Some Symptoms and Signs of ADHF

1.14. Management

1.14.1. At Home Treatment

In a number of patients simple advice to increase their doses of oral diuretics may be sufficient to restore stability and symptomatic benefit may be evident within the first few days of institution of dose changes with a return to baseline clinical state shortly thereafter. Another measure in the community that may alter course of an on-going decompensation include strict adherence to fluid and dietary salt restriction, however this strategy may be more effective if it is tailored to individual patient requirement (76). Patients may receive this advice from their usual general practitioner or from specialist heart failure nurses in hospital or within the community. A number of patients are also experienced enough to alter doses of their diuretics in response to their symptoms, without the need for formal advice.

1.14.2. In-Hospital Treatment

Some patients however may not respond to the above therapies and may require a period of hospitalisation. In patients who present with severe weight gain, signs and symptoms of pulmonary or systemic congestion; major electrolyte disturbances; repeated implantable cardioverter-defibrillator firings; or pneumonia, it may be prudent to consider hospital admissions in the first instance.
1.14.2.1. Intravenous Loop Diuretics

This is the mainstay of treatment of patients who are hospitalised for treatment of ADHF and the commonest drug used in clinical practice is intravenous Furosemide. It acts mainly on the loop of Henle and reduces sodium and water reabsorption in this section of the nephron. Its other actions are a venodilating effect similar to that of morphine, which leads to decrease pulmonary congestion before the onset of diuresis, which normally peaks about 30-60 minutes after administration (77).

Because volume overload is usually present and the major cause of the most distressing symptoms in these patients, early initiation of treatment is advisable. Better outcomes have also been reported with this prompt approach (78) (79).

Diuretics reduce intravascular volume, lowers central venous and capillary wedge pressures which decreases pulmonary oedema and results in better cardiac output. Other benefits include reductions in tricuspid and mitral regurgitation, consequent to decreases in filling volumes in the right and left ventricles (80). In the majority of patients, this is successful however, treatment may be complicated by hypotension, worsening renal function, electrolyte abnormalities and sometimes arrhythmia. These problems are more likely where aggressive and higher dose diuresis, are administered (81). Continuous infusion diuretic therapy has previously been demonstrated in some studies (82;83) to be of benefit, in avoiding these side effects. However a recent prospective randomised control trial has however shown no evidence of superiority of a bolus over a continuous infusion strategy at either low and high doses, across a broad range of efficacy and safety end points (primary efficacy end-point of patient-reported global assessment of symptoms [mean AUC, 4236±1440 with boluses and 4373±1404 with continuous infusion; P=0.47]) and primary safety end point of the change in serum creatinine level from baseline to 72 hours (mean change in creatinine level, 0.05±0.3 mg per decilitre [4.4±26.5 μmol per litre] with boluses and 0.07±0.3 mg per decilitre [6.2±26.5 μmol per litre] with continuous infusion; P=0.45). The high-dose strategy was, however associated with greater improvement in a number of secondary outcomes (including dyspnoea) but at the expense of more transient worsening of renal function (84).

In the acute stage thiazide diuretics and aldosterone antagonists are less potent when used alone and the former is known the cause more potassium losses for the same quantity of
diuresis. Furthermore, where there is severe renal insufficiency, with glomerular filtration rates less than 30ml/min, thiazide diuretics are ineffective (85). In patients with resistant peripheral oedema (and ascites), a combination of a loop and a thiazide produces a greater diuretic effect but at the expense of worsening renal function (86).

1.14.2.2. Intravenous Vasodilators

These work by stimulating granulocyte cyclase within vascular smooth muscle cells to cause both arterial and venous dilation with an attendant fall in LV filling pressures, increased stroke volume and improved cardiac output without been arrhythmogenic. They do this by denitration of GTN to produce Nitric Oxide (NO) which is a potent activator of guanylate cyclase through heme-dependent mechanisms. The most commonly used in practice is Nitroglycerin.

On large randomised control trial, The Vasodilation in the Management of Acute CHF (VMAC) evaluated the efficacy of IV nitroglycerin in AHF (87). 285 patients with dyspnoea at rest due to heart failure were randomized to IV nitroglycerin or standard care and while there was a trend toward reduced pulmonary capillary wedge pressure (PCWP) in patients receiving nitroglycerin, there was no difference in the co-primary endpoint of dyspnoea. A post-hoc analysis of these patients however showed that those patients who received a higher dose of nitroglycerin had a larger reduction in PCWP.

Where indicated it is has been demonstrated that early initiation of vasodilator therapy is beneficial as highlighted in the ADHERE trial where those who received vasoactive agents within 6 hours of hospital admission, had a significantly lower in-hospital mortality rate and length of hospital stay (62).

Other vasodilators such as Nitroprusside have been used, albeit infrequently in the Intensive care setting, but usually in experienced hands. It is a vasodilator agent that shares many features with nitroglycerin, one of these been the participation of nitric oxide in the vasodilator actions of the drug. It had been favoured because of its prompt and short-lived action allowing for rapid dose titration; however a potentially dangerous effect of the drug is cyanide accumulation during infusions. For this reason it is not commonly used. However simultaneous administration of sodium thiosulfate provides the sulphur donor to prevent cyanide accumulation without reducing the efficacy of Nitroprusside.
Nesiritide a recombinant form of BNP and vasoactive agent was recently found have neutral benefit in addition to standard treatment for ADHF. Two meta-analyses had questioned its impact on mortality and association with worsening renal function (88;89). To clarify this, the ASCEND-HF trial (Effect of Nesiritide in Patients with Acute Decompensated Heart Failure) randomized 7141 patients hospitalized with ADHF to receive either nesiritide or placebo for 24 hours to seven days on top of standard care, which could include other vasoactive drugs. The hazard ratio for death from any cause or hospitalization for heart failure, the primary clinical end point, for nesiritide vs placebo was 0.93 (95% CI 0.80-1.08) (90). This drug is therefore not recommended for routine use in the broad population of patients with acute heart failure.

The 2012 ESC Heart Failure Guidelines recommend a nitrate infusion be considered in patients with pulmonary oedema and SBP > 110 mmHg to reduce PCWP and systemic vascular resistance (4)

1.14.2.3. Inotropes

The use of inotropes such as dopamine or dobutamine or milrinone should be reserved for patients who have advanced heart failure with severe LV systolic dysfunction and severe symptoms due to low cardiac output; such as hypotension and end-organ dysfunction; or in those who are refractory to vasodilator or diuretic therapy. The reasons are the significantly higher incidence of arrhythmia, hypotension and potential to worsen in hospital mortality that is associated with this form of therapy (91). In some UK heart failure centres, a ‘low-dose’ (‘renal-dose’) dopamine is employed where anecdotal evidence shows this dose of about 2.5 - 5 mcg/kg/min is sufficient to encourage diuresis without the attendant arrhythmogenicity associated with higher doses.

1.14.2.4. Ultrafiltration (UF)

This is emerging as a useful way of treating ADHF patients, particularly those who are refractory to or develop side effects/toxicity from the use of intravenous diuretics or inotropes. The main benefit of this strategy is the adjustable fluid removal volume and rates, decreased neurohormonal activation and reduction in the development of electrolyte imbalances. It is however an invasive strategy and requires a skilled practitioner able to insert central venous catheters as well as a hospital high dependency level of care in order to manage these patients.
The UNLOAD trial demonstrated in 200 patients that UF had a sustained clinical benefit, as indicated by fewer re-hospitalizations and unscheduled HF clinic or emergency room visits in this group of patients compared with standard care with the use of IV diuretics as a bolus or infusion. This was despite both strategies having similar overall fluid losses. It was also noted by comparing isotonic fluid removed by UF to hypotonic urine removed by diuretics, that total body sodium removal was more effective in the former group (92).

More recent trials have been less impressive. The Cardiorenal Rescue Study in Acute Decompensated Heart Failure (CARRESS-HF) trial randomized 188 patients who were admitted into hospital with acute decompensation of heart failure, on-going congestion and worsened renal function to ultrafiltration or stepped pharmacologic therapy within 10 days of hospitalization (93).

The primary endpoint was the bivariate change from baseline in the serum creatinine and body weight, assessed 96 hours after randomization. UF was inferior to pharmacologic therapy, due to an increase in the serum creatinine in the UF group (mean change of +0.23 ± 0.7 mg/dL in the UF group vs. -0.04 ± 0.53 mg/dL in the pharmacologic therapy group, p = 0.003). There was no significant difference in weight loss (5.5 ± 5.1 kg in the pharmacologic therapy group vs. 5.7 ± 3.9 kg in the UF group, p = 0.58). There was also no significant difference in mortality or re-hospitalization at 60 days. Further, patients in the ultrafiltration arm had significantly more serious adverse events over 60 days of follow-up (72 % vs. 57 %, p = 0.03), including higher rates of renal failure, bleeding complications, and intravenous catheter-related complications.

There were some important differences between the two trials, which could explain the differing results. In the CARESS-HF study, patients in the pharmacologic arm had a urine output goal of 3-5 Litres a day and as such addition of thiazides, vasodilators and ionotropes were permitted to achieve this. This is in comparison to UNLOAD where a fixed dose of IV diuretic (at least twice the patients admitting oral dose) was required with further titration only at the clinician’s discretion. In addition in CARESS-HF, the UF rate was fixed at 200 mL/hour, whereas UNLOAD allowed for titration of rates up to 500 mL/hour.

The 2012 ESC Heart Failure Guidelines currently recommend that loop diuretics be given as first-line therapy to treat pulmonary congestion, and reserve ultrafiltration for those unresponsive or resistant to diuretics but this was before CARESS-HF was published (4).
1.14.2.5. Non-Invasive Ventilation

Non-Invasive ventilation (NIV) with Continued Pressure Airway Pressure (CPAP) or Non-Invasive Positive Pressure Ventilation (NIPPV) may be used to relieve symptoms of dyspnoea associated with pulmonary oedema. These techniques are not however associated with a mortality benefit (94).

The current recommendation therefore is that NIV may be used as adjunctive therapy to relieve symptoms in patients with pulmonary oedema and respiratory distress or who fail to improve with pharmacological therapy. Contraindications include hypotension, vomiting, possible pneumothorax, and depressed consciousness (4).

1.14.2.6. Monitoring

Treatments with the above strategies are most effective if guided by daily assessments of patient fluid balance and weight to assess for correction of volume overload. Frequent haemodynamic and biochemical monitoring should therefore take place during hospitalisation. These include telemetry monitoring for arrhythmia, electrolyte and serum creatinine levels. Other important blood tests that guide management include measurement of BNP, and the full blood count. These results from blood tests in particular should be examined as often as possible as a number of abnormalities may not manifest as symptoms in the patient.

The management of ADHF remains challenging even when the patient is managed in experienced hands. The main short-term goals of therapy are to relieve symptoms, treat volume overload, and correct hemodynamic abnormalities. This is achieved by reversing central volume redistribution, a reduction in cardiac filling pressures, decreasing afterload, and increasing cardiac output. Long-term goals are mainly to prevent hospitalisation for heart failure and reduce mortality.

No treatment strategy for ADHF succeeds in all cases, and treatment has to be tailored to individual patient needs. Current knowledge of the available approaches and their shortcomings is useful while results of novel therapies with potentially more favourable efficacy and tolerability profiles are currently been evaluated (95;96).
1.15. Predicting decompensation of chronic heart failure using physiological variables

Multiple admissions for the management of decompensation of heart failure are associated with worsened morbidity and increased mortality. However this continues to happen despite the advancements in the care of these patients. Subjective assessments of degree of exercise tolerance, breathlessness and changes in body weight are not perfect and in many cases unreliable as predictors of possible deterioration. As a consequence, health care systems worldwide are striving to develop other strategies that may help reduce the number of hospitalisations and this has been incorporated into various targets set by health funders (97). These newer strategies that are currently employed include telemonitoring and the use of variables from implanted devices. Some of these parameters that are can be measured are discussed below.

1.15.1. Weight

Daily weight measurements are recommended in international guidelines as a useful guide to monitoring volume overload (4;47). This is most reliable if the patients are consistent with the method and time they weigh themselves, so that an accurate trend is obtained. Furthermore, it is recommended that patients 'dry weight' are recorded at regular intervals – this is the steady weight achieved after any adjustments to diuretics and when they are least symptomatic and with no clinical evidence of fluid overload.

There is evidence that in patients who decompensate, subtle weight changes may be evident up to one week beforehand, (98), and this supports current guidelines that recommend that, rather than an absolute weight change, more sensitive and specific as a pointer towards potential HF decompensation, is a trend increase of more than 2 kg over a period of 72 hours (64).

Simple ‘rule of thumb’ guidelines have also been used to predict decompensation of heart failure by alerting clinicians to respond to a 1.36kg increase in weight over a 24-hour period for instance (99) but these are largely unreliable owing to considerable daily weight fluctuations that may not be related to worsening of heart failure.
Moreover, a more recent study which trialled an alert system based on weight thresholds that were in proportion to and individualised to each patients natural weight variability rather than a single absolute weight threshold, showed that this system was significantly more sensitive (82%) compared to guideline weight thresholds (21%) or rule of thumb thresholds of 1.36kg over 24 hours (46%). Specificity was however not significantly different between the two methods (<40%) (100).

Even so, weight measurements are not very accurate at predicting decompensation. An outpatient analysis of 77 patients found that a weight gain of more than 2 kg over 48–72 h demonstrated good specificity (97%) but poor sensitivity (9%) for predicting clinical deterioration. A weight increase of more than 2% above dry weight had a similar specificity (94%) with only marginal improvement in sensitivity (17%). In spite of the high specificities obtained, these results suggest that the lack of such a change in weight cannot be taken to exclude decompensation (101).

Even in patients studied with more severe heart failure (EF<30%), the more recent WISH (Weight Monitoring in Severe Heart Failure) trial which took place in 6 Swedish centres, demonstrated that more frequent monitoring of weight via electronic scales in the intervention group, did not result in a reduction of the primary end-point which was cardiac re-hospitalisation. [Control vs Intervention 70/153 vs 70/166; Hazard Ratio 0.90, CI 0.61-1.13; p=0.24) (102).

Weight gain on its own is therefore not sensitive enough to detect HF deterioration (101). Furthermore, it has also been shown that not all decompensation episodes are associated with observed weight gain (103). A theory explaining this is that during a decompensation of heart failure, fluid redistribution into ‘third’ spaces as opposed to an actual increase in the fluid overload, predominates (104).

Regardless of these limitations, the ease of monitoring makes it recommended in international guidelines especially in the outpatient setting to guide diuretic management and when combined with other variables may be useful in predicting episodes of deterioration (4) (105).
1.15.2. Symptoms

Common symptoms that are associated heart failure decompensation include orthopnoea, leg swellings and exercise intolerance (See Figure 8). Less specific symptoms such as fatigue may also occur. A high percentage of patients may be aware of their symptoms for a number of weeks and only seek help when their symptoms become unbearable (26).

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Number (%) with Symptom Exacerbation</th>
<th>Duration of Worsening (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mean ± SD</td>
</tr>
<tr>
<td>Edema</td>
<td>64 (77)</td>
<td>12.4 ± 11.1</td>
</tr>
<tr>
<td>Cough</td>
<td>57 (69)</td>
<td>10.1 ± 9.3</td>
</tr>
<tr>
<td>Weight gain</td>
<td>34 (41)</td>
<td>11.4 ± 9.4</td>
</tr>
<tr>
<td>Dyspnea walking</td>
<td>74 (89)</td>
<td>8.4 ± 7.5</td>
</tr>
<tr>
<td>Dyspnea lying flat</td>
<td>67 (81)</td>
<td>8.4 ± 7.7</td>
</tr>
<tr>
<td>Dyspnea at rest</td>
<td>21 (25)</td>
<td>6.4 ± 6.3</td>
</tr>
</tbody>
</table>

Figure 8: Common symptoms associated with ADHF and Duration of Worsening Symptoms before Admission for Heart Failure (n=83 Patients) (26).

Unfortunately symptoms are very subjective and attempts at standardizing responses which has been used in telemonitoring systems for instance, can be frustrating to the patient, who cannot always ‘box’ their symptoms into set categories. They are therefore not very reliable assessments. The New York Heart Association (NYHA) classification of HF is a standard scale that is utilised by health care professionals to grade the severity of HF according to patients’ functional limitation (106). It is a tool that is delivered by asking patients set questions about their exercise capacity. Again because of its subjective nature, in many cases patients over or under estimate their abilities. It is therefore limited by its poor sensitivity and poor reproducibility among clinicians and amongst patients (107).

Peripheral oedema is usually evaluated from ankle pitting and this is often done in routine clinic examinations. Most patients may notice when there is a marked increase in the size of their ankles –helped by the fact that their shoes do not fit – but by this time there may be in excess of 5 L of fluid overload. Similarly fluid accumulation in the abdomen as evident by increased girth.
may not be immediately noticeable in the initial stages to the patient and as such they may not report it.

1.15.3. Blood Pressure

Non-invasive blood pressure monitoring is relatively easy to evaluate and patients who have home monitoring systems, utilise wrist or brachial cuff measurements for this purpose (5). Poorly controlled hypertension can precipitate decompensation of CHF so this can be a useful monitoring tool. In addition, a low systemic blood pressure with resulting symptoms of postural hypotension may be an early indicator of over diuresis or high doses of neurohormonal agents used to manage heart failure.

1.15.4. Heart Rate Variability Monitoring and Arrhythmia

CHF is associated with autonomic dysfunction, which can be quantified by measuring Heart Rate Variability (HRV). This can provide independent information on the risk of death in ambulant outpatients with CHF. Patients with implanted devices such as pacemakers or defibrillators can have this parameter analysed, which can be used to guide management.

In the UK-Heart study, which was a prospective study of 433 patients with CHF, HRV was shown to be a powerful predictor of mortality, with a risk ratio for a 41.2-ms decrease in HRV- measured by the standard deviation of normal-to-normal RR intervals on 24 hour ambulatory ECG monitoring (SDNN), of 1.62 (95% CI, 1.16 to 2.44)(108). The annual mortality rate for the study population in SDNN subgroups was 5.5% for >100 ms, 12.7% for 50 to 100 ms, and 51.4% for <50 ms.

Adamson and colleagues demonstrated the usefulness of this measure, in a study of 288 patients with implanted devices and moderate to severe heart failure. They found that HRV was 70% sensitive at detecting hospitalisations but also found that it had a high false positive rate with 2.4 false-positives per patient-year of follow-up (109). A disadvantage is the requirement for sinus rhythm and non-atrially dependent pacing which may make this impractical to measure in certain patients.

Arrhythmia is a common cause of decompensation (30) so it is useful to assess for this. Ventricular arrhythmia can be fatal while atrial arrhythmia may be a precursor to deterioration in symptoms. Some home telemonitoring systems have single lead ECG as part of the recording but
perhaps much easier to assess is the continuous automatic data collected from readings of implanted devices such as pacemakers and implanted cardioverter defibrillators.

1.15.5. **Pulmonary Artery Pressure Monitoring**

This is a relatively new but invasive means of monitoring patients with heart failure. The rationale for exploring this area is based on evidence that suggest an increase in pulmonary diastolic pressures as patients move from a chronic stable to acute decompensated state of heart failure (110).

The COMPASS-HF (Chronicle Offers Management to Patients with Advanced Signs and Symptoms of Heart Failure) study was a prospective, multicentre, randomized, single-blind, parallel-controlled trial of 134 advanced HF patients (NYHA III or IV) who were randomised to receive an implantable continuous hemodynamic monitor (Chronicle, Medtronic Inc., Minneapolis, Minnesota) where continuous intra-cardiac pressure monitoring, including estimated pulmonary arterial diastolic pressures, was used to manage volume status in addition to optimal medical therapy. The control group consisted of 140 similar patients where management of HF was only by usual guideline recommended care. There was a 21% lower rate of all HF-related events compared with the control group but this was not statistically significant (p = 0.33)(111).

Further studies using this method have been more promising. The CHAMPION trial (CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA Class III Patients) randomised patients to a treatment group where their heart failure was managed based on daily measurement of pulmonary artery pressures in addition to standard care, or a control group where they were managed based on standard care alone. They were able to demonstrate a 37% reduction in heart-failure-related hospitalisation with this strategy of management compared with the control group (158 vs 254, HR 0·63, 95% CI 0·52—0·77; p<0·0001) (112).

1.15.6. **Intrathoracic Impedance (IMP)**

IMP is a measure of the resistance against electrical current passing across the lung field. Fluid conducts better than air and as such when there is accumulation of intrathoracic fluid during pulmonary congestion, this form a better conductance medium and impedance falls. The correlation between LV filling pressures and IMP is therefore inversed, that is, it decreases when there is evolving fluid accumulation within the thoracic cage. In HF patients, serial measurements
of thoracic impedance have been demonstrated to reflect pulmonary fluid status and, importantly, as shown in a small study, have the ability to predict HF decompensation even before the onset of symptoms (113). Many implanted devices can collect this data and its usefulness will be discussed in the next sections.

1.16. Home and Telemonitoring Related Variables

Telemonitoring (TM) in general refers to monitoring patients who are not at the same location as the health care provider. These patients are usually at home and send clinical information that can be used to manage their conditions by telephone to their managing health care providers. Most of these systems also involve subjective questioning regarding the patient’s health and comfort which takes place over the phone, or telemonitoring software.

A more specific definition of Telemonitoring (TM) in heart failure is the use of non-invasive measurements such as blood pressure and weight in addition to questions that cover general health and symptoms to monitor the clinical status of patients with chronic heart failure.

A Cochrane meta-analysis published by Inglis and colleagues, where 8323 patients who received Telemonitoring (Telemonitoring and/or Structured Telephone Support <STS>) as the primary component of their CHF management demonstrated a reduction in all-cause mortality [ (RR) 0.66 [95% confidence interval (CI) 0.54–0.81], P< 0.0001] in the TM arm. STS showed a similar, but non-significant trend towards improved survival [RR 0.88 (95% CI 0.76–1.01), P= 0.08]. However both TM [RR 0.79 (95% CI 0.67–0.94),P= 0.008], and STS [RR 0.77 (95% CI 0.68–0.87), P< 0.0001] reduced CHF-related hospitalizations, improved quality of life, reduced costs, and were acceptable to patients (5)

The weight monitoring in heart failure trial (WHARF-HF) was one of the first clinical trials to evaluate the impact of technologically driven interventions, which monitor weight and symptoms to manage heart failure. The end-points included hospitalisations, mortality and patients’ self-assessed quality of life.

Two hundred and eighty patients were randomised to a usual care group consisting of routine outpatient appointments and follow up with community nurses or a device care group, where they received an electronic scale that transmitted daily weights twice a day and an online daily symptoms questionnaire. There was no difference in the primary end point of hospital first re-
hospitalisation after 180 days however there was a 52% reduction in mortality for patients randomised to the device group (114).

TELE-HF represented the single largest trial, which evaluated TM of patients with chronic heart failure, and evaluated 1653 patients who were randomised equally to either receive a telephone based system of monitoring and management of their heart failure or usual care. There were no benefits seen in the primary end-point of reducing re-hospitalisation rates or mortality in the treatment group compared to usual care arm. Furthermore there was no benefit seen in any of the pre-specified secondary endpoints and sub group analysis did not demonstrate any significant differences between either groups (115).

There is the argument that the patients in the Tele-HF study were younger than in most heart failure studies (median age was 61years) however these patients had a wide range of co-morbidities and the majority were at class NYHA III at enrolment. There was also a huge commitment to adhering to the protocol and responding to system alerts by the trialists, including making a significant effort towards ensuring active patient participation. It has to be noted that adherence to intervention was still low at 45% and 14% did not even use it.

Following this, another large prospective randomised, multicentre trial, TIM-HF, examined if physician-led remote telemedical management (RTM) compared with usual care would result in reduced mortality in ambulatory patients with chronic heart failure. This study failed to confirm the benefits seen in the aforementioned meta-analysis (116).

These studies, have measured variables that include a combination of weight, blood pressure, heart rate, pulse oximetry, 12 lead electrocardiographs, in addition to symptoms. (See Table 5 for summary). Only a few of these studies have measured the outcome when investigators respond to changes in one variable and most of the results from these published studies are a consequence of outcomes relating to responses from a combination of variables.

The Whole Systems Demonstrator Telehealth trial, n=3230 was a large UK department of health funded trial designed to test the benefits of integrated health and social care supported by assistive technologies on outcomes in patients with the long-term conditions of Diabetes, COPD and Heart Failure.

The primary endpoint was an improvement in health related quality of life or psychological outcomes obtained from questionnaires that assessed generic, health related quality of life,
anxiety and depressive episodes at 4 and 12 months after recruitment. The initial report of these patients who were recruited from 3 regions in England (Cornwall, Kent and Newham) and randomised to an interventional arm (n= 845) where they received telehealth and a control arm where they continued with usual care alone (n=728) demonstrated only a small and non-significant difference for all outcomes (telecare vs usual care) either using an intention-to-treat (0.480≤P≤0.904) or per-protocol analysis (0.273≤P≤0.761). Of note, 42% of these patients had heart failure (117).

Clearly these systems can sometimes be complex and determining which components are beneficial is equally challenging especially as there is a huge variation in technological and inter-patient dynamics. There remains no real consensus on which variable or combination of, are the most useful to monitor, how often or for how long.
<table>
<thead>
<tr>
<th>STUDY</th>
<th>PAPER/YEAR</th>
<th>Patients (n)</th>
<th>HFpEF</th>
<th>Population</th>
<th>TM Variables Measured</th>
<th>Endpoint</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHARF</td>
<td>AHJ 2003</td>
<td>280</td>
<td>No</td>
<td>US</td>
<td>Weight and symptoms</td>
<td>180 day re-admission rate</td>
<td>1° Negative</td>
</tr>
<tr>
<td>TENS-HMS</td>
<td>JACC 2005</td>
<td>426</td>
<td>No</td>
<td>European</td>
<td>Weight, Symptoms, BP, HR, ECG</td>
<td>Days lost to Death/Hospitalisations</td>
<td>1° Negative</td>
</tr>
<tr>
<td>HOME-HF</td>
<td>EHJ 2008</td>
<td>182</td>
<td>Yes</td>
<td>NW London</td>
<td>Weight, Symptoms, BP, HR, Saturation</td>
<td>Number of days alive and out of hospital</td>
<td>1° Negative</td>
</tr>
<tr>
<td>TELE-HF</td>
<td>NEJM Sep 2010</td>
<td>1653</td>
<td>No</td>
<td>US</td>
<td>Weight and symptoms</td>
<td>Composite of all-cause re-admission or all-cause mortality</td>
<td>1° Negative UC- (52.3%)</td>
</tr>
<tr>
<td>COCHRANE</td>
<td>EHJ Oct 2010</td>
<td>8323</td>
<td>No</td>
<td>Worldwide</td>
<td>Weight, Symptoms, BP, HR, Saturation</td>
<td>All-cause mortality, CHF-related hospitalization, and all-cause hospitalization</td>
<td>1° Positive 34% reduction vs UC p&lt;0.0001</td>
</tr>
<tr>
<td>TIM-HF</td>
<td>Circ 2011</td>
<td>710</td>
<td>No</td>
<td>US</td>
<td>ECG, BP, Weight (sub-group 6MWT)</td>
<td>All-cause mortality</td>
<td>TM 8.4% v UC 8.7% p 0.87</td>
</tr>
</tbody>
</table>

Table 5: Summary of Key Variables from Telemonitoring Studies. (UC – Usual Care, ER-Emergency Room, TM – Telemonitoring, OPD – Outpatients Department, BP – Blood Pressure, HR – Heart Rate, ECG – Electrocardiogram, 6MWT – 6-minute walk test)
1.17. Device Related Variables

Implanted devices, which include pacemakers and defibrillators, are also able to measure other parameters that can be collected on a daily basis. These include Intrathoracic impedance (IMP), which is a surrogate for volume status, arrhythmia burden (Ventricular Tachycardia, Atrial Fibrillation), heart rate variability (HRV) as well as patients’ symptoms.

The device related variables have the advantage of not always requiring patient initiation for collection and as a result, in theory could be collected more robustly. No single system is however, completely fail-safe.

The Medtronic Impedance in Diagnostics in HF Trial (MID-Heft) study retrospectively analysed IMP data from 33 patients with NYHA III or IV heart failure and demonstrated a good correlation between decompensation episodes and a fall in IMP that occurred at the time. They also observed a good correlation between the fall in PCWP and rise in IMP that followed treatment. Interestingly, when recommended thresholds were employed; one could potentially predict these decompensation episodes up to 30 days prior to their occurrence (118).

The Fluid Accumulation Status Trial (FAST) trial looked at concurrent serial IMP measurements and weight changes, in 156 NYHA II-II patients who had an ICD or CRT-D. It demonstrated that weight gain data on its own was less sensitive than IMP data in predicting decompensation of heart failure but combining both information improved the specificity (119).

The Program to Access and Review Trending Information and Evaluate Correlation to Symptoms in Patients with HF (PARTNERS HF) was a prospective unblinded observational study that showed that a combined algorithm which included IMP and multiple non-IMP parameters such as HRV, duration of atrial fibrillation and patient activity, identified a cohort of patients at high risk of experiencing a HF event within the subsequent month. It also showed a link between patient reported HF self-management and the likelihood of IMP data crossing pre-determined thresholds suggestive of a decompensation (120).

The Sensitivity of the InSync Sentry OptiVol Feature for the Prediction of HF (SENSE-HF) and the Diagnostic Outcome Trial in HF (DOT-HF) are the more recent trials that have employed various device-based parameters to assess the potential for decompensation.
SENSE-HF was a large prospective, multicentre, double blind study that evaluated an impedance-based algorithm, OptiVol (Medtronic, Inc., Minneapolis, MN, USA), in 501 NYHA class II and class III HF patients implanted with CRT-D devices. Using OptiVol, the trial results demonstrated a low sensitivity of 42% and low positive predictive value of only 38% for future HF events that is from 6 months to 24 months post implantation. In the early period (34 days to 6 months), post implantation, the algorithm fared even worse with a sensitivity of 20.7% and positive predictive value of 4.7% (121).

(DOT-HF) was a large prospective phase IV RCT designed to test whether monitoring of intrathoracic impedance (OptiVol) could reduce morbidity and mortality in patients with chronic NYHA classes II-IV HF. All study subjects were implanted with an ICD or CRT-D capable of monitoring impedance (Medtronic Inc.), and randomised to have all device-based information (including audible alerts for preset fluid threshold crossings) available to patients and doctors (access group) or to a control group without that information. The primary endpoint was a composite of all-cause mortality and HF hospitalisation, and this occurred in 48 of 168 (29%) patients in the access arm versus 33 of 167 (20%) in the control arm (p=0.063). Unfortunately there was also a 79% increase in HF hospitalisations in the access arm (122).

In some of these studies, the excessive number of false positive alerts, which resulted in more frequent hospitalisations, remains a problem. This has resulted in difficulty in broader implementation of this technology in current clinical practice.

These algorithms for detection as well as the notifications or alerts that detected abnormalities produce, are been improved upon. The on-going OptiLink-HF Study is one such substantial study with an improved design, which would look at IMP monitoring (OptiVol) with wireless transmission of alerts versus usual care. The target is to recruit 1000 patients to demonstrate a 30% reduction in the primary outcome (composite of all-cause death or cardiovascular hospitalisation) (123)

Other invasive technologies looking at continuous hemodynamic monitoring of Left atrial pressures, right ventricular pressures and pulmonary capillary wedge pressures have produced varying results (111;112;124). There of course remains the practicability and cost effectiveness of using such measures in a day-to-day management of ambulatory heart failure patients.
Despite all these advances in technology and patient care, it would appear that there remains a major unresolved challenge in reducing the number of HF hospitalizations by our inability to adequately predict episodes of worsening HF, using the aforementioned physiological variables, from telemonitoring or device monitoring of symptoms including daily weights.

Furthermore, it appears that while each of the diagnostic variables used have the capability of stratifying patients at risk for HF hospitalizations, combination of these variables certainly improves detection rates and in particular for those at extreme ends of risk for HF hospitalizations.

The European Society of Cardiology recommends that patients with heart failure be enrolled in a multidisciplinary-care management programme to reduce the risk of heart failure hospitalization. One of the important components of such programmes is increased access to healthcare (through in-person follow-up and by telephone contact; possibly through remote monitoring)(4).

The mixed quality of evidence for remote monitoring, in particular lack of mortality benefit from telemonitoring, makes the American Heart Failure Association guidelines less definitive in their recommendations. They however also promote generic multidisciplinary team management approaches, which are designed to support patients with HF and have been shown to result in a significant improvement in outcomes including mortality (125). To this end they recommend further evaluation of the usefulness of remote monitoring (105).

Table 6 summarises some of the studies aforementioned, using device variables for prediction of ADHF.
<table>
<thead>
<tr>
<th>Study</th>
<th>Paper/Year</th>
<th>Number</th>
<th>Population</th>
<th>Device Variables Measured</th>
<th>1st Endpoint</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>MIDHeft</td>
<td>Circ 2005</td>
<td>34</td>
<td>Chinese</td>
<td>IMP, PCWP, Clinical Oedema</td>
<td>HF Hospitalisations</td>
<td>IMP vs PCWP vs Fluid Status-Good Correlation</td>
</tr>
<tr>
<td>PARTNERS-HF</td>
<td>JACC 2010</td>
<td>694</td>
<td>US</td>
<td>IMP, Arrhythmias, HRV, % of CRT pacing, Activity</td>
<td>HF Hospitalisations</td>
<td>Combined diagnostics predicts ADHF</td>
</tr>
<tr>
<td>IMPATTO</td>
<td>Pacing 2011</td>
<td>111</td>
<td>Italian</td>
<td>IMP, Echo, BNP,</td>
<td>HF Hospitalisations</td>
<td>IMP correlates with BNP</td>
</tr>
<tr>
<td>FAST HF</td>
<td>CHF 2011</td>
<td>156</td>
<td>US</td>
<td>IMP and Weight</td>
<td>HF Hospitalisations</td>
<td>IMP &gt; Weight - Sensitivity</td>
</tr>
<tr>
<td>DOT-HF</td>
<td>Circ 2011</td>
<td>225</td>
<td>Worldwide</td>
<td>IMP, Arrhythmias, HRV, % of CRT pacing, Activity (Access vs None)</td>
<td>All-cause mortality and Hospitalisations</td>
<td>IMP – did not improve outcome, increased HF Hospitalisations</td>
</tr>
<tr>
<td>SENSE-HF</td>
<td>EHJ 2011</td>
<td>501</td>
<td>European</td>
<td>IMP</td>
<td>HF Decompensation</td>
<td>IMP – low sensitivity and PPV</td>
</tr>
</tbody>
</table>

Table 6: Summary of Key Variables from Device Studies. (IMP - Impedance, TM – Telemonitoring, PCWP – Pulmonary Capillary Wedge Pressure, CRT – Cardiac Resynchronisation Therapy, HRV – Heart Rate variability, BNP – B-type Natriuretic Peptide)
SECTION THREE – Sleep Disordered Breathing in Heart Failure
1.18. Sleep Disordered Breathing in Heart Failure

There is a good body of evidence that nocturnal breathing disorders are very common in patients with chronic heart failure and at any symptomatic level of the disease (8). The majority of these abnormalities are characterised by various forms of oscillatory ventilatory patterns, the hallmark of which are rises and falls in tidal volume ($V_T$) (126).

Significantly these breathing abnormalities are associated with increased mortality, which are independent of known clinical predictors of outcome (127). The cyclical fluctuations in ventilation that are seen with these patterns have given rise to the loose term Periodic Breathing (PB) and this is described during sleep or wakefulness (128).

During sleep it is more appropriately termed Sleep Disordered Breathing (SDB), which are a group of disorders characterized by abnormalities of respiratory pattern or the quantity of ventilation during sleep. In these patients, obstructive sleep apnoea (OSA) and central sleep apnoea (CSA) form parts of a spectrum that depending on the circumstances, may take either of the two forms as the dominant mechanism. SDB occurs in up to 50% of patients with heart failure and is associated with poor prognosis (6;9)

Ventilatory instability during SDB leads to recurrent changes in intrathoracic pressures, tensions of carbon dioxide and oxygen in plasma, which result in intermittent hypercapnia and hypoxia and sharp fluctuations in sympathetic drive. These trigger repetitive arousals and sleep fragmentation, which consequently impact negatively on the heart by worsening its function. Overall these patterns are associated with poor prognosis (10;129)

Normal breathing cycle lengths range from 3 to 5 s (i.e., 0.20–0.33 Hz) while PB patterns have cycle lengths from 25 to 100 s (i.e., 0.01–0.04 Hz) (130). In the same patient however, there may often co-exist a mixture of breathing patterns, ranging from extremes of non-periodic breathing (nPB), i.e., without cyclic modulation of ventilation, through to florid Cheyne-Stokes Respiration (CSR) patterns with varying degrees of PB in between.
1.18.1. Classification of SDB

Patients with SDB have periods of apnoeas (a cessation or >90% reduction in airflow) and hypopneas (a > 50% reduction in airflow with an associated oxygen desaturation of at least 3%). SDB may be classified as obstructive sleep apnoea (OSA), where there is partial or complete collapse of the airway, or central sleep apnoea (CSA) where the airway is largely open and cessation of ventilation is due to reduced respiratory drive. In addition, patients with CSA may exhibit a Cheyne Stokes pattern of respiration (CSR) characterised by the presence of periods of central apnoeas or hypopneas alternating with periods of crescendo-decrescendo tidal volume (10;129).

Both types of SDB may co-exist in the same patient and usual practice is to label the syndrome depending on which type predominates.

The severity of SDB is generally classified by the Apnoea-Hypopnoea Index (AHI), the average number of apnoeas and hypopnoeas that occur per hour during sleep. An AHI ≥ 15 is taken to indicate clinically important disease.

1.18.2. Epidemiology

CSA is rare in patients without heart failure, but obstructive sleep apnoea is relatively common in the general population, and particularly in those who are obese, or who have hypertension or diabetes, or who have upper airways anatomically more likely to collapse (e.g. retrognathism).

The prevalence of SDB in systolic heart failure is high with estimates from population studies varying between 47% and 71% (6;131). In a prospective study of male patients with stable systolic heart failure, 51% were reported to have an AHI of 15 per hour or more (CSA 40% OSA 11%) (6). Ward and colleagues, in patients with low or preserved ejection fraction, recently reported a prevalence of 14% for CSA and 31% for OSA (132). Prevalence rates have been shown to be higher in patients who are awaiting transplantation (133), and those with implanted cardiac defibrillators (134). Several other studies in patients with systolic heart failure have shown varying prevalence rates ranging from 40% to 80% (135-137) See Table 6.
Men appear to be more likely to develop SDB than women, particularly in middle life (138). The reasons for this are not entirely clear, but presumably relate to gender differences in respiratory drive. See table 7 for summary of some landmark prevalence studies on SDB in HF patients.

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Number of Patients</th>
<th>NYHA Class</th>
<th>Male (%)</th>
<th>LVEF (%)</th>
<th>AHI severity</th>
<th>SDB (%)</th>
<th>OSA (%)</th>
<th>CSA (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lanfranchi, 2003</td>
<td>47</td>
<td>100</td>
<td>0</td>
<td>89</td>
<td>≥15/H</td>
<td>66</td>
<td>11</td>
<td>55</td>
</tr>
<tr>
<td>Sin, 1999</td>
<td>450</td>
<td>62</td>
<td>38</td>
<td>85</td>
<td>≥15/H</td>
<td>61</td>
<td>29</td>
<td>32</td>
</tr>
<tr>
<td>Ferrier, 2005</td>
<td>53</td>
<td>ND</td>
<td>ND</td>
<td>77</td>
<td>≥10/h</td>
<td>68</td>
<td>15</td>
<td>53</td>
</tr>
<tr>
<td>Javaheri 1998</td>
<td>81</td>
<td>70</td>
<td>30</td>
<td>100</td>
<td>≥15/h</td>
<td>51</td>
<td>11</td>
<td>40</td>
</tr>
<tr>
<td>Javaheri, 2006</td>
<td>100</td>
<td>II</td>
<td>100</td>
<td>25(7)</td>
<td>15/h</td>
<td>41</td>
<td>27</td>
<td>12</td>
</tr>
<tr>
<td>Oldenburg, 2007</td>
<td>700</td>
<td>ND</td>
<td>ND</td>
<td>80</td>
<td>≥15/h</td>
<td>52</td>
<td>19</td>
<td>33</td>
</tr>
<tr>
<td>Schulz, 2007</td>
<td>203</td>
<td>55</td>
<td>45</td>
<td>75</td>
<td>≥10/h</td>
<td>72</td>
<td>43</td>
<td>28</td>
</tr>
<tr>
<td>Vazir, 2007</td>
<td>55</td>
<td>100</td>
<td>0</td>
<td>100</td>
<td>≥15/h</td>
<td>53</td>
<td>15</td>
<td>38</td>
</tr>
<tr>
<td>MacDonald, 2008</td>
<td>108</td>
<td>71</td>
<td>29</td>
<td>85</td>
<td>≥15/h</td>
<td>61</td>
<td>30</td>
<td>31</td>
</tr>
<tr>
<td>Bitter, 2009</td>
<td>244</td>
<td>ND</td>
<td>ND</td>
<td>64</td>
<td>≥15/h</td>
<td>47</td>
<td>24</td>
<td>23</td>
</tr>
<tr>
<td>Yumino, 2009</td>
<td>218</td>
<td>54</td>
<td>46</td>
<td>77</td>
<td>≥15/h</td>
<td>47</td>
<td>26</td>
<td>21</td>
</tr>
</tbody>
</table>

Table 7: Landmark prevalence studies for SDB in CHF

1.18.3. Risk Factors

There are several patient characteristics that affect the likelihood of SDB. For OSA, as in the general population, male gender, increasing age, obesity, snoring and increased neck circumference increase the probability of SDB being present. For CSA, risk factors also include male gender and increasing age, but in addition the presences of arrhythmia (in particular atrial fibrillation) as well as daytime hypocapnia are features that are known to be independently associated with this condition (137).

In general, the more severe the heart failure the more likely that the patient will demonstrate CSA, particularly if they are male, older or in atrial fibrillation, but even patients with mild heart failure symptoms are likely to have SDB (8;135).
The differences in pathophysiology for these two forms of SDB may in part explain the differing risk factors. See Table 8 for a study of 193 patients newly referred with low left ventricular ejection fraction (≤45%) to a Canadian heart failure centre, who were screened for SDB.

<table>
<thead>
<tr>
<th></th>
<th>OSA – Adjusted OR</th>
<th>CSA – Adjusted OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per 10 yr Increase)</td>
<td>1.52 (1.08 – 2.14)</td>
<td>1.48 (1.01 – 2.08)</td>
</tr>
<tr>
<td>Male Gender</td>
<td>4.95 (1.74 – 14.07)</td>
<td>8.36 (2.38 – 29.38)</td>
</tr>
<tr>
<td>BMI (5kg/m2 increase)</td>
<td>1.58 (1.08 -2.33)</td>
<td>0.99 (0.62 -1.55)</td>
</tr>
<tr>
<td>Atrial Fibrillation</td>
<td>2.44 (0.56-10.55)</td>
<td>7.93 (1.76 – 35.65)</td>
</tr>
<tr>
<td>PCO2 (per mmHg Increase)</td>
<td>1.02 (0.94 – 1.11)</td>
<td>1.27 (1.15 – 1.41)</td>
</tr>
<tr>
<td>Diuretic Use</td>
<td>2.25 (0.87 – 5.82)</td>
<td>14.16 (2.7 – 72.48)</td>
</tr>
</tbody>
</table>

Table 8: Risk factors for the prevalence of SDB in heart failure (137).

1.18.4. Pathophysiology of SDB

The predominant pathological feature in all types of SDB is the presence of periodic breathing associated with pauses (apnoeas) or transient reductions (hypopneas) in ventilation during sleep. This is usually followed by a hyperpnoeic episode often leading to arousal from sleep as the patient attempts to resume normal ventilation (10;129).

These arousals produce a sharp surge in sympathetic activity, with an associated increase in heart rate and blood pressure, along with vasoconstriction of peripheral vessels. Increased circulating catecholamines may be implicated in adverse remodelling of the left ventricle and an increased propensity to arrhythmia, including paroxysmal atrial fibrillation (139).

The cycle of interrupted sleep (with frequent arousals to a lighter less refreshing stage of sleep) can leave a patient feeling tired during the day, with a tendency to nap readily. However heart failure patients do not appear to complain of this as much as non-heart failure patients with OSA. This is perhaps related to the higher background level of sympathetic activity in the former group, protecting them from daytime somnolence (140).
OSA

In obstructive sleep apnoea, ventilation is periodically interrupted by partial or complete collapse of the upper airway pharyngeal muscles at either the level of the soft palate (nasopharynx) or the level of the tongue (oropharynx). Anatomical variations in this area are associated with varying risks of development of OSA in different individuals.

It is also known that the cross-sectional area of the airway in patients with OSA is smaller than that of patients without OSA; this difference is due to the volume of the soft tissue, including the tongue, lateral pharyngeal walls, soft palate, and parapharyngeal fat pads (141).

Exaggerated negative intrathoracic pressures from continued inspiratory effort against an occluded airway is generated, increasing cardiac transmural pressures, left ventricular afterload and myocardial oxygen demand at a time when oxygen saturation may be dropping. This can lead to a worsening of cardiac function and an increased risk of arrhythmia.

Posture plays an important role in increasing the risk of respiratory events: these are more likely to occur in the supine rather than prone or lateral position. It has been suggested that the amount of rostral fluid displacement from the legs of heart failure patients during the night corresponds strongly with an overnight increase in neck circumference and increased likelihood of OSA events (142).

CSA

In patients with CSA, the predominant problem lies with instability of the feedback control of ventilation, resulting in a temporary withdrawal of central respiratory drive leading to a cessation of airflow and respiratory muscle activity (10;129).

Normal ventilation is controlled by mechanisms that keep the partial pressures of arterial carbon dioxide (PaCO2) in plasma within a tight range. Alterations to this homeostasis results in the development of periodic breathing both during sleep and wakefulness. Intermittent cessation of inspiratory drive occurs due to a fall in PaCO2 below the apnoea threshold (the minimum partial pressure of carbon dioxide in plasma that is sufficient to stimulate ventilation) (Figure 9). The main contributor to this process in heart failure patients appears to be an increased chemoreceptor sensitivity to CO2 (resulting in hyperventilation driving down PaCO2 below the
apnoeic threshold) and perhaps an increased arterial circulation time due to low cardiac output in some patients increasing the feedback time in the homeostatic control mechanism (143).

**Figure 9:** Mechanism of CSA – As PCO2 levels fall below apnoeic thresholds, airflow ceases

### 1.18.5. The Diagnosis of Sleep Disordered Breathing in Heart Failure

SDB is under diagnosed in patients with chronic heart failure even though it remains a prevalent condition and associated with increased morbidity and mortality. One of the main reasons for this is that cardiologists are reluctant to send their patients in for a diagnostic test that is seen as cumbersome and sometimes tedious for a group of patients who are usually very frail. The other factor is that the symptoms patients present with, which are suggestive of the presence of SDB can be confused with the usual symptoms of heart failure and as such it is not easily recognised.

It should also be noted that there is no correlation between the NYHA class and the presence of SDB (8).

Attended in-hospital polysomnography (PSG) provides the best available tool for making a diagnosis of SDB and it is currently the ‘gold’ standard. A variety of other devices have been
developed to offset the resource and labour intensiveness of PSG and these generally rely on their portability, but at the cost of the number of signals they can output and therefore information that can be provided towards a diagnosis. These tools include overnight oximetry(132) and the use of apnoea link device(144), which combines pulse oximetry with thoracoabdominal plethysmography, but a formal diagnosis would still require a PSG/PG recording. As such in practice these devices are generally used only as screening tools.

1.18.5.1 Types of Portable Monitors

The 1994 American Sleep Disorders Association classifies portable monitors based on the number and type of signals they record (145). This has recently been reviewed by the American Academy of Sleep Medicine, the American College of Chest Physicians, and the American Thoracic Society (146).

**Type 1: Standard attended in-hospital polysomnography (PSG)**

These monitors are usually the reference standard to which other monitors are compared. A minimum of 7 channels are recorded including EEG, Electrooculogram, chin EMG, ECG or heart rate, airflow, respiratory effort, and oxygen saturation. I will discuss PSG in detail in the next section.

**Type 2: Comprehensive Portable Polysomnography**

These monitors incorporate sleep staging as well as respiratory analysis. They rely on recordings from a minimum of seven channels as Type 1 sleep studies, the main difference being that they are unattended.

**Type 3: Modified Portable Sleep Apnea Testing**

This type of monitor incorporates at least four channels (with at least three being respiratory), including ventilation or airflow (at least two channels of respiratory movement, or respiratory movement and airflow), heart rate or ECG, and oxygen saturation.
Type 4: Continuous Single or Dual Bio parameters

These monitors measure a single parameter or two parameters, for example, oxygen saturation or airflow. A monitor that did not meet the criteria for type 3 (i.e., a monitor that measured one to three channels or did not include airflow despite having four channels) was classified as type 4. The SleepMinder™ device used in this thesis would be classified as a Type 4 Portable Monitor. Tables 9 and 10 below show some examples of Type 4 portable monitors and relevant studies. As a result of on-going development, some of the models of monitors used in these validation studies may have updated marketing versions that may include additional or alternative-recording channels.
<table>
<thead>
<tr>
<th>Name</th>
<th>Author/Year</th>
<th>Number</th>
<th>Failure Rate (%)</th>
<th>Parameter</th>
<th>Outcome Measure</th>
<th>Reference Standard (PSG)</th>
<th>Correlation (r)</th>
<th>Sensitivity(%)</th>
<th>Specificity(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apnoea Link (ResMed Australia)</td>
<td>Erman, JCSM, 2007</td>
<td>63</td>
<td>6.3</td>
<td>Airflow</td>
<td>Device AHI</td>
<td>AHI&gt;15</td>
<td>0.89</td>
<td>91</td>
<td>95</td>
</tr>
<tr>
<td>Pro-Tech Portable (USA)</td>
<td>Ayappa, Sleep, 2004</td>
<td>59</td>
<td>5</td>
<td>Airflow, O2 Sats</td>
<td>ODI 4%</td>
<td>AHI&gt;18</td>
<td>NA</td>
<td>88</td>
<td>92</td>
</tr>
<tr>
<td>OxiFlow</td>
<td>Baltzan, Sleep, 2000</td>
<td>97</td>
<td>8</td>
<td>O2 Sats</td>
<td>ODI 4%</td>
<td>AHI&gt;15</td>
<td>0.75</td>
<td>73</td>
<td>83</td>
</tr>
<tr>
<td>MESAM IV (Germany)</td>
<td>Esnaola, ERJ, 1996</td>
<td>152</td>
<td>1</td>
<td>O2 Sats, HR, Snoring, Body Position</td>
<td>ODI, HRV, ISI</td>
<td>AHI&gt;15</td>
<td>0.57</td>
<td>68</td>
<td>97</td>
</tr>
<tr>
<td>WatchPAT 100 (Israel, USA)</td>
<td>Pittman, 2004</td>
<td>30</td>
<td>3</td>
<td>O2 Sats, HR, Actigraphy, PAT</td>
<td>RDI</td>
<td>AHI &gt;15</td>
<td>0.89</td>
<td>91</td>
<td>86</td>
</tr>
<tr>
<td>Somnocheck™ (Germany)</td>
<td>Ficker, Respiratior, 2001</td>
<td>51</td>
<td>NA</td>
<td>O2 Sats, PR, Airflow</td>
<td>Device AHI</td>
<td>AHI&gt;10</td>
<td>0.83 (all values)</td>
<td>83</td>
<td>100</td>
</tr>
<tr>
<td>SleepStrip™ (S.L.P. Israel)</td>
<td>Shochat, ERJ, 2002</td>
<td>402</td>
<td>26.5</td>
<td>Airflow</td>
<td>Device AHI</td>
<td>AHI&gt;10</td>
<td>0.73 (for all values)</td>
<td>86</td>
<td>57</td>
</tr>
<tr>
<td>AVL-Minolta Pulsox-7 (Switzerland)</td>
<td>Golpe, 1999</td>
<td>125</td>
<td>7.2</td>
<td>O2 Sats</td>
<td>CT O2 sats &lt;90%</td>
<td>AHI&gt;10</td>
<td>NA</td>
<td>84</td>
<td>48</td>
</tr>
<tr>
<td>Oximatoor Durasensor, DS-100A (USA)</td>
<td>Jobin, 2007</td>
<td>104</td>
<td>10</td>
<td>O2 Sats</td>
<td>ODI 4%</td>
<td>RDI&gt;15/h</td>
<td>NA</td>
<td>63</td>
<td>96</td>
</tr>
<tr>
<td>Biox 3740 (Ohmeda UK)</td>
<td>Wiltshire, 2001</td>
<td>100</td>
<td>NA</td>
<td>O2 Sats</td>
<td>ODI 4%</td>
<td>ODIe15/h</td>
<td>NA</td>
<td>94</td>
<td>74</td>
</tr>
<tr>
<td>Stowood Scientific Instruments (UK)</td>
<td>Ward, Thorax, 2012</td>
<td>171</td>
<td>NA</td>
<td>O2 Sats</td>
<td>ODI 3%</td>
<td>AHIe15</td>
<td>NA</td>
<td>97</td>
<td>32</td>
</tr>
</tbody>
</table>

Table 9: Examples of Type 4 Portable Monitors using predominantly O2 saturation and Airflow as parameter for detecting SDB. (Abbreviations: AHI – Apnoea Hypopnea Index, ODI – Oxygen Desaturation Index, HRV – Heart Rate Variability, ISI – I Snoring Index, PR – Pulse Rate, HR- Heart Rate, PAT – Peripheral Arterial Tone, CT- Cumulative Total, NA – Not Available, RDI – Respiratory Disturbance Index O2 Sats – Oxygen Saturation)
### Table 10: Examples of Type 4 Monitoring using HRV as measure for detecting SDB

(Abbreviations: VLFI – Very Low Frequency Increment, RR – R – R Interval on Electrocardiogram, LF – Low Frequency, HF – High Frequency, HR – Heart Rate, AHI – Apnoea Hypopnea Index, NA – Not Available, OSA – Obstructive Sleep Apnoea)
Polysomnography/Polygraphy (PSG/PG)

Laboratory based Polysomnography or polygraphy usually involves an overnight inpatient hospital stay. A standard PSG should have at least seven recording channels, which should include Electroencephalogram (EEG), Electrooculogram (EOG), submental electromyogram (EMG), Electrocardiogram (ECG), Oro-nasal airflow, Respiratory Inductance Plethysmography (RIP), and Pulse Oximetry. Body position is obtained from the recording device and additional data may be obtained from anterior tibialis electromyogram and a snore electrode.

The main output from an overnight PSG typically recorded for about 4-6 hours is information on sleep architecture, including the total sleep time (TST); which is an important metric in calculating the main index for estimating the severity of SDB, the apnoea and hypopnea index (AHI), which is simply a fraction of the total number of apnoeas and hypopneas divided by TST; sleep efficiency, sleep stages and frequency of arousals. Respiratory effort signals help to distinguish central from obstructive events. Other important information that can be obtained includes, number of periodic leg movements, number of oxygen desaturations and snoring and these extra data may be invaluable especially where there is diagnostic doubt.

Many studies classify SDB severity by the AHI into Mild (>5 <10), Moderate (>10 <30) and Severe (>30). However when treatment is been considered, an AHI of >15 is usually considered clinically significant.

PSG studies are time and resource expensive due to the need for a well-equipped sleep laboratory and the trained personnel who perform the studies but also to interpret the results. It is also particularly obtrusive and sometimes is not representative of patients normal sleep pattern/habit due to the laboratory setting and the extensive electrodes attached.

There is also the limitation of making a diagnosis on a single nights recording, as studies have shown that a high proportion of patients shift their type of sleep disordered breathing over consecutive nights (147). Even where the facilities exist to do so, it is often expensive and impractical to perform PSG studies on consecutive nights.
1.18.6. The Variability of the Apnoea Hypopnea Index (AHI)

The Apnoea Hypopnea Index (AHI) is the most frequently used measurement for diagnosis and classification of severity of sleep-disordered breathing. The gold standard and recommended technique for obtaining this value is from a single night in-hospital Polygraphy or Polysomnography (148).

The AHI may however be variable over a period of time in the same patient who has heart failure. This therefore raises the question about whether the use of a single night Polysomnogram to make a diagnosis of SDB and to classify the severity and type of SDB. One possible reason for this variability is due to breathing pattern changes that may occur during the course of the heart failure syndrome; no doubt contributed in part by the effects of changes in medical and device treatment strategies; that could potentially influence a change in this value.

Only a few studies have investigated the variability of the AHI, in the short term, in patients with heart failure, mainly due to the complexities of multiple night polygraphy or polysomnography examinations. Furthermore, these studies are largely heterogeneous in the techniques used, the variables examined for variability assessment, and intervals between measurements. Therefore, results from these published studies are largely contradictory.

Le Bon and colleagues studied 243 patients who were referred to a Brussels Sleep Centre for screening of suspected sleep apnoea. They underwent sleep studies on two consecutive nights and it was noted that the detection rate for SDB in this cohort was improved by a second night PSG, by about 15 – 25 % when the result of the first night was negative (149). As a result, the main conclusion from this study was that one night’s sleep study might be insufficient to make a definitive diagnosis of SDB.

In a much larger but retrospective North American study of 1091 adult patients, who underwent sequential sleep studies over 3 nights, there was a high consistency in the AHI, across the 3 nights of measurement with an Intra Class Correlation Co-efficient (ICC) value of 0.90 (95% CI 0.89-0.91). However, at least 1 in 10 of these patients were reclassified into a different SDB severity group based on the highest AHI obtained on any of the 3 nights. The AHI thresholds used in this study were 5, 10 and 15 (150).
At the Royal Brompton Hospital in London, Vazir and colleagues, studied 19 men with stable CHF and found that over a period of four nights, the AHI and Oxygen Desaturation Index (ODI) demonstrated minimal variability (Intra-class Correlation Co-efficient 0.94 [0.76-0.97]; 0.94 [0.88-0.97] respectively. They however found that 37% (95% CI 20-64%) of their patients moved from one severity group to the next of Sleep Disordered Breathing (SDB) over the four nights of monitoring. The severity thresholds used in this study were based on the AHI; mild-(5-14.9), Moderate (15-29.9) and severe (≥30). In addition there was a change in the predominant type of SDB, shifting from CSA to OSA and vice versa in 42% (8/19) of these patients (147). Using night one as a reference, 3 patients moved from a reference classification of CSA to OSA on any other night of study while 5 patients moved from an index classification of OSA on night one to CSA on subsequent nights.

Contrastingly, another study which investigated patients across 2 consecutive nights, found excellent correlation in the AHI (r=0.948 p<0.001) and Apnoea Index (AI) r=0.842 p<0.001. In addition they found that the more severe the SDB, the more reproducible these indices were and the more likely the patients were to be classified correctly by type of SDB. (151) The results on these patients with stable CHF led the authors to conclude that in this patient group, a single night of cardiorespiratory monitoring was a true representation of severity and type of SDB.

Maestri and colleagues investigated variability in the AHI, AI and Periodic Breathing (PB) across two nights using the Embletta device, which is a portable sleep monitor that measures airflow and ventilatory effort via elasticated chest and abdominal bands. They measured variability using 95% limits of random variation (LoV) and found significant night-to-night intra-subject variation (95% LoV, ±10.6, ±7.7, ±11.3 for AHI, AI and ODI). However, the majority of these patients were classified correctly according to severity using conventional cut-offs for the AHI.(152)

Similarly, Bittencourt and colleagues found high variability when comparing the AHI values obtained over 4 consecutive nights in 20 adult patients with OSA referred from the respiratory sleep disorders clinic in Sao Paulo Brazil. They observed a large scattering of values using a Bland Altman analysis. (Night 1 vs Night 2; Night 1 vs Night 3; Night 1 vs Night 4 – 95% CI -19.37 to +21.27, -22.3 to +25.27, and -22.04 to +25.24 respectively). In addition 50% of these patients changed the severity classification of SDB on at least one follow up night. (153)
In the Sleep Heart Health Study, 91 participants underwent 2 sleep studies 4 months apart. The Respiratory Disturbance Index (RDI 3%), which was the number of apnoeas and hypopneas per hour of sleep associated with a >3% desaturation, was the variable measured. Using thresholds of 5, 10 and 15 events per hour, the investigators found little variability even when the threshold for desaturation was increased to >4% (Intra-class correlation co-efficient 0.77-0.81). (154).

To summarize, the aforementioned studies show largely discrepant results in terms of variability and misclassification of SDB according to severity or type. Further, most of these studies have only followed up patients between 2 and 4 nights and at varying intervals between sleep studies and most have not included heart failure patients.

One of the aims of this thesis is to observe nocturnal respiratory patterns in heart failure patients over a prolonged period of monitoring using the SleepMinder™ device, which is a non-contact continuous monitor of nocturnal respiration, and to examine the variability of the AHI and other measures of SDB and the clinical implications such variations may have.

1.18.7. Treatment of SDB

It is important to treat heart failure optimally, before labelling a patient as having SDB. Effective treatment of heart failure with contemporary drug and device therapy has been shown to attenuate SDB (155-158); improving the heart failure will often improve the SDB. The use of diuretics to control fluid retention, in addition to disease modifying therapy (such as angiotensin converting enzyme inhibitors, beta-blockers, and aldosterone antagonists for systolic heart failure), and the control of co-morbidities such as hypertension, diabetes or obesity are central to a treatment strategy. If the patient has a broad QRS complex and left ventricular systolic dysfunction, cardiac resynchronisation therapy should also be considered.
1.18.7.1. Oxygen

Administration of supplemental overnight oxygen via nasal cannula improves overnight mean saturation but does not always significantly reduce the amount of SDB (159;160). For this reason, this is therefore not a recommended treatment option.

1.18.7.2. Benzodiazepines

These have been used to treat SDB, but although they blunt arousals, they also reduce the amount of slow wave and REM sleep and paradoxically worsen SDB (161).

1.18.7.3. Non-Invasive Ventilation

Continuous positive airway pressure (CPAP) is recommended to treat symptomatic patients with OSA (162). It helps improve SDB (and any attendant symptoms), and may also improve the control of co-existing hypertension, angina or arrhythmia. There is also increasing evidence that it may help improve left ventricular function in patients with heart failure and OSA (58). There is no evidence that using a strategy of CPAP for CSA in heart failure improves outcome. In one medium sized randomised trial – the Canadian Positive Airways Pressure Trial (CAN-PAP) – there was no improvement in mortality or hospitalisation for heart failure, and the study was stopped early because of, amongst other issues, low event rates and difficulty in recruitment (163). A post-hoc analysis of those patients in whom the CPAP therapy had effectively suppressed the CSA, there was statistical evidence of benefit, (164) and this encouraging signal led to the design of a much larger randomised trial of adaptive servo ventilation (ASV) in predominantly CSA in systolic heart failure (SERVE-HF) (165). This study has finished recruitment (1325 patients) with results expected in 2015 regarding the effect of this form of ventilation on mortality and hospitalisation, ventricular function, control of the heart failure syndrome, and quality of life.

Unlike CPAP, ASV provides varying amounts of ventilatory support during different phases of CSR: minimal during the hyperpnoeic phase and maximal during periods of apnoea or hypopnea. This provides steady ventilation and abolishes CSA very effectively (Figure 10). Small studies have shown that this treatment is safe, more efficient at normalising CSR than CPAP, and is better tolerated than CPAP or oxygen therapy.
Another randomised trial (ADVENT – Effect of Adaptive Servo Ventilation (ASV) on Survival and Hospital Admissions in Heart Failure) is currently recruiting patients, and will test whether CPAP Improves outcome for patients with heart failure and SDB – whether OSA or CSA (166)

![Graph showing respiratory events before and after ASV treatment]

Figure 10: 3-minute epoch recordings showing how treatment of Central Sleep Apnoea using ASV treatment abolishes respiratory events. Top Image – Untreated CSA. Bottom Image – Treated CSA with ASV.

1.18.8. Ventilatory Changes as a Marker of Deterioration

The main function of the respiratory system is gas exchange however a broad range of factors can affect ventilation including influences the nervous system, the cardiovascular system, the respiratory system, and the excretory system.

The respiratory rate on its own is a broad indicator of major physiological instability and can help identify patients at risk of serious adverse events such as cardiac arrest and unplanned ICU admission. In a small study, Fieselmann et al retrospectively examined 59 inpatients from 12 wards at a single centre in an American hospital that had experienced cardiopulmonary arrest and had at least 72 hours of inpatient vital signs recorded. They demonstrated that a respiratory
rate higher than 27 breaths a minute had a sensitivity of 0.54 and a specificity of 0.83 (odds ratio = 5.56, 95% CL = 2.67-11.49) in predicting cardiopulmonary arrest (167).

Subbe and colleagues prospectively studied 1695 acute medical admissions in UK medical unit who had their risk of clinical deterioration stratified according to the modified early warning score (MEWS). This tool records parameters that also included the systolic blood pressure, heart rate and oxygen saturations (168). While there was no statistically significant difference in mortality between the different risk groups, they found that the RR was best at discriminating between these patients. (169).

Alveolar ventilation, which is a product of the respiratory rate and tidal volume, is normally under strict control of chemoreceptors centrally in the medulla and peripherally in the carotid bodies as well as lung baroreceptors. These mechanisms monitor changes in these parameters and when there is an alteration or imbalance in the partial pressures of oxygen (PaO2) and in particular carbon dioxide (paCO2), one way the body corrects for this hypoxaemia or hypercarbia is to increase ventilation.

Therefore any condition that results in a metabolic acidosis, which results in an increase in the concentration of hydrogen ions and consequently increased CO2 production, would precipitate an increase in tidal volume and respiratory rate. This makes the respiratory rate a broad indicator of severe derangement in these organ systems, as well as an indicator of respiratory disorders.

Not only is the absolute respiratory rate important, RR trends are also very useful markers of potential ill health. The RR trend can indicate progression of cardiopulmonary illnesses, including acute respiratory distress syndrome, pulmonary oedema, pulmonary embolism, pneumonia, COPD, and severe heart failure. Changes in respiratory rate can also indicate sepsis, systemic inflammation, low blood volume, and malfunctions of the excretory system or central nervous system disorders, including intracranial pressure, neurogenic, pain, and opioid-induced respiratory depression.

Ventilatory changes, which are the hallmark of Sleep Disordered Breathing (SDB), are therefore potentially useful in the context of predicting heart failure deterioration.
1.18.9. Sleep Disordered Breathing as a predictor of Acute Decompensation of Heart Failure

Hospitalisations related to decompensation of chronic heart failure have significant cost implications to healthcare systems and lead to increased morbidity and mortality. For this reason, a lot of emphasis is now being placed on the early identification of these patients who are deteriorating so that potential hospital admission can be averted.

In the United Kingdom, community heart failure services, which involve the specialist heart failure nurses and patients have been shown to reduce hospitalisation (3). This system operate by empowering patients with information regarding their disease, and is thought to be a useful way of managing recurrent hospitalisation, by creating the ‘expert patient’ who could adjust their diuretics in particular; in response to their symptoms. However the continued socioeconomic burden of recurrent hospital admissions for managing decompensation of heart failure suggests that these measures on their own may not be adequate. Identifying other means to prevent such admissions therefore becomes desirable.

Sleep disordered breathing (SDB) and in particular central sleep apnoea (CSA) associated with Cheyne’s Stokes Respiration (CSR) is prevalent in patients with heart failure and may be found at any symptomatic stage of the condition (8). The presence of CSR therefore reflects severity of CHF and prognosis. It is also an independent predictor of mortality and cardiac transplantation in several studies (9;127).

Nocturnal rostral fluid shifts have been shown to increase the predisposition to upper airway collapse in stable CHF patients with OSA or CSA (170). Upper airway instability is also known to follow central apnoeas leading to obstructive events towards the end of the central event (171).

There is an increase in cervical venous congestion during a decompensated state of heart failure as part of overall fluid overload. As patients with ADHF are a distinct group compared to ambulatory patients, it is possible to speculate that worsening of upper airway collapsibility may result in more respiratory events of apnoeas and hypopnoeas leading to an increased overall prevalence of SDB.
Majority of the studies that have reported on the prevalence of SDB in patients with chronic heart failure, have however examined mainly ambulant and euvoalaemic patients (6;7). Only a few studies have assessed the significance of the presence of SDB in patients who are in acute decompensated heart failure (ADHF).

Padeletti and colleagues performed overnight in-hospital Polysomnography (PSG) studies in 29 patients who had been admitted within 48 hours of an acute decompensation of heart failure and found a high prevalence of SDB, with 76% of their cohort having an Apnoea Hypopnea Index (AHI) >15 events per hour. These patients had predominantly CSR (Central events 39±29/hour; Obstructive events 2±2/hour p<0.001). The mean ejection fraction in this group of patients was 20±6% (172), so they were notably a sicker group.

Similarly Khayat and colleagues found 75% of their cohort of 395 patients, had evidence of SDB defined by an AHI of ≥15 events/hour (173). These patients had been admitted following new-onset acute heart failure or an exacerbation of already recognised chronic heart failure. In this study, the prevalence of obstructive SDB (57% 95% CI [52-62]) exceeded that of predominantly central SDB (18% 95% CI [14-22]) by up to a third. In these patients only apnoeas were employed in the scoring criteria, which grouped patients as central SDB and this could have contributed to this finding.

It has also been shown by Solin and colleagues, that central sleep apnoea episodes were more frequent and more severe in patients with increased preload as is the case with decompensation of heart failure (155). The mechanism for this finding is thought to relate to increased minute ventilation from pulmonary congestion and the resultant hypocapnia, leading to respiratory control instability, which is the key mechanism that drives CSA (174;175).

They demonstrated that in patients who had higher pulmonary capillary wedge pressures (PCWP), determined by right heart catheterisation studies, central events predominated. (Mean ±SEM; central 22.8±1.2; obstructive 12.3±1.2; non-apnoea 11.5±1.5 events per hour). Additionally, in the central apnoea group, PCWP correlated with the frequency and severity of central apnoea indexed by the AHI (r=0.47, p=0.006). They also noted a significant reduction in the PCWP (29±2.6 to 22±1.8 mmHg p<0.001) and central apnoea frequency (38.5±7.7 to 18.5±5.3 events per hour p=0.005) following intensive medical treatment that reduced pulmonary congestion.
Similarly in 105 patients with symptomatic but stable heart failure studied by Oldenburg and colleagues, they found that SDB of the Central variety predominated. In these patients mean PCWP was higher in CSA and OSA patients compared to those with heart failure but without SDB. Furthermore mean PCWP correlated with AHI ($r=0.409$, $p=0.005$) in CSA patients but not in OSA patients.

Overall, these studies suggest that during a decompensation of heart failure, there is an increase in the amount of sleep disordered breathing measured by the Apnoea Hypopnea Index and in some cases the amount of Cheyne-Stokes respiration present. This results in a predominantly CSA-CSR pattern of SDB from increased pulmonary venous load or OSA pattern from cervical venous congestion.

It is important to note that all of the studies described above have utilised single night PG/PSG for determination of the presence of SDB during the index hospital admission or the period marked as decompensation. In addition, none of these studies have made direct comparisons of the amount of SDB or CSR in stable state of CHF and with patients when decompensated.

One of the aims of this thesis is to investigate how the amount of SDB varies from a stable to decompensated state by continuous measurements of the AHI and CSR over a prolonged period of monitoring, using a non-contact monitor, the SleepMinder™ device.
SECTION FOUR — Digital Signal Processing in Medicine
Glossary

Active window: The window that is currently selected for moving, sizing, editing, closing, or some other function.

Algorithm: This is a well-defined, step-by-step set of instructions for calculating a specific function

ALU: Arithmetic logic unit.

Amplitude: the maximum extent of variation from the zero or mean value of a signal

Binding: Associating or linking together two complementary software objects.

Boot: The process of loading a program into program memory.

Cache: A fast memory into which frequently used data or instructions from slower memory are copied for fast access. Fast access is facilitated by the cache’s high speed and its on-chip proximity to the CPU.

Central processing unit (CPU): The CPU is the portion of the processor involved in arithmetic, shifting, logic operations, as well as the generation of data- and program-memory addresses.

Classifier: A Classifier is essentially a mathematical function that can map those sets of features extracted from the raw signals into a category

Code: A set of instructions written to perform a task; a computer program or part of a program.

Convolution: A time or frequency domain reference for digital filtering that makes extensive use of sum-of-products.

Digital mixing: The mixing together of two digital signals into one; the algebraic sum of two digital signals.

Domain: This is an administrative area where signal analysis and processing takes place

DSL: Stands for Digital Subscriber Loop. It shares the same phone line as the telephone service, but it uses a different part of the phone line’s bandwidth.
Feature: A feature is a characteristic of the raw signal that helps us identify its morphology and place it into a physiological group, for instance, the heart rate or respiratory rate.

Filters: These are devices or digital processes that aim to eliminate noise or unwanted interference from signals.

Frequency: The number of cycles per unit of time, denoted by Hertz (Hz). One Hz equals one cycle per second.

Frequency Domain: the analysis of mathematical functions with respect to frequency.

JPEG (Joint Photographic Experts Group): An industry standard for compressing images.

Load: To enter data into storage or working registers.

Noise: This refers to artefact or interference that corrupts signals.

Time Domain: the analysis of mathematical functions with respect to time.

Vector: A vector is a set of numerical values that mathematically represent a signal.
1.19. The Challenge of Digital Signal Analysis and Processing in Medicine

A signal is any variable that carries or contains some kind of information that can, for example, be conveyed, displayed or manipulated. Examples include Speech, Biomedical signals such as EEG, echocardiography, Sound and Music, Video and Image and Radar signals, which determine range and bearing of distant targets.

The specific reasons for processing a signal may be to remove noise/interference, obtain a spectrum of the data or to transform the data into a more suitable form. Digital signal processing (DSP) refers to the digital representation of signals and the use of digital processors to analyse, modify or extract information from signals.

Most signals found in nature vary continuously with time and represent the variations of physical quantities such as sound for example. They may be represented in an analog or digital fashion.

**Analog Signals**

An analog signal is any continuous signal for which the time varying feature (variable) of the signal is a representation of some other time varying quantity, i.e., analogous to another time varying signal. For example, in an analog audio signal, the instantaneous voltage of the signal varies continuously with the pressure of the sound waves. The main advantage of analog signals is that it is continuous and an exact representation of the information collected. The main disadvantage is that because every system has noise – i.e., random unwanted variation, as the signal is copied and re-copied, or transmitted over long distances, or electronically processed, the unavoidable noise introduced by each step in the signal path is additive, progressively degrading the signal-to-noise ratio, until in extreme cases the signal can be overwhelmed.

**Digital Signals**

A digital signal is a representation of a sequence of discrete values of an analog signal. These values are obtained from samples or segments of the original analog signal. They are not continuous because they only use specific values to represent samples of the original information and so may not be an exact copy. The fidelity of a digital signal is however retained with current technology that allow for more frequent samples of the original analog signal to be
collected which means that there is an insignificant loss of information. The cost implications and need for expertise in designing these systems is one notable disadvantage.

The signals used in most forms of DSP are derived from analog signals, which have been sampled at regular intervals and converted into a digital form. See Figure 11.

![Figure 11: Digital signals are transformed analog signals sampled at regular intervals: Steps](image)

The advantages of DSP over analog techniques are that they are more accurate and therefore reproducible. This is because noise or interference can be eliminated at various steps of collection, to produce a much cleaner signal. The performance is unaffected by temperature or age, and it is flexible meaning that you do not need to modify hardware following programming and re-programming.

DSP has developed increasing importance in many key areas of technology including telecommunication, media, financial markets and biomedicine. It is now at the core of many emerging technologies that produce digital products that we use in everyday functions such as digital phones, television media, cameras, and banking.

In medicine, perhaps greater advancement is expected as the medical community is persuaded to collaborate with the engineering industry to continue to develop appropriate technology that would enhance patient experience, improve quality of life, prevent development or worsening of illness and as a harder end point, reduce mortality. This collaboration is the basis of Bioengineering, which is the application of concepts and methods of biology to solve real-world problems by using engineering methodologies.
Biomedicine therefore represents an important and fertile area for both the application of conventional DSP and more importantly for the development of new and robust DSP algorithms that could improve patient care.

Biomedical scientists utilise DSP in developing algorithms for patient monitoring, scanners, EEG brain mappers, ECG analysis, X-rays amongst a few. Medicine poses a unique problem however as its data is one of the most complex forms recorded. The reason being that they are generated from patients who are inherently different in their physical and constitutional characteristics and expectedly produce different outputs. The data produced from patients are also affected by changes in individual physiology on a daily basis and particularly from healthy to non-healthy states as well as interactions with environmental factors. This represents a challenge to the engineer who must come up with novel ways of manipulating and interpreting these complex medical data.

1.19.1. Properties of a signal

Any physiological parameter can be described by a frequency which is measured in Hertz (Hz) and this represents the number of times that parameter occurs in a second. An example is the respiratory rate, which in a normal healthy adult occurs about 12 times a minute. A device that measures it may therefore produce a signal that occurs at least 0.2 times per second = 0.2Hz. It is also described as an inverse of time:

\[ T = \frac{1}{f} \] (where \( T \) = time in seconds and \( f \) = frequency)

In DSP the term sampling frequencies of signals is used representing the number of times per second a signal is sampled during processing. It is important that the sample frequency (\( f \)) is greater than twice the maximum frequency (\( f_{\text{Max}} \)) of the signal otherwise it may be impossible to record that signal especially if it is prone to variation. This is known as the Nyquist limit, a concept that is similarly employed in transthoracic echocardiography for Doppler assessment of valvular incompetence (\( f \geq 2 f_{\text{Max}} \)).

The other properties that are of importance in signal analysis include the amplitude, the time frequency behaviour, and regularity. This list is non-exhaustive especially as signal processing is usually specific to the functional parameter we want to measure.
1.19.2. Key Digital Signal Processing (DSP) Operations

In this segment I will discuss a few key DSP operations (176), some of which I have used in some detail in this thesis. I have focused on the main techniques that I have employed in generating some of the algorithms for SleepMinderTM estimation of respiratory parameters used in diagnosis and prediction of ADHF, which I will discuss in the next chapters.

I have also excluded the finer details of the mathematical permutations that are generated to produce these algorithms as they are outside the focus and beyond the scope of my thesis.

1.19.2.1. Digital filtering and Signal Enhancement

Both techniques essentially involve the removal of noise/artefact from the wanted signal.

Digital Filtering

Biomedical signals may sometimes contain high frequency distortion and digital filtering preserves necessary components by using filters, which are devices or digital processes that remove from a signal some unwanted component or feature.

In DSP, it is common to use a combination of various filters to achieve better results. These filters act intelligently to remove some frequencies and not others in order to suppress interfering signals and reduce background noise.

The main aim is to eliminate as much noise as possible so that the signal to noise ratio is increased i.e. less noise is present. A high-pass filter is one where signals of higher frequencies are passed through, while low frequency signals are attenuated or eliminated (Figure 12). The converse is true for Low-pass filters.
Figure 12: A high pass filter removing noise from the raw signal to produce a cleaner signal

**Signal Enhancement**

The need for signal enhancement arises from a similar problem of artefact or signal contamination, which is pervasive in biomedicine. Artefacts can be generated by either external (mains supply or conflicting medical equipment) or internal (body movements, cardiac activity or illness) factors and these reduce the quality of the signals, which consequently affects clinical usefulness.

Analysis of these signals whether done manually or automatically can thus become very difficult to perform and sometimes impossible. Therefore a great deal of care is taken to enhance the signals of interest to tackle the dual problem of low signal to noise ratio and overlap between signal and noise spectra (Figure 13). This is done in the hope that clinical information of interest is not distorted.
Figure 13: A. Greater overlap of noise and signal spectra and smaller signal to noise ratio before signal enhancement. B. Lesser overlap of noise and signal spectra and higher signal to noise ratio.

Pattern recognition/Feature Extraction

The goal of pattern recognition is to classify objects of interest into one of a number of categories or classes. These objects of interest are generically called patterns, which in biomedicine may be from signals generated from a number of physiological parameters. An algorithm is generated and implemented on a specific hardware which when applied to these patterns would produce a result.

Supervised pattern recognition is a commonly utilized system in developing algorithms that are effective in biomedicine and one that has been used in this project. A dataset may contain a number of signals related to a physiological parameter, respiration for instance, that we are interested in analysing. The important signals we are interested in are first removed from the raw signals to create a set of labelled patterns and these comprise the ‘training set’. This process is known as feature extraction. (See Glossary – Page 96). A portion of these labelled signal patterns are then extracted and used to develop a classification algorithm. The remaining
patterns, collectively referred to as the ‘test set’ are then used to test the derived classification algorithm. Since the correct classes of the individual sampled patterns are already known, it is easy to evaluate the performance of the algorithm (Figure 14).

Depending on the results of the classification, the developer may make modifications to the algorithm until a desired level of performance is achieved; which is measured in terms of misclassification rates. Following on from this, the algorithm can now be used on unlabelled data. Spot-checking of results, as the feedback loop involving the developer is formally broken, may be provided by an alternative classification algorithm or in some cases waiting a length of time until the correct classification reveals itself.

![Figure 14: Schematic showing the processes involved in Pattern recognition.](image)

### 1.19.2.2. Discrete transformation

This is used in many DSP applications to allow for a more efficient implementation of DSP algorithms.

In some situations, it may be necessary to transform the observed raw signal vector \( x \) to a transformed features vector \( y \) for the classifier to produce a result (Figure 15).

Transformation is necessary to reduce the number of features obtained from the original signal, which are required to produce a result. It is important that while the features in the transformed vector \( y \) are intended to be fewer than the observations, it should collectively contain most of the information for classification of patterns.
The feature extraction procedures that are used now become very important here, so that potentially important features are not discarded. This can be very difficult to achieve perfectly especially if there are many variables and depending on the experience of the developer/selector. In general features extraction procedures are either based on intuition, physical consideration of the problem based on some prior knowledge or education about that physiological parameter. It is also sometimes purely a mathematical technique that performs a random selection.

Whatever mode is employed, the features vector \( y \) would be passed through the classifier, which will make a decision about the pattern and as discussed earlier, the results can guide in modifying either feature selection of classification algorithm especially if this was a development phase of the program.

### 1.19.2.3. Correlation

Cross correlation is a measure of similarities or shared properties between two signals. Applications include detection of signals buried in noise, pattern matching and delay measurements.

When you want to compare two signals of varying frequencies for instance, this becomes very important as we try to align or match their properties. For this process to work, a lot of the previously discussed processes are employed initially to remove noise and to digitally transform both signals onto similar vector planes from where they can be matched. Figure 16 below shows how a 32Hz respiratory signal is divided into segments from which integral absolute values are obtained to form a new vector plane \( V1, V2, \ldots, Vn \). A similar process is performed on another signal that may have similar properties but has been sampled at a different frequency to obtain a second vector plane. The two are then slid on top of each other to achieve a match.

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**Figure 15: Schematic showing of transformation of vectors**
Auto correlation in the other hand involves only one signal and provides information about the structure of the signal or its behaviour in the time domain.

I have defined some other DSP operations, some of which I have used in small detail in this project including:

1.19.2.4. Convolution

This is a frequently used operation in DSP particularly to filter signals by multiplication of signals in the frequency and time domains. Essentially Convolution is a mathematical way of combining two signals to form a third signal. More insight is gained and broader analysis can be made because we can look more closely at the structure of the integrand signal.

1.19.2.5. Modulation

This process involves varying a property of a high frequency signal (the carrier) in sympathy with the signal we wish to transmit known as the modulating signal. This is frequently employed in the digital audio industry where signals are modulated to match the frequency characteristics of those of the transmission and or storage media in order to minimize signal distortion, and maximize available bandwidth.
SECTION FIVE - Introduction to the SleepMinder™ Study
1.20. The SleepMinder™ Study

The SleepMinder™ study aims to validate the usefulness of a novel non-contact device which placed by a patient’s bedside is able to analyse respiratory patterns during sleep that may be indicative of an upcoming decompensation episode in patients with chronic heart failure (CHF).

The SleepMinder™ device (ResMed Ltd) utilises a biomotion sensor for contactless and convenient measurement of sleep and breathing in the home. It contains a non-contact radio-frequency sensor that continuously measures the biomotion due to breathing and body-movement of a subject in bed. The sensor operates in a license-free band at 5.8 GHz, emits an average power less than 1 mV and is capable of sensing movement and breathing over a distance ranging from 0.3 to 1.5 meters; in the case of two people in the bed, a combination of sophisticated sensor design and intelligent signal processing results in measuring only the respiration of the person nearest to the sensor.

There is evidence from pilot analyses that show that the SM is able to estimate accurately breathing rates and the AHI, which is the key parameter in making a diagnosis of SDB (177;178). Certain nocturnal respiratory signals have also been suggested to be useful in predicting ADHF from a small pilot study in Dublin.

I am carrying out SM analysis on a population of chronic heart failure patients from a west London tertiary centre who are at moderate to severe risk of decompensation. The primary goal of this study is to validate the diagnostic accuracy of the SM device in detecting ADHF events by identifying sleep respiratory patterns that are peculiar to these episodes and correlating the SM diagnosed events with clinical information. I will also examine how early these respiratory patterns that are suggestive of ADHF appear in the build-up to an overt deterioration.

To enable me achieve this, firstly I will validate the SM device against PSG in identifying and classifying varying types of respiratory patterns associated with SDB. I will accomplish this by developing event-based algorithms, signal protocols and classifiers, which would detect SDB events, by using, phase demodulation, amplitude, and correlation-based signal processing methods. Following the development of these algorithms identifying SDB, I would then use these events occurring during sleep as ADHF episodes evolve and resolve to develop a SM predictor algorithm for Acute Decompensation of Heart Failure (ADHF).
SUMMARY OF THE LIST OF STUDIES

STUDY ONE – Chapter 3

The validation of SleepMinder™ analysis of nocturnal respiratory patterns against Polysomnography for diagnosing Sleep Disordered Breathing in patients with Chronic Heart Failure

Main Hypothesis:

I hypothesised that there is a difference in the Apnoea Hypopnea Index (AHI) and quantity of Cheyne-Stokes Respiration (CSR) measured by the SleepMinderTM device compared to in–hospital Polysomnography (PSG).

STUDY TWO – Chapter 4

A Longitudinal Observation of Nocturnal Respiratory Patterns in patients with Chronic Heart Failure using a Non-Contact Breathing Monitor

Main Hypothesis:

I hypothesised that due to potential on-going changes in the pathophysiology of CHF patients, the AHI would have a high variability over a longer period of monitoring. My ‘Null’ hypothesis was therefore that there is a low variability in the Apnoea Hypopnea Index from night to night in patients with Chronic Heart Failure over a long (12months) period of monitoring.

STUDY THREE – Chapter 5

The Prediction of Acute Decompensation of Heart Failure Using a Non-Contact Monitor of Nocturnal Respiratory Patterns

Main Hypothesis:

I hypothesised that there is a measurable increase in the Apnoea Hypopnea Index (AHI) and the % overnight Cheyne-Stokes Respiration (CSR) by the SleepMinderTM device, within a 7-day period, and which can be utilised as a predictor of acute decompensation of heart failure.
CHAPTER TWO – General Methods
2.1. Ethical Considerations

This study received ethical approval from the National Research Ethics Service (NRES), London-Chelsea committee (REC Ref number 08/H1307/41) as well as Site Specific Assessment by the Research and Development department at the Royal Brompton and Harefield NHS Foundation Trust prior commencing all aspect of this study (Ref number 2008EP001B). An international ethics approval for screening patients for sleep disordered breathing in heart failure patients was also in place and this covered all patients recruited from the German centres, in Study 2 (Ref: Freiburger IRB/IEC. FECCI Code 010/1553). The group of patients recruited from Dublin, Ireland were covered by local ethical approval from St. Vincent’s Hospital in Dublin.

The studies in this project have been conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki, 1964, and later revisions, and are conducted in accordance with the principles of Good Clinical Practice.

In addition, all patients in the study signed a written consent form before they were recruited to take part and in line with strict data confidentiality, each participant was allocated an individual study number for data collection and subsequent analysis. Further, all data relevant to the study, was placed in a separate case record file for each participant and this was stored in our secure research office unit based at the Royal Brompton Hospital London. Copies of ethical approval letters, consent forms, patient information sheet and case record forms are included in Appendix Section 1-4.
2.2. Study Participants

2.2.1. Study One – The validation of SleepMinderTM analysis of nocturnal respiratory patterns against Polysomnography for diagnosing Sleep Disordered Breathing in patients with Chronic Heart Failure

Patients in study one were consecutive adult patients from two tertiary heart failure units, one in South-West London, United Kingdom and the other in Essen, Germany. These patients had presented for screening, to the heart failure clinic with recognized typical symptoms of Sleep Disordered Breathing (SDB), including witnessed apnoeas and daytime somnolence.

They all had systolic heart failure defined by a recent transthoracic echocardiogram with an ejection fraction (EF) of <45%. Patients with significant obstructive lung disease defined by an FEV1 of <50% or who were on treatment with any form of positive airway pressure were excluded.
2.2.2. Study Two – A Longitudinal Observation of Nocturnal Respiratory Patterns in patients with Chronic Heart Failure using a Non-Contact Breathing Monitor

Study Three – The Prediction of Acute Decompensation of Heart Failure Using a Non-Contact Monitor of Nocturnal Respiratory Patterns

Patients in Study three comprised of a development group enrolled from chronic heart failure patients attending St. Vincent’s Hospital in Dublin Ireland and a validation group of patients who were enrolled from the heart failure disease-monitoring programme at the Royal Brompton in London, United Kingdom. They were all recruited based on identical inclusion and exclusion criteria aimed to identify patients with a moderate to high risk of decompensation. Participants were aged over 18 years with a diagnosis of CHF in accordance with the European Society of Cardiology guidelines (4), with a BNP at recruitment of >58pmmol/L or a recent hospitalisation for worsening heart failure in the last 24 months. Exclusion criteria were cognitive impairment, unpredictable sleep patterns likely to affect the collection of sleep data and concurrent use of continuous positive airway pressure (CPAP). Recruitment for the Dublin group of patients started in October 2010 and finished in September 2012, while the first and last London patients were recruited in September 2011 and June 2012 respectively.

Patients in study two, which examined longitudinal variations in nocturnal respiratory patterns, comprised of the entire validation group of patients enrolled into study three from the Royal Brompton Hospital London.
2.3. Investigations and Assessments

2.3.1. Polysomnography

Attended in-hospital overnight PSG (Somnoscreen PSG Tele, Somnomedics GmbH) was performed in our sleep laboratories using standard techniques and scoring criteria (148;179).

Thoracoabdominal motion was measured by respiratory inductance plethysmography (Mux RIP Adaptors, Somnomedics GmbH with RIP belts, SLP Inc., USA), and nasal airflow was monitored by nasal pressure cannula and an oral flow thermistor. Arterial oxyhaemoglobin saturation (SaO₂) was monitored by pulse oximetry (Somnomedics Somnoscreen using Nonin PureLight Oximeter technology).

Sleep was monitored using a standard neuro electrode placement system to include EEG references (C4/A1), (C3/A2) and (O1/A2) (179). Submental and anterior tibialis Electromyogram (EMG) were also recorded. Electrooculogram (EOG) electrodes placed on both lateral canthi measured rapid eye movements (REM). Figure 17 shows a patient with a typical sleep laboratory setup for an overnight PSG study.

The transducers and lead wires permitted normal positional changes during sleep as well as movement out of bed. Bedtime and awakening time were at each subject’s discretion; and the Polysomnography was terminated after final wakening. This system was similar at both centres where PSG was performed.
Figure 17: Example of Patient setup for overnight Polysomnography

Polysomnography Scoring

Two expert respiratory physiologists scored the PSG data independently to determine $\text{PSG}_{\text{AHI}}$ and $\text{PSG}_{\text{CSR}}$ and using standard scoring criteria (180).

An apnoea was defined as cessation of airflow or reduction $>90\%$ for $\geq 10$ s, and a hypopnea as a reduction of $\geq 50\%$ in flow amplitude lasting $\geq 10$ s or a 30% reduction in flow amplitude with a $>3\%$ desaturation measured on the pulse Oximeter channel. The respiratory event was scored as obstructive apnoea, if it met apnoea criteria and was associated with continued or increased respiratory effort throughout the entire period of absent airflow or central apnoea if respiratory effort was absent throughout the entire period of absent airflow.

Cheyne – Stokes Respiration was scored as present when there were 3 consecutive central apnoeas and hypopneas in a 10-minute epoch. The % overnight CSR was calculated by dividing the number of epochs scored as CSR by the Total Sleep Time (TST). The apnoea-hypopnea index (AHI) was a fraction of the total number of apnoeas and hypopneas over the scored TST.
2.3.2. SleepMinder™ Recordings and Data Transmission

The SleepMinder™ is a non-contact bio-motion recording system interpreting body movement and breathing via two sinusoidal electromagnetic wave signals (factor 10-100 less compared to common household devices). The sensor operates in a license-free band at 5.8 GHz and emits an average power less than 1 mV. It sends and receives this reflected wave from the SM sensor to the patient and back again to record the patient’s body movement and breathing associated with sleep.

The SM emits two signals named I and Q, which are out of phase by 90 degrees with each other. This maximizes its sensitivity within its cone of operation. This means that at any given point, when the signals hit the subject, one component would be larger in amplitude than the other enabling the sensor to capture all possible dynamics of patient's movement. (Figure 18)

![Image](image)

**Figure 18: SleepMinder™ I and Q channels**

The SM device sensor also has range gate, which is capable of sensing movement and breathing over a distance ranging from 0.3 to 1.5 meters. Further, due to its intelligent sensor design, it ensures that in the case of two people sleeping in the bed, only the person nearest the sensor would have signals recorded.

The signals hit this first subject and are reflected immediately back to the SM sensor which now trains recording on this subject alone. This is shown in Figure 19.
Figure 19: Schematic showing Cone of Operation of SM Device

Study Environment

For the purposes of the validation in study 1, simultaneous PSG and SM recordings took place during an overnight hospital stay at the Royal Brompton Hospital in London and the University Hospital Duisburg-Essen Germany. The device was placed at a height of about 10cm from the patients’ bed and 100cm from the patients’ chest. (See Figure 20)

Figure 20: Schematic of SleepMinderTM placed by patients bedside

In the studies 2 and 3, each patient was provided with a SM device, which they took home and positioned at their bedside as aforementioned. They also received a set of scales to record their daily weights with. They were instructed to weigh themselves at the same time every day, preferably in the morning. The SM and scales transmitted this information collected via a study
mobile phone using Bluetooth connectivity. This phone then automatically transferred this data via a 3G mobile network to the data collection centres in Dublin and Sydney for later analysis. (See Figure 21)

The data collection centre was a real time database and was quality controlled in Dublin. When there were interruptions in recordings from either SM or scales, I was able to respond to this by contacting the patient(s) involved and troubleshooting.

![Figure 21: Schematic of SleepMinderTM showing data transmission](image)

**2.3.3. Transthoracic Echocardiography**

Transthoracic echocardiography was performed mainly to make an assessment of the patient’s global left ventricular function systolic function by measuring the left ventricular ejection fraction (LVEF). This was mainly for the purposes of classification of heart failure patients into low or preserved EF categories but also a surrogate for severity of heart failure (181). CHF may be also present in patients with a normal ejection fraction especially women and older patients (182).

The echocardiograms performed as part of this study were all part of routine clinical care. In study one where I excluded patients with Heart failure with preserved or normal ejection fraction (HFpEF, HFnEF), participants were required to have this assessment done if it had not been performed. A Simpson’s biplane method was used to assess global left ventricular function were possible otherwise a 2D Teicholtz method was employed. However, the latter methods using LV linear dimensions may result in inaccuracies due to the geometric assumptions required
to convert a linear measurement to a 3-D volume. With reference to sex and body surface area, a patient is considered to have a normal LVEF with a value above 45% (183).

2.3.4. B-type Natriuretic Peptide (BNP)

BNP is released by the ventricular myocytes as a response to stretch due to volume overload. Its actions include natriuresis and diuresis and antagonism of the renin angiotensin system leading to a reduction in cardiac preload and afterload (43). BNP is used for diagnosis, risk stratification and prognostication in heart failure (184). BNP was measured as part of inclusion criteria in study three. Patients who had a BNP level of >200pg/ml (58pmol/L) were eligible for this study provided there were no other exclusion criteria. This measurement was carried out at the baseline visit, in the biochemistry laboratory at the Royal Brompton Hospital London, using an Alere™ Triage immunoenzymatic assay.

2.4. Statistical Analysis

All SleepMinder™ algorithm development, analysis and testing was performed using MATLAB version 15. All other statistical analyses were undertaken using IBM SPSS Statistics version 21. For studies 1, 2 and 3, I have described in detail, in the relevant chapters (3, 4 and 5), the specific statistical tools I have employed to analyse my results.
CHAPTER THREE – The validation of SleepMinder™ analysis of nocturnal respiratory patterns against polysomnography for diagnosing Sleep Disordered Breathing in patients with Chronic Heart Failure
3.1. Introduction

Sleep Disordered Breathing (SDB) is prevalent in patients with chronic heart failure (CHF) occurring in 50-80% of patients (6-8;185).

The current gold standard for making a diagnosis of SDB is attended in-hospital polysomnography or polygraphy (PSG/PG).

The SleepMinder™ device is a novel non-contact bedside monitor that contains a biomotion sensor transceiver that utilises ultra-low power radiofrequency signals to detect movement and breathing of a patient sleeping next to it.

3.2. Hypothesis

The ‘Null’ Hypothesis for this study is that there is no difference between the Apnoea Hypopnea Index (AHI) and quantity of Cheyne-Stokes Respiration (CSR) measured by the SleepMinder™ device compared to in–hospital Polysomnography (PSG).

3.3. Aim

The main aim of this study was to evaluate the SM’s accuracy in identifying and quantifying SDB in patients with CHF compared to full in hospital PSG, by developing specialised algorithms from the reflected SM signals, which can calculate metrics of SDB.

This validation would be important as the algorithms generated and measurements obtained from the SM, would be utilised in other areas of this thesis particularly in the chapter 5 looking at predicting acute decompensation of chronic heart failure.

3.4. Study Population

The study population was made up of 59 consecutive adult patients with CHF enrolled from two tertiary heart failure units, one in South-West London, United Kingdom and the other in Essen, Germany. They had presented to the heart failure clinic for screening for SDB with recognized typical symptoms including witnessed apnoeas and daytime somnolence.

They all had systolic heart failure, with a recent transthoracic echocardiogram measured left ventricular ejection fraction (EF) of <45%. Patients with significant obstructive lung disease
defined by an FEV1 of <50% or who were on treatment with any form of positive airway pressure were excluded.

3.5. Methods

3.5.1. Overnight Polysomnography (PSG)

Each patient underwent simultaneous SleepMinder™ recordings and an overnight PSG (Somnoscreen PSG Tele, Somnomedics GmbH) performed in our sleep laboratories using standard techniques and scoring criteria (148). This has been described in detail in the Chapter Two – General Methods.

To summarise, the PSG data acquired, included signals from respiratory effort bands at the chest and abdominal level, airflow via nasal cannula, arterial oxygen saturation, electrocardiogram, electroencephalogram (for staging of sleep), and electromyogram (for detecting arousals). In addition a microphone was connected to detect snoring events.

A minimum of 4 hours was considered satisfactory for each study and this system was similar at both centres.

3.5.2. PSG Scoring

Two independent experts who were blinded to each other, the patients’ medical history or SM recordings, performed the scoring of PSG signals. The specific criteria for scoring respiratory events have been described in Chapter 2 – General Methods.

The main output from the scorers for the purpose of validation was the PSGahi and PSGcsr.

3.5.3. SleepMinder™ Recording

The SleepMinder™ (SM) device is a non-contact device that sits by the patient’s bedside. It emits low frequency electromagnetic waves from an in-built sensor to the patient, which is reflected back to the SM sensor. Through this, it is able to record signals that pertain to breathing and movement of the subject lying closest to it. Detailed description of this mechanism of operation has been given in Chapter 2 – General Methods.
On the night of the PSG study, the SleepMinder™ was positioned by the patients’ bedside at a height of 10cm and 3 foot from their chest. It was turned on at the start of the PSG recording and then turned off at final patient wakening. SM recordings were logged onto a Secure Digital card, which was downloaded at the end of the study.

3.5.4. Sample Size

Based on previous validation studies of home screening devices for SDB (186;187), I predetermined that a combined diagnostic accuracy of 90% (sensitivity=specificity=0.90), would be an acceptable measure of accuracy of the SleepMinder™ device.

Therefore using a prevalence rate of 40% of CHF patients in the population who have SDB, and for a maximum width of 15% for a 95% confidence interval, a sample size of 40 patients was calculated as adequate for this study. I achieved higher than this target, recruiting 66 patients into this study with 7 excluded due to incomplete or corrupted PSG (4) or SM (3) data.

3.5.5. Statistical Analyses

The combined data generated from the overnight studies at both centres were divided into two datasets. A combination of the 1st two thirds of each dataset from each centre made up the ‘Development’ Set (London -20, Essen- 20, n = 40 patients), for algorithm development. We then validated our results on a combination of the final third of the remainder dataset in each centre, which formed our ‘Validation’ Set (London-10, Essen- 9, n = 19 patients).

Normally distributed and continuous data are presented as means ± Standard Deviation (SD), otherwise as Medians and Interquartile Ranges (IQR). Student’s t-tests were used to compare non-paired continuous variables. For categorical variables, the χ2 test with Yates’ correction or Fisher’s exact test, if necessary, was used.

Algorithm development and signal analyses were performed using Mat Lab version 7.13. All other statistical analyses were performed with IBM SPSS Statistics v.21 software. All P values are asymptotic two-sided. Statistical significance was considered when P< 0.05.

The correlation between the two diagnostic tools for the AHI was tested by Pearson’s correlation co-efficient and the degree of agreement was tested using a Bland and Altman analysis examining for any systematic bias in scoring by either tool.
Furthermore, I constructed Receiver Operator Characteristic (ROC) curves for various thresholds of SleepMinder™ determined AHI (SM_{AHI}), according to SDB severity, to obtain the best cut-off point compared to expert PSG scoring (PSG_{AHI} and PSG_{CSR}) in terms of sensitivity, specificity, and positive and negative predictive values (188;189). I used a similar method for predetermined thresholds of SleepMinder™ determined % overnight CSR (SM_{CSR}). The accuracy of our algorithm was the number of true positive and true negative cases divided by all cases and represented by the area under the ROC curve.

Inter-rater variability to assess agreement of sleep scoring between scorers of the PSG signals was derived from Pearson’s correlation co-efficient and Intra-class correlation coefficients.

3.6. Development of SleepMinder™ Algorithms

3.6.1. Alignment of PSG/SM Signals

The first step in developing the AHI and CSR Algorithms used in this study was to align signals from both SM and PSG devices as accurately as possible and to a common timing stamp because both signals were collected at different sampling frequencies – 16GHz for the SM and 20Hz/32Hz for the PSG.

To achieve this, we have used a cross correlation and sliding window method to align feature vector transformation of these signals. I have described these digital signal-processing techniques previously in section 1.19. To summarise, the SM signals were initially combined into one single channel to reduce computational costs i.e. the amount of time required to analyse the SM signals in two separate channels as they are essentially identical signals but only collected at different angles. The PSG signals were utilized in its single channel. The entire lengths of both signals (SM and PSG) were then broken down into consecutive 1-second segments and an Integral Absolute Value (IAV) for each segment was obtained based on the sampling frequency and amplitude of each signal. Therefore each 1-second segment of PSG data for instance, would contain 20 or 32 samples upon which the IAV was calculated and 16 samples for the SM.

The result of this process was the production of two vectors, one each for PSG flow and SM signals. (Figure 22) The IAV’s obtained for segments of both PSG and SM signals were then cross
correlated to find the highest correlation value which corresponded to the best alignment points of both signals. Once this vector alignment was achieved and because the timings had now been unified, it was now possible to adjust the raw signals using our sliding window to achieve a reasonable fit. This was achieved by essentially sliding one vector window V1 for PSG over the vector window V2 for SM.

Figure 22: Integral Absolute Values created from 1-second samples of signals. (V1-PSG Vector, V2-SleepMinder Vector)

The alignment drift; which refers to how one vector is moved to align with the other; is measured in seconds and this is what is subsequently applied to the RAW signals to obtain a final result (Figure 23). Even when there was an excess of signal (usually with the SM, as that was turned on first before the PSG started), this could be trimmed at the end of alignment of the both RAW signals. Figure 24 is a schematic showing a summary of the entire alignment process.
Figure 23: Aligned RAW PSG and SM Signal

Figure 24: Summary of SM/PSG Alignment process
3.6.2. AHI Algorithm Development

The first step in developing the AHI algorithm was to combine, both I and Q channels of SleepMinder™, into a single RAW channel (Z) as shown in Figure 25. This was done to in order to reduce computational time and resources. It was within this single channel that all operations relating to algorithm development took place.

The combined channel was pre-processed to filter noise and zero the baseline (also known as detrending). Further, using pattern recognition and cycle interval techniques the pure respiratory signals were then isolated. The SM’s proprietary Sleep/Wake analysis and integrated movement detector algorithms were then applied to this signal to determine the SM calculated Total Sleep Time (SM\(\text{TST}\)). This algorithm has been described in detail elsewhere (190). In summary, this algorithm makes an estimate of the patients total sleep time, by measuring the patient’s presence and movement away from the SleepMinder™ through the night of recording.

![Diagram of AHI algorithm development process](image)

**Figure 25: AHI algorithm development process**

The pure sleep respiratory signal was then divided into segments for AHI algorithm development and analysis. These segments are also known as epochs, which are time-defined segments upon which gold standard PSG is routinely scored. Typically an epoch for scoring is usually 30 seconds to 5 minutes long.
We developed a new event based algorithm for the detection of SDB events; apnoeas or hypopneas; with the fundamental criteria defining the detection of a disturbed breathing event being a reduction in magnitude of 50% or more in the amplitude of the non-contact measure of overall body breathing effort, lasting for 10 seconds.

To achieve this, we created a respiratory event detection envelope that mapped the entire overnight SM respiratory signal channel (Figure 26). This was then analysed using markers of peaks and troughs to detect and label all potential events.

**Figure 26: Signal Envelope Generation**

Final confirmation of these events was based on the duration and amplitude of these SDB events based on the pre-defined criteria (Figure 8). The $\text{SM}_{\text{AHI}}$ was then determined as a fraction of $\text{SM}_{\text{TST}}$ as shown in figure 27. Severity of SDB was defined as mild AHI >5, moderate AHI >15 and severe AHI >30.

**Figure 27: Confirmation of SDB Event**
During development, the algorithm was trained to ignore non-respiratory event signals such as high amplitude, but low frequency signals that may arise from periodic leg movements (PLM), which could potentially mimic a hyperpnoea.

3.6.3. CSR Algorithm Development

The SleepMinder™-based CSR algorithm used in this study was designed based on a framework of pattern recognition [28], where sets of statistical descriptors, usually referred to as features, were extracted from the raw SM signals, processed and then used to determine the probability of CSR within a 10 minute epoch of SM signal.

The initial stages of this algorithm development are similar in process to those used in developing the AHI metric in terms of combination of SM channels and identification of respiratory events. We concentrated development mainly over these areas where there were confirmed respiratory events, examining them for modulatory patterns of respiration which may be representative of CSR.

The single combined SM channel was first pre-processed to remove local trends that may cause baseline wandering. The signals were then passed through a first order Band-Pass Butterworth filter with cut off frequencies [0.1Hz, 0.7Hz], to remove any irrelevant effects of non-respiratory frequencies that may induce some CSR-like modulated shapes in our SM signal.

Following this, all the apnoea/hypopnoea events were then detected using our previously developed AHI algorithm. These events were subsequently labelled and then examined carefully for any possible crescendo-decrescendo modulations that qualify these sections of the signal to be scored as CSR.

The main module of the CSR algorithm we have developed utilises a combination of the following key statistical descriptors of the patterns of Apnoeas or hypopnoeas identified for possible modulation. This is shown in Figure 22.
Statistical Descriptors

- Number of zero crossings (ZC) – This is a measure of how many times the SM signal crosses the x-axis at zero point and an indicator of how fast the CSR signal oscillate within a specific cycle.

- Energy of the CSR pattern (En) – the energy of the signal when divided into segments looking for any possible crescendo-decrescendo pattern (terminal regions exhibit lower energy than middle regions).

- Slope of the CSR Envelope (Slope) – This feature examines the upward and downward trends of the potential CSR segment anticipating a positive slope for the first half of the cycle and a negative slope for the latter half. The angle of each slope against the x-axes is also examined.

- Phase locking Value (PLV) – This feature describes the amplitude and phase of the CSR cycle. A typical cycle would exhibit high phase similarity between two halves as opposed to one that is corrupted, been dissimilar.

Figure 28: Statistical descriptors for CSR Algorithm development
These above extracted features/statistical descriptors contribute a probability value or ‘vote’ that the segment should be scored as CSR. Each descriptor was of equivalent weight. The final result was a probability score between 0 and 1. The closer to 1, the vote was, the higher the probability that those segments should be scored as CSR.

During development of the algorithm the probability threshold was adjusted depending on expert PSG scoring and to reduce the number of false positives. We selected a fairly high probability value of >0.85 as acceptable indication of CSR and this was used on the validation set of patients. This threshold selection was based on strict scoring behaviour of the expert PSG on valid CSR sections.

In the final module, we divided the entire overnight signal length into consecutive 10-minute segments and employing universal scoring criteria (148), a section was scored as CSR where there are at least 3, or more, consecutive cycles of cyclical crescendo-decrescendo change in breathing amplitude. Figure 29 summarises this entire development process.

![Figure 29: Schematic showing summary of entire CSR Algorithm development process](image-url)
3.7. Results

3.7.1. Demographics

66 patients (London 30) and (Essen 36) had simultaneous PSG and SM data collected (Figure 30). 7 patients from the Essen dataset were excluded from analysis due to incomplete or corrupted data (4 PSG, 3 SM). In total 59 patients had adequate paired data (>4 hours) suitable for analysis. The median age (IQR) of all studied patients was 71 (60-74) years. The mean (SD) ejection fraction, NYHA class and Body Mass Index were 31 (9) %, 2.5 (0.5) and 29 (8) Kg/m2 respectively.

There were no significant demographic or clinical differences between the London and Essen population of patients (Table 11). There was also no significant difference between Development and Validation group of patients with more than half of patients in both groups treated with Beta-blockers, ACE-inhibitors or Mineralocorticoid receptor antagonists (Table 12).

Figure 30: Consort Chart of recruitment
<table>
<thead>
<tr>
<th>Group</th>
<th>Total (59)</th>
<th>London (30)</th>
<th>Essen (29)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Years)</td>
<td>71 (60-74)</td>
<td>71 (31-87)</td>
<td>72 (41-84)</td>
<td>0.43</td>
</tr>
<tr>
<td>Male Sex n (%)</td>
<td>51 (86)</td>
<td>28 (93)</td>
<td>23 (79)</td>
<td>0.16</td>
</tr>
<tr>
<td>BMI (Kg/m2)</td>
<td>29 ± 8</td>
<td>29.4 ± 5.1</td>
<td>29.3 ± 4.3</td>
<td>0.91</td>
</tr>
<tr>
<td>Ejection Fraction (%)</td>
<td>31 ± 9</td>
<td>33.6 ± 6</td>
<td>27.9 ± 11.2</td>
<td>0.02</td>
</tr>
<tr>
<td>NYHA</td>
<td>2.5 ± 0.5</td>
<td>2.3 ± 0.4</td>
<td>2.8 ± 0.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ischaemic n (%)</td>
<td>41 (70)</td>
<td>23 (77)</td>
<td>18 (62)</td>
<td>0.10</td>
</tr>
<tr>
<td>HTN n (%)</td>
<td>35 (59)</td>
<td>15 (50)</td>
<td>19 (66)</td>
<td>0.02</td>
</tr>
<tr>
<td>COPD n (%)</td>
<td>7 (12)</td>
<td>4 (13)</td>
<td>3 (10)</td>
<td>0.34</td>
</tr>
<tr>
<td>DM n (%)</td>
<td>12 (20)</td>
<td>7 (23)</td>
<td>5 (17)</td>
<td>0.33</td>
</tr>
<tr>
<td>BetaBlocker n (%)</td>
<td>41 (70)</td>
<td>22 (73)</td>
<td>19 (66)</td>
<td>0.27</td>
</tr>
<tr>
<td>ACEi or AIIRB n (%)</td>
<td>47 (80)</td>
<td>26 (86)</td>
<td>21 (72)</td>
<td>0.05</td>
</tr>
<tr>
<td>MRA n (%)</td>
<td>36 (61)</td>
<td>21 (70)</td>
<td>15 (52)</td>
<td>0.22</td>
</tr>
</tbody>
</table>

**Table 11: Demographic Chart – London versus Essen Group of Patients, (BMI – Body Mass Index, NYHA – New York Heart Association Classification of Heart Failure, DM – Diabetes Mellitus, B-Blocker – Beta Blocker, ACEi – Angiotensin Converter Enzyme Inhibitor, AIIRB – Angiotensinogen II Receptor Antagonist, MRA – Mineralocorticoid Receptor Antagonist, COPD –Chronic Obstructive Pulmonary Disease and HTN – Hypertension)**
### Table 12: Demographic Chart – Development versus Validation Group of Patients

<table>
<thead>
<tr>
<th></th>
<th>Total (59)</th>
<th>Development (40)</th>
<th>Validation (19)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Years)</td>
<td>71 (60 - 74)</td>
<td>72 (31-87)</td>
<td>72 (47-78)</td>
<td>0.43</td>
</tr>
<tr>
<td>Male Sex n (%)</td>
<td>51 (86)</td>
<td>34 (85)</td>
<td>16 (84)</td>
<td>0.63</td>
</tr>
<tr>
<td>BMI (Kg/m²)</td>
<td>29 ± 8</td>
<td>29.7 ± 5.4</td>
<td>28.6 ± 2.9</td>
<td>0.42</td>
</tr>
<tr>
<td>Ejection Fraction (%)</td>
<td>31 ± 9</td>
<td>30.4 ± 9.3</td>
<td>31.8 ± 9.2</td>
<td>0.61</td>
</tr>
<tr>
<td>NYHA</td>
<td>2.5 ± 0.5</td>
<td>2.5 ± 0.5</td>
<td>2.6 ± 0.6</td>
<td>0.55</td>
</tr>
<tr>
<td>Ischaemic n (%)</td>
<td>41 (70)</td>
<td>27 (68)</td>
<td>16 (84)</td>
<td>0.49</td>
</tr>
<tr>
<td>HTN n (%)</td>
<td>35 (59)</td>
<td>20 (50)</td>
<td>14 (74)</td>
<td>0.08</td>
</tr>
<tr>
<td>COPD n (%)</td>
<td>7 (12)</td>
<td>3 (0.1)</td>
<td>4 (0.2)</td>
<td>0.64</td>
</tr>
<tr>
<td>DM n (%)</td>
<td>12 (20)</td>
<td>7 (0.2)</td>
<td>5 (0.3)</td>
<td>0.28</td>
</tr>
<tr>
<td>B-Blocker n (%)</td>
<td>41 (70)</td>
<td>26 (65)</td>
<td>15 (79)</td>
<td>0.26</td>
</tr>
<tr>
<td>ACEi/AIIrb n (%)</td>
<td>47 (80)</td>
<td>33 (83)</td>
<td>14 (74)</td>
<td>0.67</td>
</tr>
<tr>
<td>MRA n (%)</td>
<td>36 (61)</td>
<td>21 (53)</td>
<td>15 (79)</td>
<td>0.05</td>
</tr>
</tbody>
</table>

(BMI – Body Mass Index, NYHA – New York Heart Association Classification of Heart Failure, DM – Diabetes Mellitus, B-Blocker – Beta Blocker, ACEi – Angiotensin Converter Enzyme Inhibitor, AIIrb – Angiotensinogen II Receptor Antagonist, MRA – Mineralocorticoid Receptor Antagonist, COPD – Chronic Obstructive Pulmonary Disease and HTN – Hypertension)
3.7.2. Prevalence of SDB

The prevalence of clinically significant Sleep Disordered Breathing (SDB) (AHI>15), as determined by expert PSG scoring in this cohort was 47%. In this group of patients 36% of them also exhibited a Cheyne - Stokes Respiration suggesting a central variety of SDB. (Table 13)

<table>
<thead>
<tr>
<th>SDB AHI&gt;15</th>
<th>CSR %&gt;0</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>NO</td>
<td>20</td>
<td>11</td>
</tr>
<tr>
<td>YES</td>
<td>18</td>
<td>10</td>
</tr>
<tr>
<td>TOTAL</td>
<td>38</td>
<td>21</td>
</tr>
</tbody>
</table>

Table 13: A 2 by 2 table showing prevalence of clinically significant SDB (AHI>15) and Cheyne – Stokes Respiration based on expert PSG scoring.

3.7.3. AHI Algorithm Performance

There was good correlation between SleepMinder™ Algorithm scored AHI (SM_AHI) and Expertly scored AHI from Polysomnography (PSG_AHI) with a correlation co-efficient of 0.91 and 0.80 in the development and validation set of patients respectively. (Figure 31 & 32)

Figure 31: Pearson’s Correlation Development set of Patients r=0.91
I have further constructed a Bland – Altman plot to examine the agreement and systematic bias between the two AHI scoring techniques. This demonstrated that while there was a tendency for a higher estimation of the AHI by SM, across the range of values overall agreement between SM$_{AHI}$ and PSG$_{AHI}$ was good and consistent even as severity of SDB increased. The mean diff between the two scores was 5.6 events per hour (95% Confidence Interval -2.1 -13.4) and where there was overestimation compared to gold standard PSG, this was not by more than 10 events per hour in 72% of patients, which is therefore unlikely to put the patient into a different severity category of SDB. (Figure 33)
Figure 33: Bland-Altman Plot of agreement between SM$_{AHI}$ and PSG$_{AHI}$. Shaded area is the agreement band within 10 events per hour for both tests.

In terms of diagnostic accuracy, the SleepMinderTM was 91% sensitive and 50% specific for identifying patients with SDB ($AHI>15$). It has a positive predictive value of 71% and a negative predictive value of 80%. (Table 12) The overall accuracy of the SM AHI algorithm was 82% as shown by the area under a Receiver Operator Characteristic (ROC) Curve constructed for this diagnostic threshold. (Figure 34) The performance of the algorithm was marginally improved when the threshold for diagnosis was changed to an AHI of >30 (i.e. Severe SDB – AUC 0.88, Figure 35) or >5 (i.e. any SDB at all – AUC 0.85, Figure 36).
Table 14: A 2 by 2 Plot of diagnostic accuracy of SleepMinder™ for SDB (AHI>15) on Validation set of patients (n=19)

<table>
<thead>
<tr>
<th>Patient with AHI &gt;15 PSG (gold standard)</th>
<th>AHI&gt;15 by Sleep Minder Algorithm</th>
<th>Sensitivity = 91%</th>
<th>Specificity = 50%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Positive</td>
<td>Negative</td>
<td>Total</td>
</tr>
<tr>
<td>Positive</td>
<td>10</td>
<td>1</td>
<td>11</td>
</tr>
<tr>
<td>Negative</td>
<td>4</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>Total</td>
<td>14</td>
<td>5</td>
<td>19</td>
</tr>
</tbody>
</table>

PPV = 71%  NPV = 80%

AUC – 0.82  (95% CI 0.63 – 1.0)

Figure 34: ROC curve for diagnostic threshold of SDB of AHI>15
Figure 35: ROC curve for diagnostic threshold of SDB of AHI>30

AUC – 0.88 (95% CI 0.68 – 1.0)

Figure 36: ROC curve for diagnostic threshold of SDB of AHI>5

AUC – 0.85 (95% CI 0.61 – 1.0)
3.7.4. CSR Algorithm Performance

The SleepMinder™ CSR algorithm was 71% sensitive and 75% specific for identifying the presence of Cheyne-Stokes Respiration (CSR >0%). The positive and negative predictive value of this algorithm was 63% and 82% respectively. (Table 15) Overall the accuracy of the CSR algorithm was 0.76 as determined by the area under a ROC curve plotted at this threshold (See Figure 37). For a diagnostic threshold of CSR >5%, the accuracy was marginally worse with an AUC of 74%. (Figure 38)

<table>
<thead>
<tr>
<th>Patient with CS&gt;5% PSG (gold standard)</th>
<th>CSR&gt;0% by Sleep Minder Algorithm</th>
<th>Sensitivity = 71%</th>
<th>Specificity = 75%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>Positive</td>
<td>Negative</td>
<td>Total</td>
</tr>
<tr>
<td>Positive</td>
<td>5</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>Negative</td>
<td>3</td>
<td>9</td>
<td>12</td>
</tr>
<tr>
<td>Total</td>
<td>8</td>
<td>11</td>
<td>19</td>
</tr>
</tbody>
</table>

PPV = 63 %  NPV = 82 %

Table 15: A 2 by 2 Plot diagnostic accuracy of SleepMinder™ for presence of CSR on Validation set of patients (n=19)

![ROC Curve for CSR>0%](image)

Figure 37: ROC curve for diagnostic threshold of overnight CSR >0%
The SM estimated Total Sleep Time (TST) did not correlate well with that obtained from PSG scored by experts (Intra-class Correlation Co-efficient 0.22). To evaluate further, I constructed a Bland-Altman plot to evaluate agreement and for any systematic bias between this two techniques (Figure 39). Overall the SleepMinder™ tended to overestimate the TST compared to the PSG but this trend was consistent with increasing TST suggesting no systematic bias. The mean difference between the two scoring systems was 87.35 (minutes) but the limits of agreement were quite wide suggesting that the two tests did not agree particularly well in obtaining this parameter (95% Limits of Agreement 39.8 – 134.8).
3.7.6. Inter-Rater Variability

To assess the reliability between the two independent scorers of the PSG signals, I calculated correlation coefficients and intra-class correlation coefficients for both scorers.

There was good agreement between the 2 scorers for the AHI as shown in figure 40 and supported by the ICC. While the CSR correlation value seemed reasonable, it was evident from the ICC of 0.203, that agreement was poor between scorers, with one observer coding no CSR while the other coded a variable degree of CSR in many of the same patients. (See Figure 41)
**Figure 40:** Correlation between 2 PSG Scorers for AHI Correlation Coefficient $r=0.907$. Intra-class Correlation Coefficient = 0.879 (95% CI 0.747, 0.936)

**Figure 41:** Correlation between 2 PSG Scorers for CSR. Correlation Coefficient $r=0.625$ Intra-class Correlation Coefficient = 0.203 (95% CI -0.083, 0.469)
3.8. Discussion

In this study I have developed and validated two algorithms using signals obtained from the SleepMinder™ (SM) device and shown that it is capable of identifying Sleep Disordered Breathing (SDB) based on the Apnoea Hypopnea Index (AHI) with a reasonable diagnostic accuracy (High Sensitivity-91%, but very modest Specificity -50%). To a lesser degree, it is also able to identify Cheyne-Stokes Respiration (CSR) (Sensitivity 71%, Specificity 75%). This has been achieved using a mixed population of patients with Chronic Heart Failure (CHF) and compared to the gold standard in-hospital Polysomnography.

I successfully collected paired SM/PSG signals from 59 patients. In the 7 patients whom we excluded, this was due to signal failure of the SM in 3 patients and loss of PSG signals in the other 4. The failure rate for SM was therefore 4.5%, which is comparable to other contact devices used either at home, or in-hospital (See Table 9, Chapter 1) (146).

The clinical value of this method is the potential to simplify the sometimes-laborious diagnostic process for SDB as a result of the non-contact and thus patient-friendly design of the SM. It is cheaper than PSG to perform and can be performed in the patients’ home requiring minimal engagement and competence from patients.

In addition, the performance of SM in detecting and diagnosing SDB in a heart failure cohort is comparable to other forms of portable/home contact-screening devices (132;144;191-203).

In majority of these studies of portable home screening devices that are comparable to SleepMinder™ – (i.e Type 4 portable monitors, See Table 9 and 10, Chapter 1), patients with heart failure were not included. Most of these patients who were recruited into these studies had suspected symptoms of Obstructive Sleep Apnoea (OSA) and had been referred to the sleep clinics for further investigations. I will discuss two of these studies which have included a predominantly heart failure population for their validation purposes (See Table 16 below)(132;144;191).
Table 16: Studies of Portable Monitoring for the diagnosis of SDB in Heart Failure patients

(Abbreviations: HR – Heart Rate, AHI – Apnoea Hypopnea Index, ODI – Oxygen Desaturation Index, CSR – Cheyne Stokes Respiration, VLFI – Very Low Frequency Increment, O2 Sats – Oxygen Saturation, NA – Not Available)

The ApneaLink (ResMed, Sydney, Australia) is a single-signal screening device, which measures flow via a nasal cannula connected to a pressure transducer. It has been validated for detecting CSR compared against PSG in a population of heart failure patients (Sens 87%, Spec 94%) (191). In this study 70 patients were recruited as part of screening for SDB and sleep studies took place in a German sleep centre. 58% of these patients had a diagnosis of CHF. It has also been previously validated against PSG for calculating the AHI (Sens 91% Spec 95%), in a population of 59 Type II diabetic patients, 3% of whom had heart failure (144).

Ward and colleagues investigated the utility of overnight pulse oximetry and Heart Rate Variability (HRV) for detecting SDB in a population of 178 stable CHF patients recruited from a UK tertiary HF centre. The median left ventricular ejection fraction was 40% and 77% of these patients had NYHA class I or II symptoms. They measured the percentage of Very Low Frequency Increments (%VLFI) in heart rate from an ambulatory ECG worn by patients and a 3% Oxygen Desaturation Index (ODI) which was calculated as the mean number of ≥3% oxygen desaturations per hour, using the ‘time in bed’ as denominator. A pre-specified 3% ODI cutoff of >7.5 desaturations/hour was used to diagnose SDB.
In comparison to PSG and at a cutoff of ≥2.23%, the %VLF1 had a sensitivity of 58% and specificity of 48%, for diagnosis of SDB (AHI≥15). Overnight pulse oximetry performed better with a sensitivity of 97% and specificity of 32% for diagnosis of clinically relevant SDB.

While the Apnoea Link and the use of a 3% ODI as reported by Ward et al, have published better results in comparison to the SleepMinder™, a major advantage of the SM over these methods is that it is unlikely to influence sleeping due to its non-contact design, and therefore several nights would be convenient to undertake and this could be used to identify clinically important SDB. The ability of the SM to be used in the patient’s home as well also increases its acceptability as a screening tool.

The SM is also validated for sleep/wake scoring against PSG (190) and therefore uses the Total Sleep Time (TST) as the denominator for calculating the AHI, unlike other PM devices which use the 'Time In Bed' (TIB) or 'Total Recording Time' (TRT), which could result in underestimation of SDB. Therefore theoretically it should present a more accurate assessment of SDB.

I have however utilised the SM-TST proprietary algorithm in the determining the SM calculated AHI. This algorithm was developed and tested in 14 normal healthy volunteers (mean age 27±5 years) and as yet is not validated in a heart failure population (190). The algorithm makes an estimate of the total sleep time by detecting the patient’s presence in front of the SleepMinder™ and the patient’s gross movement patterns through the night. This is in contrast to PSG, where EEG recordings are used to determine the TST more accurately.

The SM has recently been validated against PSG for the diagnosis of OSA in a heart failure-free population of 74 patients who were referred for screening for SDB at a sleep centre in Dublin, Ireland. Utilizing the current TST algorithm but a different version of AHI algorithm developed and used in this thesis, the performance at detecting clinically important SDB (AHI>15) was excellent (Sens 0.90, Spec 0.92, AUC 0.97) (204).

From my results, I have demonstrated that the SM tended to overestimate the TST, compared to expertly scored PSG, in more than half of our heart failure patients (see Figure 39). While the final result of the SM-AHI does not seem to reflect this, it is possible that refining of the SM-TST to reflect the sleep patterns in a heart failure population may improve the diagnostic accuracy of the SM in calculating the AHI.
The AHI algorithm has a PPV of 71% meaning that 7 out of 10 patients diagnosed by the SM would be confirmed on formal testing. Therefore clinicians can rely on the results of the SM and appropriately prioritize patients with a high pre-test probability of SDB for a formal PSG study. But a NPV of 82% means that 2 out of 10 patients who the SM indicates no SDB will have this on formal PSG.

Portier and colleagues in a previous study observed individual differences between the portable and the laboratory PSG AHI’s values obtained from consecutive nights of studying, of less than 10events/hour in 65% of the 78 subjects participating to the study (205). SM’s AHI estimate was within 10 events per hour in 72% of the cases.

The CSR algorithm was only 71% sensitive at detecting Cheyne Stokes respiration and the false positive rate was also high in the validation set of patients (37%). We found some situations where our algorithm had scored CSR in some patients, who seemed to fulfil these criteria even on PSG, but were not scored as so by the ‘expert’ scorer. An example is shown in the figure below. (Figure 42)

![Figure 42: SM vs PSG – ‘Obvious’ CSR pattern seen on both PSG and SM signals. Scored as present by SM algorithm but scored as 0 by expert](image)

The AASM provide guidelines for scoring CSR but this is fraught with varying interpretations due to variations in scoring hypopnoeas (180). This may contribute to significant inter rater variability. As a consequence, there are no firm rules in place for marking and quantifying CSR in everyday clinical practice. It is therefore not surprising that our CSR algorithm which follows strict rules in design and pattern recognition would overestimate the presence of CSR while an expert may be more or less flexible in their definitions.
This problem is less obvious with scoring of respiratory events (Apnoeas or Hypopneas) as definitions in guidelines are clearer. This is confirmed by a much lower Inter observer variability for AHI scoring compared to CSR. (AHI vs CSR Intra Class Correlation Coefficient – 0.879 vs 0.203).

We also observed more noise within the Essen dataset compared to the London dataset. The reasons were not clear, as techniques used for both sleep studies were similar. This may however have reduced the performance of the CSR algorithm. We appeared to confirm this by testing solely on the London validation population (n=10), who had cleaner signals. This resulted in a drop in the False Positive Rate (FPR) from 37% to 11%.

The overall diagnostic accuracy for the CSR algorithm for the entire dataset was 76%, which is still comparable to other screening strategies (191).

The prevalence of SDB in our study population, using an AHI >15 was 47%, which is comparable to published studies (7;137), but lower than some other studies that show a higher prevalence of SDB in patients with CHF (127;136). This is however a relatively small cohort and good contemporary drug and device therapy in these patients may have controlled the heart failure syndrome better. Our sample size was however not powered to answer specific prevalence questions.

The presence of Cheyne – Stokes Respiration is usually associated with Central Sleep Apnoea (CSA) and sometimes used as a surrogate for classifying patients who have SDB, into this group, particularly those with an AHI >15. 36% of the patients in our cohort fitted this criterion, which is lower than some documented literature that suggests CSA is the predominant form of SDB in patients with CHF (7;9;206). However more recent data in contemporary cohorts of CHF patients similar to ours suggest that OSA is as common as CSA (132).
3.9. Limitations

The main limitation from this study was that at this stage of development, the SleepMinder™ device does not formally discriminate between obstructive and central events. The presence of Cheyne-Stokes Respiration (CSR) has been used a surrogate to categorise patients into a Central Sleep Apnoea group.

Our results would have been strengthened by an algorithm that differentiates the two major types of SDB, as there are implications for treatment. Accurate separation of respiratory events into obstructive and central would however not matter a great deal, if there was a device that could treat both types of SDB.

The patients recruited in this study did not also have any clinical risk assessments of SDB performed, for instance using a physician administered Epworth Sleep Score (ESS). For this reason, our study population may not represent a true at-risk population for SDB and so the number of patients with CSR may have been underestimated. The ESS is however notably very subjective and not very sensitive (66%) or specific (32%) (207). In addition HF patients notably have less subjective daytime sleepiness despite significantly reduced sleep time, whether or not they have SDB (208). Perhaps screening our study population using a more objective clinical risk assessment tool like the Oxford Sleep Resistance Test (OSLER) (Sensitivity 85%; Specificity 94%) may have been useful to increase our pre-test probability for identifying patients with SDB (209).

The TST in heart failure patients compared to a normal population is usually shortened by haemodynamic and autonomic mechanisms that result in frequent arousals (ref – Bradley Circulation). In this study, we have utilised the SM-TST proprietary algorithm validated in a heart failure-free population, to estimate the SM-AHI. Our results would perhaps have been more accurate using a TST- algorithm specifically developed using heart failure patients.

We have also only included patients with low left ventricular ejection fraction. It would therefore be valuable to know if these algorithms are applicable to the group of heart failure patients with normal or preserved ejection fraction (HFnEF, HFpEF) as this patient population are also known to have SDB.
Further research is needed to extend this work to involve a larger study cohort to confirm the diagnostic value of this new tool, and improve the algorithm to enable grouping of SDB events by type.

3.10. Conclusion

This validation study has confirmed the null hypothesis that there is no difference in the Apnoea Hypopnea Index (AHI) and quantity of Cheyne-Stokes Respiration (CSR) measured by the SleepMinder™ device compared to in–hospital Polysomnography (PSG).

SDB is prevalent in an unselected population of patients with chronic heart failure and this diagnosis can be made with a reasonable degree of accuracy using a non-contact monitor of nocturnal respiratory patterns – SleepMinder™ device, compared to full in-hospital PSG. The AHI algorithm seems robust and has been tested on a mixed population of patients with CHF. This study should be extended to a larger and more varied cohort of patients including more women. The quantification of CSR using this system needs further refinement to improve its accuracy.

Multi-national randomised control trials (165;166) may demonstrate mortality benefit from treating patients with CHF and SDB and this would increase the need for easier and convenient diagnostic tools to aid this process.

The SM seems to be able to achieve this as a screening tool and the potential ability to observe variations in SDB metrics such as AHI and CSR over long periods is also welcome to improve our understanding of how these physiological parameters influence the course of the heart failure syndrome over a long period of time.

In the next chapter, I will examine how nocturnal respiratory patterns including variations in SDB metrics such as AHI and CSR vary over a longer period of monitoring. This may provide potentially important data that has not been available due to the impracticalities of performing nightly PSG.
CHAPTER FOUR – Longitudinal Observation of Nocturnal Respiratory Patterns in patients with Chronic Heart Failure using a Non-Contact Breathing Monitor
4.1. Introduction

The Apnoea Hypopnea Index (AHI) is the most commonly measured parameter for diagnosis and classification of Sleep Disordered Breathing (SDB). However in small studies and over short periods of monitoring, it is has been shown to be subject to variations in patients with or without heart failure (147;154).

It however remains unknown what the true variation of the AHI is over a longer and consecutive period of monitoring is, how often these variations take place and what the clinical significance might be. This is because up till now, it has been difficult to accurately monitor patients’ respiratory patterns on a consecutive night-to-night basis and for a prolonged period due to the impracticalities of consecutive nightly Polysomnography (PSG) studies. Specific respiratory parameters including rates and duration of various components of SDB have also not been described in literature on a longitudinal basis, due to this similar constraint.

The SleepMinder™ device is a non-contact biomotion respiratory monitor that is capable of recording signals related to breathing and movement when placed by the patient’s bedside. In the previous chapter, I have validated its accuracy in measuring the Apnoea Hypopnea Index and quantifying CSR in patients with CHF against ‘gold’ standard Polysomnography. It can be used in the patient’s home and can provide continuous measurements of nocturnal respiratory parameters over several nights.

4.2. Hypothesis

I hypothesised that due to potential on-going changes in the pathophysiology of CHF patients, the AHI would have a high variability over a longer period of monitoring. My ‘Null’ hypothesis was therefore that there is a low variability in the Apnoea Hypopnea Index from night to night in patients with Chronic Heart Failure over a long (12months) period of monitoring.
4.3. Aim

The main aim of this study was to determine the variability of the AHI over a prolonged period of monitoring by employing the SleepMinder™ device (SM) to analyse nocturnal respiratory patterns in CHF patients over a period of 12-month period.

The SM device is a non-contact, biomotion sensor monitor that placed by the patient’s bedside, is capable of recording signals that pertain to breathing and movement. In the previous chapter, I have validated its diagnostic accuracy in measuring the Apnoea Hypopnea Index (AHI) and quantifying CSR in patients with CHF against ‘gold’ standard PSG.

4.4. Methods

4.4.1. Participants

All patients who were recruited into the validation arm of the SleepMinder™ study were used in this analysis. (See Figure 43) I have described in detail the recruitment process for these patients in Chapter 2 and Chapter 4. These patients had consented to receive a SleepMinder™ device, which they took home and placed by their bedside. They also received a set of weighing scales which they measured their weights with daily. A mobile phone was provided which provided wireless transmission of SM and weight data. All three devices were ‘paired’ or connected to each other via a Bluetooth wireless connection. (See Figure 15 – Chapter 2)

The SM device recorded all activity related to breathing and movement during a window from 7pm in the evening till 10am the following morning onto a removable Secure Digital (SD) memory card. Periodic downloading of SM data occurred during a separate ‘Log Window’ the following day onto a live study database. Recording and transfer of data did not occur simultaneously. Weight data were transferred immediately following measurement with the scales. All data were transferred via a 3G wireless mobile network.
Follow-Up

The SM device was left switched on throughout the duration of the study. The mean follow up period for all patients was 11.2 \( \pm \) 3.6 months. Figure 44 shows a sample of the SleepMinderTM recording in one patient over a 12-month period.

**Figure 43: Consort Chart for patient recruitment into Validation Arm of SleepMinder™**

827 patients screened from Heart Failure Database

75 patients Eligible

752 patients excluded
Did not Fit Inclusion Criteria

43 patients Enrolled

32 patients declined
10 - Did Not want Equipment at Home
7 - Unsure about use of technology
15 - Did not want to participate in research
Figure 44: Sample SleepMinder™ recording over a 12-month period. Brown Lines represent periods of decompensation of heart failure

4.4.2. Trouble shoot and Loss of Data

Problematic acquisition or transfer of data occurred due to three main reasons.

- Loss of electrical power to SM, usually from being accidentally switched off
- Loss of battery power to scales
- Mobile Phone Signal Loss leading to un-pairing with SM and scales resulting in inability to transfer data

Our database was a live one, so we were informed early when data acquisition was inadequate. The first two problems relating to power were easy to deal with, by replacing scale batteries and reconnecting the SM to power.

The other problem relating to un-pairing of equipment was resolved by placing a phone call to the patient, to talk them through a phone/SM and scales reset, or a home visit that I performed.
4.4.3. Nocturnal Respiratory Parameters Analysed

In this study the Apnoea Hypopnea Index (AHI) was the main measure I examined, for assessing variability of sleep-disordered breathing (SDB). I have, however, also examined the variability in other nocturnal respiratory parameters including the Respiratory Rate (RR), quantity of Cheyne-Stokes Respiration (CSR), and Total Sleep Time (TST).

4.4.4. Statistical Analyses

Baseline characteristics of patients were described by means and standard deviations for continuous variables and as a number or percentages for categorical variables.

In order to assess variability of the AHI in this period, I have used a number of methods in order to be comparable to reports in literature.

Intra-patient variability was first determined by computing the distribution of the AHI using box-plot representation of interquartile ranges, and medians over the entire follow up (FU) period.

I then examined within-subject means ($\text{Mean}_{\text{AHI}}$) and standard deviations of the AHI, over 3 groups of FU periods; 2 weeks, 3 months and 12 months; and compared these by using an independent sample student t-test with a significance level set at $p<0.05$.

I further assessed Inter-patient variability, by calculating the co-efficient of variation (CoV). (210) The coefficient of variation is useful because the standard deviation of data must always be understood in the context of the mean. In contrast, the actual value of the CoV is independent of the unit in which the measurement has been taken, so it is a dimensionless number. It is sometimes used as a percentage. Highly variable data has been described where the CoV was $>15\%$ (211).

As an alternative to the Mean, I have further described as proportions of the overall follow up period, periods when the AHI was above a commonly used treatment threshold of $\text{AHI}>15$ ($\text{FU}_{\text{AHI15}}$). Correlation between the $\text{FU}_{\text{AHI15}}$ and $\text{Mean}_{\text{AHI}}$ was made by the Pearson’s correlation co-efficient.
The Intra-class correlation co-efficient (ICC) together with the 95% confidence interval was used to determine inter-patient AHI variability. I derived this by selecting consecutive nights of simultaneous patients SM recordings and computing this value. \((212;213)\) The ICC is defined in this case as the ratio of between-patient variances to the total variance, which is a combination of the between- and within- patient variances and was used to measure consistency in the AHI over the FU period.

I also assessed if the prevalence of clinically important (AHI>15) SDB in our cohort using a single night AHI measurement was comparable to that from a longer period of monitoring. I achieved this by comparing the Mean\(_{\text{AHI}}\), over the 3 FU periods used, with results from a Monte Carlo simulation, which provided a probability estimate of the highest proportion of patients who would have a clinically important AHI based on a single nights study.

To determine which patients had the most variable data for the AHI and because I elected not to use an arbitrary determination of what may be considered highly variable based on the CoV, I proposed that the more highly variable patients would be those whose mean AHI over the follow up period was less than twice their standard deviation (Mean\(_{\text{AHI}}< 2\times\text{SD}\)). 95% of data points are expected to lie within 2SD of the mean and when the SD is greater than the mean, the dataset is considered as skewed. Exploring my original dataset, I found that most patients had a mean\(_{\text{AHI}}\) that was greater than the SD suggesting minimal variability in each patient. However, to test the strength of this assumption and to create the categories for analysis, I have increased this threshold by doubling the SD. If the patients mean AHI was still >2SD then, I have accepted that in this patient there was minimal variability for this parameter.

Using this criterion, I was able to divide the patients into two variability groups for the AHI (high and low). I then assessed whether the severity of heart failure using surrogates such as the ejection fraction and BNP levels had any influence on AHI variability.

Finally I have defined the severity of SDB by commonly used AHI cut-offs, \(\geq5\) mild, \(\geq15\) moderate, \(\geq30\) severe, with the clinical treatment groups been the latter two. By doing this I was able to calculate the percentage of patients who were misclassified into a different severity or treatment category from night to night.
4.5. Results

4.5.1. Demographics

In total, 43 adult patients with CHF were recruited into this study. They were mainly male (72%) with a mean age of (76.7 ± 9 years) and left ventricular ejection fraction of (38.3 ± 13.7 %). Table 17 summarises their other characteristics.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Years)</td>
<td>76.7 ± 9</td>
</tr>
<tr>
<td>Male Sex n (%)</td>
<td>31 (72)</td>
</tr>
<tr>
<td>EF (%)</td>
<td>38.3 ± 13.7</td>
</tr>
<tr>
<td>NYHA III or IV n (%)</td>
<td>11 (26)</td>
</tr>
<tr>
<td>Ischaemic n (%)</td>
<td>20 (47)</td>
</tr>
<tr>
<td>BNP (pmol/L)</td>
<td>134.6 ± 89.5</td>
</tr>
<tr>
<td>Weight (Kg)</td>
<td>78.5 ± 18.5</td>
</tr>
<tr>
<td>Anaemia n (%)</td>
<td>19 (44)</td>
</tr>
<tr>
<td>Renal Impairment n (%)</td>
<td>29 (67)</td>
</tr>
<tr>
<td>DM n (%)</td>
<td>6 (14)</td>
</tr>
<tr>
<td>HTN n (%)</td>
<td>14 (32)</td>
</tr>
<tr>
<td>CRT-Pacing n (%)</td>
<td>17 (40)</td>
</tr>
<tr>
<td>AF n (%)</td>
<td>12 (28)</td>
</tr>
<tr>
<td>ACEi or AIIRB n (%)</td>
<td>34 (79)</td>
</tr>
<tr>
<td>BB n (%)</td>
<td>34 (79)</td>
</tr>
<tr>
<td>MRA n (%)</td>
<td>14 (33)</td>
</tr>
</tbody>
</table>

Table 17: Patient characteristics of all 43 patients recruited into the study (EF – Ejection Fraction, NYHA – New York Heart Association Classification of Heart Failure, BNP – Brain Natriuretic Peptide, Anaemia – HB <13g/dl women, <14 g/dl men, DM – Diabetes Mellitus, HTN – Hypertension, AF – Atrial Fibrillation, ACEi – Angiotensin Converting Enzyme Inhibitor, AIIRB – Angiotensin II Receptor Blocker, BB – Beta Blocker, MRA – Mineralocorticoid Receptor Antagonist, Renal Impairment – eGFR <60ml/min/1.73m²)
4 patients were excluded from further analysis, from the original 43, due to a combination of less than 3 months’ worth and corrupted data collected. Therefore for further statistical analysis used in this chapter unless otherwise stated, this relates to the 39 patients who were eligible. The mean (SD) follow up period for these patients was 11.2 ± (3.6) months. There were no meaningful differences in terms of baseline characteristics between the 4 patients excluded and the 39 analysed.

4.5.2. Intra-Patient Variability in AHI – Distribution and Prevalence

Figure 45 shows box-plots in all 39 patients, showing the range of distribution in AHI over the follow-up period. The ‘whiskers’ of the plot represent the range of values, that is, maximum and minimum values of AHI. The boxes represent the values between the lower and upper quartiles while the horizontal line in the middle of the box represents the median value. This analysis demonstrates a wide variation in the value of the AHI with such ranges in some patients giving the suggestion that a patient could record clinically important SDB (AHI≥15) on one night and in some cases no SDB on another night.

![Box-Plots showing distribution of AHI over a 12-month follow-up period.](image)

**Figure 45**: Box-Plots showing distribution of AHI over a 12-month follow-up period. Mean Stdev

11.3 events per hour (95% CI 10.08-12.95). Reference Line represents an AHI of 15, which is clinically significant SDB
Further I divided the follow-up period into 3 groups as described earlier to assess if there was a significant change in the percentage of patients whose Mean AHI was $> 15$ as the FU period shortened. Figure 46 represents scatter plots that shows how the mean AHI of each patient changes as the FU period is shortened.

![Scatter plots showing proportion of patients with AHI≥ 15 as FU period is increased.](image)

Reference line represents mean AHI of 15 events/hour

57%, 60% and 74% of all patients had a mean AHI≥ 15 when monitored over a 2-week, 3-month and 12-month FU period respectively. There was however was no significant statistical difference in the actual mean value of the AHI in all 39 patients over the different FU periods. (2wk vs 3mth; 20 vs 19 p=0.84, 2wk vs 12mth; 20 vs 24 p=0.11, 3 mth vs 12mth; 19 vs 24 p=0.06). Figure 47 is a line plot that illustrates this similarity in the mean AHI over the 3 different FU periods examined.
Mean AHI over different follow up periods in all patients n=39

Figure 47: Line Plots showing change in mean AHI over different FU periods

4.5.2.1. Age and Sex Distribution

Male patients had a consistently higher mean AHI compared to the female patients regardless of the duration of FU (Figure 48). More patients however had a higher AHI in the 12-month FU group. There was no specific distribution of the AHI according to patient’s age group (Figure 49), however similarly more patients who were followed up for 12 months had a higher mean AHI across all age groups.
Figure 48: Mean AHI according to Sex and period of follow-up

Figure 49: Mean AHI according to Age Group and period of follow-up
4.5.2.2. Prevalence of SDB (AHI>15) – Monte-Carlo Simulation

We created a computational model that would select the best possible night with the highest proportion of patients who have scored an AHI of 15 or more.

![Monte-Carlo Simulation](image)

**Figure 50: Monte-Carlo simulation for the incidence of SDB (AHI>15) based on a single nights study**

Based on that best single night screening, the incidence of SDB in the cohort was 62%. This means that if all the patients in this study underwent Polysomnography/Polygraphy on that night, 62% of them would have clinically relevant SDB (Figure 50). This is in comparison to 74%, 60% and 57% of patients who would have an AHI of 15 or more, using the mean AHI over 12 months, 3 months, and 2 week follow up respectively. This model does not individualise patients and makes its simulation on the group as a whole.
4.5.3. Intra-Patient Variability – Other Nocturnal Respiratory Parameters

The box plots below show the distribution of the Respiratory Rate (RR), quantity of Cheyne-Stokes Respiration (CSR) and Total Sleep Time (TST) over a 12-Month Follow-up period.

4.5.3.1. Respiratory Rate

![Box-Plots showing distribution of Respiratory Rate (breaths per minute) over a 12-month follow-up period. Mean ± SD (18 ± 3) breaths per minute. 95% CI (17-19)](image)

The mean nocturnal respiratory rate over the 12-month period (18 ± 3) breaths per minute (Figure 51) was above normal adult respiratory rates (10-12 breaths per minute). This may represents hyperventilation associated with alveolar oedema as well as autonomic dysfunction that are seen in heart failure patients and a proposed mechanism for the development of CSA. This distribution does not take into account periods of decompensation where RR may be expected to be higher.
4.5.3.2. Total Sleep Time

Figure 52: Box-Plots showing distribution of Mean estimated Total Sleep Time (hours) over a 12-month follow-up period. Mean ± SD (7.5 ± 1.5) hours.

The mean Total Sleep Time (TST) in the group as a whole was 7.5 hours. In individual patients, there were wide variations over the 12-month period of follow up with a range of between 4-11 hours of TST (See figure 52).
Cheyne Stokes Respiration (CSR) occurred during a mean of 4.4% of total sleep time in all patients. Over the 12-month period there was wide variation in the amount of CSR that was recorded. In some patients there were days when CSR was recorded for over 40% of the TST and days when CSR was not present. This distribution is demonstrated in the box plots in Figure 53. However this is not unexpected as previous data in chapter 3 showed that the SM diagnostic accuracy for CSR is not well established.

4.5.4. Intra-patient Variability in AHI – Co-Efficient of Variation

The coefficient of variation was determined as a ratio of the standard deviation to the mean AHI and it is a useful way of assessing variability within a subject. Highly variably data are those with a variation >15% (210).

The mean CoV in this group of patients was 54% indicating a significant intra-patient variability for the AHI. Figure 54 shows the distribution of patients according to the CoV ranges and this show that the majority of patients (59%) had a CoV above 50%.
4.5.5. Proportion of Follow-Up period with clinically significant SDB

I also determined what proportion of the follow-up period that each patient had meaningful SDB that may have warranted treatment. Figures 55 and 56 show this distribution. 49% and 41% of patients had an AHI>15 in over 30% of the nights of a 12-month and 2-week FU period respectively.
Figure 55: Proportion of 12-month FU period when individual patients had an AHI>15

Figure 56: Proportion of 2-week FU period when individual patients had an AHI>15
Furthermore I proposed what proportion of the FU period, when a patient who had an AHI>15 may be considered clinically important or used as a diagnostic threshold. 49% had an AHI>15 for >30% of Nights of a 12 month follow up period and 59% of patients when this period is shortened to 2-weeks. Figure 57 and 58 show the number of patients who would be in each group respectively (<10%, 10-30% and >30% of the FU period).

Figure 57: Proportion of patients with and AHI>15 according to proportion of Nights of FU – 12 Month

Figure 58: Proportion of patients with and AHI>15 according to proportion of Nights of FU – 2 Week
4.5.5.1. Age and Sex Distribution

Figures 59 and 60 show that there was no sex or age-specific distribution, in terms of the proportion of FU period. However in the group with the proportion of the FU period when the AHI>15 was over 30%, there were more men.

Figure 59: Sex distribution according to proportion of FU period

Figure 60: Age distribution according to FU period
4.5.6. Correlation between Mean AHI and Proportion of FU period

There was a good correlation ($r=0.79$) between the mean AHI ($\text{Mean}_{AHI}$) and proportion of FU ($\text{FU}_{AHI>15}$) period when patients had clinically significant SDB ($\text{AHI}>15$). This is demonstrated in Figure 61 which showed that patients with a higher mean AHI also had a higher proportion of the FU period where the $\text{AHI}>15$. This was as expected suggesting that both mean AHI and proportion of FU period can be used interchangeably.

![Correlation Between Mean AHI and Proportion Period AHI>15](image)

Figure 61: Correlation between $\text{Mean}_{AHI}$ and $\text{FU}_{AHI>15}$. Shaded area represents 28% of patients who had clinically important SDB for less than 30% of follow up period and whose overall mean AHI for the follow up period was less than clinical threshold for treatment ($\text{AHI}>15$).
4.5.7. Intra-patient Variability in AHI – intra-Class Correlation Co-efficient (ICC)

The ICC is used to measure the consistency in Apnoea Hypopnoea Index (AHI) for each patient throughout the follow-up period. The ICC is defined as the ratio of between-patient variances to the total variance, which is a combination of the between- and within-cluster variances.

To preserve the independence and accuracy of this statistical tool I have selected only consecutive nights where patients were simultaneously recorded by the SleepMinder™ device. To this end, I have analysed 218 consecutive nights in 34 patients (7,412 patients' nights). (See Figure 62)

![Patient selection for Intra Class Correlation analysis](image)

Figure 62: Patient selection for Intra Class Correlation analysis

The AHI had an ICC value of 0.33 (95% CI 0.23-0.49) suggesting a high variability. Table 18 shows the ICC values for the other nocturnal parameters analysed. The most variable parameter was the Total Sleep Time (TST) with an ICC value of 0.26 (95% CI 0.17-0.40). As discussed in Chapter 3 of this thesis, the SM-TST algorithm used in calculating the Total Sleep Time is validated in a heart failure –free population and could in part explain this observation of high variability in this parameter.
Table 18: Intra-class correlation co-efficient for respiratory parameters. A value > 0.75 represents excellent reproducibility. (AHI-Apnoea Hypopnea Index, CSR- Cheyne Stokes Respiration, TST- Total Sleep Time, RR – Respiratory Rate)

4.5.8. Misclassification of Sleep Disordered Breathing

I proposed a misclassification rate according to severity (MRsev), as the number of times each patient shifted from one severity category of SDB to the next, over the follow up period (2 weeks). The baseline severity category at the start of this period was used as the reference. I have employed conventional cut-offs for grading SDB with Mild ≥5 Moderate ≥15 and Severe ≥30.

In addition I have further determined the misclassification rate according to treatment grade of SDB (MRrx). This was determined as the number of times a patient shifted from a non-treatment grade of SDB (i.e. AHI<15) to a treatment one (AHI>15) and vice-versa.

The mean MRsev was 35% ± 24%. This means that on average, in the 2-week period of follow-up, a patient shifted from one severity category of SDB to the next, 35% of the time. Only 3 of the 39 patients (8%) did not have any shift in severity of SDB at all during this follow-up period. Further, using the baseline severity of SDB as diagnostic, there was no statistically significant differences in the MRsev based on whether the patient was initially diagnosed as having No, Mild, Moderate or Severe SDB.

The mean MRrx was 21% ± 19%. This means that on average, for 21% of the 2-week follow-up period, a patient shifted from a treatment to non-treatment category of SDB. 6 out of the 39
patients (15%) remained in the same treatment category for SDB throughout the follow up period.

4.5.9. **Severity of Heart Failure and Variability in AHI**

We hypothesised that patients with a more severe form of heart failure may show more variability in the AHI. To examine this, we divided the patients into two groups of High and Low variability in AHI. To determine which patients had the most variability in the AHI and because we elected not to use an arbitrary determination of what was considered ‘highly’ variable using the CoV, we proposed that the least variable patients would be those whose mean AHI over the follow up period was > 2 times their standard deviation. 15 patients had highly variable AHI by this criterion.

I have also used single baseline measures of B-type Natriuretic Peptide (BNP), Ejection Fraction (EF), and estimated Glomerular Filtration Rate (eGFR) as surrogates for severity of heart Failure and analysed the means using independent sample Student’s t-test.

<table>
<thead>
<tr>
<th>AHI Variability</th>
<th>Number</th>
<th>Mean</th>
<th>Std Dev</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BNP</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>24</td>
<td>129</td>
<td>80.2</td>
<td>0.54</td>
</tr>
<tr>
<td>High</td>
<td>15</td>
<td>148</td>
<td>105.8</td>
<td></td>
</tr>
<tr>
<td>EF</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>23</td>
<td>38</td>
<td>13.9</td>
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<tr>
<td>High</td>
<td>15</td>
<td>37</td>
<td>14.7</td>
<td></td>
</tr>
<tr>
<td>eGFR</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>24</td>
<td>47</td>
<td>25.1</td>
<td>0.88</td>
</tr>
<tr>
<td>High</td>
<td>15</td>
<td>46</td>
<td>18.7</td>
<td></td>
</tr>
</tbody>
</table>

Table 19: Variability of AHI according to severity of heart failure. EF- Ejection Fraction, BNP- B-type Natriuretic Peptide, SGFR- estimated Glomerular Filtration Rate.

From the results the variability of the AHI appears to be unaffected by the severity of heart failure using the surrogates of severity used in Table 19.
4.5.10. Longitudinal nocturnal respiratory parameters and survival

This study was not powered to assess survival however we made an observation of how the respiratory parameters we collected related to survival.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Survivors (31)</th>
<th>Non-Survivors (8)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean AHI</td>
<td>22</td>
<td>33</td>
<td>0.008</td>
</tr>
<tr>
<td>Peak AHI</td>
<td>32</td>
<td>42</td>
<td>0.04</td>
</tr>
<tr>
<td>Mean CSR &gt;1% (number)</td>
<td>15</td>
<td>7</td>
<td>0.04</td>
</tr>
<tr>
<td>Cycle Length CSR (s)</td>
<td>54</td>
<td>59</td>
<td>0.17</td>
</tr>
<tr>
<td>TST (hours)</td>
<td>7.2</td>
<td>8.3</td>
<td>0.07</td>
</tr>
<tr>
<td>Mean Respiratory Rate</td>
<td>17</td>
<td>20</td>
<td>0.009</td>
</tr>
<tr>
<td>Residual Effort (mv)</td>
<td>21</td>
<td>13</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Table 20: Relationship between survival and longitudinal respiratory patterns

There were 8 deaths in the 12-month follow up period and in these patients, the mean AHI, maximum AHI, mean Respiratory rate and number of apnoeas (residual effort) were significantly higher. Table 20 highlights this result.

4.6. Discussion

The main result from this study was that the AHI, which is the most commonly used index to measure SDB, is highly variable in patients with CHF observed over a long period of follow up (Intra-class Correlation Coefficient – 0.329 95% CI 0.229 – 0.488). I also found that other indices measured as part of nocturnal PG/PSG monitoring were also characterised by large night-to-night variability. The ICC for TST, %CSR and RR were (0.256, 0.398, 0.361) See Table 15.

The reason for this high variability is not clear. It is possible that changes in the pathophysiology of the heart failure syndrome and how they affect the measures of SDB are more apparent over a longer period of monitoring, which is why some studies over shorter periods of monitoring have shown excellent consistency in these measures.
Studies have shown that as heart failure worsens, particularly with fluid overload, the amount of SDB increases (155). These patients may not necessarily have symptoms and clinical signs may also not be overt. In this study, we have studied a sicker cohort of patients (mean EF 38.3 ± 13.7 %; mean BNP 134.6 ± 89.5) who are more likely to have frequent changes in their syndrome, particularly fluid shifts. This in turn may influence the amount of SDB measured by the AHI, the quantity of CSR and its variability.

Further I have employed the SleepMinder™ (SM) device to calculate the indices we have analysed for variability assessment, including the AHI. This has been validated in the previous chapter, with good diagnostic accuracy (Sens 91%; Spec 50%; AUC 82%) against PG/PSG in calculating the AHI. While it is unlikely that there would have been a significant error contribution from using the SM as opposed to PSG/PG, which has been used in other studies to assess variability, it is not implausible.

I also do not expect any significant contribution by ‘inter-rater’ variability, as each patient used identical SM devices for the duration of the study. I cannot however totally exclude small manufacturing differences in the SM devices.

The Total Sleep Time (TST) was the denominator used in making the SM-estimates of the AHI. I have shown in chapter 3 that the SM-TST algorithm did not correlate well with expertly scored PSG TST in our heart failure patients and this could have contributed to some of the variability seen in some of the parameters investigated.

I have also shown that over different follow-up periods, the mean AHI was consistently above the generally accepted threshold for treatment (AHI>15) in a high proportion of patients, and this was irrespective of the follow up period chosen. This raises the suggestion that the mean AHI rather than a single night’s value may be more representative of a true diagnosis when screening for SDB.

92% of all the patients studied shifted from one severity of SDB to the next; using conventional cut-offs for the AHI; at any time during a 2-week follow up period. This percentage is significantly higher than the 37% of patients who varied severity in the cohort studied by Vazir and colleagues (147). Theirs was however a small group of patients (n=19) and sleep studies were performed over 4 consecutive nights compared to the 14 nights I used in this analysis. Both cohorts were however similar with predominantly less symptomatic heart failure (NYHA II – 74% of patients in
both studies). This suggests that the AHI is longitudinally a rather variable phenomenon in heart failure patients and consistent with other literature (149;152;153). Comparing our findings with a heart failure free population with the OSAHS, 14% (Dean and Chaudhary 1992), 32% (Mendelson 1994) and 54% (Lord et al 1991) of these patients changed severity category of SDB, following a second night of nocturnal cardiorespiratory monitoring (214-216).

The average misclassification rate from one severity category to the other, for each patient was 35% of the follow-up period.

In addition, 84% of patients shifted from one treatment group of SDB (AHI>15) to the other with an average misclassification rate of 21% for each patient during this follow up period. When compared to a similar population of patients with moderate to severe heart failure, but who were studied on two consecutive nights, 18% of patients were misclassified from one treatment group to the next (152).

The presence of SDB in patients with CHF confers a worse prognosis. It is therefore it is important that the severity of SDB is accurately diagnosed as this may have implications for treatment. This study has demonstrated that patients may move, from a category of SDB that may warrant treatment, to one, which may not. This seems to happen frequently and is identifiable even over a short follow up period of 14 nights.

Based on these findings, it may seem a reasonable strategy for clinicians to be given the ability to respond to changes in the amount of SDB by altering the management of these patients. However it is impractical and cost-ineffective to incorporate nightly PSG studies into any treatment pathway. The SM device due to its novel design may proffer a realistic option for monitoring SDB in this manner but its value may have to be tested on a larger and more varied cohort of patients. This study has however highlighted the need to factor in the potential for these changes into on-going follow up and management plans for these patients. One current real world solution is to perform interval PSG/PG studies either to confirm diagnosis or to see how treatment is affecting the grade of SDB.

Treatment of SDB with newer devices such as Adaptive Servo Ventilation (ASV) has been shown in small studies (217) and a meta-analysis (218) to be beneficial to patients with CSA and HF. It is currently been investigated in two large multicentre and multinational trials, one looking at its effect on mortality in patients with CSA and HF (165) and the other looking at its effectiveness in
patients with any form of SDB and HF (166). ASV has the potential to solve the problem of frequent daily changes in severity of SDB in patients with heart failure. This is because this form of positive airway pressure is designed to adapt therapy to patient’s minute ventilation delivering more therapy when there are more episodes of apnoeas and hypopneas and reducing therapy when these respiratory events are fewer.

I did not find any significant association between the severity of HF using surrogates such as BNP levels, and Ejection Fraction and the variability of the AHI in this group of patients. These surrogates used were however single point measures and while they have been shown in studies to have prognostic importance, (181;184) it is pertinent to note that in this study, their changes during the course of the follow up period was not assessed in relation to AHI variability.

Finally, in our small cohort and over the follow up period (mean 11.2 +/- 3.6 months) non-survivors had a significantly higher mean AHI, Respiratory Rate, number of apnoeas and percentage of Cheyne Stokes Respiration (CSR) overnight. Paradoxically these patients had a tendency towards a higher Total Sleep Time (TST). This finding is in keeping with other studies that assign prognostic importance to the presence of Cheyne Stokes Respiration and a high AHI (9;127).

This observational study has shown that over a prolonged period of monitoring in patients with heart failure, the AHI is highly variable. Based on these results, I am therefore recommending that obtaining the mean AHI over a 2-week follow up period would be a practical, feasible and more robust assessment of the severity of sleep disordered breathing in patients with heart failure as opposed to a single night study.
4.7. Limitations

We have not separated these patients based on the predominance of Central or Obstructive events but we have demonstrated that Cheyne Stokes Respiration (CSR) was present in up to a third of our patients who had clinically important SDB (AHI>15). As CSR predominates in patients with the central variety of sleep-disordered breathing, we have used its presence as a surrogate for classifying this group of patients into this category but have not assessed shifts in SDB type based on this. Our study may therefore have been strengthened if we were also able to show misclassification of SDB according to these broad types, as current treatments are different.

It is also important to note that the patients we have analysed in this study had moderate to severe CHF and whether our findings are generalizable to patients with milder form of the heart failure syndrome remains unknown.

4.8. Conclusion

To our knowledge, this is the first time that a group of patients with chronic heart failure has been studied longitudinally to assess the nocturnal variations in respiratory patterns and in achieving this, we have raised important points that may influence how these patients should be diagnosed and managed in the future. In particular we have shown that the AHI shows high variability over a number of nights. We have also highlighted the frequent changes in the severity of SDB that occur on a night-to-night basis as a result.

The next steps would be to study a larger and more varied cohort of CHF patients including those with milder disease syndromes and to investigate the shifts in SDB from one type to the next, observed over a longer period of monitoring.
CHAPTER FIVE – The Prediction of Acute Decompenation of Heart Failure Using a Non-Contact Monitor of Nocturnal Respiratory Patterns
5.1. Introduction

Until recently it was not possible to monitor changes in sleep disordered breathing on a day to day basis easily, as formal assessment of SDB required attachment to multiple electrodes and usually an overnight stay in hospital, ultimately making it a cumbersome process.

The magnitude of change and durations of components of the ventilatory cycle might however provide relevant information on the clinical impact of nocturnal breathing disorders; in particular the likelihood of significant worsening of cardiovascular function; in patients with chronic heart failure.

I have previously shown that the SleepMinder™, through low frequency electromagnetic waves, is able to measure the AHI and quantify the CSR based on a single night study and validated against full in-hospital PSG (219;220). Further, using an extended dataset in chapter 3 of this thesis, the SM performed with a good combined diagnostic accuracy of 82% and 76% respectively for these measures.

Due to its non-contact nature, it appears to be a more convenient way of measuring SDB and may be a useful means of detecting early deterioration of the heart failure syndrome, which can be utilised in the patient’s home.

A preliminary analysis using this device in a heart failure unit in Dublin, and following up 40 patients for six months, demonstrated that there might be some signals from changes in respiratory patterns at night that may presage clinical deterioration (unpublished data K. McDonald et al Dublin 2011).

In this chapter, I will be describing the prediction of acute decompensation of chronic heart failure (ADHF) by developing a predictor algorithm using features extracted from the SM signals.
5.2. Hypothesis

My main hypotheses in this study is that as patients with chronic heart failure decompensate, particularly in the weeks or days before they seek intervention, there may be a measurable rise in the Apnoea Hypopnea Index (AHI) or the amount of Cheyne-Stokes Respiration (CSR) present and that this can act as a signal for predicting a potential acute decompensation.

The ‘Null’ hypothesis therefore for this study is that there is a measurable increase in the AHI and the % overnight CSR by the SleepMinder™ device, within a 7-day period, and which can be utilised as a predictor of acute decompensation of heart failure.

5.3. Aims

5.3.1. Primary Objective

The primary objective of this study is to validate whether a simple bedside device (SleepMinder™), that monitors the breathing patterns during sleep in the participant’s home can be used to identify deterioration in heart failure reliably by confirming the diagnostic accuracy, sensitivity and specificity of the device for this purpose.

With the SleepMinder™ device, I am afforded a unique opportunity to record nocturnal respiratory patterns over consecutive nights, and this data can be analysed and utilised for prediction.

I therefore plan to examine and use the serial changes in nocturnal respiratory metrics, including the AHI, quantity of CSR, respiratory rates and total sleep time (TST), as ADHF episodes evolve and resolve, to develop a SM ADHF predictor algorithm (SMApA).

Finally I will seek to show whether these SM signalled respiratory abnormalities incorporated into the SMApA, predict ADHF by measuring its diagnostic accuracy in terms of sensitivity and specificity against clinically detected ADHF episodes. This would validate the signals identified as potentially valuable in the Dublin preliminary analysis in a different heart failure population and over a longer period of time.
5.3.2. Secondary Objective

To determine whether the bedside SleepMinder™ device monitoring is acceptable to patients with chronic heart failure. I aim to measure this by calculating what proportion of patients approached regarding the study agree to take part (‘recruitment proportion’), and the proportion of patients who request that the SleepMinder™ be removed before the end of the study (‘withdrawal proportion’), as measures of patient acceptability of this form of monitoring.

5.3.3. Study Design

This was a prospective observational study over an 18-month period seeking to validate in heart failure patients at the Royal Brompton Hospital in London, potential signals predictive of Acute Decompensation of Heart Failure, using the SleepMinder™ device, that were obtained from a prior analysis of nocturnal respiratory signals in CHF patients from St. Vincent’s hospital in Dublin, Ireland.

5.3.4. Sample size and Statistics

I have calculated that for this pilot study, and in order to achieve a combined accuracy of 85% (sensitivity=specificity=0.85), which would be qualitatively rated ‘very good’ to ‘excellent’, and to achieve a 15% width of a 95% confidence interval, I would need to recruit 40 patients. I have also made an ADHF event rate estimation of 30% per year, based on the severity of disease in the group that I am studying. I therefore expected that at least 12 out of 40 patients would have an episode of decompensated heart failure in the follow up period, which would give a reasonable number of events (12 events) for ADHF prediction.
5.3.5. Study Population

The data used in this study was from a ‘development’ dataset obtained from 61 chronic heart failure patients attending St. Vincent’s Hospital in Dublin, Ireland, and a ‘validation; dataset obtained from 43 chronic heart failure patients who were enrolled in the heart failure disease-monitoring programme at the Royal Brompton Hospital in London, United Kingdom. Recruitment for the Dublin group of patients started in October 2010 and the last patient was recruited in September 2012. As above, preliminary observational findings from an initial sample of 40 of these patients informed this formal validation study. Recruitment of patients into the development dataset was overseen by a separate clinical research team based in Dublin, which was not involved with enrolment or follow up of patients into the validation dataset.

I screened, recruited and collected follow-up data for all the patients used in the validation dataset. The first patient was recruited in September 2011 and last patient in June 2012. (See Figure 63) In total 827 patients were screened from our heart failure programme database. 75 patients were eligible who fulfilled the inclusion criteria and 43 patients consented to take part in the study while the remainder 32 patients who were approached, declined. The primary reason for failure of enrolment was patients who did not want to take part in research or who had a perceived inconvenience at having medical equipment placed within their home environment.

**Figure 63: Sleep Minder Recruitment Chart – Validation Arm**
5.4. Inclusion and Exclusion Criteria

Both development and validation sets of patients were selected based on identical inclusion and exclusion criteria listed below. These criteria aimed to identify patients with a moderate to high risk of decompensation. (Table 21)

<table>
<thead>
<tr>
<th>INCLUSION</th>
<th>EXCLUSION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma BNP&gt;200pg/ml (58pmol/litre) when reviewed in heart failure clinic</td>
<td>• Unpredictable sleep patterns based on work schedules e.g. night shifts</td>
</tr>
<tr>
<td>OR</td>
<td>• Age &lt;18 years</td>
</tr>
<tr>
<td>History of any hospitalization due to heart failure within the preceding 24 months</td>
<td>• Cognitive impairment sufficient to interfere with proper use of study equipment</td>
</tr>
<tr>
<td></td>
<td>• Already on therapy for obstructive sleep apnoea i.e. CPAP</td>
</tr>
</tbody>
</table>

Table 21: SleepMinder™ ADHF Study Inclusion and Exclusion criteria

5.5. Definition of Acute Decompensation of Heart Failure

The primary endpoint of this study was decompensation of chronic heart failure. The secondary endpoints related to acceptability of SleepMinder™ monitoring to patients attending a heart failure clinic.
5.5.1. ADHF Criteria

The definitions used in this study were as follows:

I) **DEFINITE:** Non-elective heart failure hospitalisation

This is the most definite evidence for decompensation of chronic heart failure, with admission to hospital for management of deterioration in symptoms and signs of heart failure. To determine if this was a definite heart failure decompensation, it was required that there was evidence of the following:

- Evidence for symptom deterioration,

And

- Objective evidence of fluid overload: such as elevated jugular venous pressure and/or lung crackles and/or dependent oedema and/or ascites; or chest radiograph evidence of pulmonary oedema or at least 50% increase in the plasma BNP value from euvolaemic level,

And

Requirement for at least one administration of intravenous diuretic

ii) **PROBABLE:** Deterioration in the chronic heart failure syndrome was accepted if the following criteria were met:

- Symptom Deterioration (development of new symptom of dyspnoea or worsening of established dyspnoea manifest as reduction in functional capacity and/or worsening orthopnoea and/or increasing or new paroxysmal nocturnal dyspnoea),

OR

- Evidence of weight gain of at least 2Kg level within 48 hours,

And

- Decision taken to increase diuretic therapy,
- Response of symptoms and/or weight within 48 hours to the increase in diuretic therapy (if symptoms did not respond within this time course, the patient was routinely reviewed in the heart failure clinic, where the decompensation could be confirmed and if appropriate the patient was admitted to hospital to regain control of the syndrome).

5.5.2. Adjudication of ADHF Events

A panel of two independent experts formed an adjudication committee. They were heart failure consultants who were blinded to the outcomes of the study, and using the event criteria, adjudicated every episode of suspected acute decompensation of heart failure. Where there were individual disagreements, both adjudicators met to discuss this to reach a consensus, and where this did not happen, a 3rd independent adjudicator was entrusted with the final decision.

To aid the adjudication committee, each ADHF event was presented with anonymised supporting documentation regarding that episode. These documents included discharge letters, GP contact letters, investigations (Chest radiographs, Blood tests, and echocardiograms), drug charts, and correspondence (telephone and text contacts) with the heart failure specialist nurses.

Similarly information for all Non-heart failure admissions (non-ADHF event) were collected and passed on to the committee for adjudication and to ensure that events were not misclassified into a non-ADHF event group.

5.6. Methods

All patients enrolled into both development and validation arm of this study continued their usual heart failure care management according to the NICE and the European Society of Cardiology heart failure guidelines (4;47)

Usual care within this service is that patients (and their partner or principal carer) are educated to recognise symptoms and signs of emerging clinical deterioration, with specific attention given to instructions on the meaning of weight change and how to react to increasing symptoms. All patients were provided with the contact number for the heart failure service for easy access during working hours Monday to Friday from 8am to 5pm.
In addition to this usual care, all patients were provided with the SleepMinder™ device, for bedside monitoring of nocturnal breathing patterns during sleep in the patient’s home, a weighing scale, and a study mobile phone that communicated by Bluetooth technology with the SM device and scales. The data from these devices was transmitted first to the central data collection centre in Dublin, Ireland for collation, and then into a secure database in Sydney Australia for later analysis. This process of recording and data transmission has been described in detail in Chapter 2.

At commencement of the study all patients attended a recruitment visit in hospital and in some cases, the study team comprising a research nurse and myself attended the patients home; where they were instructed on how to use these devices. Baseline blood tests were performed at that visit if in clinic or within a week of device collection if home recruitment. Patients were also provided with contact details of the research office in case they needed to ask any questions or for trouble shooting purposes.

5.6.1. Development Data Set and Follow-up

61 consecutive patients were enrolled from the heart failure clinics at St. Vincent’s hospital in Dublin, into this arm of the study.

This purpose of this dataset was mainly for exploratory data analysis. We identified key features and metrics from this dataset and developed methods for feature extraction, feature selection and training and testing of the classifiers. Because this was a novel algorithm, it was not clear at the start how much data would be needed to develop an algorithm development. Therefore the follow up period was kept open initially, to allow time for events to accumulate.

We, however, placed an algorithm development embargo at 12 months into the start of the validation study where no further input into development of the predictor algorithm was permitted

Formal follow-up of patients in the development dataset, took place at St. Vincent’s hospital in Dublin; however I participated in clinical data collection and analysis regarding all acute decompensation of heart failure episodes in these patients. This information was made available concurrently during development of the SM ADHF predictor algorithm.
5.6.2. Validation Data Set and Follow-Up

43 patients were enrolled into the validation arm of this study. (See Figure 61) They were followed up for a pre-specified minimum period of 12 months and a maximum of 18 months and took place in the heart failure clinics at the Royal Brompton Hospital London. During the follow up period, I collected information relating to all decompensation episodes, from hospitalisation records and contact with community heart failure nurses or the heart failure service at the Royal Brompton Hospital. In addition, the patients also kept a diary of any change in their diuretic dosages, weight gain or increased symptoms, which provided supplementary data on decompensation. No part of these data in the validation arm were used in developing the SM ADHF predictor algorithm, and as mentioned previously, was kept blind from algorithm developers until the testing period of this study.

5.7. Development of The SleepMinder™ ADHF Predictor Algorithm (SMApA)

Development of SM ADHF predictor algorithm (SMApA) was achieved using clinical and SleepMinder™ information from the Dublin development dataset only.

My main input into the SM ADHF predictor algorithm development was during signal features selection and extraction, based on my clinical knowledge of the medical literature and the clinical behaviour of chronic heart failure patients. My experience as a specialist registrar in cardiology, who has been involved in the pharmacological and device management of patients with acute decompensated heart failure was also utilised.

To this end, I provided clinical support to a small team of engineers at the applied research unit of ResMed Ltd. (Sydney) and on two occasions travelled out to the research centre in Sydney for algorithm development training and meetings. This was in addition to several telephone conference meetings regarding the same. Some of these meetings involved the algorithm development team and clinical team at St. Vincent’s hospital in Dublin, Ireland when we sought to clarify data from the development arm of patients.
Further, even though I was directly involved in the collection of suspected clinical episodes of ADHF in the validation dataset, the final results of the adjudication committee on this events were not available to me until one week before testing of the ADHF predictor by which time no further changes were permitted to our developed algorithm.

5.7.1. Features and Classifiers

The Sleep Minder collects and records data, which are represented as raw signals for every night throughout the patients’ participation in the study. This raw signal contains information including those that are related to breathing, thoraco-abdominal movement, leg movement, ocular activity and patient presence or absence amongst others. Artefactual information is also invariably collected. (Figure 64)

![Diagram of data transmission and feature extraction](image)

Figure 64: Data Transmission (‘A’–‘Z’ – are features extracted from RAW data: Breathing rates, cycle length, sleep efficiency, HR, AHI, TST, CSR, Apnoea length, number of sleep sections etc.)
**Features**

A feature is a characteristic of the raw signal that helps us identify its morphology and place it into a physiological group, for instance, the heart rate or respiratory rate. A feature vector is then produced which is a set of numbers that mathematically helps to classify these signals.

Generally the features quantify something about the morphology of the signal in either the time or frequency domain and based on existing knowledge of frequencies of physiological parameters, theoretically, this should easily be characterized. In practice however, due to noise and other artefacts the signals can be complex and difficult to analyse.

Several features were collected on a nightly basis for each patient and a features database was generated containing data for every night of the patient’s enrolment in the study. (Figure 65)

![Features Database](image)

**Figure 65: Features Database for all nights of the study. (’A’-’Z’- Features. PAT – Patients)**
Classifiers

A Classifier is essentially a mathematical function that can map those sets of features extracted from the raw signals into a category. In the simplest sense, a classifier can be described by its topology and a set of parameters, which are “learnt” during training. (Figure 66)

Figure 66: Features Vector to Classification

There were 2 main classifier types, which we used in development; State Space Principle Component Analysis (SSPCA) and Linear Discriminant Analysis (LDA) and we investigated around 131 features. (Table 22)

In terms of Feature selection, both intuitive and information theoretic methods were used for feature selection and only the assumed best features were then passed through the classifier. Pattern recognition as well as machine learning algorithms was used for training of the classifiers. The unblinded clinical ADHF data from the development set was also utilised during selection of the features and classifiers.
<table>
<thead>
<tr>
<th>No.</th>
<th>Feature Names</th>
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<td>'FreqCSQuarters(1,:)’</td>
<td>67</td>
<td>'activityMean'</td>
<td>11</td>
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<td>19</td>
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<td>'activityStd'</td>
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<td>'activitySkewness'</td>
<td>11</td>
<td>'cycleLengthObwSkewness'</td>
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<td>'activityKurtosis'</td>
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<td>'cycleLengthObwKurtosis'</td>
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<tr>
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<td>'BWCSQuarters(1,:)’</td>
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<td>'activity5th'</td>
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<td>'cycleLengthObw5th'</td>
</tr>
<tr>
<td>23</td>
<td>'BWCSQuarters(2,:)’</td>
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<td>'activity25th'</td>
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<td>'cycleLengthObw25th'</td>
</tr>
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<td>'activity50th'</td>
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<td>74</td>
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<td>Column 3</td>
<td>Column 4</td>
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<td>---------</td>
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<td>---------</td>
</tr>
<tr>
<td>26</td>
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<td>'activity95th'</td>
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<td>'cycleLengthObw95th'</td>
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<tr>
<td>27</td>
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<td>12</td>
<td>'sdbTimeHrs'</td>
</tr>
<tr>
<td>28</td>
<td>'MDCSQuarters(3,:)'</td>
<td>77</td>
<td>'sdbAnalysisTime'</td>
<td>12</td>
<td>'sdbTimeRatio'</td>
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<tr>
<td>29</td>
<td>'MDCSQuarters(4,:)'</td>
<td>78</td>
<td>'sdbAnalysisTimeLowQuality'</td>
<td>12</td>
<td>'sdbTimeMinsPerHour'</td>
</tr>
<tr>
<td>30</td>
<td>'HiQuarters(1,:)'</td>
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<td>12</td>
<td>'DutyCycleApneaLengthRatio'</td>
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<tr>
<td>31</td>
<td>'HiQuarters(2,:)'</td>
<td>80</td>
<td>'sdbEventLengthMean'</td>
<td>12</td>
<td>'AHISlope5days'</td>
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<tr>
<td>32</td>
<td>'HiQuarters(3,:)'</td>
<td>81</td>
<td>'sdbEventLengthStd'</td>
<td>13</td>
<td>'EventDay'</td>
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<tr>
<td>33</td>
<td>'HiQuarters(4,:)'</td>
<td>82</td>
<td>'sdbEventLengthSkewness'</td>
<td>13</td>
<td>'EventSpan'</td>
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<td>'sdbEventLengthKurtosis'</td>
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<tr>
<td>35</td>
<td>'FreqHiQuarters(2,:)'</td>
<td>84</td>
<td>'sdbResidualAmplitudeMean'</td>
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<td></td>
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<tr>
<td>36</td>
<td>'FreqHiQuarters(3,:)'</td>
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<td></td>
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<td>37</td>
<td>'FreqHiQuarters(4,:)'</td>
<td>86</td>
<td>'sdbResidualAmplitudeSkewness'</td>
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<td></td>
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<td>38</td>
<td>'BWHiQuarters(1,:)'</td>
<td>87</td>
<td>'sdbResidualAmplitudeKurtosis'</td>
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<td></td>
</tr>
<tr>
<td>39</td>
<td>'BWHiQuarters(2,:)'</td>
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<td>'cycleLengthNumber'</td>
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<td></td>
</tr>
<tr>
<td>40</td>
<td>'BWHiQuarters(3,:)'</td>
<td>89</td>
<td>'cycleLengthPeriodMean'</td>
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</tr>
<tr>
<td>41</td>
<td>'BWHiQuarters(4,:)'</td>
<td>90</td>
<td>'cycleLengthPeriodStd'</td>
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<td></td>
</tr>
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<td>42</td>
<td>'MDHiQuarters(1,:)'</td>
<td>91</td>
<td>'cycleLengthPeriodSkewness'</td>
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<tr>
<td>43</td>
<td>'MDHiQuarters(2,:)'</td>
<td>92</td>
<td>'cycleLengthPeriodKurtosis'</td>
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<td>44</td>
<td>'MDHiQuarters(3,:)'</td>
<td>93</td>
<td>'cycleLengthPeriod50th'</td>
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<td></td>
</tr>
<tr>
<td>45</td>
<td>'MDHiQuarters(4,:)'</td>
<td>94</td>
<td>'cycleLengthPeriod25th'</td>
<td></td>
<td></td>
</tr>
<tr>
<td>46</td>
<td>'anfRate5th'</td>
<td>95</td>
<td>'cycleLengthPeriod50th'</td>
<td></td>
<td></td>
</tr>
<tr>
<td>47</td>
<td>'anfRate25th'</td>
<td>96</td>
<td>'cycleLengthPeriod75th'</td>
<td></td>
<td></td>
</tr>
<tr>
<td>48</td>
<td>'anfRate50th'</td>
<td>97</td>
<td>'cycleLengthPeriod95th'</td>
<td></td>
<td></td>
</tr>
<tr>
<td>49</td>
<td>'anfRate75th'</td>
<td>98</td>
<td>'cycleLengthPeriodNormMean'</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 22:** List of Features extracted from SM signals used in ADHF predictor algorithm development
5.7.2. Developing and Training the SM ADHF Predictor Algorithm (SMApA)

Developing the SMApA

The ADHF predictor algorithm was developed from 21,659 nights of data from 51 patients in the Dublin development dataset, using some of the features identified in Table 18. (See Figure 67)

During development a ‘Leave One Out Cross Validation’ (LOOCV) system was used to make a more robust assessment of the features selected (221). It is a tedious but robust system that involves systematically removing a single feature from the original dataset, which is then used as a validation on the remainder feature set to see if there were significant changes to the SMApA. This is repeated such that each feature in the sample is used once as the validation data. This way the best features are selected and inputted into the final algorithm.

At the end of development, 3 SMApA Classifiers, which contain a feature set and a trained classifier, were selected based on their sensitivity, specificity & ROC as potential predictors for validating the London group of patients (Tables 23, 24 & 25). The target was to correctly identify an ADHF episode within the 7-day window before it was clinically detected.

Figure 67: Consort chart for Algorithm development – Development Set
SM ADHF Predictor Algorithm 1 – CLASSIFIER 1

Type of Classifier – SPCCA

Features

<table>
<thead>
<tr>
<th>Feature Index</th>
<th>Feature Name</th>
<th>Brief Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MovCUM</td>
<td>Total Movement duration during the Session.</td>
</tr>
<tr>
<td>2</td>
<td>HICUM</td>
<td>Total Regular Breathing duration during the Session.</td>
</tr>
<tr>
<td>3</td>
<td>FreqCSQ4</td>
<td>Breathing Frequency duration during the 4th Quarter of the night.</td>
</tr>
<tr>
<td>4</td>
<td>BWCSQ4</td>
<td>CS Breathing Bandwidth duration during the 4th Quarter of the night.</td>
</tr>
</tbody>
</table>

Table 23: Features used for SM ADHF Predictor Algorithm 1

SM ADHF Predictor Algorithm 2 – CLASSIFIER 2

Classifier – LDA

Features

<table>
<thead>
<tr>
<th>Feature Index</th>
<th>Feature Name</th>
<th>Brief Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>totSleepTime</td>
<td>Total estimated Sleep Time during the night.</td>
</tr>
<tr>
<td>2</td>
<td>activity75th</td>
<td>75th centile of all detected activity.</td>
</tr>
<tr>
<td>3</td>
<td>cycleLengthPeriodNorm50h'</td>
<td>Median of the duration of all periodic breathing.</td>
</tr>
<tr>
<td>4</td>
<td>'RE 2nd - 1st'</td>
<td>Difference between the mean Residual Effort (of detected periodic breathing) between the second part and the first part of the night.</td>
</tr>
<tr>
<td>5</td>
<td>AL mean/std</td>
<td>A measure of the variability of apnea length.</td>
</tr>
<tr>
<td>6</td>
<td>CycleLength Range</td>
<td>Cycle length range.</td>
</tr>
<tr>
<td>7</td>
<td>activity95th</td>
<td>95th percentile of all detected activity.</td>
</tr>
<tr>
<td>8</td>
<td>sdbEventNumber'</td>
<td>Number of detected SDB events.</td>
</tr>
<tr>
<td>9</td>
<td>Resp 95th - 50th'</td>
<td>Difference between the 95th and the 50th percentile of all the respiration rates estimated during the night.</td>
</tr>
<tr>
<td>10</td>
<td>Residual effort range</td>
<td>Residual effort range.</td>
</tr>
</tbody>
</table>

Table 24: Features used for SM ADHF Predictor Algorithm 2
SM ADHF Predictor Algorithm 3 – CLASSIFIER 3

Classifier – LDA

Features

<table>
<thead>
<tr>
<th>Feature Index</th>
<th>Feature Name</th>
<th>Brief Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PercentCS'</td>
<td>Percent CS during the night.</td>
</tr>
<tr>
<td>2</td>
<td>CSQuarters(2,:)</td>
<td>CS in 2nd quarter of the night.</td>
</tr>
<tr>
<td>3</td>
<td>BWCSQuarters(1,:)</td>
<td>Bandwidth of the CS in the first quarter of the night.</td>
</tr>
<tr>
<td>4</td>
<td>MDCSQuarters(3,:)</td>
<td>Modulation depth of the CS in the 3rd quarter of the night.</td>
</tr>
<tr>
<td>5</td>
<td>HIQuarters(3,:)</td>
<td>Entropy in the 3rd quarter of the night.</td>
</tr>
<tr>
<td>6</td>
<td>'respRate25th'</td>
<td>25th percentile of all respiration rates during the night.</td>
</tr>
<tr>
<td>7</td>
<td>sdbEventNumber'</td>
<td>Number of detected SDB events.</td>
</tr>
<tr>
<td>8</td>
<td>sdbEventLengthMean'</td>
<td>Mean length of all detected SDB events during a night.</td>
</tr>
<tr>
<td>9</td>
<td>sdbEventLengthStd'</td>
<td>STD of the duration, of all detected SDB events during a night.</td>
</tr>
<tr>
<td>10</td>
<td>sdbResidualAmplitudeStd'</td>
<td>STD of the residual effort of all detected SDB events during a night.</td>
</tr>
<tr>
<td>11</td>
<td>sdbResidualAmplitudeStd2nd'</td>
<td>STD of the residual effort of all detected SDB events during the second part of the night.</td>
</tr>
<tr>
<td>12</td>
<td>sdbEventLengthMean1st'</td>
<td>Mean duration of all detected SDB events during the first part of the night.</td>
</tr>
<tr>
<td>13</td>
<td>cycleLengthPeriodNorm25thY</td>
<td>25th percentile of the duration of all cycles of modulated breathing detected during the night.</td>
</tr>
<tr>
<td>14</td>
<td>cycleLengthPeriodNorm50thY</td>
<td>50th percentile of the duration of all cycles of modulated breathing detected during the night.</td>
</tr>
<tr>
<td>15</td>
<td>cycleLengthPeriodNorm75thY</td>
<td>75th percentile of the duration of all cycles of modulated breathing detected during the night.</td>
</tr>
<tr>
<td>16</td>
<td>cycleLengthPeriodNorm2ndHalfMean'</td>
<td>Mean duration of all cycles of modulated breathing detected during the second part of the night.</td>
</tr>
<tr>
<td>17</td>
<td>cycleLengthPeriodNorm2ndHalfStd'</td>
<td>STD of the duration of all cycles of modulated breathing detected during the second part of the night.</td>
</tr>
<tr>
<td>18</td>
<td>sdbTimeMinsPerHour'</td>
<td>AHI x mean Cycle Length.</td>
</tr>
<tr>
<td>19</td>
<td>Resp 95th - 50th'</td>
<td>Difference between the 95th and the 50th percentile of all the respiration rates estimated during the night.</td>
</tr>
<tr>
<td>20</td>
<td>CL 95th - 75th'</td>
<td>Difference between the 95th and the 75th percentile of the duration of all the cycles of modulated breathing detected during the night.</td>
</tr>
<tr>
<td>21</td>
<td>'RE 2nd - 1st'</td>
<td>Difference between the mean residual effort of detected SDB events between the second part of the night and the first part of the night.</td>
</tr>
<tr>
<td>22</td>
<td>AL 2nd - 1st'</td>
<td>Difference between the mean duration of detected SDB events between the second part of the night and the first part of the night.</td>
</tr>
<tr>
<td>23</td>
<td>CL 2nd - 1st'</td>
<td>Difference between the mean duration of the residual effort of detected SDB events between the second part of the night and the first part of the night.</td>
</tr>
<tr>
<td>24</td>
<td>RespRate50thVsBaseline'</td>
<td>Difference between the 50th percentile of all estimated respiration rate during a night versus baseline from previous days.</td>
</tr>
<tr>
<td>25</td>
<td>RespRate75thVsBaseline'</td>
<td>Difference between the 75th percentile of all estimated respiration rate during a night versus baseline from previous days.</td>
</tr>
</tbody>
</table>

Table 25: Features used for SM ADHF Predictor Algorithm 3
5.7.2.1. Testing the SMApA

Once the SM ADHF predictor algorithm (SMApA) development was completed, testing commenced on the London database. Only ADHF events that had been recorded, completed and adjudicated upon at commencement of testing (20/01/2013) were included. There were 20 such adjudicated ADHF events and 13 were usable, which translated to 10,730 nights that were available for testing the SMApA. The mean (SD) FU at this stage was 10.2 ± 4.6 months. In a similar fashion only the best features, which had been selected a priori during development, were extracted from this validation set and put through the classifier algorithm to give a prediction. Figure 68 is the consort chart for ADHF event selection while Figure 69 summarises the entire development and testing process of the SMApA.

Figure 68: Consort chart for Algorithm development – Validation Set
Figure 69: Schematic showing summary of entire development and validating of the SleepMinder™ ADHF predictor algorithm. (LOOCV – Leave One Out Cross Validation, ADHF – Acute Decompensation of Heart Failure)
5.8. Results

5.8.1. Patient Characteristics

There were 61 patients in the development and 43 patients in the validation arms of this study. The characteristics of these patients are shown in Table 26. All patients had chronic heart failure secondary to left ventricular systolic dysfunction and majority were on contemporary heart failure therapy with a beta-blocker, ACE inhibitor or Angiotensin II Receptor Blocker.

There were significantly more patients in the validation set who were treated with cardiac resynchronisation therapy (CRT) (40% versus 5%. p<0.001). Furthermore, the baseline BNP was significantly higher in the development arm (mean±SD-170±179) compared to the validation set of patients (mean±SD-134±89). In addition, significantly more patients in the development arm of the study had atrial fibrillation and hypertension however more patients in the validation set had documented renal impairment or anaemia.
Table 26: Showing baseline characteristics of Development and Validation set of patients. Values are expressed as mean ± SD or percentages.

There were no significant differences in the key respiratory parameters used in the development of the SMApA, compared to the number of events in the validation set of patients as shown in Table 27.

Table 27: Showing comparisons between Development and Validation set of patients of key respiratory parameters used in SM ADHF predictor algorithm. Values are expressed as mean ± SD
5.8.2. Acute Decompensation of Heart Failure

In the validation set of patients, there were 29 documented ADHF episodes, which occurred in 15 of the 43 patients recruited, over the entire follow up period [mean(SD) 11.2 ± 3.6 months]. The adjudication committee deemed one event, as not being a true ADHF episode as it did not fulfil all of the pre-specified event criteria. There were therefore 28 true ADHF episodes in 15 patients. This gave an ADHF event rate for this group of patients in this period of 35%, which was higher than our projected rate (30%) in our sample calculation.

Multiple ADHF episodes occurred in 8 of these patients up to a maximum of 3 episodes as shown in Figure 70.

Figure 70: Number of ADHF Episodes per patient

Compared to those patients who did not decompensate, ADHF patients were more symptomatic at baseline in terms of NYHA grading and more (67%) had an ischaemic substrate as the aetiology of their heart failure as shown in the table 28 below, compared with those who did not decompensate.
### Table 28: Comparison of patients who did or did not have an ADHF episode

<table>
<thead>
<tr>
<th>Group/Patients</th>
<th>had ADHF (15)</th>
<th>did not ADHF (28)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>77.62 ± 11</td>
<td>76.7 ± 7</td>
<td>0.88</td>
</tr>
<tr>
<td>NYHA III or IV n (%)</td>
<td>7 (47)</td>
<td>3 (11)</td>
<td>0.008</td>
</tr>
<tr>
<td>Ischaemic Etiology n (%)</td>
<td>10 (67)</td>
<td>9 (32)</td>
<td>0.03</td>
</tr>
<tr>
<td>HTN n (%)</td>
<td>5 (33)</td>
<td>9 (32)</td>
<td>0.93</td>
</tr>
<tr>
<td>DM n (%)</td>
<td>3 (20)</td>
<td>3 (11)</td>
<td>0.40</td>
</tr>
<tr>
<td>COPD n (%)</td>
<td>0 (0)</td>
<td>2 (7)</td>
<td>0.28</td>
</tr>
<tr>
<td>BNP (SD)</td>
<td>160 ± 126</td>
<td>113 ± 122</td>
<td>0.19</td>
</tr>
<tr>
<td>EF (SD)</td>
<td>34 ± 11</td>
<td>38 ± 16</td>
<td>0.35</td>
</tr>
<tr>
<td>eGFR</td>
<td>42 ± 16</td>
<td>46 ± 26</td>
<td>0.61</td>
</tr>
<tr>
<td>B-Blockers n (%)</td>
<td>13 (87)</td>
<td>22 (78)</td>
<td>0.56</td>
</tr>
<tr>
<td>ACE or AllRB n (%)</td>
<td>10 (67)</td>
<td>22 (78)</td>
<td>0.23</td>
</tr>
<tr>
<td>MRA n (%)</td>
<td>5 (33)</td>
<td>10 (36)</td>
<td>0.54</td>
</tr>
</tbody>
</table>

### 5.8.2.1. Hospital Managed ADHF

An ADHF episode resulted in a hospital admission in 19 of the 28 ADHF episodes. The mean time to intervention, which is from documented symptom onset as recorded by the patients in their diary or reported to the admitting medical team, to hospital admission, was 6.3 ± 4.2 days (Mean ± SD). Following hospital admission the average length of stay (LOS) for each episode of ADHF was 18 ± 15 days (Mean ± SD). 83% of these patients managed in-hospital received intravenous loop diuretic Furosemide and 47% of these patients received this in combination with ‘renal dose’ dopamine. Ultrafiltration was used as adjunctive therapy to manage 2 patients who had failed to respond to the initial combination treatment with IV diuretics and Dopamine and to help preserve renal function as shown in Table 29. Arrhythmia and sepsis were causative of the ADHF episodes in 22% and 11% of these events, respectively, and in one patient an acute coronary event was deemed important. The exact trigger for a decompensation episode was unidentified (‘other’) in 52% of patients. Examination of records by the adjudication committee however suggested that non-adherence to fluid balance management and/or non-compliance with medication may have been causative in these patients.
Table 29: Showing characteristics of ADHF events managed in hospital. ‘Other’ – Non-compliance with fluid balance or medication management (IV = Intravenous, LOS – Length of Hospital Stay, Pre-Adm-LOS – Time to hospital admission/intervention, UF – Ultrafiltration, Loop- Loop Diuretic, Furosemide)

5.8.2.2. Home Managed ADHF

Home management of ADHF occurred in 9 of the 28 ADHF episodes and was initiated by the patient based on expert knowledge of their condition or following a call to the heart failure nurse (community/hospital) or GP. They had complained of weight gain or increased symptoms (dyspnoea or orthopnoea), which led to an intervention. It was difficult to obtain a definite trigger for decompensation in these patients but from interviewing patients and obtaining GP notes I established that most of these episodes were triggered by a loss of control of a usually strict fluid balance by these patients. On average, these patients delayed intervention by up to 6 days before initiating treatment (6.2 ± 3.5 days; Mean ± SD). See table 30.
Table 30: Showing characteristics of ADHF events managed at home. ‘Other’ – Non-compliance with fluid balance or medication management (Loop – Loop Diuretic, Furosemide, Pre-I-Adm – Time at home from symptom onset to intervention)

5.8.3. Non Heart Failure Related Admissions

Table 31 below shows the reasons for admissions to hospital that were not related to heart failure decompensation (non-ADHF admissions). 19 such events occurred in 11 patients. 5 (26%) events were elective and 14 (74%) were emergency admissions. The average LOS was 5.3 ± 4.2 nights (mean ± SD)
Table 31: Aetiology of Non-Heart Failure Admissions (UTI = Urinary Tract Infection, LOS – Length of Hospital Stay, PPM – Permanent Pacemaker, PCI – Percutaneous Coronary Intervention, LRTI – Lower Respiratory Tract Infection)

5.8.4. Mortality

During the entire follow up period 9 (21%) patients died. The cause of death was end-stage Heart Failure in 8 (89%) of these patients. One death was following complications from a pulmonary embolus following a hip operation.
5.8.4.1. Overall Mortality versus ADHF episodes

5 of the patients who died suffered at least one ADHF episode prior to their demise and 3 of these patients had 2 or more ADHF episodes as shown in Figure 71.

![Mortality – ADHF Episodes](image)

Figure 71: Patients who died in relation to the number of ADHF episodes (Mean FU Period 11.2 ± 3.6 months) LON 010 was patient who died following emergency Hip Operation.

5.8.5. Compliance with Diary Documentation

We had instructed patients at the start of the study to document changes in diuretic therapy and symptoms into provided diaries. Compliance with diary documentation was assessed by comparing patient entries into the diaries regarding change in diuretic therapy and symptoms with information regarding actual clinical events, obtained from outpatient letters or hospital notes, and contact with HF nurses and GPs. Overall compliance was very poor with only 10 (23%) of eligible recruited patients making an entry at all. Of these only 6 patients appropriately correlated their entries with clinical information, which we had, access to. The remaining four patients who documented anything at all entered non-relevant information
5.8.6. Sleep Minder Acceptability

5.8.6.1. Recruitment Proportion

There were 43 patients who consented to take part in this study and the pre-specified follow up period was for a minimum of 12 months. Comparatively, our recruitment proportion for this study was high (222) at 57% with 43 of the 75 eligible patients approached, who agreed to take part in the study. The primary reason for failure of enrolment was patient’s perceived inconvenience at having medical equipment placed within their home environment. (See Figure 63)

5.8.6.2. Withdrawal Proportion

3 patients, who had initially consented to take part in the study, returned their devices after 1 day due to unexpected family reasons (2) or unexpected travel abroad (1).

Of the 40 remaining patients, only 2 patients pulled out voluntarily before the end of the follow up period. One patient found the SleepMinder™ device a constant reminder of their medical problems and dropped out of the study after 122 days. The other patient entered a palliative phase of their management and dropped out after 118 days of the study, as they could no longer actively participate.

Therefore, apart from patients who died or who were excluded as a result of early return of study equipment, acceptability of the SM device was excellent with 95% of patients using the device throughout the study period. Our withdrawal proportion was therefore only 5%.
5.8.7. SM ADHF Algorithm Prediction

We developed 3 SleepMinder™ ADHF predictor Algorithms (SMApA) using the techniques described earlier in Section 5.7. Table 32 shows the results of all three algorithms in terms of sensitivity, specificity and diagnostic accuracy by means of the area under receiver operator characteristic curve (AUC). Due to the design of SMApA 1, we were only able to produce binary predictions. With SMApA 2 and 3 however, we were able to generate prediction probabilities, which enabled us to plot ROC curves.

Of the 3 algorithms, the SM ADHF predictor algorithm 2 was deemed to have the best combination in terms of accuracy parameters and was selected as the final algorithm or prediction. The sensitivity and specificity of this algorithm was 38% and 71%, respectively, in the validation group of patients. Positive predictive value (PPV) and Negative Predictive Value (NPV) was 1% and 99% respectively. The False Positive Rate (FPR) was 71%.

The AUC for this classifier was 53%. See Figure 72.

<table>
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<tr>
<th>Measure</th>
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<th>Validation (London)</th>
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<tr>
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<td>0.538 [0.291 .. 0.768]</td>
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<td>Specificity</td>
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<td>0.574 [0.550 .. 0.598]</td>
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<tr>
<td>AUC</td>
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<td>n/a</td>
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<tr>
<td>Weeks</td>
<td>3376</td>
<td>1812</td>
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<tr>
<td>Events</td>
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<td>13</td>
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<td>FN</td>
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<tr>
<td>TN</td>
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<tr>
<td>FP</td>
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<td>676</td>
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<tr>
<td>Sensitivity</td>
<td>0.821 [0.702 .. 0.900]</td>
<td>0.385 [0.177 .. 0.645]</td>
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<td>Specificity</td>
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<tr>
<td>AUC</td>
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<td>0.5304</td>
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<td>FP</td>
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Table 32: SleepMinder™ ADHF Predictor Results all classifiers.
Figure 72: Receiver Operator Characteristic (ROC) curve for SMApA 2, (Blue line – ROC curve for Development Set, Red Line – ROC curve for Validation set. AUC – Area Under Curve=0.53)
5.8.8. Weight Analysis

I also compared the changes in weight seen before an ADHF episode compared to Non – ADHF episodes. There was no statistically significant difference between the two events with a mean difference of 1kg weight change between the two event types but this is underpowered as there were fewer non-ADHF events. This is shown in table 33.

![Table 33: Weight change between ADHF event and Non-ADHF event days.](image)

5.9. Discussion

An effective tool for predicting acute decompensation of chronic heart failure (ADHF) should be one using a parameter or a combination of parameters, which has a high positive predictive value for ADHF. It should also be detectable early enough to allow for intervention by the physician in order to institute management changes that could prevent further deterioration of heart failure.

In this study we have shown that our SM ADHF predictor algorithm (SMApA), which incorporates components of nocturnal respiration obtained from a non-contact bedside monitor – the SleepMinder™ device, is not clinically useful for predicting decompensation of heart failure. Our best SMApA had a sensitivity of 38% and specificity of 71% with a PPV of 1% and NPV of 99%, for predicting ADHF in the week before a clinical event, in the validation group of patients. The AUC was 53% which suggests its predictive value is only a little better than chance. Overall and on its own, its clinical use is therefore of little clinical value.

The results of the SMApA in the development set of patients alone were better than published weight–based algorithms for predicting ADHF with a sensitivity and specificity of 82% and 80% respectively. These weight-based algorithms shown in Table 34 (101) were developed and validated on the same group of patients and as a result, may have been artefactually optimistic in their results. It is therefore more robust to develop and test on different sets of patients.
<table>
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<th>Auth/Paper/Year</th>
<th>Criteria</th>
<th>Sen</th>
<th>Spec</th>
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<td>Zhang Ten-HMS EHJ 2009</td>
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<td>Kataoka Futures 2009</td>
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<td>Blair EVEREST Trial EHJ 2009</td>
<td>180 day post discharge hosp. risk &gt;2kg in 24-72h</td>
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<td>Lewin Weight and BNP EHJ 2005</td>
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<td>Ledwidge Heart Phone EHJ 2013</td>
<td>7 day Moving Average of weight</td>
<td>0.82</td>
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Table 34: Comparison of SM ADHF predictor algorithm with Weight based algorithms – developed and validated in same group of patients

When our results are compared with other studies on ADHF prediction, (Table 35) which were developed and validated on different groups of patients, the SM ADHF predictor algorithm was not as accurate (121)
Table 35: Comparison of SM ADHF algorithm with ADHF algorithms – developed and validated in different group of patients.

Cowie and colleagues developed a dynamic HF risk score (low ≤5%, Medium 5-20%, High>20%), derived from combining diagnostic parameters monitored in implantable devices for predicting HF hospitalisations in the next 30 days. The parameters used in this study included intra-thoracic impedance (IMP), atrial fibrillation (AF) burden, ventricular rate during atrial fibrillation (VRAF), ventricular tachycardia (VT) episodes, patient activity (ACT), day and night heart rate (NHR), and heart rate variability (HRV) (223).

They developed this score using data from a development set of 921 HF patients with an average follow-up duration of 10.6±5.8 month and validated their findings on 1310 HF patients who were followed up for an average of 8.1±5.0 months. All patients had an implanted CRT-D or ICD and were derived from Europe, Hong Kong and the USA.

In patients with a low to medium HF risk score (5%), the sensitivity and specificity of the score for predicting a future HF hospitalisation in the next 30 days was 83% and 46% respectively.

The COMPASS-HF (Chronicle Offers Management to Patients with Advanced Signs and Symptoms of Heart Failure) study was a prospective, multicenter, randomized, single blind, parallel-controlled trial of 274 New York Heart Association functional class III or IV HF patients who received an implantable continuous hemodynamic monitor (ICHM). Patients were randomized to a Chronicle (Medtronic Inc., Minneapolis, Minnesota) (n = 134) or control (n = 140) group (111). All patients received optimal medical therapy, but the hemodynamic information from the
monitor was used to guide patient management only in the Chronicle group. The ICHM continuously monitored and stored information including heart rate, body temperature, patient activity and changes in right ventricular systolic and diastolic pressure. **There was a 21% reduction in HF related events in the Chronicle group but this did not reach statistical significance, (See Table 32).**

SENSE-HF was a large prospective, multicentre, double blind study that evaluated an impedance-based algorithm, OptiVol (Medtronic, Inc., Minneapolis, MN, USA), in 501 NYHA class II and class III HF patients implanted with CRT-D devices. Using OptiVol, the trial results demonstrated a low sensitivity of 42% and low positive predictive value of only 38% for future HF events that is from 6 months to 24 months post implantation (121).

We have developed the SM ADHF predictor algorithm by using various components of respiration derived from nocturnal monitoring with the SM device and then incorporated them into a ‘yes’ or ‘no’ predictor. These respiratory parameters are essentially a reflection of pulmonary congestion and in theory should give a good indication of a patient’s fluid status. We however know that in the days or weeks preceding an ADHF episode, there may be a significant increase in extracellular fluid volume, without evidence of peripheral oedema or pulmonary congestion (104). We have not incorporated other physiological parameters into our algorithm, which have been shown to have some added advantage in ADHF prediction such as heart rate monitoring or oxygen saturation (121;132). Other studies that have combined multiple parameters that assess not only fluid status, have produced arguably better results (223) and it is possible that by adding more diagnostic variables, the performance of the algorithm may be improved.

There was a 44% drop in sensitivity of the algorithm when tested on the validation group of patients. The reason for this is not clear. In terms of baseline characteristics, there were some differences between the two groups of patients (development and Validation) that could account for this. In particular, the BNP, which is a reliable marker of severity of heart failure, was significantly higher in the development group of patients (Validation vs Development; 135 ± 89; 170 ± 179). Conversely a significant number of patients in the validation arm were treated with cardiac resynchronisation therapy (CRT), which may also suggest the presence of severe heart failure despite optimal medical therapy (Validation vs Development; 40% vs 5% p<0.00). There are some small studies that show that CRT reduces the amount of SDB in heart failure (224) and
perhaps this may have had some undetected effect on the number of respiratory events in the validation group of patients, which may have influenced the manner in which the SMApA performed. Despite the higher use of CRT in the validation arm, the event rate of 35% was still high, so they were still notably a ‘sick’ group of patients. The mean AHI was marginally higher at 26.4 events per hour in the development set of patients compared to the validation group (24 events per hour). This difference is probably not enough to cause such a sharp drop in performance but it is worth noting this.

Overall however, there was no clear difference in clinical or demographic characteristics, which contrasted either development or validation group of patients. Neither was there any statistically significant difference in terms of other nocturnal respiratory patterns utilised for the purpose of developing the predictor that demarcated either group of patients. (Table 24)

I have shown in the previous chapter that amongst other respiratory parameters, the Apnoea Hypopnea Index (AHI) was highly variable over a prolonged period of monitoring. As the SMApA was derived from components of this, it is possible that this large variability may have influenced the performance of the algorithm in the validation group.

Another possible explanation for the drop in performance of the SMApA in the validation group, may be from ‘over fitting’ of the algorithm during development such that it becomes too trained or moulded on one particular group of patients. In statistics and machine learning, over fitting occurs when a statistical model describes random error or noise instead of the underlying relationship. Over fitting generally occurs when a model is excessively complex, such as having too many parameters relative to the number of observations. A model which has been over fitted will generally have poor predictive performance, as it can exaggerate minor fluctuations in the data (225).

This, in theory, should however not affect the performance of the algorithm particularly if there was no major clinical difference between the two groups. It is however the most likely explanation because not all factors that could have influenced the final development of the SMApA can be accounted for, even if the design of the study involved matching clinical characteristics of the validation group to the development group.

There were fewer usable events in the validation group of patients with 13 adjudicated events that the SM ADHF predictor Algorithm (SMApA) was tested on compared to the 56 events from
which it was developed. We speculate that by testing the SMApA on a larger dataset with more ADHF events, it is possible that the results may have been slightly better. Perhaps this is an area where further work needs to be carried out.

67% of the validated ADHF episodes resulted in a hospital admission while the remainder 23% were successfully managed at home without the need for a hospital admission. This supports guidelines that encourage patient education empowering them to manage their heart failure at home (3). These patients who were managed at home adjusted their diuretics in response to their symptoms or signs on their own, or did so following advice from the heart failure nurse specialists or general practitioners.

The mean length of stay for a hospital admission for heart failure decompensation was longer at 18 days compared to 13 days nationally (63). But this is comparing our group of patients who potentially had a more severe heart failure syndrome, with a general heart failure population.

We have also shown that the SM device as a novel non-contact monitor was convenient to use and acceptable by heart failure patients with only a 5% withdrawal during the follow up period (mean 11.2 ± 3.6 months). This is encouraging and suggests that patients are agreeable to the use of technology in the management of their chronic conditions. Majority of our patients were elderly (mean age 76.7 ± 8.9 years) and were still able to use the various components of the equipment provided including the SM device itself, a mobile phone and a set of scales, without much difficulty. This is in line with reviews of studies that have shown success and good compliance when technology was utilised as a tool for improving management of chronic disease regardless of the age of the patient (226).

There was no clear differentiation in weight gain compared to non-ADHF events. Again this is in agreement with majority of studies that weight is not a sensitive predictor of decompensation (103).

This study has added to the body of evidence, which suggests that the prediction of Acute Decompensation of Heart Failure (ADHF) remains a challenge. More research is needed to determine what optimal diagnostic parameters would reliably identify decompensation and which may be robust enough to be clinically useful in practice by physicians. This may help reduce the incidence of ADHF and potentially overall mortality in chronic heart failure patients.
The development of multimodality monitoring of heart failure patients in on-going studies such as the MULTISENSE trial (Boston Scientific) may be a useful way of collecting more information that may be useful for predicting decompensation of heart failure (227). This trial is evaluating the predictive power of multiple physiological parameters obtained from implanted CRT-D devices that have a multi-sensor design. This would be used in combination with its remote monitoring system (Latitude) where this clinical information from the implanted devices may be available to physicians to enable them take clinical action sooner to avoid hospitalization due to heart failure.

REM-HF (Remote Monitoring in Heart Failure) is another on-going UK multi-centre trial which aims to evaluate the effectiveness of automatic remote monitoring using implanted device technology (Medtronic, St.Judes) for the management of chronic heart failure in the home, compared to usual care involving face-to-face hospital visits. Patients with stable CHF and who have had an implantable device (CRT-D or ICD), for at least 6 months are being randomized to receive device-based care, where Information from periodic downloads from these devices would be made available to clinicians to aid management of these patients or usual care according to ESC guidelines. They will be followed up for a minimum of 2 years. In addition all patients will be asked to complete quality of life questionnaires at regular intervals. This study is due to complete its findings in 2015 and it is hoped that the results from this study will help to provide robust evidence of the clinical and cost-effectiveness of remote monitoring of patients with such devices (228).

The signs and symptoms that constellate to the development of ADHF results from disturbances in multiple intersecting processes including neurohormonal circuits, inflammatory mediators, cardiorenal interactions, and myocardial performance (229). In theory therefore, there are multiple opportunities for detecting early changes in the processes that lead to ADHF. Further research is therefore required to develop ideal predictive tools incorporated with remote monitoring programmes that monitors and detects early and subtle changes in these physiological parameters, which may lead to earlier intervention to abort the ADHF cascade.
5.10. Conclusions

I have shown that the non-contact monitoring of Sleep Disordered Breathing is unreliable in detecting Acute Decompensation of Heart Failure (ADHF). Although an algorithm could be developed in one cohort of HF patients, its value was no better than chance when tested in a second cohort of similar patients.

There are no simple SM parameters that provide a clear differentiation between stable and acutely decompensated heart failure. Limited but non-statistically significant trends in some respiratory parameters such as the mean nightly respiratory rate, duration of SDB and cycle length of CSR, have been noted but these are not consistent for all patients or all events.

Further work with the addition of other physiological parameters and possibly implanted device variables may provide a more clinically useful method for ADHF prediction.
CHAPTER SIX – CONCLUSIONS
6.1. Summary of Main Aims

Sleep Disordered Breathing (SDB) is an important but under-diagnosed co-morbidity that is prevalent in patients with chronic heart failure (CHF). The need for simple and reliable tools for screening and diagnosis is therefore desirable.

To this end, the first aim of this thesis was to validate the SM device as a diagnostic tool for SDB in these patients compared to in-hospital Polysomnography (PSG). This may provide a suitable alternative for clinicians towards improving identification of this important condition.

The second aim was to describe the variability of nocturnal respiratory parameters in CHF patients (in particular the Apnoea Hypopnoea Index (AHI)) over a prolonged period of monitoring. The value of this analysis was to improve our experience of how changes in these parameters may influence the diagnosis and management of SDB.

In addition, Acute decompensation of Chronic Heart Failure (ADHF) leads to increased morbidity and mortality and early diagnosis has the potential to improve survival outcomes in these patients. The Third aim of this thesis was to investigate the predictive value of a non-contact respiratory monitor – the SleepMinder™ device (SM) for early identification of ADHF, using a prediction algorithm derived from SM signals.

6.2. Summary of Main Results

I studied 59 patients with chronic stable systolic heart failure to investigate the accuracy of the SleepMinder™ device for the diagnosis of Sleep Disordered Breathing (SDB). To achieve this, these patients underwent simultaneous overnight Polysomnography (PSG) and SM recordings in our sleep laboratories. I then developed algorithms from the SM signals for the calculation of the Apnoea Hypopnoea Index (AHI) and % overnight Cheyne-Stokes Respiration (CSR). The algorithms generated as a result of this study formed the baseline metrics for developing the SM ADHF predictor algorithm evaluated in chapter five.

The results from this study showed that the SM was accurate for the diagnosis of clinically relevant SDB (AHI>15) with a sensitivity of 0.91 and less moderately a specificity of 0.50. The area under the receiver operator characteristic curve (AUC) at this threshold was 0.82 (95% CI 0.63-1.0). The SM was less accurate for identifying CSR in this population of patients with a sensitivity
of 0.71 and specificity of 0.75 The AUC using a threshold of % overnight CSR of 0 was 0.76 (95% CI 0.56-1.0).

In comparison to PSG, even where there was a disagreement in the AHI score between the two techniques, this was not more than 10 events per hour in over 70% of these patients. This means that even with this difference, these patients were unlikely to be categorised into a different severity group of SDB. The mean difference between the two techniques was 5.6 events per hour (95% CI -2.1 -13.4)

Based on the high sensitivity (0.91) but at the expense of a negative predictive value (0.80) of the SM AHI algorithm, I have argued that it would be a reliable indicator when the test result was negative, and can therefore be used as a screening tool to rule out SDB or select patients for further confirmatory tests such as PSG. This would reduce the burden on overstretched sleep laboratories for formal sleep studies by excluding patients who may not require further investigations.

To determine the variability of the AHI over a prolonged period of monitoring, I have analysed 13,104 consecutive patient nights of nocturnal respiratory data in a group of 39 patients with moderate to severe CHF. The mean (SD) follow up period was 336 ± (108) days and this is the first study in the published literature that has been able to make an observation of this nature, based on more than four nights’ recording. I have demonstrated that there was a substantial night-to-night intra- and inter- patient variability in the AHI. [Mean Stdev 11.3 events per hour (95% CI 10.08-12.95)] [Intra Class Correlation Co-efficient 0.329 (95% CI 0.229-0.488)].

Based on these results, I have argued that a single night’s assessment may be insufficient to make a definitive diagnosis of SDB. I have therefore investigated alternative diagnostic thresholds using the mean AHI or the proportion of the follow up period where there was clinically relevant SDB (AHI>15). I observed that there were a high percentage of patients whose mean AHI was above treatment thresholds for SDB (AHI>15) and this percentage was consistent over varying follow-up periods. For this reason, I have recommended the mean AHI over a 2-week period as an alternative diagnostic criterion.

My argument is strengthened by the high individual patient misclassification rate for SDB that was observed. I found that on average a patient was misclassified into a different severity group
for 35% of a 2-week follow-up period and into a different treatment group for 21% of the analysed FU period. These results may have significant implications for the diagnosis and management of SDB in heart failure patients.

Finally, I have demonstrated that the SleepMinder™ ADHF predictor algorithm, which uses a combination of nocturnal respiratory parameters, has no value in predicting acute decompensation of chronic heart failure. This algorithm had a sensitivity and specificity of 38% and 71% respectively. The false positive rate was observed to be significantly high (71%) rendering the algorithm of no utility in identifying a higher risk of ADHF.

6.3. Clinical Relevance and Future Directions

This thesis has evaluated the usefulness of a novel non-contact monitor of nocturnal respiration in heart failure patients, for diagnosing Sleep Disordered Breathing (SDB) and predicting acute decompensation of chronic heart failure (ADHF). It has also described, for the first time, the variability of nocturnal respiratory and sleep parameters over a prolonged period of monitoring. The results of my studies may have some important clinical implications for how heart failure is managed in the near future.

6.3.1. Diagnosis of SDB using the SleepMinder device

Increased survival from acute coronary syndromes and sudden cardiac death, has led to an increased prevalence of heart failure (230). Advancement in contemporary drug and implanted device therapy has been associated with improved outcomes in patients with left ventricular systolic dysfunction in particular, but attendant morbidity or mortality remains high (63). As a consequence, newer therapeutic targets for managing this condition are being investigated. Due to its high prevalence (40-50%) and negative prognostic association in patients with CHF (6) (9), the treatment of SDB is one such area that is continuing to attract a lot of interest. Further, studies (165;166) investigating newer treatment options for SDB may provide morbidity and mortality data that would persuade the introduction of clear treatment strategies for SDB into current heart failure management guidelines.

In clinical practice however, there remains a large percentage of patients who remain under diagnosed due to lack of investigation by the clinician (231). Attended in-hospital overnight
Polysomnography (PSG) remains the gold standard for diagnosing SDB, which is expensive and not always readily available. It is arguable that amongst clinicians, the low awareness and drive to diagnose this co-morbidity may be in part due to the lack of clear guidelines, available sleep services or the cumbersomeness of referring frail heart failure patients for the intrusive investigation of in-hospital polysomnography which they do not consider valuable.

I have found that the SM has a high diagnostic value for clinically relevant SDB (AHI>15) in heart failure patients and a negative result may be used to rule out the presence of SDB. This study potentially provides a novel exclusion tool that is convenient and easy to use by patients and can be interpreted by clinicians. One of the major advantages of this method is its novel non-contact feature, which means it can also be used in the home environment. As this validation study was undertaken in the hospital setting, it may be useful to further compare the SM with existing home portable monitors. The addition of a qualitative assessment evaluating patients’ preference of either device, as one of the outcomes of this proposed study, would be useful.

The SM device is able to diagnose SDB based on the AHI calculated from its algorithms. It does not separate respiratory events of apnoeas or hypopnoeas into central or obstructive components. Further work to improve the algorithm for this discrimination is warranted. This would be an important addition to the algorithm, as appropriate categorisation of SDB has important treatment implications.

Due to a lack of firm guidelines in place, there are limited clinical management pathways for SDB in heart failure. The SM device is a convenient tool that has the potential to be introduced in to diagnosis and clinical management pathway of SDB in CHF patients. It would also be easy to perform a clinical trial to evaluate the performance of a diagnostic pathway including SleepMinder™ against that of conventional PSG. A proposed diagnostic pathway is shown in Figure 73 below. In this model, I have made allowance for false negative patients by adding symptoms into the screening pathway. While not very sensitive or specific, some symptoms such as witnessed apnoeas have been shown to increase the odds ratio of making a diagnosis of SDB (132).
6.3.2. Diagnosis of SDB using the Mean AHI

In Study two, using the SleepMinder™ device, I have shown that the AHI was highly variably over prolonged periods of monitoring in heart failure patients. In addition, I demonstrated that a high percentage of patients were reclassified into a different severity and treatment group of SDB over several nights. The clinical implications are that a single night PSG study may not be a sufficient risk assessment for this group of patients.

The mean AHI over a 2-week follow up period is proposed as an alternative and potentially more robust measure of the presence of SDB. To evaluate the diagnostic value of this measure it may be necessary to perform a randomised controlled trial that evaluates the outcomes of patients who have been managed for SDB based on their mean AHI compared to a single night measure.
In theory this should be a straightforward study to perform, however the follow up period would be expected to be long, as the outcomes would invariably include mortality. In addition, the sample size for a trial like this would be expected to be large for it to sufficiently collect data on these endpoints to detect a significant difference in the two pathways.

The potential utility of this diagnostic criterion using the mean AHI would need to be evaluated further.

6.3.3. Predicting decompensation of ADHF using the SleepMinder™ device

In Study three, I have utilised a combination of nocturnal respiratory parameters to develop the SleepMinder™ ADHF predictor algorithm (SMApA) and found that its predictive value was of little value. The algorithm performed with a sensitivity of 0.38 and specificity of 0.71.

We have only utilised respiratory parameters in developing this algorithm but we observed some limited but non-statistically significant trends in some of the respiratory features when comparing ADHF event days to Non-Event Days. I found in particular that the duration of SDB, number of apnoeas, and Cycle length of CSR, tended to be higher in the week before an ADHF episode but this was not consistent for all event days and not in all patients. This may in part explain why the prediction algorithm was not successful.

Perhaps the addition of other easily measurable physiologic parameters such as heart rate and blood pressure, could improve the predictive value of the SM. Further research is required.

6.4. Conclusions

The prediction of Acute Decompensation of heart failure is challenging and further research is required to identify clinically relevant parameters that may aid early identification. The use of the SleepMinder™ device, which is a non-contact bedside monitor of nocturnal respiration, for this purpose, is limited.

This device is however acceptably accurate at detecting SDB in patients with heart failure. Its value as part of a clinical diagnostic and management pathway however, needs to be further evaluated.
CHAPTER SEVEN – REFERENCES
Reference List


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CHAPTER EIGHT – APPENDIX
8.1. Copy of SleepMinder™ Ethics Approval

NHS
National Research Ethics Service
NRES Committee London - Chelsea
Room 4W/12, 4th Floor West
Charing Cross Hospital
Fulham Palace Road
London W6 8RF
Telephone: 020 331 17261
Facsimile:

18 August 2011

Professor Martin R Cowie
Professor of Cardiology and Honorary Consultant Cardiologist
Imperial College London
Royal Brompton Hospital
Sydney Street
London
SW3 6NP

Dear Professor Cowie

Study title: Diagnostic utility of the Sleep-Minder bedside monitor of respiratory patterns for the prediction of heart failure decompensation: a validation study.

REC reference: 11/LO/1205
Protocol number: SleepMinder Validation

Thank you for your letter of 11 August 2011, 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 Vice-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

NHS 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).

Non-NHS sites

The Committee has not yet been notified of the outcome of any site-specific assessment (SSA) for the non-NHS research site(s) taking part in this study. The favourable opinion does not therefore apply to any non-NHS site at present. We 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 non-NHS sites.

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.
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 ("R&D approval") should be sought from all NHS organisations involved in the study 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 a NHS organisation’s role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

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:

<table>
<thead>
<tr>
<th>Document</th>
<th>Version</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence of insurance or indemnity</td>
<td>Accord</td>
<td>14 July 2011</td>
</tr>
<tr>
<td>GP/Consultant Information Sheets</td>
<td>1</td>
<td>24 June 2011</td>
</tr>
<tr>
<td>Investigator CV</td>
<td></td>
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<td>Other: SleepMinder BM07 User Manual</td>
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<td>Participant Information Sheet</td>
<td>2</td>
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<td>11 August 2011</td>
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<tr>
<td>Response to Request for Further Information</td>
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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

Reporting requirements

The attached document "After ethical review – guidance for researchers" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:
National Research Ethics Service

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- 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.

Feedback

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.

Further information is available at National Research Ethics Service website > After Review

| 11/LO/1205 | Please quote this number on all correspondence |

With the Committee's best wishes for the success of this project

Yours sincerely

[Signature]

pp.Mrs Tricia Pank
Vice Chair

Email: Rosalind.cooke@imperial.nhs.uk

Enclosures: "After ethical review – guidance for researchers" (SL-AR2)

Copy to: Professor Klaus Schindhelm
Dr Ginette Hoare, Royal Brompton Hospital
8.2. Copy of International Approval for Screening of SDB

CERTIFICATE

Study Title: Serve - HF
Treatment of sleep-disordered breathing with predominant central sleep apnoea by adaptive servo ventilation in patients with heart failure

Study Code: 001

feci Code: 07/2330

Sponsor: ResMed GmbH & Co. KG

Date of meeting: November 05, 2007

Place of meeting: Mozartstrasse 21, 79104 Freiburg, Germany

The freiburg ethics commission international (fecI) has completed a careful review of the study protocol, the informed consent and other submitted documentation, in particular from ethical and legal points of view and with impartial expertise. The regulations of the German Medical Device Law (MPG) § 20 Abs. 8 (MPG § 23) are reviewed and the bylaw about protection against damages caused by X-rays (RoV) have also been reviewed. (The sum insured stated in the documents fulfills the demands of risk assessment according to MPG).

A list of those members actively involved in the review process and present during the meeting at which the ethical and legal soundness of the study protocol were discussed and voted on, as well as their professional designations, appear below.

The fecI requests the submission of an interim report after one year (should the study last longer than one year) and a brief final report upon completion of the study.

With regard to proposed clinical study, the fecI hereby

∞ grants approval
( ) grants conditional approval (refer to following page)
( ) does not grant approval (refer to following page)

Prof. Hans Peter Graf, MD PhD

Freiburg, November 05, 2007
8.3. SleepMinder™ Patient Information Sheet

Royal Brompton & Harefield NHS Foundation Trust
Royal Brompton Hospital
Sydney Street
London
SW3 6NP

PATIENT INFORMATION SHEET

Utility of SleepMinder monitoring of respiratory patterns in heart failure.

Chief / Principal Investigator
Professor Martin R Cowie
Professor of Cardiology and Honorary Consultant Cardiologist
Royal Brompton Hospital,
Sydney Street,
London SW3 6NP.

Study Coordinator
Dr Henry Oluwaseguni Savage
Clinical Research Fellow
Clinical Cardiology
Royal Brompton Hospital
Sydney Street
London SW3 6NP

Invitation paragraph

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

Thank you for reading this.

What is the purpose of the study?

People with heart failure are at risk of their heart problem deteriorating or "decompensating". Your overnight breathing pattern can be an indicator of how well controlled the heart failure is, and changes in the breathing pattern may allow early identification of deterioration, sometimes even before you would notice any changes in symptoms such as increasing breathlessness or ankle swelling.
A small study of the use of a bedside monitoring unit (The 'SleepMinder') in patients with heart failure in Dublin has suggested that this monitor can help identify when heart failure may be worsening. The aim of the study at the Royal Brompton Hospital is to check whether the findings in Dublin can be confirmed in another hospital and in another group of people with heart failure.

Information from this study will be used to check whether monitoring the overnight breathing pattern might be useful for people with heart failure in the future. The study will not be of any direct benefit to you at the present time.

Why have I been invited?

You are being asked to participate in this research study because you have heart failure and you have been identified as a potential candidate for this research study. We hope to recruit a maximum of 40 participants.

Do I have to take part?

It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form to show you have agreed to take part.

You may choose not to participate in this study or you may leave the study at any time without giving a reason. This would not affect the standard of care you receive.

What will happen to me if I take part?

The research procedures will be conducted at the Royal Brompton Hospital. The first day you come in you will be checked by a member of the research team and asked to sign a consent form to confirm your willingness take part in the study. This visit is expected to take 45 minutes to one hour. The following tests will be performed at the start of the study:

1. You will be physically examined by the doctor
2. We will then show you how to use the Sleep Minder monitoring device, the weighing scales, and the study mobile phone. If you have any problems with using any of the devices at home, you will be able to contact us and ask any questions.
3. We will also give you instructions on how to record any change in your water intake dose in the study diary.

You will not need to attend the Royal Brompton Hospital for the purpose of the study at any time after this initial visit. You will receive your usual care related to your heart failure, including regular follow-up with your heart failure cardiologist and your GP as necessary.

The SleepMinder kit will be set up by yourself in your home and you will be shown how to do this. It needs to be plugged into the mains, and has a small green light on the back that shows when it is switched on. The machine needs to be placed close to your bed.
within 5 feet of where you sleep, and would sit easily on a bed-side table. It weighs around 500 grams (1lb) and is smaller than most clock radios.

In total you will have the device in your home for 18 months. During this time, we will ask you to check your weight each day on the weighing scales, complete a small diary containing information about any changes to your diuretic (water tablet) dose, and the SleepMinder device will sit beside your bed and monitor your breathing pattern while you sleep at night. Each morning you will need to check that the study mobile phone is switched on and charged to make sure that all the information collected is sent on to the study centre. No information that could identify you or where you live is sent by the study phone.

You will need to make sure that the study mobile phone is charged up from time to time, just like a personal mobile phone. You will not be charged for the call that the study mobile phone makes, but it cannot be used to make ‘normal’ calls as it is set to only transmit the study information to the central study number.

At the end of the study we will arrange for removal of the SleepMinder kit from your home.

If at any time during the study either you or your doctor feels that it is in your best interest to withdraw from this study, you may do so without any penalty or loss of benefits to which you are otherwise entitled at this hospital, including the present and future standard of medical care that you receive.

If you decide to withdraw from the study, study data collected before your withdrawal will be processed along with other data collected as part of the clinical study. No new data will be collected and added to the study database.

**Will I be reimbursed for my expenses?**

You will not receive any payment for taking part in this study. There will be reimbursement of any out-of-pocket expenses incurred.

**What will I have to do?**

Involvement in this study should not impose any restrictions to your current lifestyle. There are no specific dietary restrictions. You can drive, drink, take part in sport or indeed do anything that your doctor thinks is safe for you to do. You will continue taking the usual medications that your doctor prescribes unless instructed otherwise. You will need to check your weight each morning using the scales provided, and to switch on the study phone each morning to make sure the information collected overnight is sent to the study centre. You will also be asked to make a note in the study diary if you change the dose of diuretic (water) tablets you are taking. If you go away on holiday there is no need to take any of the equipment with you.

**What is the drug, device or procedure that is being tested?**
The name of the device being tested is the 'SleepMinder BM06'. This product has been designed to be used as a sleep assessment device, and monitors breathing patterns. It has a CE Mark, meaning it is allowed to be used in the European Union. The SleepMinder is a specially designed motion sensor that detects your breathing pattern, without any physical contact with your body.

**What are the alternatives for diagnosis or treatment?**

You do not have to participate in this study to receive treatment for your condition.

**What are the possible disadvantages and risks of taking part?**

There are no risks involved in taking part in this study. It does mean that you will need to weight yourself each day, and switch on the study mobile phone for a few minutes, and make a note in the study diary if you have changed the dose of water tablets you’re taking. This should only take a few minutes each morning. Except for the initial visit there will be no additional visits to hospital for this study.

**Are there any benefits to me if I participate in the study?**

There are no benefits to you by taking part in this research.

**What happens when the research study stops?**

At the end of the research, the device will be removed and your care will continue as usual.

**Are there any reasons why I should not participate in the study?**

You will not be able to participate in any other clinical trial for the entire period you are participating in this trial.

**What if relevant new information becomes available?**

Sometimes during the course of a research study, new information becomes available about the treatment that is being studied. If this happens, we will tell you about it and discuss with you whether you want to continue in the study. If you decide not to carry on we will make arrangements for your care to continue. If you decide to continue in the study you may be asked to sign an updated consent form. Also, on receiving new information we might consider it to be in your best interests to withdraw you from the study. We will explain the reasons and arrange for your care to continue.

**What if I do not want to carry on with the study?**

If you do not want to take part in this study, you will receive standard care as determined by your doctor. Your participation in this study is voluntary and you may withdraw from the
study at any time without prejudice to your future medical care. Should you decide to withdraw from the study for any reason, you are asked to contact Dr Henry Savage as soon as possible on telephone number 0207 351 8856. Should your participation in the study be terminated, regardless of the reason, you will not suffer any penalties or loss of benefits to which you are otherwise entitled.

What if there is a problem?

If you have a concern about any aspect of this study, you should ask to speak to the researchers who will do their best to answer your questions: Professor Martin Cowie or Dr Henry Oluwasefunmi Savage, available by telephoning 0207 351 8856. If you remain unhappy and wish to complain formally, you can do this through the NHS Complaints Procedure and speak with the Royal Brompton Hospital PALS service on 0207 349 7715.

Harm

In the event that something does go wrong and you are harmed during the research and this is due to someone’s negligence then you may have grounds for legal action for compensation against the sponsor of the study, ResMed Ltd, but you may have to pay your legal costs. The normal National Health Service complaints mechanisms will still be available to you. NHS indemnity does not offer no-fault compensation i.e., for non-negligent harm, and NHS bodies are unable to agree in advance to pay compensation for non-negligent harm.

Will my taking part in the study be kept confidential?

All information which is collected about you during the course of the research will be kept strictly confidential. Any information about you which leaves the hospital will have your name, address and personal details removed so that you cannot be recognised from it. We will request your consent before informing your GP about your participation in the study.

Data collected during the study may be sent to associated researchers in countries where the laws don’t protect your privacy to the same extent as the Data Protection Act in the UK. However ResMed Ltd, the sponsor of this study will take all reasonable steps to protect your privacy.

Will my General Practitioner / Family doctor (GP) be informed of my involvement?

Provided you consent to this, your GP will be informed that you are participating in the study and kept informed of your medical progress.

What will happen to the results of the research study?
Your medical records will be made available for review by the study investigators and regulatory authorities (who periodically check that the studies are being carried out correctly). The information in these records will be kept confidential but on rare occasions the law may require disclosure to third parties. At the end of the project all the research results are gathered together and analysed. The researchers have a professional responsibility to publish their findings, however your identity will not be revealed. Most research is published in the medical press – if you are interested in knowing the overall results of the study, ask the researchers about this. You are entitled to see any results or information about you under the Freedom of Information Act.

Who is organising and funding the research?

ResMed Ltd is sponsoring and paying for this research to be carried out. The doctors conducting the research are not being paid for including you in the study but the hospital will be reimbursed for the tests and work carried out in this study.

Who has reviewed the study?

All research in the NHS is looked at by an independent group of people, called a Research Ethics Committee, to protect your safety, rights, wellbeing and dignity. This study has been reviewed and given favourable opinion by [enter name of REC]. In addition approval has been gained from the Royal Brompton and Harefield NHS Foundation Trust Research and Development Office.

Contact for Further Information

If you would like any further information about the study, either now or at any time during the course of the study, please contact Dr Henry Savage, Clinical Research Fellow, Clinical Cardiology, Royal Brompton Hospital, Sydney Street, London SW3 6NP on 0207 351 9356.

Thank you for taking the time to consider this study. If you do choose to participate, you will be given a copy of this information sheet to keep and also a copy of the consent form that you will be asked to sign.
8.4. **SleepMinder™ Consent Form**

Royal Brompton & Harefield NHS Foundation Trust
Royal Brompton Hospital
Sydney Street
London
SW3 6NP

**CONSENT FORM**

Utility of SleepMinder monitoring of respiratory patterns in heart failure

Centre Number 001
Patient Identification Number for this trial:
Name of Researcher: Professor Martin R Cowie

Please initial box if you agree

1. I confirm that I have read and understand the information sheet dated 24 August 2011
   (version 3.0) 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 ResMed, 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 GP being informed of my participation in the study. ☐

5. I agree to take part in the above research

   Name of Patient
   Date
   Signature

   Name of Person taking consent (if different from researcher)
   Date
   Signature

   Researcher
   Date
   Signature

When completed: 1 for patient; 1 for researcher site file; 1 (original) to be kept in medical notes

Consent Form

Version 3.0

24 Aug 2011
8.5. SleepMinder™ Case Record Form

Case Record Forms (CRF)

Form: Baseline / Initiation Visit:  
Date of visit:  

Patient ID  

Assigned Patient Serial No: (study entry date/site/consecutive number)  
[rob/ddmmyy/#01]

General Patient Data

DOB:  

SEX:  Male  Female

Form: Confirmation

1. Confirm Inclusion and Exclusion criteria

inclusion Criteria

Plasma BNP>200pg/ml (58pmol/L) when reviewed in the heart failure clinic, OR

History of any hospitalisation due to heart failure

within the preceding 24 months  

\[ \text{Y or N} \]

Date of last hospitalisation:  

BNP levels & Date:  

Date:  

Signature:  

Must sign and date every sheet of this document

Diagnosis: utility of the Sleep Minder™ bedside monitor of respiratory patterns for the prediction of heart failure decompensation: a validation study Version 23/06/2011
Patient ID

Exclusion Criteria
Unpredictable sleep patterns based on work schedules (e.g. night shifts)  O Y O N
Age < 18 years  O Y O N
Cognitive impairment sufficient to interfere with proper use of study equipment  O Y O N
Already on therapy for obstructive sleep apnoea (such as CPAP therapy)  O Y O N

2. Confirm patient has Patient Information Sheets and understands them

3. Consent form
→ Make 3 copies; one copy for medical notes, one copy for the patient, one copy for Patient Research File

4. Complete instructions Demo
( Remember to fill device checklist and advise patient to take device in for hospitalisation)
→ Weighing scales
→ SleepMinder
→ Study Phone

4a. Has Contact numbers for heart failure nurse

4. GP letter
→ Make 3 copies; Send original to GP, one for Medical notes, one for Cardiology consultant [+/- cover letter]


Date: ______________ Signature: ____________________

Must sign and date every sheet of this document
Patient ID

Form: Diagnostics

Co-Morbidities

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Type of Heart failure

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Pacemaker

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Biventricular

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Physical Examination

Systolic blood pressure

Diastolic blood pressure

Sleep Times:

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LVEF %

Date of Echo:

NYHA status: I

II

III

IV

ECG

Date of ECG:

Heart Rate:

Rhythm:

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Date: ____________

Signature: ________________

Must sign and date every sheet of this document.
Patient ID

Form: Medication

Medication at Initiation Visit:

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Form: Laboratory: (ensure done at entry)

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<tr>
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<tr>
<td>Na:</td>
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<tr>
<td>Cr:</td>
<td>mmol/L</td>
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<tr>
<td>BNP:</td>
<td>pmol/L</td>
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Date: ____________________ Signature: ____________________

Must sign and date every sheet of this document
Form: Scheduled Visits:

Date: 

Reason: Routine o Requested o

NYHA Status: 

Physical Examination: 

Weight ______ BP ______ HR ______ ECG [ ] Bloods [ ] 

Prior to visit:
1. Any Drug changes (Diuretics, Beta blockers, ACE I, Aldosterone antagonists)

Details (What change)

Crosscheck with Symptoms Diary [ ]

Date: ______________ Signature: ____________________________

Must sign and date every sheet of this document

Diagnostic utility of the Sleep Minder™ bedside monitor of respiratory patterns for the prediction of heart failure decompensation: a validation study Version 23/08/2011
Patient ID

2. Any Hospitalisations
   "If Yes, Go to Form, Hospitalisations"

At the end of visit:

1. Any Drug changes (Diuretics, Beta blockers, ACE-i, Aldosterone antagonists)

Details (What change)

Remind to fill Symptoms Diary

Lab: Hb Cr Na BNP WCC Urate

Date: __________________ Signature: _______________________

Must sign and date every sheet of this document

Diagnostic utility of the Sleep Minder™ bedside monitor of respiratory patterns for the prediction of heart failure decompensation: a validation study Version 25/08/2011
Patient ID [ ]

Form: Hospitalisations:

Date: Hospital: Duration of admission:

Admission weight: Discharge weight:

CXR: ____________________________

Admission Events:

Date: __________________ Signature: ____________________________

Must sign and date every sheet of this document.
Patient ID

Bloods:
BNP:
Na:
Cr:
WCC:
Urate:

Change in Medication:
Received IV Diuretics
Increased oral diuretics
Change in B-Blocker
Dose Increase Decrease Stop
Change in ACE-I
Dose Increase Decrease Stop
Change in Aldosterone antagonist
Increase Decrease Stop

Other (Details Below)

Discharge Diagnosis:
True Heart failure decompenstation

(Notes to be assessed by investigators)

Date: ______________ Signature: __________________

Must sign and date every sheet of this document

Diagnostic utility of the Sleep Minder™ bedside monitor of respiratory patterns for the prediction of heart failure decompenstation: a validation study Version: 25/09/2011
Patient ID: 

Form: Adverse Events/Technical Problems

Form: Consent Withdrawal

Date of withdrawal:

Reason for withdrawal:

Has equipment been returned?

☐ Y  ☐ N

Does patient agree to allow data already collected to be analysed for study?

☐ Y  ☐ N

Patient Signature: ______________________ Date: ______________________

Date: ______________ Signature: ______________________

Must sign and date every sheet of this document
Patient ID: 

Form: Mortality

Brief Description of events leading to death: (Particular information on prior heart failure decompensation)

________________________________________________________

________________________________________________________

________________________________________________________

________________________________________________________

Discharge Summary (if hospital death) ☐

Post Mortem (if carried out) ☐

Date: ___________________  Signature: ___________________

Must sign and date every sheet of this document