Thesis submitted for the degree of MD (Res.)

Sleep-Disordered Breathing in Patients with Implanted Cardiac Devices: Validation of the ApneaScan™ Algorithm and Implications for Prognosis

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Abstract

Aims

Sleep-disordered breathing (SDB) is common in heart failure (HF) and frequently undiagnosed. The ApneaScan™ algorithm, available on certain ICD and CRT devices, uses changes in transthoracic impedance with breathing to quantify SDB. This research tests 3 hypotheses:

1) The ApneaScan™ algorithm can accurately detect moderate-to-severe SDB in patients with HF
2) There is minimal night-to-night variability in the ApneaScan™-determined severity of SDB
3) Those with moderate-to-severe SDB, assessed by ApneaScan™, have a higher rate of adverse cardiovascular events than those without.

Methods

Patients with EF≤40% and ICD or CRT devices incorporating ApneaScan™ were recruited. For hypothesis 1, 54 subjects underwent a successful sleep polygraphy study and simultaneous download of ApneaScan™ data. 22 subjects (44%) had undiagnosed moderate-to-severe SDB. The area under the ROC curve was 0.84 for the diagnosis of moderate-to-severe SDB. The optimal ApneaScan cut-off was 30.5/hour (sensitivity 95%, specificity 69%, positive predictive value 68%, negative predictive value 95%).

For hypothesis 2, ApneaScan™ data over 28- and 92-nights in 35 patients was reviewed. There was minimal variability in SDB and no significant difference between durations.

For hypothesis 3, 72 patients were followed up at a median of 532 (IQR 386-736) days. Mean event-free survival was 660±344 days (95% CI 535-785 days) in the insignificant

SDB group and 854±413 days (95% CI 730-978 days) in the significant SDB group (p=0.25 by log rank test).

Conclusions

ApneaScan™, with an optimal cut-off of 30.5 events/hour, is a sensitive means of screening for SDB in patients with HF with a high negative predictive value. Readings above 30.5/hour require further investigation with a sleep study. Night-to-night variability in SDB is minimal and repeat sleep studies should be reserved for those with 'borderline' AHI. In this cohort, the presence of SDB was not associated with adverse cardiovascular outcomes. Recruitment is on-going to test this further.

Copyright Declaration

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Statement of originality

Contributions to the work

The original idea and design for the study was by Dr Ali Vazir, Dr Rakesh Sharma and Professor Michael Polkey, of the Royal Brompton Hospital and Imperial College London. There was also valuable input from Dr Tom Wong.

Professor Martin Cowie helped shape the project and was an important part of the project committee, helping steer the project and achieve the aims. Professor Cowie, along with Dr Vazir and Prof Polkey, gave important guidance and review of this thesis.

I was responsible for obtaining Research Ethics Committee and Research and Development approval for the project. I recruited most of the patients in the study, with help from Rebecca Lucas and Sarah Kingham (research nurses). I performed and analysed the sleep studies, obtained ApneaScan data from the device programmers, took patient histories and examinations and organised echocardiography and blood tests where required. The prognosis follow-up data collection was performed by Rebecca Lucas.

I was responsible for writing this thesis, including performing the statistical analysis. The thesis was reviewed by Professor Cowie, Dr Vazir and Professor Polkey. Where included, the work of others is all appropriately referenced.

Originality

There is no other published work assessing the validity of the ApneaScan algorithm for the diagnosis of significant sleep-disordered breathing (SDB). This is the first public study to determine the value of ApneaScan for the investigation of SDB in heart failure (HF). This is also the first study to determine the variability in SDB over 28 nights in those with HF. Previous studies have monitored for shorter periods, or for fewer nights more separated in time. This is also the first study to determine whether the presence of significant SDB, as

diagnosed by ApneaScan, correlates with prognosis in patients with HF and thus whether it is a useful risk-stratification tool for clinicians.

List of abbreviations

AA: Aldosterone Antagonist
ACEi: Angiotensin converting enzyme inhibitor
AF: Atrial fibrillation/flutter
AHI: Apnoea-Hypopnoea Index
AP-RDI: ApneaScan Respiratory Disturbance Index
ARVC: Arrhythmogenic right ventricular cardiomyopathy
ASV: Adaptive servo-ventilation
ANP: Atrial natriuretic peptide
ARB: Angiotensin receptor blocker
AT: Atrial tachycardia/tachyarrhythmia
ATP: Anti-tachycardia pacing
BB: Beta blocker
BiPAP: Biphasic positive airway pressure
BMI: Body mass index
BNP: B-type natriuretic enzyme
CCB: Calcium channel blocker
CI: Confidence interval
CIED: Cardiac implantable electrical device
CO_2: Carbon dioxide
CPAP: Continuous positive airway pressure
CRT(-P/D): Cardiac resynchronization therapy (-pacemaker/-defibrillator)
CSA: Central sleep apnoea
DCM: Dilated cardiomyopathy
ECG: Electrocardiogram
EF: Ejection fraction
ESS: Epworth sleepiness scale
HCM: Hypertrophic cardiomyopathy
HF: Heart failure
HFREF: Heart failure with reduced ejection fraction
HFPEF: Heart failure with preserved ejection fraction
HR: Hazard ratio
ICC: Intra-class correlation coefficient
ICD: Implantable cardioverter defibrillator
IHD: Ischaemic heart disease
LBBB: Left bundle branch block
LV: Left ventricle
LVEF: Left ventricular ejection fraction
MLwHF: Minnesota living with heart failure (questionnaire)
MRA: Mineralocorticoid receptor antagonist
NYHA: New York Heart Failure (grade)
ODI: Oxygen Desaturation Index
OR: Odds ratio
OSA: Obstructive sleep apnoea
$PaCO_2$/PaO_2: arterial partial pressure of carbon dioxide/oxygen
PAP: Positive Airway Pressure
PG-AHI/RDI/ODI: Polygraphic-Apnoea-Hypopnoea Index/-Respiratory Disturbance Index/-Oxygen Desaturation Index
RAAS: Renin-angiotensin-aldosterone system
RDI: Respiratory Disturbance Index
RR: Relative Risk
RV: Right ventricle

SD: Standard deviation
SDB: Sleep-disordered breathing
SE: Standard error
SNS: Sympathetic nervous system
VT/VF: Ventricular tachycardia/fibrillation

Chapter 1: Introduction

1.1 Chronic Heart Failure

1.1.1 Definition

Heart failure (HF) is a clinical syndrome in which there are typical symptoms (including dyspnoea, fatigue, orthopnoea, oedema) and signs (such as elevated venous pressure, pulmonary crackles, displaced apex beat) with evidence of abnormal cardiac function on investigation (1). The spectrum of HF includes patients with reduced ejection fraction on cardiac imaging (HF with reduced ejection fraction – HFREF) and those in whom ejection fraction is normal but there is impairment of cardiac filling during diastole (HF with preserved ejection fraction – HFPEF, previously termed 'diastolic heart failure'). Many patients have abnormalities of both elements of the cardiac cycle, as well as prolongation of the isovolumic contraction and relaxation phases. HF may also be present when heart muscle function is normal, but other factors (such as valve disease) impair cardiac output, or where metabolic demand is so great that a normal heart is unable to compensate ('high-output heart failure'). HF is a clinical syndrome and cannot be diagnosed on the basis of imaging tests alone.

1.1.2 Aetiology

The commonest causes of heart failure vary depending on geographical location and the age, sex and vascular risk factors of the patient. The major causes of HF are listed in Table 1. In Europe, ischaemic heart disease and hypertension account for the majority of cases (2). Valve disease, chiefly aortic stenosis, increases in prevalence with age. In younger patients, the cardiomyopathies and congenital heart disease are a more common cause of HF. Drug-induced cardiomyopathy is increasingly recognised, in particular with powerful cancer chemotherapy agents. In South America, Chagas disease remains an important cause. In the developing world, rheumatic valve disease used to be a common aetiology of

HF, but with increasing westernisation of lifestyles, ischaemic heart disease and hypertension are increasingly the predominant aetiologies (3).

These underlying aetiologies result in heart failure through different mechanisms. Cardiac dysfunction in ischaemic heart disease is usually regional, affecting the area of myocardium supplied by one or more diseased coronary arteries and creating the characteristic 'regional wall abnormalities' on cardiac imaging. Hypertensive heart disease tends to have a global effect on the left ventricle (LV), associated with hypertrophy and impaired diastolic filling. In more advanced hypertensive heart disease, systolic ventricular function also deteriorates. The hypertrophy in hypertensive heart disease often affects the base more than the apex and can make differentiation from hypertrophic cardiomyopathy challenging.

The effect of valve disease on the heart depends on the valve or valves involved and whether the valve is regurgitant or stenotic. Aortic stenosis creates a pressure gradient opposing LV output and leads to a hypertrophied, pressure-loaded left ventricle that eventually fails in systole and diastole. Aortic regurgitation leads to volume loading of the LV with consequent dilatation and dysfunction. Mitral stenosis restricts LV filling and results in high pulmonary pressures, which may ultimately cause right ventricular (RV) failure. Mitral regurgitation leads to volume loading and dilatation of the LV in a similar way to aortic regurgitation with a reduction in forward cardiac output due to the regurgitant volume. Pulmonary and tricuspid valve disease are less common causes of HF, but have similar effects on RV function.

Dilated cardiomyopathies (DCM) usually affect the whole myocardium, resulting in global ventricular dysfunction and dilatation, and may be genetic or acquired. Hypertrophic cardiomyopathy (HCM) typically causes predominant thickening of the basal septal and results in impaired diastolic filling in the early stages. As basal septal hypertrophy increases, the left ventricular outflow tract may become narrowed and, in severe cases, may occlude during systole thus limiting stroke volume. Systolic anterior motion of the mitral valve in this condition can also result in mitral regurgitation, further impeding cardiac function. Restrictive cardiomyopathy is rare and usually associated with infiltrative

conditions such as amyloidosis. In this condition, the ventricle is usually small with dilated atria due to a non-compliant myocardium with marked diastolic dysfunction. Systolic function may appear preserved until late in the disease process. In arrhythmogenic right ventricular cardiomyopathy (ARVC), there is fibro-fatty infiltration of the RV with consequent hypertrophy and dysfunction. In severe cases the LV is also affected.

The functional consequences of congenital heart disease are complex and vary depending on the nature of the abnormality. Discussion of the wide range of possible abnormalities is beyond the scope of this thesis. Arrhythmias can cause heart failure acutely, either with supra-ventricular or ventricular tachyarrhythmias, or bradyarrhythmias such as complete heart block. Patients with abnormal cardiac function are more susceptible to acute decompensation in the presence of an arrhythmia and have a high incidence of arrhythmia. Chronic tachyarrhythmia may also lead to ventricular dilatation and dysfunction.

Pericardial constriction or tamponade impairs cardiac filling and causes characteristic swings in trans-tricuspid and trans-mitral flow with breathing. Finally, high output cardiac failure is seen in conditions in which cardiac function is normal, but there is either an impairment of oxygen delivery (as seen in severe anaemia) or a demand beyond the abilities of the heart (as in severe thyrotoxicosis or Paget's disease).

Table 1. Causes of heart failure

- Ischaemic heart disease
- Hypertension (systemic and pulmonary)
- Valvular heart disease
    - Age-related/degenerative
    - Congenital
    - Infective Endocarditis
    - Immunological (e.g. post-rheumatic fever)
    - Connective tissue disease (chiefly Marfan's syndrome)
    - Neoplastic (carcinoid, metastases)
- Cardiomyopathy
    - Dilated cardiomyopathy
    - Hypertrophic cardiomyopathy
    - Restrictive cardiomyopathy
    - Arrhythmogenic right ventricular cardiomyopathy
- Congenital heart disease
- Arrhythmias
- Pericardial disease
    - Constrictive pericarditis
    - Pericardial effusion with tamponade
- High output cardiac failure
    - Anaemia
    - Thyrotoxicosis
    - Pregnancy
    - Arteriovenous fistula
    - Liver cirrhosis
    - Paget's disease
    - Renal cell carcinoma

1.1.3 Epidemiology of Heart Failure

The prevalence of heart failure depends on the exact definition used. In a community-based cross-sectional study of 1640 participants aged between 25 and 74, McDonagh et al (4) found a mean LV ejection fraction (LVEF), measured by Simpson's bi-plane method on echocardiography, of 47.3% (which would be classified as mild LV dysfunction by current definitions (5)). Severely impaired LVEF (≤30%) was found in 2.9% of the population and around half of these patients were considered asymptomatic. In a cross-sectional study of over 2000 participants in a community in the USA aged 45 and above, the prevalence of HF (defined as clinical signs or symptoms of HF with abnormal systolic or diastolic function on

echocardiography) was 2.2% (6). 44% of those with a diagnosis of HF had normal LV systolic function (i.e. HFPEF). The prevalence of both systolic and diastolic ventricular dysfunction increases markedly with age – systolic dysfunction (EF<50%) was found in 3% of those aged 45-54 but 12.9% of those over 75. Over half of those above 75 years old had diastolic dysfunction on echocardiography and 18% severe diastolic dysfunction. HF is more common in men than women at all ages, particularly HFREF. The prevalence of HF is projected to increase by around half in the next 20 years as the population ages and survival from cardiovascular disease improves.

The incidence of HF also increases with age. In the Hillingdon heart failure study, the incidence of HF was 1.2 per 1000 population per year in those aged 55-64, 3 per 1000 in those 65-74, 7.4 per 1000 in those 75-84 and 11.6 per 1000 in those 85 and over (7). This incidence would equate to over 80,000 new cases of HF per year in the UK. In England and Wales, around 250,000 in-hospital deaths or discharges per year include HF in the coding and in around 65,000 deaths or discharges HF is the principal cause. HF accounts for over 2.5 million bed days per year in England and Wales (8). In the 2014-15 national HF audit, median length of hospital stay was 9 days for those admitted with HF, the mean age at admission was 78 years and in-hospital mortality 9.6%. The 1-year mortality rate for patients admitted to hospital with HF was 29.6% (9).

1.1.4 Pathophysiology of Heart Failure

In HFREF, the LV is unable to adequately expel its internal blood volume during systole. The ventricle thus dilates with stretching of myocardial fibres. This initially increases the force of contraction according to Starling's law, with an increase in stroke volume. However, eventually the wall stress exceeds this compensatory mechanism and the ventricle dilates further and fails. This change in dimensions and shape of the heart in HF is termed 'remodelling'. In milder HFREF, diastolic filling may be normal, but as the LV deteriorates and LV diastolic pressure rises, filling inevitably becomes compromised. There may be loss of myocardial mass and inco-ordinate contraction within and between the ventricles, as well as between the atria and the ventricles. Microscopic changes include

altered myocyte morphology, disorganised muscle fibre orientation and inflammatory infiltration and fibrosis (10). In HFPEF, systolic function is preserved but the LV is unable to fill adequately during diastole, usually due to reduced compliance of the myocardium (11,12).

The consequence of both HFREF and HFPEF is a fall in cardiac output (CO), or (more usually) a failure to increase CO adequately on exertion. The body's response to both types of heart failure is broadly similar, although the evidence base for treatment is much stronger in the former. Baro-receptor activation and under-perfusion of organs leads to a complex neurohumoral response. In the short-term, this can improve organ perfusion through augmentation of cardiac output via tachycardia, increased stroke volume, peripheral vasoconstriction and increased circulating volume. However, in the longer-term these mechanisms are deleterious and accelerate cardiovascular decline. The following mechanisms are implicated in the pathophysiology of heart failure:

- **The sympathetic nervous system (SNS).** Falling pressure sensed at the baroreceptors in the aortic arch and carotid bodies leads to an increase in SNS tone and decrease in parasympathetic tone. The SNS stimulates tachycardia and increased stroke volume, initially increasing CO. It also leads to peripheral vasoconstriction, renin release and consequently increased salt and water retention. In the acute setting of left ventricular failure or hypovolaemia, this mechanism maintains perfusion, but in chronic HF the increased afterload exacerbates the work of the failing heart and the high catecholamine concentrations increase the risk of arrhythmia and may be directly toxic to the myocardium.
- **The renin-angiotensin-aldosterone system (RAAS)**. Under-perfusion of the juxtaglomerular apparatus in the kidney leads to release of renin. This protein cleaves two amino acids from angiotensinogen to create angiotensin I. This is further cleaved by Angiotensin Converting Enzyme (ACE), predominantly produced in the lung, to form angiotensin II (ATII). ATII is a powerful vasoconstrictor, stimulates noradrenalin release and increases the sensitivity of the vasculature to its actions. ATII also

stimulates the release of aldosterone from the adrenal cortex, which leads to increased sodium retention, potassium loss and fluid retention from the distal convoluted tubule and collecting ducts of the kidney. The result is increased water and salt retention, increased circulating volume with increases in both pre- and after-load. This has a short-term benefit, as with the SNS, but in the longer-term leads to further decline.

- **Arginine vasopressin** stimulates translocation of the aquaporin II receptor in to the membrane of the renal collecting ducts with subsequent water resorption. The trigger is thought to be reduced pressure at the baroreceptors and the end result water retention with hyponatraemia - an adverse finding in HF.
- **Endothelins** are a group of peptides found in high concentration in HF. They are potent vasoconstrictors and enhance aldosterone release. They are active at the vascular endothelium where **nitric oxide**, a major vasodilator, is diminished thus predisposing to the endothelial dysfunction found in HF.

In partial counterbalance to these mechanisms, atrial natriuretic peptide (ANP) and B-type natriuretic peptide (BNP) are released from the atria and ventricles respectively. These proteins are vasodilators, reduce noradrenalin release and promote sodium loss in the kidney. In advanced HF, however, these beneficial mechanisms are overwhelmed. Salt and water retention leads to peripheral oedema. Increasing pulmonary venous pressure coupled with decreased plasma oncotic pressure predispose to pulmonary oedema. Increased pre- and after-load distends the myocardial fibres beyond the elastic phase of the Starling curve and the heart dilates and fails. Remodelling of the heart may result in tricuspid and mitral regurgitation, as the papillary muscles and valve structure distorts, further impairing function.

These mechanisms are summarised in Figure 1.

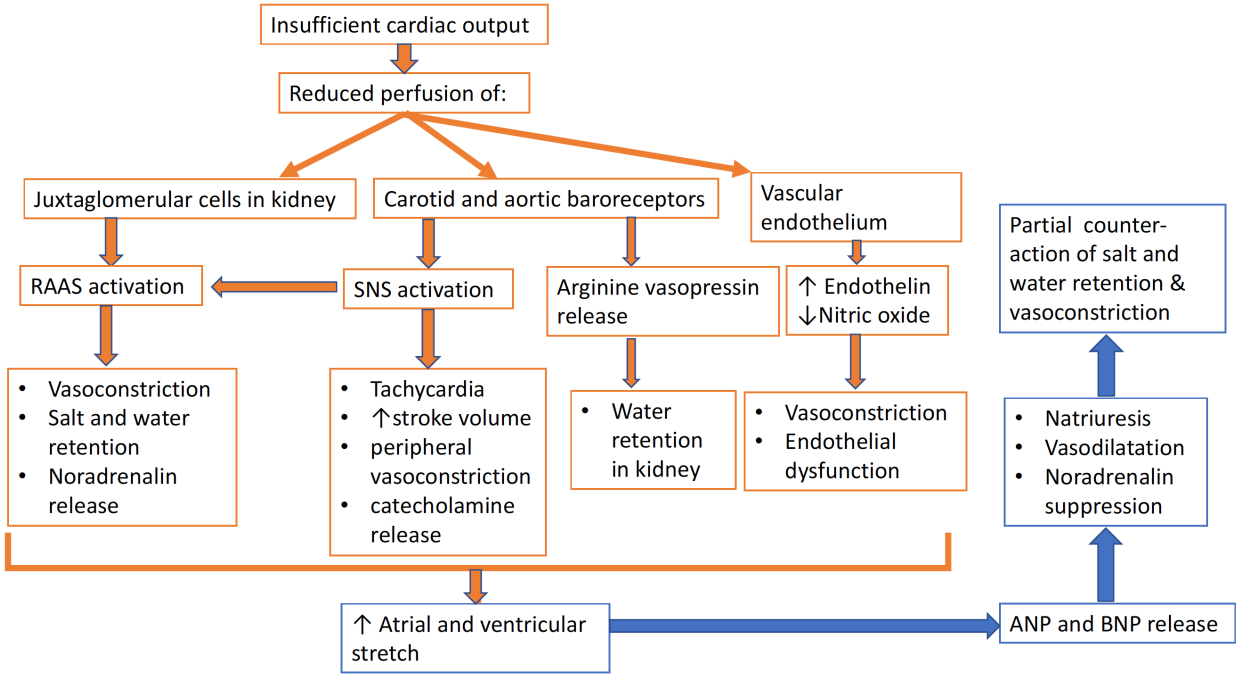


Figure 1. Pathophysiological mechanisms implicated in heart failure. RAAS – renin-angiotensin-aldosterone system; SNS – sympathetic nervous system; ANP – atrial natriuretic peptide; BNP – B-type natriuretic peptide. Original figure.

1.1.5 Pharmacological management of Heart Failure

The goal in managing patients with HF is to prolong survival, minimise rates of hospitalisation and relieve symptoms, thus improving health-related quality of life. General measures recommended in international guidelines include moderating fluid and salt intake, encouraging exercise and weight loss where appropriate (13). Avoidance of factors that might exacerbate breathlessness, such as smoking, is important. Several drugs are detrimental in HF, either through negative inotropic effects (e.g. rate-limiting calcium channel blockers) or increased salt and water retention (e.g. non-steroidal anti-inflammatory drugs).

Loop diuretics are effective at reducing oedema and dyspnoea in HF. In more advanced HF, absorption from the gut may be impaired and action on the kidney impeded by renal

failure. The addition of a thiazide and/or aldosterone antagonist may stimulate diuresis (so-called "sequential nephron blockade"). Intravenous loop diuretics may be required in resistant cases. The lowest diuretic dose that maintains euvolaemia should be used in the long-term.

The following drug classes have been shown to be of benefit in chronic HF with reduced ejection fraction:

- **Angiotensin converting enzyme inhibitors (ACEi).** Several large randomised controlled trials have demonstrated a benefit for ACEi in terms of symptoms, LVEF and dimensions, hospitalisation rates and mortality compared with placebo in patients with HFREF (14,15). ACEi remain first line therapy for patients with LV systolic dysfunction, although the emerging evidence for sacubitril-valsartan (Entresto™) has lead to European and US guidelines recommending it as an alternative to ACEi in certain patients with HFREF (please see below) (13,16).
- **Angiotensin receptor blockers (ARBs).** ARBs have been shown to reduce hospitalisation and, in some studies, mortality in HFREF (17,18). The evidence–base is not as strong as for ACEis and in the Val-HeFT study, valsartan did not improve mortality (19). They are generally used if side-effects (most commonly cough) develop with an ACEi. There is limited evidence for improved outcomes if ARBs are used in addition to and ACEi, but with increased risk of hyperkalaemia, and this is therefore not recommended in current international guidelines (20).
- **Beta-blockers.** Owing to bradycardia and negative inotropy, beta-blockers were long considered contra-indicated in HF. However, they have the benefit of countering the over-active SNS in HF and reducing risk of arrhythmia and ischaemia. With long-term use, beta-blockers improve systolic function, symptoms and mortality in HFREF (21–23). Care must be taken when initiating beta-blockers to prevent decompensation of the HF syndrome – a 'start-low, go-slow' approach is recommended (13).
- **Aldosterone Antagonists.** Aldosterone antagonism with either spironolactone (24) or eplerenone (25) has been shown to reduce symptoms, hospital admission rates and mortality in those with severe HF symptoms. The Emphasis trial also demonstrated

survival and hospitalisation benefit for those with severely impaired LV function and milder (NYHA II) symptoms (26).

- **Ivabradine** is a drug that slows conduction in the I_f channel of the sinus node, thus reducing heart rate without other effects on myocardial or vascular function. Ivabradine only slows heart rate in sinus rhythm. The BEAUTIFUL trial enrolled almost 11000 patients with coronary artery disease and an EF of less than 40%, and randomised to Ivabradine or placebo plus standard medical therapy. This trial demonstrated a reduction in ischaemic events in those with a heart rate above 70 beats per minute (bpm) prior to treatment, but there was no improvement in heart failure outcomes (27). The SHIFT trial, however, did demonstrate a significant reduction in heart failure hospitalisation in those with HF and a resting HR of 70bpm or greater despite maximal possible treatment with beta-blockers (28). Based on these data, Ivabradine has been introduced to current ESC guidelines for those with on-going symptoms of heart failure and a heart rate of 70 or above despite optimal treatment with angiotensin system blockade, beta-blockade and aldosterone antagonism (13).
- **Hydralazine and isosorbide dinitrate** as a combination therapy has been shown to improve symptoms, hospitalisation for HF and survival in African-American patients with systolic HF and NYHA III or IV symptoms in addition to standard care (29). There is limited evidence for its use in Caucasian patients. This may be because Afro-American patients respond less well to ACEi, possibly due to lower renin levels.
- **Digoxin** has been demonstrated to reduce hospitalisation rates, but not mortality, in patients with HF in one randomised control trial, including only those in sinus rhythm (30).
- **Sacubitril-Valsartan** (formerly known as LCZ696 and now marketed as 'Entresto™') is a drug combining the angiotensin receptor blocker valsartan with sacubitril, a neprilysin inhibitor. Neprilysin is an endogenous enzyme responsible for degradation of several peptides including the natriuretic peptides, which are thought to be protective in HF. The PARADIGM-HF trial was stopped early due to benefit of sacubitril-valsartan over enalapril in terms of heart failure hospitalisation and all-cause mortality (31). The National Institute for Health and Care Excellence (NICE) has recently recommended

sacubitril-valsartan as a treatment option for patients with severely impaired LV systolic function (EF≤35%) and persistent NYHA II to IV symptoms despite stable treatment with and ACEi or ARB, which is consistent with current European and US guidelines (13,16,32).

The current ESC guidance for treatment of HFREF is presented in Figure 2 (13). The NICE guidelines for chronic heart failure date from 2010 and will be revised in 2018 (33).

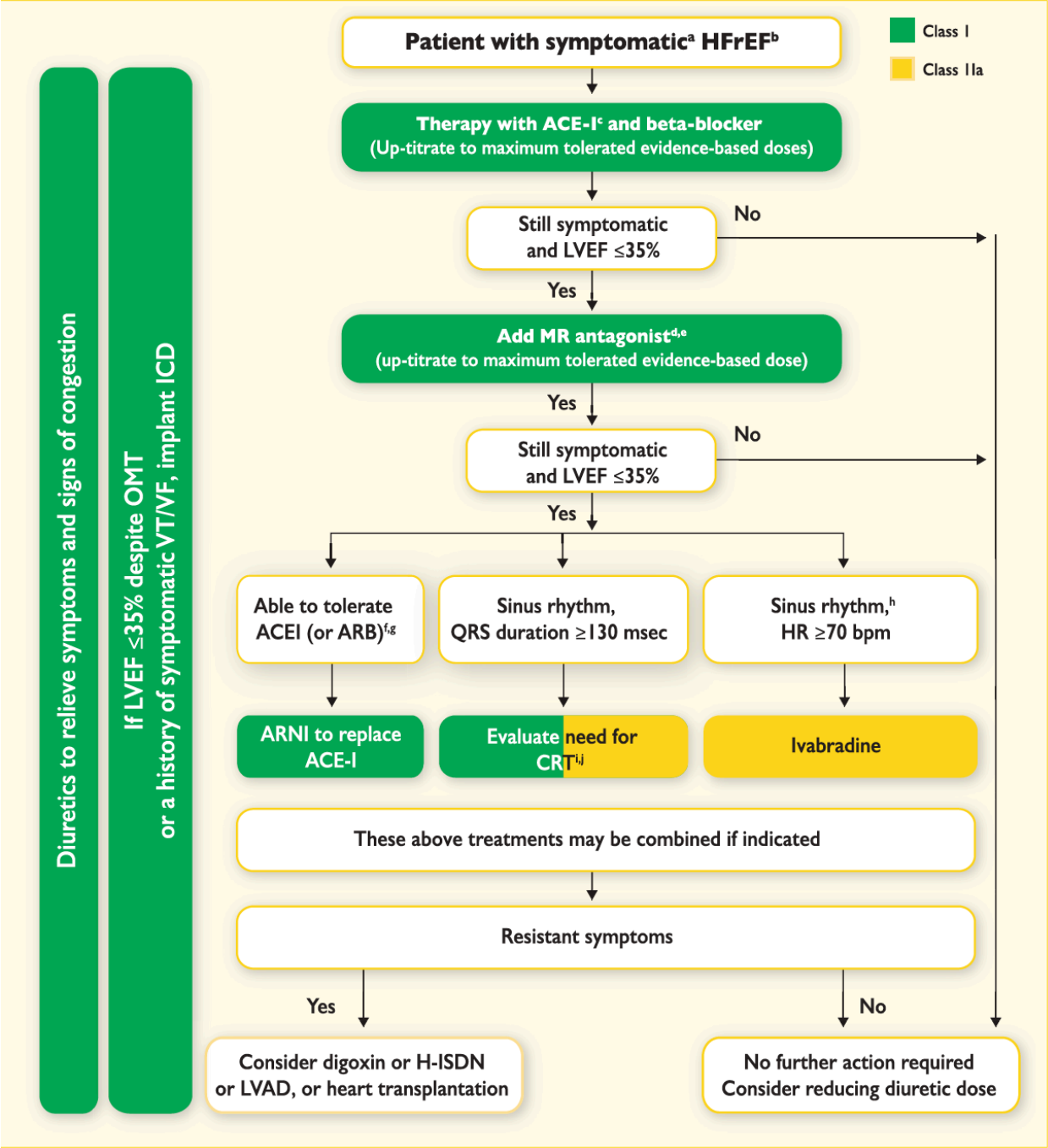


Figure 2. Therapeutic algorithm for chronic HFREF from the *ESC guidelines for the investigation and management of acute and chronic heart failure 2016*. Reproduced with permission from Ponikowski et al. *Eur Heart J* 2016; 37 (27): 2129-2200.

The evidence base for pharmacological therapy of HFPEF is not strong and no treatment has yet been shown to reduce mortality. As this study did not recruit patients with HFPEF, further discussion is beyond the scope of this Thesis. [Section on HFPEF deleted]

1.1.6 Device Therapy in Heart failure

Cardiac implantable electronic device (CIED) therapy for HF comprises implantable cardioverter-defibrillators (ICDs) and cardiac resynchronisation therapy with or without defibrillator function (CRT-D or -P). Other electronic devices for the management of HF, such as vagal nerve stimulators and pulmonary artery pressure sensors, are currently under investigation.

Implantable Cardioverter-Defibrillators

Many deaths in those with HF occur due to spontaneous ventricular tachycardia or fibrillation. In studies reporting mode of death, 25-30% of deaths in those with severely impaired LV function were deemed 'sudden cardiac deaths' (34). The proportion of sudden cardiac death due to primary ventricular arrhythmia varies according to the population studied and definition used, and in a meta-analysis of trials in those with ICDs suffering an apparent sudden-cardiac death, 76% had a ventricular arrhythmia as the cause, the remaining 24% dying of non-arrhythmic causes (35).

ICDs are designed to detect VT and VF and attempt to terminate the rhythm through rapid pacing of the right ventricle (anti-tachycardia pacing (ATP) - for VT only) or through delivery of an internal shock between coils in the RV lead and generator. ICDs offer proven survival benefit above optimal medical therapy for those who have survived a cardiac arrest or suffered haemodynamic instability due to ventricular arrhythmia without a reversible cause (36). Meta-analysis of the early trials of ICDs in patients who had survived a cardiac arrest due to VT or VF demonstrated a 28% relative risk reduction (RR 0.72, 95% CI 0.60-0.87; p=0.0006) compared to medical therapy including amiodarone (36).

Research also shows that ICDs are more effective than medical therapy alone for primary prevention of sudden cardiac death in those at high risk (37). Trials randomised patients with HFREF (EF either <35% or <30%) but without a history of sustained VT or VF to ICD therapy or optimal medical therapy alone. Meta-analysis of the randomised-controlled primary prevention trials found a relative risk reduction of 60% (RR 0.40, 95% CI 0.31–0.50, p=0.0001) for arrhythmic death and 28% (RR 0.72, 95% CI 0.64–0.82, p=0.0001) for all-cause death in those receiving ICDs versus medical therapy alone (38). No statistical heterogeneity was found amongst the trials analysed for either arrhythmogenic or all-cause mortality. In this meta-analysis, there was no difference in the benefit conferred on those with ischaemic and non-ischaemic HF.

The benefit of ICDs for primary prevention in those with non-ischaemic HF has recently been brought in to doubt by the results of the DANISH trial (39). In this study, 1116 patients with non-ischemic HF and EF≤35% were randomised to standard therapy or standard therapy plus ICD. 58% of patients in both groups received CRT therapy. At a mean follow-up of 68 months, there was no difference in all-cause mortality between the groups (21.6% for the ICD group vs 23.4% for the controls; HR 0.87, 95% CI 0.68 to 1.12, p=0.28). ICDs did reduce the risk of sudden cardiac death (4.3% vs 8.2% of patients; p=0.005) but the relatively low number of events did not translate in to an overall survival advantage. 4.9% of ICD patients suffered a device infection. This would be supported by data from the smaller DEFINITE trial in 2004, which showed similar results in patients with non-ischaemic HF and frequent ventricular ectopy or non-sustained VT. It may be that, with current evidence-based therapy including CRT where appropriate, those with non-ischaemic HF have a low risk of sudden cardiac death and therefore the benefit of ICDs for primary prevention is minimal. The low all-cause mortality in both the DANISH and DEFINITE populations contrasts with that in the post-myocardial infarction population. In the MADIT II trial, comparing ICDs to standard therapy for those with EF≤30% following MI, mortality in the control group approached 20% at 20 months follow-up and ICDs conferred a significant survival advantage. How international guidelines will interpret these data is awaited with interest.

ICDs are currently recommended in the ESC and NICE guidelines for primary prevention in those with an ejection fraction of 35% or less and symptoms not worse than NYHA III and both ischaemic and non-ischaemic aetiologies (13,40).

In the primary prevention patient group, higher numbers of shocks or ATP for slower ventricular arrhythmias and inappropriate therapies (e.g. for misidentified supra-ventricular tachycardia) are associated with increased mortality and it has been shown that conservative programming of the ICD to only treat the fastest and most persistent ventricular arrhythmias improves outcomes (41).

Cardiac Resynchronisation Therapy

In patients with severe LV dysfunction and left bundle branch block (LBBB), electrical activation and consequently contraction of the lateral and posterolateral wall of the LV is delayed, thus inducing dyssynchrony which further reduces cardiac output. This dyssynchrony may also increase the degree of mitral regurgitation due to effects on the papillary muscles and mitral valve function. Dyssynchrony may be demonstrated between the atria and the ventricles (due to atrio-ventricular (AV) conduction delay), within the ventricle (intraventricular, e.g. between the LV septum and lateral wall) or between the RV and LV (interventricular). Cardiac resynchronisation therapy aims to correct this dyssynchrony by pacing both the RV apex or septum and the LV posterolateral wall, restoring co-ordinated contraction. For patients in sinus rhythm, AV synchrony may also be optimised. To achieve this, pacing leads are placed at the RV apex or septum and a lateral branch of the coronary sinus. If the patient is in sinus rhythm, a right atrial lead is also employed. The device is programmed to optimise AV delay (often done with echocardiographic guidance for maximal LV filling) and ventriculo-ventricular timing (although evidence for using echocardiography to optimise this is debated) (42). The aim is to pace both ventricles close to 100% of the time.

A large number of studies have demonstrated an advantage for CRT over medical therapy in terms of survival, symptoms and LV remodelling for those with severely impaired LV function (EF≤35%), symptoms of HF (NYHA I-IV) and a LBBB on ECG (QRS duration ≥130ms) (43–46). In the CARE-HF trial, for example, patients with NYHA III or IV HF of all aetiologies in SR with EF≤35% and LBBB>120ms (and echo evidence of dyssynchrony if QRS 120-149ms) were randomised to optimal medical therapy with or without CRTP. At 29 months follow-up, both mortality and HF hospitalisation rates were significantly lower in the CRTP group than the medical therapy group (39 percent vs. 55 percent; HR 0.63; 95% CI 0.51 to 0.77; P<0.001 for the combined endpoint; 20% vs. 30%; HR 0.64; 95% CI, 0.48 to 0.85; P<0.002 for mortality). This demonstrated a significant mortality benefit for CRT, even without ICD function (43).

The Echo-CRT study found that those with a narrow QRS complex (<130ms) but with evidence of dyssynchrony on echocardiography do not benefit from CRT and, in fact, CRT may be detrimental (47). CRT is also associated with improvement in cardiac sympathetic nervous activity as measured by positron emission topography (PET), which may be of significance in central sleep apnoea (CSA – see below) (48).

The current ESC and NICE guidelines recommend CRT for those with symptomatic systolic heart failure (EF≤35%) with LBBB on ECG and QRS ≥130ms expected to survive more than 1 year with good functional status (Fig. 3). CRT may also be considered for those with QRS≥150ms in a non-LBBB morphology (13,40).

Despite an overall benefit for carefully selected patients undergoing CRT, up to a third of patients are classified as ‘non-responders’ and do not demonstrate clear clinical improvement. In some cases this may be due to a severe underlying clinical trajectory which, whilst ameliorated by CRT, is not entirely reversed. Echocardiographic parameters have not proved reliable in predicting those who will respond (49) and techniques to optimise placement of the LV lead using cardiac magnetic resonance (CMR) to avoid areas of scar, as well as echo strain measurements to guide placement at the site of most-delayed activation are being developed (50). Endocardial LV lead placement, via a trans-septal

puncture, which avoids the anatomical restrictions of the cardiac venous system, is also under investigation (50).

	NYHA class			
QRS interval	**I**	**II**	**III**	**IV**
<120 milliseconds	**ICD if there is a high risk of sudden cardiac death**			**ICD and CRT not clinically indicated**
120–149 milliseconds without LBBB	ICD	ICD	ICD	CRT-P
120–149 milliseconds with LBBB	ICD	CRT-D	CRT-P or CRT-D	CRT-P
≥150 milliseconds with or without LBBB	CRT-D	CRT-D	CRT-P or CRT-D	CRT-P
LBBB, left bundle branch block; NYHA, New York Heart Association				

Figure 3. Summary of the NICE guidance for selection of device therapy in patients with HFREF (EF<35%). Reproduced with permission from *National institute for health and care excellence. Implantable cardioverter defibrillators and cardiac resynchronisation therapy for arrhythmias and heart failure 2014* (40).

1.2 Sleep-Disordered Breathing in Heart Failure

1.2.1 Introduction

Sleep-disordered breathing (SDB) affects over half of patients with heart failure, which is approximately five times the prevalence in the general population (51,52). It may comprise obstructive sleep apnoea (OSA), due to collapse of the pharynx during sleep leading to airway obstruction, or central sleep apnoea (CSA) in which the regulation of breathing at the brainstem is abnormal. Many patients have a mixed pattern or may progress from predominant OSA to CSA or vice-versa during the night, thought to be due to progressive pulmonary congestion, sympathetic stimulation and rostral fluid shift (53,54). SDB is

associated with a more severe clinical course and significantly increased mortality (55,56). OSA is thought to accelerate heart failure though a variety of mechanisms as detailed below. CSA was traditionally thought to be a marker of severity of HF and, although evidence exists that CSA may itself be detrimental, the unexpected results of the recent SERVE-HF study have caused a re-evaluation of CSA in HF (57).

1.2.2 Definition and Classification

The term 'Sleep-Disordered Breathing' encompasses a group of disorders characterised by an abnormal respiratory pattern during sleep and including episodes of apnoea and hypopnoea. An apnoea is defined as the reduction of oro-nasal airflow of over 90% from baseline for 10 seconds or more and a hypopnoea as a reduction in oro-nasal airflow of more than 30% from baseline associated with a fall in arterial oxygen saturation of ≥3% (58). Apnoeic-hypopnoeic events are further classified as 'obstructive' if there is significant thoraco-abdominal movement during the episode (especially when there is paradoxical movement of the chest and abdominal sensors) or 'central' if there is a cessation or proportionate decrease in respiratory effort (Figures 4 and 5). Episodes may also be a combination of obstructive and central and are termed 'mixed'. By convention, ≤5 events/hour is classified as normal, 5-14/hour as mild, 15-30 moderate and ≥30/hour severe SDB. The mean number of events per hour of sleep is the 'apnoea-hypopnoea index' (AHI). If more than 50% of events in a study are central, the subject is said to have predominant CSA (and vice—versa for OSA). However this is an oversimplification and there are, in fact, two separate pathophysiological processes co-existing in 'mixed' sleep apnoea and there may be value in adressing the central apnoea index and obstructive apnoea index separately.

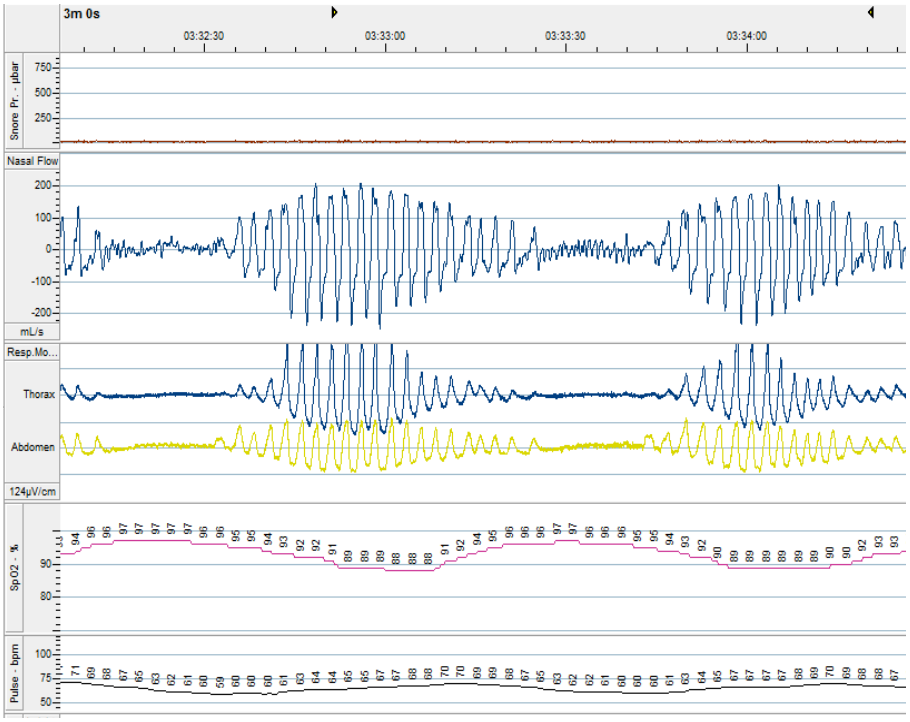


Figure 4. Sleep polygraphy study demonstrating central sleep apnoea/Cheyne Stokes respiration. Top line indicates no snoring. Line 2 shows waxing-waning nasal airflow, Lines 3 and 4 demonstrate absence of chest or abdominal excursion during apnoea, line 5 shows arterial oxygen desaturation following apnoea and the bottom line indicates mild fluctuations in heart rate.

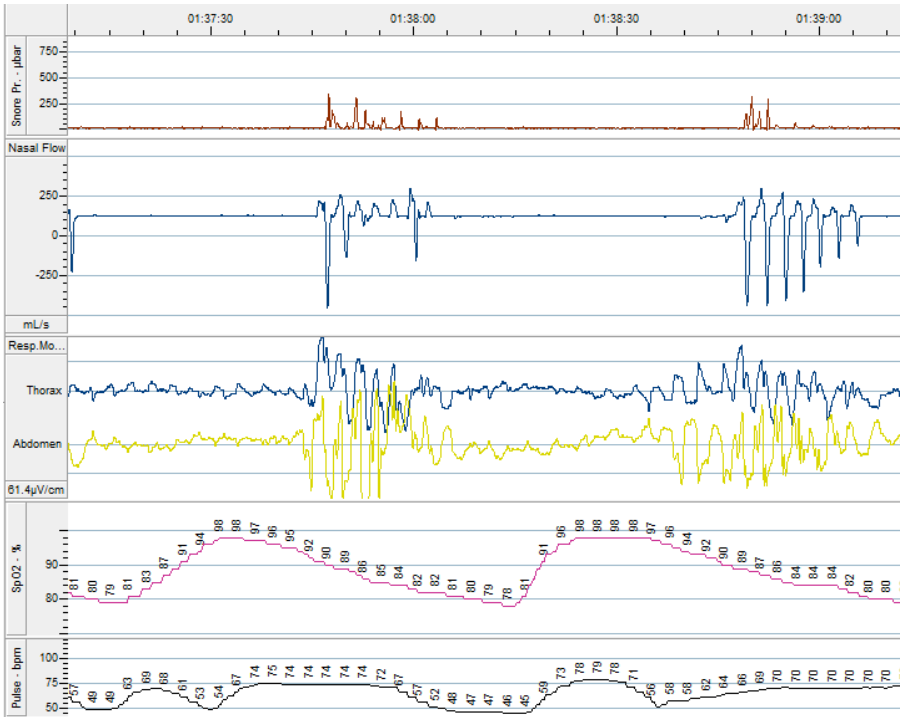


Figure 5. Sleep polygraphy study demonstrating obstructive sleep apnoea. The top line indicates intermittent snoring, the second line abrupt cessation in nasal airflow, the third and fourth lines show persistence of chest and abdominal movement during apnoea, the fifth line shows marked desaturations during apnoea and the bottom line shows the swings in heart rate with apnoea.

1.2.3 Epidemiology of Sleep-Disordered Breathing in Heart Failure

The prevalence of SDB in HF varies according to the population examined and definitions applied. In a study of 700 patients with symptomatic HF (NYHA II-IV) and LVEF ≤40%, Oldenburg et al found SDB (AHI>5/hour) in 76% of participants (56). In 40% of subjects, the SDB was predominantly OSA and in 36% CSA. CSA was found more frequently in those with severe symptoms, lower EF, lower peak oxygen consumption on cardiopulmonary exercise testing and lower 6-minute walk test distance. Vazir *et al* found a prevalence of 53% (38% CSA, 15% OSA) in men with mild (NYHA II) HF and LVEF ≤ 45%. SDB was associated with higher B-type natriuretic peptide (BNP) concentrations, suggesting more severe HF (51). Another study performed sleep polygraphy on 108 patients with NYHA II to IV symptoms and LVEF≤40% attending a general HF clinic. This study reported moderate to severe SDB (AHI >15/hour) in 61% of subjects (31% CSA, 30% OSA), with higher rates in those with atrial fibrillation and more advanced symptoms (59). Similarly, Javaheri and colleagues found moderate to severe CSA in 40% and OSA in 11% of 81 patients with stable HF and LVEF ≤45% (60). Those with OSA were more likely to be obese and snore. In those admitted to hospital with acute decompensate HF, a degree of SDB is an almost universal finding and in one study moderate to severe CSA was found in 75% of patients tested within 48 hours of admission (61).

In the large prospective German Schla-HF registry of almost 7000 patients with symptomatic HF and EF<45%, moderate-to-severe SDB was more common in men than women (49% vs. 36%) and was increasingly common with age (31% in those under 50 vs. 59% of those over 80 years) (62). Risk factors for the development of SDB included increased BMI, low EF, male sex, AF and increased age.

The prevalence of SDB in patients with HFPEF is similar. Bitter and colleagues examined 244 patients from a general heart failure clinic with HFPEF and found SDB (AHI>5/hour) in 69.3% (63). 39.8% had predominant OSA and 29.5% CSA. SDB, particularly CSA, was associated with poor capacity on cardiopulmonary exercise testing, more severe diastolic

dysfunction on echocardiography, higher NT-proBNP and higher pulmonary capillary wedge pressure on right heart catheterisation.

Whilst SDB affects 53-75% of patients with moderate to severe symptomatic LV dysfunction, it is also highly prevalent in other cardiovascular disorders. Moderate to severe SDB is found in 30% of those with ischaemic heart disease, 45% with hypertension, 60% with atrial fibrillation and as many as 90% of people with resistant hypertension (64). For reference, in a population cross-sectional study in Lausanne, Switzerland, moderate to severe SDB was found in around 38% of people (65). This figure is higher than previous studies, which may reflect improved diagnostic sensitivity of sleep polygraphy devices and the new American Academy of Sleep Medicine (AASM) diagnostic criteria, which broadened the definition of hypopnoea. Previous studies, such as the Wisconsin cohort study, placed the prevalence of moderate-to-severe SDB in the general population at 9.1% (95% CI 6.4-11%) in men and 4.0% (95% CI 1.5-6.6%) in women aged 30 to 60 in 1993 (66). This figure is rising, possibly due to the increased rates of obesity, and it is now estimated that moderate-to-severe SDB is present in up to 17% (95% CI 15-21%) of men aged 50 to 70 in the Wisconsin cohort (67). The relative increase in rates of moderate-to-severe SDB between 1993 and 2012 was between 14% and 55% depending on the sub-group.

1.2.4 Aetiology of Sleep-Disordered Breathing in Heart Failure

Although the mechanism by which OSA and CSA produce apnoeas and hypopnoeas is very different, both may be exacerbated by the internal physiological state produced by failure of the heart.

Obstructive Sleep Apnoea

While awake, medullary neural stimulation of the muscles of the upper airway, especially the genioglossus, maintains airway patency against the negative pressure of inspiration

(68). During sleep, this neural stimulation decreases and the supine position predisposes to posterior displacement of the tongue and soft palate, narrowing the airway (69).

In OSA, the pharynx partially collapses during sleep and causes partial or total airway occlusion, usually during the period of negative pressure generated by inspiration (70). As in the general population, obesity and retrognaithism may result in a narrowed airway more prone to occlusion, although these factors are less prevalent in patients with HF and OSA (71). Sedation relaxes pharyngeal muscles and predisposes to collapse (72) and, in heart failure, rostral shift of oedema fluid from the peripheries to the neck further narrows the airway, evidenced by a progressive increase in neck circumference matched by a reduction in leg circumference overnight in those with HF and OSA (54). Venous congestion in the neck in those with HF may also contribute to airway narrowing (73). The respiratory muscles thus attempt to inspire against a closed pharynx, generating negative intrathoracic pressure, causing arousals and increasing sympathetic stimulation. As a consequence of arousal, pharyngeal muscle tone increases and the airway re-opens. OSA is thus characterised by abrupt partial or complete cessation in airflow as the pharynx collapses, usually preceded and followed by snoring, with subsequent hyperventilation due to stimulation of the respiratory centre by high arterial partial pressure of carbon dioxide ($PaCO_2$), which is consequently returned to normal.

Central Sleep Apnoea

In CSA, the abnormal breathing pattern is mediated by maladjustment of the homeostatic feedback loop at the respiratory centres in the brainstem. In normal physiology, $PaCO_2$ is maintained within a narrow range to facilitate removal from tissues and release into the alveolar space, as well as maintaining the pH so essential to normal enzyme function. This tight regulation of $PaCO_2$ is achieved by a feedback loop between the respiratory centres in the pons and medulla, with neural input from chemosensors in the carotid bodies and aortic arch. A rise in $PaCO_2$, such as occurs during a period of apnoea, stimulates the chemosensors and thus the respiratory centre to increase neural output to the intercostal muscles and diaphragm. The consequent rise in tidal volume and frequency increases

minute ventilation and leads to increased diffusion of CO_2 in to the alveolar space and expulsion. The $PaCO_2$ thus returns to normal and the neural drive to breathe decreases to maintain equilibrium.

In CSA, there is an exaggerated respiratory response to rising $PaCO_2$, such that small rises in $PaCO_2$, as occur during sleep, stimulate relative hyperventilation (74). This drives the $PaCO_2$ down, which is sensed by the chemoreceptors and there is an abrupt decrease in neural drive to breathe, resulting in hypopnoea. The $PaCO_2$ then rises again as minute ventilation falls and the cycle repeats (Figure 6). The fall in $PaCO_2$ may be great enough to go below the 'apnoeic threshold', at which point the neural drive to breathe is so diminished that an apnoea occurs (75). Secondary to chronic hyperventilation, patients with HF and CSA tend to have a low baseline $PaCO_2$ and consequently the margin between baseline and apnoeic threshold is small, increasing the risk of apnoea (63,76). In addition, patients with HF have a prolonged circulation time between the alveolar capillaries and the chemosensors, so that there is a lag phase in the feedback loop. This further impairs fine control of $PaCO_2$, as the $PaCO_2$ sensed and acted-upon may not represent the level at the lung.

In addition to this over-shoot of the feedback loop, pulmonary congestion stimulates juxta-pulmonary capillary (J) receptors which subsequently trigger reflex hyperventilation (77). High pulmonary capillary wedge pressure (PCWP) is associated with CSA (but not OSA) and hypocapnoea in those with HF, and a strong relationship exists between the PCWP and severity of CSA (78).

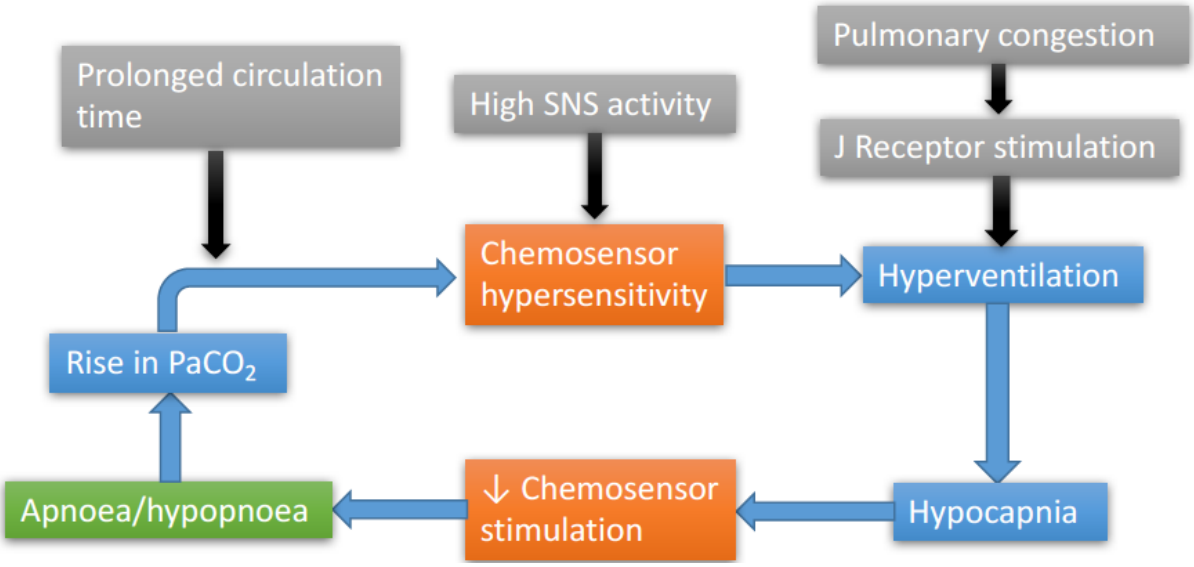


Figure 6. Flow diagram of the mechanisms causing central sleep apnoea in heart failure. SNS = sympathetic nervous system, $PaCO_2$ = arterial partial pressure of carbon dioxide. Original figure.

This unstable negative feedback loop produces episodes of hyperventilation, in response to rising $PaCO_2$ and pulmonary congestion, followed by hypopnoea or apnoea as respiratory drive decreases. In contrast to the abrupt cessation of breathing seen with airway collapse in OSA, CSA tends to create a more gradual transition from apnoea to hyperventilation and back again. Apnoea and hypopnoea in CSA is accompanied by a marked reduction or cessation in respiratory muscle effort (Figure 5), as opposed to OSA where the muscles attempt to inspire against a closed or narrowed airway, often causing snoring (Figure 6). Classical cyclical waxing-waning ventilation is termed 'Cheyne Stokes respiration'.

Whilst HF increases the risk of CSA and treatment of HF with CRT improves CSA, the relationship between LVEF and AHI is complex and non-linear (79,80). Worsening LVEF is, however, associated with increasing cycle length, apnoea and ventilation length and circulatory delay (measured as the time lag between the end of an apnoeic episode and the subsequent nadir of oxygen saturation). These parameters subsequently improved in parallel with improvement in LVEF with treatment. Another study found that circulatory delay in HF correlated with hyperpnoea duration but not with duration of apnoea (81).

These data suggest that AHI alone may be a crude measure of severity of SDB and factors such as cycle length may be at least as important. In the severest HF, AHI may paradoxically decrease as the very long cycle length limits the number of events that can occur per hour.

1.2.5 Pathophysiological Effects of Sleep-Disordered Breathing in Heart Failure

Whilst OSA and CSA have different effects on the circulation, they share some common sequelae, which may be detrimental in HF. The traditional view that OSA accelerates HF whilst CSA is merely a marker of severity in HF has been challenged by accumulating evidence of the consequences of CSA and, most recently, by the results of the SERVE-HF trial (57).

Obstructive Sleep Apnoea

In OSA, apnoea and hypopnoea are accompanied by marked negative intrathoracic pressure as the respiratory muscles attempt to inspire against a closed airway. This may be as high as 70cmH_2O (82,83). This negative pressure increases venous return to the right heart and thus RV preload. In addition, hypoxia induces pulmonary vasoconstriction which increases RV afterload (84) and may reduce LV preload during the apnoea. The volume and pressure-loaded RV dilates and the interventricular septum is pushed to the left, compromising both LV filling and systolic dynamics. In addition, the negative intrathoracic pressure increases the LV transmural pressure during systole, effectively increasing LV afterload. It is also thought that the swings in intrathoracic pressure in OSA affects renal blood flow and stimulates the juxtaglomerular cells to increase renin release, known to be pathological in HF (85).

Recurrent episodes of apnoea and hypopnoea cause swings in heart rate and blood pressure, oxygen desaturation and sympathetic nervous system activation with arousals that disturb normal sleep architecture (86) (Figure 5). Urinary catecholamines are raised in those with OSA compared to matched controls without OSA, suggesting sympathetic stimulation (87). Direct measurement of sympathetic activity by microneurography reveals

increased activity in those with OSA compared to obese controls which persists during the day, and a fall in activity with treatment by continuous positive airway pressure (CPAP) (88,89).

Debate has persisted regarding whether OSA is itself a risk factor for the development of hypertension, fuelled by the difficulty of recruiting an appropriate control group given the multi-factorial nature of the condition. In a physiological study of healthy subjects, however, nocturnal autonomic arousal index was driven by the frequency of apnoeic events and was associated with increased BP, and this was independent of other known risk factors for hypertension on regression analysis (90). In addition, nocturnal hypoxia in a hypobaric chamber has been shown to cause an elevation in blood pressure which persists in to the day (91). CPAP therapy effectively suppresses AHI in OSA and withdrawal of CPAP in those with OSA results in a significant rise in systolic blood pressure (mean rise 5-7mmHg in trials) (92,93). Nocturnal hypoxia may also directly affect myocardial diastolic function, although systolic function appears to be relatively spared (94).

OSA is associated with vascular endothelial dysfunction, inflammation and atherosclerosis. The severity of nocturnal desaturation correlates directly with carotid intimal thickness and prevalence of atherosclerotic plaque (95). The vasodilatory response to acetylcholine is blunted in patients with OSA (96). In mouse models, intermittent hypoxia accelerates atherosclerosis (97) and in humans, vascular inflammatory mediators are elevated in those with OSA (98). Linked to this vascular dysfunction is an enhancement of lipid peroxidation, thought to contribute to atherosclerosis, but the exact mechanism remains to be determined (99). Whilst withdrawal of CPAP therapy in those with OSA appears to increase blood pressure, the effect on endothelial function and inflammatory markers is complex and incompletely understood (100,101).

OSA is independently associated with type 2 diabetes, itself a strong risk-factor for cardiovascular disease (102). Evidence from mouse studies suggests that this effect is most marked when there is co-existent obesity (103). Some studies have shown improvement in

insulin sensitivity with CPAP therapy, but others have not (104,105). Dyslipidaemia is also more common amongst those with OSA but a causal relationship has not been proven (82).

Given these pathological processes, it is perhaps not surprising that patients with OSA and HF have a significantly increased mortality compared to those without OSA, particularly with co-existent ischaemic heart disease (106). In one prospective cohort study of patients with chronic stable HF, the mortality rate per 100 patient-years was 12.2% in those with moderate-to-severe SDB and 8.1% in those without, and this mortality rate was closely associated with the amount of time spent overnight with arterial oxygen saturations <90% (107). In the Sleep Heart Health Study, OSA was associated with cardiovascular disease in the general cohort, largely owing to the high prevalence of other atherosclerosis risk factors in those with OSA. In the prospective arm of the study, after adjustment for co-morbidities, OSA was only independently associated with incident cardiovascular disease in men under 70 years of age (108). Further research has demonstrated an increased plaque burden on coronary CT in patients with moderate to severe OSA attending a sleep clinic compared to those with mild or no OSA with otherwise comparable cardiovascular risk factors (109).

Both ventricular and atrial arrhythmias are more common in patients with HF and OSA than those without SDB. Bitter et al. demonstrated an increased frequency of appropriate ICD therapies for VT and VF in those with OSA and CSA compared with those without SDB (55). Further research demonstrated that ventricular arrhythmias were more likely to occur during the night in those with OSA, but during the day in those with CSA or no SDB (110). Atrial fibrillation (AF) is also more common in those with OSA than matched controls and paroxysms of AF are more likely to occur during the night in those with OSA (111). One study found OSA in 75% of patients attending for direct current cardioversion (DCCV) for AF (112). Possible mechanisms include increased sympathetic activation and atrial distension.

Central Sleep Apnoea

CSA is associated with a severe clinical course in HF. In one study of patients with ejection fraction <45%, the presence of any CSA (including mild disease) was associated with a significantly shorter mean survival – 45 months vs 90 months (113). The traditional view has been that CSA is a marker of severe cardiac dysfunction, rather than a cause. However, there are pathological processes in CSA that might be expected to cause deterioration in heart failure, as well as possible beneficial effects, and the relationship appears to be more complex than previously thought.

CSA is accompanied by desaturation and swings in heart rate in a similar fashion to OSA (Figure 4). CSA is associated with higher sympathetic nervous system activity, known to be maladaptive in HF (114). There is debate as to whether this is due to the CSA itself or due to the underlying HF (115,116), although reduction in the severity of CSA with oxygen and CPAP therapy is accompanied by reduced sympathetic tone, suggesting that the respiratory pattern itself is at least partially responsible (117). Intermittent hypoxaemia and arousals are the likely mechanism. The episodes of hyperventilation in CSA may also increase demand on the failing heart. However, as there is greatly reduced neural drive to breathe during apnoeas and hypopnoeas, there is minimal negative intrathoracic pressure and thus the acute haemodynamic changes are not as marked as in OSA.

CSA is an independent risk factor for arrhythmia. Research has shown an increase in ventricular ectopy during episodes of CSA, particularly during the hyperventilation phase (118). In a study of 472 patients receiving a CRTD device for the management of heart failure, Bitter and colleagues demonstrated that CSA is an independent risk factor for both monitored and treated VT and VF episodes compared to controls, and is a stronger predictor than OSA (55). It is likely that the increased mortality observed in those with CSA and HF is primarily due to ventricular arrhythmia.

Despite the association of CSA with adverse events in HF, the relationship is complex and CSA itself may, in some cases, be protective in HF. This has recently received great

attention due to the unexpected results of the SERVE-HF trial (57). In this study, treatment of patients with HF and predominant CSA with adaptive servo-ventilation (ASV), a non-invasive ventilation technique known to be very effective at reducing AHI in CSA by normalising the peaks and troughs of ventilation, had no impact on the combined endpoint of all-cause mortality, life-saving cardiovascular intervention or unplanned HF hospitalisation. ASV did, however, significantly increase all-cause and cardiovascular mortality (Hazard Ratios 1.28 [95% CI, 1.06 to 1.55; P = 0.01] and 1.34 [95% CI, 1.09 to 1.65; P = 0.006] respectively) compared with controls. This increased mortality seemed to be driven by a higher rate of sudden (presumable arrhythmogenic) cardiac death, which occurred more frequently during the day as well as during the night in those treated with ASV. Further analysis of these data by Eulenberg and colleagues found that ASV confers the greatest relative risk of cardiovascular death in those with the lowest ejection fractions and those with the greatest proportion of central apnoeic events (119). This analysis confirmed a greater risk of death following a life-saving event (e.g. ICD therapy) and without prior hospitalisation in those treated with ASV – both suggesting that sudden cardiac death was significantly more common in the treatment group.

CSA is rare in the non-HF community and may be idiopathic or associated with chronic opioid use or some neurological conditions. In the Sleep Heart Health Study of 6441 community patients without HF, OSA was associated with increased cardiovascular and all-cause mortality, but there was no association between CSA with mortality (120). Whether this implies that some of the increased risk seen in those with CSA and HF is related to difficulties recruiting an appropriate HF control group is debated.

There are several possible mechanisms through which CSA may be protective in HF, principally related to the beneficial effects of intermittent hyperventilation (121). Episodes of hyperventilation result in hypocapnia and a respiratory alkalosis. In a canine model, hypocapnia preserves myocardial function in the presence of hypoxia (122) and alkalosis partially preserves myocardial performance during hypoxia in vitro (123). Additionally, hypocapnia and alkalosis both increase the oxygen-carrying capacity of haemoglobin, according to the Bohr and Haldane effects. As hypercapnia and acidosis are frequent

findings in acute decompensated heart failure, this may have a protective role. Intermittent hyperventilation also leads to end-tidal volume increases of 400ml on average (124). Oxygen storage in the lung is thus increased which reduces hypoxaemia in the presence of pulmonary oedema and improves lung compliance in a similar way to CPAP therapy. The hyperventilation phase of CSA has also been shown to reduce sympathetic and increase vagal tone, and the elevated sympathetic tone seen in those with HF and CSA relates more closely to the severity of HF than of CSA (116). Swings in intrathoracic pressure with hyperventilation may also augment cardiac output via pump-like variations in pre- and after-load. Yumino et al found that stroke volume increased during episodes of CSA, but decreased during OSA (125). In addition, hyperventilation is thought to reverse oedema-induced bronchoconstriction (126). During apnoeic episodes in CSA there is also a slight elevation of intrathoracic pressure, which may prevent alveolar collapse (127). Furthermore, recurrent episodes of hypoxaemia may stimulate erythropoiesis and it is postulated that alternating high and low workload may reduce respiratory muscle fatigue and improve oxygenation compared with constant effort (128). The effect of ASV on these protective mechanisms may explain the surprising increase in cardiovascular mortality found in the SERVE-HF trial.

Another possible reason for the increased mortality in the SERVE-HF trial relates to the effects of positive airway pressure (PAP) on venous return to the heart. In those with low pulmonary capillary wedge pressure, high intrathoracic pressure due to PAP may compromise RV pre-load and thus LV filling and lead to a fall in cardiac output, exacerbated by any increase in pulmonary vascular resistance caused by alveolar expansion. In the SERVE-HF trial, ASV pressures were up-titrated to effectively suppress CSA, resulting in relatively higher pressures than in some previous studies. In the Saviour-C study, the PAP was maintained at or below the default level for the ASV device (129). This study found ASV to confer no additional advantage in improving ejection fraction compared to the control group, but did demonstrate clinical benefits in terms of NYHA class and activity of daily living scores. It has been postulated that high minute ventilation volumes in the SERVE-HF trial, secondary to high airway pressure support, may have predisposed to

arrhythmia through hypocapnia, as the ventricular ectopy that occurs during episodes of CSA is suppressed by inhaled carbon dioxide (118).

However, there are several counter-arguments. The mean pressures used in the SERVE-HF study were similar to several other trials demonstrating improvements in cardiac function in those with CSA treated with ASV. The mean inspiratory/expiratory pressures were 10/6 cm of water, which would not be considered excessively high for bi-level ventilation. On further analysis, no association was found between depressed RV function and mortality in those treated with ASV. A previous study on the ASV algorithm used in SERVE-HF did not demonstrate high minute ventilation in those with HF, partially due to decreased lung compliance, and the change in $PaCO_2$ was negligible (130). Further analysis of events by compliance with ASV did not change the outcome, nor did restricting the analysis to those actually treated with ASV (as opposed to intention to treat analysis) (131–133).

Therefore, whether CSA is truly beneficial in HF or whether ASV is inherently detrimental remains to be elucidated. On-going research in to phrenic nerve stimulators may inform this debate. This pacemaker-like device stimulates a branch of the phrenic nerve and delivers electrical stimulation to the nerve if intrinsic stimulation is not detected for a set period of time (i.e. if there is a central apnoeic event). This stimulation triggers contraction of the diaphragm and inspiration. Early studies have shown a significant reduction in central apnoeic events with this device (please see section 1.2.9). This device thus reduces the severity of CSA without using positive airway pressure, which may allow conclusions to be drawn about whether CSA itself is beneficial or detrimental and whether negative effects of positive airway pressure may have influenced the results of SERVE-HF. Regardless of this, it is likely that a cardiovascular outcomes study will be required to demonstrate that ameliorating CSA does not increase cardiovascular mortality.

<u>Daytime somnolence in the HF population</u>

In the non-HF population, OSA is associated with daytime somnolence (134). This may be demonstrated subjectively by the Epworth sleepiness score (ESS, with scores of ≥11

considered to represent excessive sleepiness) or objectively by the 'multiple sleep latency test' (in which subjects are placed in a dark room at different times of the day and instructed to fall asleep – an average time to sleep (by EEG criteria – the sleep latency) of 7 minutes or less is considered to be abnormal, or by the 'maintenance of wakefulness test' in which the subject is instructed to stay awake for as long as possible in a similar setting, with a normal delay before sleep being around 30 minutes (135).

In the HF population, however, daytime somnolence is reported less frequently in those with SDB and the Epworth questionnaire is not a useful screening tool. In one study comparing 155 patients with HF (and no prior diagnosis of SDB) against a large community sample, Epworth scores were significantly lower at all degrees of SDB in those with HF despite having shorter total sleep time on polysomnography (71). In another study of 267 patients with stable HF (mean EF 34±10%), only 19 of 122 patients (15.6%) with moderate-to-severe CSA reported an ESS of ≥11 and there was no difference in Epworth scores between those with CSA and those without (136). This study did find a significant correlation between NYHA class and excessive daytime somnolence, suggesting that the severity of the HF syndrome may be a greater driver of sleepiness in this population than the severity of CSA.

The absence of reported daytime somnolence in those with HF and SDB is the primary reason for the under-diagnosis of SDB in the HF population. However, poor sleep quality, both subjectively and objectively, is associated with poor functional capacity and mental health measures in patients with HF (137). It is unclear from current data in the HF population whether treatment of SDB can improve this and if this should be a treatment goal in the absence of daytime somnolence. This may also explain why physicians are reluctant to screen for SDB in this population.

Current American and British guidelines for the treatment of OSA in the non-HF population focus on alleviation of daytime somnolence, which may not be so relevant in the HF population (138,139). Optimal treatment of CSA is even less clear. In the absence of daytime somnolence, robust evidence of clinical benefit should be demonstrated before

specific treatment for SDB can be recommended. This is discussed in more detail in section 1.2.9

1.2.6 Investigation of Sleep-Disordered Breathing

Given the high prevalence of SDB in HF, a high index of suspicion is appropriate as SDB is associated with poor outcomes and may be a useful risk-stratification tool. In addition, those with OSA may be considered for CPAP therapy, although optimal management of CSA is uncertain (please see section 1.2.9). Screening questionnaires, such as the Epworth sleepiness score, show poor sensitivity and specificity in the HF population (140,141), possibly due to the complex array of symptoms experienced in HF. Subjective fatigue and observed apnoeas and snoring are reported to be useful diagnostically (140).

The gold standard diagnostic test for SDB is polysomnography. This is performed in hospital and usually involves effort belts around the chest and abdomen, a finger saturation probe, nasal cannulae, oral thermistor, snore sensor, ECG and electroencephalography (EEG). Many centres also video the patient during sleep. Whilst this provides comprehensive data it is laborious and expensive to perform and is only available in specialist sleep centres. It is also argued that the patient is unlikely to have a representative night of sleep in a hospital environment with so much equipment attached. Many sleep centres now use sleep polygraphy as a first-line test, reserving full polysomnography for more complex cases. Polygraphy can be performed in the patient's home and set-up by the patient themselves. The standard equipment (Figure 7) includes elastic effort belts around the chest and abdomen, a finger saturation probe and nasal cannulae to measure airflow. An oral thermistor to detect mouth breathing, a snore sensor taped to the neck and ECG electrodes are available if required. This has the advantages of the patient sleeping in their own bed, probably giving a more representative sleep pattern, and is considerably more economical than polysomnography. A study comparing diagnostic accuracy of polygraphy compared with polysomnography in HF found good correlation - area under the receiver operating characteristic (ROC) curve for the detection of moderate-to-severe SDB was 0.86,

with sensitivities of 68.4-82.5% and specificities of 88.6-98.8% depending on the cut-off used for the detection of SDB (142).

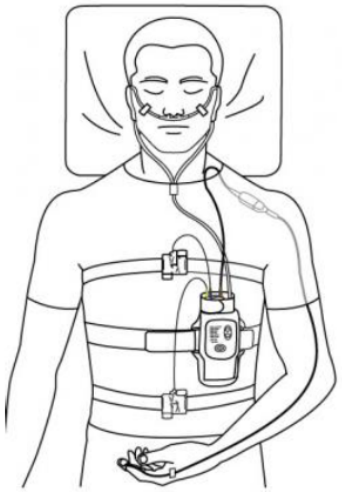


Figure 7. Home sleep polygraphy study. The device directly records nasal airflow, chest and abdominal excursion and arterial oxygen saturation. The device also deduces heart rate, snoring and body position.

Even simpler screening for SDB may also be achieved by overnight pulse oximetry. Compared to formal polysomnography, Ward and colleagues reported a sensitivity of 93% and specificity of 77% using desaturations of ≥3% at a cut-off of 12.5 events/hour for significant SDB (143). Pulse oximetry cannot, of course, differentiate between OSA and CSA and if the test is positive further investigation with polygraphy or polysomnography is mandated.

Non-contact monitors which use ultra-low energy radiowaves to detect respiratory movement during sleep have been developed. These can diagnose significant SDB with a sensitivity and specificity of around 90% (144) but are not yet common in clinical practice. Very recently, data from these monitors has suggested that there may be considerable night-to-night variability in SDB in patients with HF (please see chapter 4) (145).

Sleep studies may be analysed to give different measures of SDB, and there is debate over which measure is of greatest clinical relevance. AHI is the most commonly used unit of SDB, but oxygen desaturation index (ODI – the mean hourly frequency of arterial oxygen desaturation of ≥3% from baseline) and respiratory disturbance index (RDI – the mean

hourly frequency of apnoeas and hypopnoeas irrespective of oxygen desaturation) are also used. In a study of 963 patients, Oldenburg and colleagues found that total hypoxaemic time (time spent with arterial oxygen saturation ≤90%) was most closely predictive of adverse outcomes in patients with HF (107,146).

Other research suggests that oxygen desaturation index (ODI) may correlate more closely with adverse outcomes in those with HF and CSA than AHI (147). Sympathetic nervous system activity and noradrenaline excretion are also more closely correlated with ODI and nocturnal hypoxaemic burden than with AHI in HF (116,117). In fact, AHI may fall in those with the most severe CSA as cycle length becomes increasingly prolonged with increasing circulation time (79). This also affects ODI but not the total hypoxaemic time. At present, AHI remains the standard measure of SDB but this may change in the future (146).

1.2.7 Pacemaker Algorithms for the Diagnosis of Sleep-Disordered Breathing

Cardiac implantable electrical devices (CIEDs) are able to detect exercise and appropriately increase heart rate for patients with chronotropic incompetence by two means, which can be independently turned on or off depending on the patient's heart rate profile. Firstly, there is an accelerometer or piezoelectric crystal system in the pacemaker generator which increases heart rate in proportion to movement of the generator. Secondly, there is the minute ventilation sensor which increases heart rate in proportion to the product of respiratory rate and tidal volume, which would be expected to increase on exertion. To achieve this, the pacemaker emits a fixed, low-current high-frequency pulse of electricity (e.g. 320 μA, 5 μs, 20 Hz) from the RV lead tip cathode that is conducted across the chest to a sensor in the generator box. During inspiration, the increased volume of air in the lungs increases transthoracic impedance (and thus increases the potential difference between the RV lead tip and generator in proportion, according to Ohm's law: potential difference = current x resistance [V=IR]). The inverse occurs on expiration. The pacemaker thus records the sinusoidal changes in impedance which reflect respiratory frequency and tidal volume.

Different device manufacturers employ different sensors and it may vary between devices. Whilst respiration causes the greatest fluctuation in transthoracic impedance, changes in position, myopotentials and breathing pattern can interfere with the recording and lead to under- or over-pacing in response to exercise. Sitting position, shallow breathing and cycling rather than walking produced a lesser increase in pacing rate for a given increase in minute ventilation in one study (148).

For more than 10 years there has been interest in the use of the pacemaker minute ventilation algorithms for the detection and quantification of SDB. In a study of 20 patients with Guidant pacemakers implanted for the treatment of bradycardia (but not HF) in 2003, Simon and colleagues demonstrated that the pacemaker transthoracic impedance sensor, compared against a pneumotachometer, was highly accurate at measuring respiratory rate and minute ventilation at rest and on exercise (mean difference in respiratory rate between the pacemaker and pneumotachometer 0.2±2.1 breaths/minute, correlation coefficient for respiratory rate 0.99 and for minute ventilation 0.96) (149). A year later, Scharf et al went on to visually analyse overnight recordings of transthoracic impedance from pacemakers in 22 patients, comparing the respiratory disturbance index (RDI – events per hour) from the impedance trace against simultaneous polysomnography (150). They found excellent diagnostic accuracy for moderate to severe SDB (area under ROC curve 1.0; all 12 cases correctly identified).

Defaye and co-workers analysed an early automatic pacemaker algorithm for the detection of SDB (Talent 3, ELA Medical, Montrouge, France) (151). This was the earliest commercially available algorithm that produced data on SDB on a standard programmer at the time of pacemaker interrogation. In a study of 42 patients with conventional indications for dual chamber or biventricular pacing, they compared the severity of SDB from polysomnography with the RDI from the pacemaker. 42% of the patients had HF but only 18% received a biventricular device. At the optimal pacemaker-derived RDI cut-off of 30.6/hour, they found 75% sensitivity, 94% specificity, 75% positive predictive value and 94% negative predictive value for the diagnosis of severe SDB (AHI>30), indicating that the algorithm could reliably exclude severe SDB with a high negative predictive value.

Subsequently in 2006, Shalaby and colleagues developed a similar computer algorithm which automatically recorded a respiratory disturbance event if the amplitude of the transthoracic impedance vs time graph fell by >30% from baseline for >10 seconds (152). In a study of 60 patients, the Pearson's correlation coefficient (r) between the pacemaker RDI and polysomnography AHI was 0.80 ($p<0.01$), suggesting reasonable correlation. The pacemaker algorithm was most sensitive and specific at diagnosing moderate to severe SDB at a RDI cut-off of 37 events per hour, giving an area under the ROC curve of 0.85 and a sensitivity and specificity of around 80%.

The recently published DREAM study assessed the accuracy of another commercially available pacemaker algorithm for the diagnosis of SDB (the "Sleep Apnoea Monitoring/SAM" algorithm on REPLY 200 devices, Sorin CRM SAS, Clamart, France) (153). This algorithm was initially available on single or dual chamber brady pacemakers only, but is now available on the REPLY CRTP device (but not yet ICDs). Defaye and colleagues compared the RDI from the SAM algorithm (on single and dual chamber pacemakers only) against polysomnography on the same night in 40 patients with a conventional indication for brady pacing, 78% of whom had moderate to severe SDB by polysomnography and 40% had otherwise unspecified 'heart failure'. In 14% of patients, there was no SAM data available due to significant artefact (data are automatically discarded by the device if a certain number of non-physiological changes in transthoracic impedance are detected, indicating noise or poor signal) and a further 10% were unable to complete polysomnography or withdrew consent. 31 of the 40 patients therefore had complete data and were included in the analysis. Using a ROC curve, the optimal RDI cut-off for diagnosing severe SDB was 20/hour, yielding sensitivity of 89%, specificity of 85% and positive predictive value 89%.

Data from this pacemaker algorithm is currently being collected in the RESPIRE registry (NCT01922726) to determine the predictive power of pacemaker-diagnosed SDB for the development of atrial fibrillation. In this study, patients are divided in to those with severe-

and non-severe SDB based on SAM data from the CIED and followed up at a year for the primary outcome of paroxysmal, persistent or permanent AF. Results are awaited.

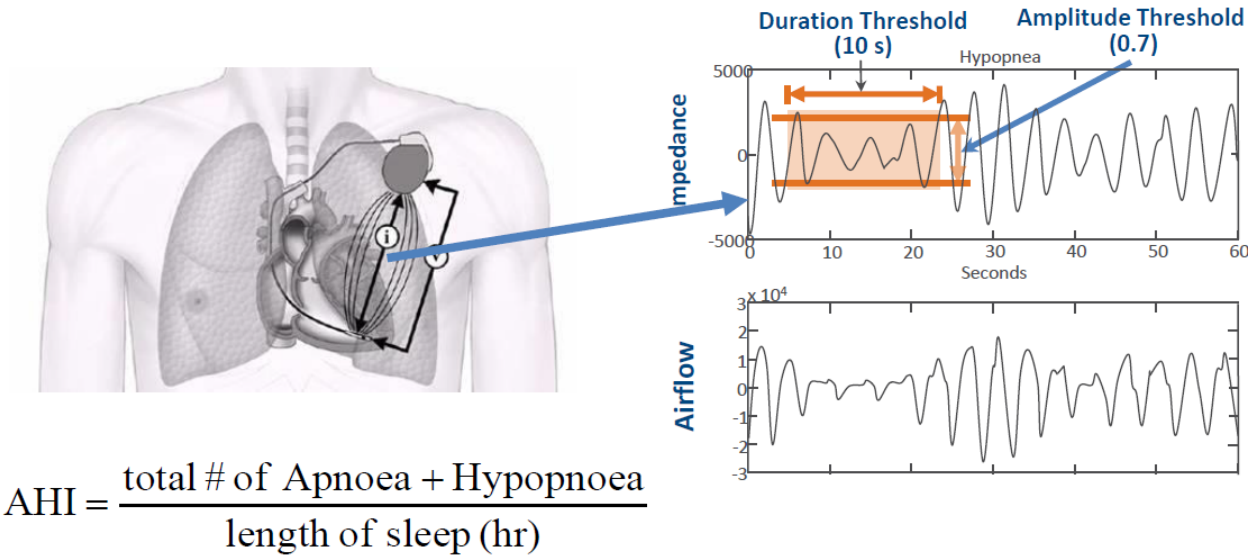
1.2.8 The ApneaScan™ Algorithm

Increasing number of patients with heart failure receive ICD and CRT devices. In the 2013-14 financial year, the implant rate for all pacemaker, ICD and CRT devices in the UK was 837 per million population, of which 72 were ICDs, 151 CRT devices and 614 simple pacemakers (154). ICD and CRT devices are implanted in to the highest risk patients with HF and information gained from these devices via remote monitoring and pacemaker clinic attendance, such as frequency of arrhythmia, activity level or oedema accumulation, is used to adjust patient care.

Trials to date have produced variable results on the value of these data in changing clinical outcomes (155,156). The recent REM-HF trial, for example, which randomised 1650 patients with HF and a CIED to usual care or usual care plus weekly download of data from the CIED (±intervention based on these data), showed no outcome benefit from weekly data downloads (157). However, the MultiSENSE study, using a combined score derived from several parameters downloaded from Boston Scientific CIEDs - including transthoracic impedance - showed promise in predicting adverse HF events (sensitivity of 70% for predicting HF hospitalisation) (158). However, this has not yet been tested in prospective randomised trial. There remains clinical interest in the use of CIEDs to monitor patient physiology as a means of tailoring care and reducing hospital admissions, morbidity and mortality. With the increasing prevalence of HF, such data may be a powerful tool in the management of a growing HF population which will inevitably place pressure on health care resources.

Boston Scientific plc (Marlborough, MA, USA) have developed an algorithm on implanted devices, called “ApneaScan”, designed to detect and quantify SDB. This algorithm is currently included on most new generation ICD and CRT devices including Autogen™, Incepta™, Invive™ and Dynagen™ devices, although it may soon be available on brady

pacemakers also. ApneaScan uses changes in transthoracic impedance with respiration to monitor respiratory rate and tidal volume (Figure 8). If the amplitude of the transthoracic impedance wave falls by more than 27% from the baseline of the previous 100 seconds for more than 10 seconds, the algorithm records one respiratory disturbance event. The mean number of events per hour overnight is given as the respiratory disturbance index (RDI). The timing of sleep on the pacemaker algorithm can be adjusted via the programmer for those with unusual sleep patterns or night shift workers, with the default setting being 11pm to 6pm. The algorithm automatically subtracts the first and last hour so that the actual recording period is midnight to 5am, unless re-programmed.



$$\text{AHI} = \frac{\text{total \# of Apnoea + Hypopnoea}}{\text{length of sleep (hr)}}$$

Figure 8. Illustration of ApneaScan function by measurement of potential difference and current (and thus impedance) between the generator and the RV lead tip. The algorithm detects an event of the amplitude of the transthoracic impedance wave with ventilation falls by >27% from baseline for >10 seconds, corresponding to an apnoea or hypopnoea. Reproduced with permission from Boston Scientific plc.

At pacemaker download, the most recent 3 months of data are displayed as a graph with each point representing the mean RDI for a single night (Figure 9). Sliding the cursor over the graph gives the exact reading. ApneaScan data is also transmitted by the new generation Latitude™ transmitters, which allow automatic or manually-activated download of data via a telephone line or mobile link to a secure Boston Scientific server,

which is then accessible online via a secure log-in. Older generation Latitude transmitters are not compatible with the ApneaScan algorithm.

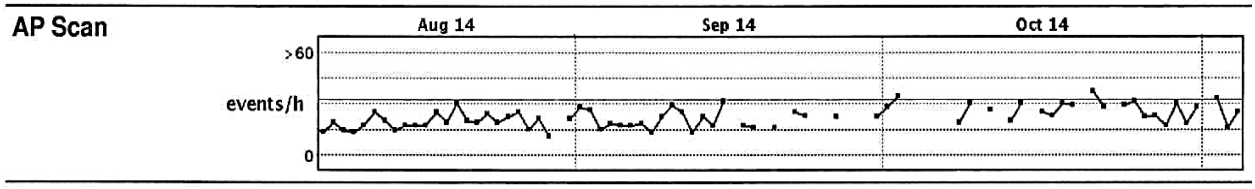


Figure 9. The ApneaScan graph as displayed on a device programmer or print-out (actual size). Each dot represents the mean RDI (events/hour) for a single night. A line at 32 events/hour is provided by the manufacturer.

Boston Scientific plc recommend using a cut-off of 32 events per hour as the threshold for significant SDB. This is based on unpublished and confidential commercial data on a limited number of patients. This is represented by a line on the ApneaScan graph seen at pacemaker download (Figure 9).

There are no published data on the validity of the ApneaScan algorithm for the diagnosis of SDB. The primary aim of this research is to determine the performance of ApneaScan compared with sleep polygraphy for the diagnosis of moderate-to-severe SDB in patients with HF.

1.2.9 Management of Sleep-Disordered Breathing

Management of SDB in HF can be broadly divided in to lifestyle interventions, pharmacological therapy, device therapy and non-invasive ventilation treatment. OSA and CSA are managed differently and are discussed separately below.

Obstructive Sleep Apnoea

CPAP Therapy

Patients without Heart Failure

Current US and British guidelines (for those without HF, although this is not specified) recommend treatment with CPAP for those with moderate-to-severe OSA (AHI≥15/hour) in the presence of significant daytime somnolence (138,139). In the SIGN guidelines, excessive daytime somnolence is defined as an Epworth Sleepiness Score ≥11 or patients falling asleep in dangerous situations (such as driving) even with a normal ESS (159).

The recommendation for CPAP therapy in such patients is based on several randomised trials showing significant improvements in the Epworth Sleepiness Score in those treated with CPAP, as well as improved AHI and oxygen desaturation index (ODI) (138). CPAP therapy has not been shown to reduce the incidence of hypertension or vascular disease, and the guidelines do not support the use of CPAP for patients without excessive somnolence.

Observational studies have found a reduction in cardiovascular mortality associated with the use of CPAP, including increased mortality in those non-compliant with CPAP therapy (160,161). However, the randomised data are at odds with this finding.

Although the majority of deaths observed in the OSA population are cardiovascular, prospective randomised controlled trials have not shown a conclusive reduction in cardiovascular events with CPAP therapy. A study of 723 patients with moderate-to-severe OSA followed up for 4 years did not find any difference in the incidence of hypertension or cardiovascular events in those treated with CPAP versus controls (162). In 47 patients with OSA but without heart failure, Colish et al found that CPAP therapy for 1 year improved pulmonary hypertension, right ventricular dimensions and left ventricular mass but did not affect NTpro-BNP concentrations (163).

In the more recent SAVE trial, McEvoy and colleagues randomised 2717 adults with moderate-to-severe OSA and known coronary or cerebrovascular disease to CPAP therapy or standard medical therapy (164). Patients were excluded if the ESS was >15 or if CSA was present. Mean CPAP use was only 3.3 hours per night, but this is typical of many OSA populations studied (165). After a mean follow up of 3.7 years, there was no difference in the combined endpoint of death from cardiovascular causes, myocardial infarction, stroke, or hospitalisation for unstable angina, heart failure, or transient ischemic attack between those treated with CPAP and those not (17% vs. 15%, HR with CPAP 1.10; 95% CI 0.91 to 1.32; p= 0.34). CPAP was effective at reducing AHI (from a mean of 29/hour to 3.7/hour), reducing Epworth scores, improving quality of life measures and reducing snoring.

Meta-analysis of trials on cardiovascular outcomes in OSA shows no overall benefit from CPAP therapy, although sub-group analysis suggests that there may be improved cardiovascular outcomes in those with the highest CPAP compliance (166). There is insufficient evidence to compare CPAP with bi-level positive airway pressure (BiPAP) for the treatment of OSA.

Patients with Heart Failure

Some investigators have examined the efficacy of CPAP in the population with HF and OSA specifically. There is evidence from small randomised controlled trials that CPAP is beneficial for cardiac function in OSA with HF. Mansfield et al randomised 55 patients with

HF and OSA to CPAP for 3 months or standard therapy (167). Those receiving CPAP had a greater improvement in LVEF (5.0±1.0% vs. 1.5±1.4%, p=0.04), reduced urinary noradrenaline and improved quality of life scores. Kaneko et al randomised 24 patients to CPAP for one month or standard therapy (168). In the CPAP group there was improvement in left ventricular ejection fraction (LVEF) from 25.0 ± 2.8% to 33.8 ± 2.4% (p<0.001), reduced LV end systolic diameter from 54.5 ± 1.8mm to 51.7 ± 1.2mm (p=0.009) and reduced heart rate and blood pressure in parallel with a significant decrease in AHI (37.1±6.4/hr to 8.3±2.8/hr, p<0.001).

Cardiac stroke volume decreases acutely during obstructive apnoeas (125). Patients with OSA and HF have greater total reductions in stroke volume and cardiac output overnight compared with matched controls without OSA. This overnight reduction in cardiac performance is attenuated by the use of CPAP (169). CPAP has also been shown to reduce sympathetic nervous system activity, thought to be detrimental, in those with HF and OSA (170).

Data on the impact of CPAP on survival in OSA and chronic HF is currently observational only, although the prospective ADVENT-HF trial (NCT01128816) has randomised patients with OSA and CSA to treatment with ASV and is powered to detect a mortality difference with NIV. The results of ADVENT-HF are awaited.

Kasai et al followed 88 patients with symptomatic systolic heart failure and OSA for a mean of 25 months (171). Those who were not receiving CPAP therapy had around twice the risk of death or hospitalisation compared with those on treatment (HR 2.03; 95% CI 1.07 to 3.68; p = 0.03). Those with poor CPAP compliance had an even higher adverse event rate (HR 4.02; 95% CI, 1.33 to 12.2; p = 0.01). Damy et al found a similar difference in prognosis with CPAP therapy in another registry study of patients with HF and OSA (172). They reviewed 384 patients over a mean of 48 months and found that those treated with CPAP were around half as likely to have died, undergone heart transplantation or implantation of a left ventricular assist device compared with controls, adjusted for confounding factors (HR 0.56; 95% CI 0.33–0.95 P = 0.03). A large observation study of 30,719 Medicare

patients found similar results – those with OSA and HF treated with CPAP had around half the mortality over 2 years compared to matched controls not treated with CPAP (HR 0.49; 95% CI 0.29–0.84, P<0.01) (173).

A major barrier to successful CPAP therapy is compliance. Patents on CPAP for OSA (without HF) use their devices for under 5 hours a night on average, and are therefore frequently asleep without the protection of positive airway pressure (174). Around a third of patients prescribed CPAP for OSA will have stopped within 5 years (175). In the trials of CPAP in those with HF, compliance appears similar –a mean of 6.2 ± 0.5 hours of CPAP per night in one randomised study and 4.9 hours in an observational study (168,171).

As discussed above, OSA is particularly associated with adverse outcomes in patients with HF and the guidance applicable to the general population may not be appropriate in HF. CPAP may be of greater benefit in a HF population, as the positive intrathoracic pressure generated reduces venous return and thus cardiac pre-load. It may also improve lung compliance, reduce alveolar collapse and gas trapping in the context of pulmonary oedema and impaired surfactant action. The role of CPAP in acute pulmonary oedema is unclear, with the 3CPO trial reporting no improvement in 7-day mortality in those presenting to hospital with acute cardiogenic pulmonary treated with CPAP or BiPAP therapy vs. oxygen therapy (176).

There is currently no consensus on the use of CPAP therapy for the treatment of OSA in those with HF in the absence of excessive daytime somnolence. None of the studies found increased mortality with CPAP therapy in HF, suggesting that its use is safe in treating daytime somnolence (possibly in contrast to ASV – see below), although this must be interpreted with caution given the lack of large prospective studies. Larger randomised trials powered to detect differences in mortality and morbidity would influence opinion but none are currently underway. Should the ADVENT-HF trial demonstrate improved clinical outcomes in those with OSA treated with ASV compared with controls, this may become standard care and debate should be had as to whether the results can be extrapolated to the use of the more economical and widely available CPAP therapy.

Lifestyle Interventions

Intensive weight loss programmes are associated with significant improvements in OSA in obese subjects, although there is little or no improvement in Epworth sleepiness scores (177,178). This improvement is less marked after 4 years but those who had undergone a weight loss programme still had a lower AHI than controls, despite 50% of the initial weight lost returning. The impact on mortality is not known. Similarly, advice on 'sleep hygiene' such as avoiding alcohol and other sedatives is of use where applicable. In selected patients with retrognaithism, mandibular advancement devices have been shown to be beneficial (179).

Weight loss interventions are less likely to be appropriate to the HF population, who are less likely to be obese compared with the general OSA population (62). Careful maintenance of euvolamia through the use of diuretics and medications to optimise cardiac function is a cornerstone of the management of OSA in HF. Minimising peripheral oedema, and therefore the overnight rostral shift, would be expected to reduce pharyngeal oedema and thus OSA, but trial evidence is lacking.

Device Therapy

As CRT improves cardiac performance in selected patients with HF, it might be expected to reduce oedema, rostral fluid shift and thus the severity of OSA. The evidence for benefit in OSA is, however, conflicting with the majority of research reporting no significant change following CRT, in contrast to those with CSA (80,180).

A novel therapy for OSA is hypoglossal nerve stimulation. In this technique, a pacemaker-like device is implanted in the right infraclavicular region with a sensing lead adjacent to the lung and a stimulation lead adjacent to the hypoglossal nerve in the neck. If the device detects apnoea, it produces electrical stimulation to the hypoglossal nerve, which acts to increase tone in the pharyngeal muscles and restore airway patency. In a prospective

cohort study of 126 patients who were non-compliant with CPAP therapy, Strollo et al found that this technique reduced AHI by a mean of 68% (29.3 events per hour to 9.0 events per hour, P<0.001). In those who responded to hypoglossal nerve stimulation, subsequent withdrawal of the stimulus resulted in a relapse to previous levels of OSA. The impact of this new therapy on patients with heart failure and on clinical outcomes is not known.

Central Sleep Apnoea

Our understanding of CSA is developing rapidly and there is currently no consensus on how to manage CSA, or even whether CSA should be treated at all, especially in light of the findings of the SERVE-HF trial (57,121,181). This section presents the current trial data but it should be noted that none of these interventions can be recommended currently for the treatment of CSA alone, although some of them may be appropriate for the treatment of the HF syndrome.

Pharmacological Therapy

Optimisation of pharmacological therapy for HF would be expected to reduce the severity of CSA through amelioration of the sympathetic drive and prevention of pulmonary congestion, thus removing the drivers of CSA.

Acetazolamide improves CSA, presumably through both diuretic and respiratory stimulating actions. In one double-blind cross-over study of 12 patients with chronic HF and moderate-to-severe CSA, acetazolamide significant decreased mean AHI (49±28 vs. 23±21/hour, p=0.004) and reduced hypoxaemic time (with arterial saturation ≤90% - 19±32 vs. 6±13%; p=0.01) compared with placebo (182). In a subsequent study, Javaheri et al found that acetazolamide significantly decreased AHI in 6 male patients with stable HF and moderate-to-severe CSA (mean AHI 65±32 with placebo vs. 31±19/hour with acetazolamide) (183). Interestingly, acetazolamide actually enhanced the HCVR in those with CSA and HF, which might be expected to increase the severity of CSA and possibly

implies that the respiratory stimulating and diuretic effects of the drug over-ride this mechanism, although this cannot be concluded from the limited data.

Treatment for 6 months with carvedilol in a trial of 16 patients with HF and CSA also reduced AHI (mean AHI 34±13 to 14±13, P=0.003), although this trial was observational and the improved CSA may have merely reflected improved LV function (mean LVEF increased from 32±7.4% to 45±9.8%, P<0.001) (184).

In a placebo-controlled cross-over trial of theophylline for the treatment of moderate-to-severe CSA in 15 men with stable HF, the drug significantly decreased mean AHI (18±17, vs. 37±23 with placebo; p<0.001) (185). There are, however, concerns regarding its safety in a HF population owing to inotropic, chronotropic and possibly arrhythmogenic effects and it is therefore not in routine use.

Non-invasive ventilation

Non-invasive ventilation has proved disappointing in improving survival in CSA. In fact, given the possible beneficial effects of CSA in HF, it has to be questioned whether normalising the respiratory pattern should be a treatment goal at all, other than as a consequence of treating the HF syndrome itself.

Continuous Positive Airway Pressure (CPAP)

The CANPAP trial assessed the role of CPAP in patients with HF and CSA (186). In this study, 258 patients on optimal medical therapy for HF were randomised to nocturnal CPAP or no CPAP. The trial was terminated early due to an early divergence in survival favouring the control group, a slow recruitment rate and low event rate. After 3 months, the CPAP group had a greater reduction in AHI (-21±16 vs. –2±18 per hour, P<0.001), reduced noradrenaline levels (-1.03±1.84 vs. 0.02±0.99 nmol/l, P=0.009), increased mean nocturnal oxygen saturation (1.6±2.8% vs. 0.4±2.5%, P<0.001), increased LVEF (2.2±5.4% vs. 0.4±5.3%, P=0.02) and increased 6-minute walk test distance (20.0±55 vs. 0.8±64.8 m,

P=0.016). In the first 18 months, the Kaplan-Meier curve for transplant-free survival favoured the control group, however at 2 years there was no difference in survival and this persisted in those followed up for 60 months, although with a trend towards improved survival in those treated with CPAP (HR for transplantation-free survival 0.66; P=0.06). The authors conclude that, based on the results of the CANPAP trial, CPAP cannot be recommended for the treatment of CSA in HF.

Post-hoc analysis of the CANPAP results found that adequate compliance with CPAP and effective suppression of CSA (to <15 events/hour) was associated with a survival advantage (187). This raised the possibility that a more efficacious form of NIV may confer a overall survival advantage in those with HF and OSA.

BiPAP has been shown to improve LVEF and AHI in CSA with HF more effectively than CPAP, but is often poorly tolerated and there are no data on mortality (188).

Adaptive Servo-Ventilation (ASV)

Adaptive servo-ventilation (ASV) is an advanced form of NIV in which the device monitors the patient's minute ventilation and provides increased bi-level positive airway pressure during hypopnoeas and apnoeas (including mandatory breaths), and withdraws pressure support during hyperventilation. It also provides positive end expiratory pressure (PEEP) in the same manner as CPAP. It therefore effectively normalises the breathing pattern in both CSA and OSA. Additional benefits in CSA include treatment of pulmonary oedema (and thus lessening J receptor stimulation) through positive intrathoracic pressure and prevention of alveolar collapse, as well as reducing hypocapnia during hyperventilation. Research has shown ASV to be significantly more effective at reducing AHI in CSA than CPAP, BiPAP or oxygen therapy (130). Compared with CPAP, patients treated with ASV have a greater reduction in AHI, improvement in LVEF and better compliance with treatment at 6 months (189).

Research by Pepperell and colleagues found that 1 month of nocturnal ASV reduced day time somnolence and urinary metadrenaline secretion, as well as reducing plasma BNP concentration in patients with HF and CSA (190). In a non-controlled cohort of 29 male patients with moderate-to-severe LV systolic dysfunction and CSA, Oldenburg et al demonstrated that ASV for around 6 months significantly reduced AHI (from 37.4±9.4/h to 3.9±4.1/h, $p<0.001$), improved cardiopulmonary exercise test performance (peak VO_2 from 58±12% to 69±17% of predicted, $p=0.007$) and improved LVEF (from 28.2±7% to 35.2±11%, $p=0.001$). There was also an impressive reduction in NTpro-BNP (from 2285±2192 pg/ml to 1061±1293 pg/ml, $p=0.01$) with ASV therapy (191).

ASV is also effective at treating CSA in patients with HFPEF. Bitter et al studied 60 patients with HFPEF and CSA for 1 year, 21 of whom either rejected ASV therapy or were non-compliant, thus acting as an (observational) control group (192). They demonstrated that ASV significantly reduces AHI in patients with HFPEF (43.5±14.7 to 3.5±1.7 events/h; $p<0.001$). The treatment group also had significant improvements in BNP, cardiopulmonary exercise test parameters and LV filling pattern on echocardiography compared with the 'control' group.

Some research also suggested that ASV reduced the risk of ventricular arrhythmia in patients with HF and CSA. In a registry study of 403 patents (of whom 96 received ASV) over 21 months, Bitter and colleagues showed that ASV was associated with a reduced incidence of treated and monitored ventricular tachyarrhythmias in patients with HF, CSA and an ICD (193). Compared to those with HF but no SDB, those with untreated CSA were around twice as likely to have a monitored or treated ventricular arrhythmia (HR 1.99, 95% CI 1.46–2.72, $p<0.001$), whereas ASV therapy reduced the risk down to a similar level (HR 1.06, 95% CI 0.74–1.50, $p=0.77$).

Following on from the significant physiological and clinical benefits of ASV described above (although perhaps with some publication bias), the randomised controlled SERVE-HF trial was undertaken with adequate power to detect a survival and hospitalisation benefit of ASV (Resmed, San Diego) in patients with HF and CSA compared with controls on optimal

medical therapy only (57,194). This study enrolled 1,325 patients with EF≤45%, NYHA II to IV symptoms and moderate-to-severe CSA (AHI>15/hour, >50% of events central) and randomised them to ASV therapy or optimal medical therapy only. Contrary to expectation, there was no difference in the combined endpoint of all-cause mortality, life-saving cardiovascular intervention or hospitalisation for worsening heart failure between the ASV and control groups (HR 1.13, 95% CI 0.974 to 1.325, p = 0.10). However, both all-cause and cardiovascular mortality were higher in those treated with ASV (HR 1.28; 95% CI, 1.06 to 1.55; p = 0.01 and HR 1.34; 95% CI, 1.09 to 1.65; p = 0.006 respectively). The most common mode of mortality was sudden cardiac death (presumably arrhythmogenic) and this occurred during the day as well as the night (119,133).

The exact relationship between ASV and ventricular arrhythmia is therefore unclear, given the previous data on reduced ventricular arrhythmia in those on ASV (193). The full implications of this result are still being appreciated, but as a consequence patients on treatment with ASV for CSA in HF have been advised to stop this therapy. At this stage, it is only possible to speculate as to the reasons for the result. Suppression of the postulated beneficial effects of CSA is a possible theory, as is the effect of PAP on those with normal or only modestly elevated pulmonary capillary wedge pressure.

The CAT HF trial, examining the effect of ASV initiated after a hospital admission for acute decompensated HF (with reduced or preserved ejection fraction) with moderate-to-severe SDB (predominantly CSA), was terminated early due to safety concerns following the results of SERVE-HF (195). One hundred and twenty-six of the anticipated 215 patients were recruited and analysed. The data collected at 6 months follow-up showed that ASV was effective at suppressing SDB (from 35.7/h to 2.1/h in the ASV group vs. 35.1/h to 19.0/h in the control group (p < 0.0001)). There was no overall difference in the global rank score endpoint of death, cardiovascular hospitalisations, and percent changes in 6-min walk distance at 6 months. There was, however, a statistically-significant improvement in the composite endpoint in the pre-specified sub-group of those with HFPEF treated with ASV compared with controls (HR 0.36, 95% CI 0.14-0.93, p=0.04). There was no safety

signal with ASV treatment but conclusions on hard clinical endpoints cannot be made from these data (196).

Based on these data, ASV should not be used for the treatment of CSA in those with HFREF. A further study of ASV (Respironics, Pennsylvania, USA) for the treatment of CSA and OSA in HF is underway (ADVENT-HF,(197)) which may further inform the debate.

Oxygen and Carbon Dioxide Therapy

The CHF-HOT trials randomised patients with HF and CSA to receive overnight home oxygen therapy (HOT) or not (198). They demonstrated that HOT reduces AHI (−11.4 ± 11.0 vs. −0.2 ± 7.6 events/h, $p < 0.01$) and NYHA functional class with a trend towards improved LVEF. Ventricular ectopic beats were reduced by HOT in those with more severe HF symptoms and CSA at baseline, but not the remainder of the cohort. A randomised study of HOT in patients with moderate-to-severe LVF and predominantly NYHA III symptoms (but without known SDB – although a high percentage of these patients would be expected to have SDB) found no improvement in Minnesota Living with Heart Failure (MLwHF) scores (a patient-reported measure of heart failure symptoms and impact on activities of daily living) and noted poor compliance (mean use 5.4 hours per day) (199).

Overnight inhalation of carbon dioxide, which might reduce the propensity to apnoea due to hypocapnia following hyperventilation in CSA, is also effective at reducing AHI. In one study AHI fell from 74.4±12.4 events/h during air breathing to 25.8±7.8 events/h with CO_2 inhalation ($p = 0.002$), but there was no impact on arousal index and this has not been adopted in to clinical practice (200). The impact of oxygen and carbon dioxide therapy on prognosis and hospitalisation are not known.

Cardiac Resynchronisation Therapy (CRT)

Cardiac resynchronisation therapy (CRT) improves prognosis, symptoms and cardiac performance in selected patients with HFREF. CRT has also been shown to reduce the

severity of CSA. Sinha and colleagues performed sleep polygraphy on 24 patients before and 17 weeks after implantation of a biventricular pacemaker (201). In the 15 patients with CSA (AHI>5/hr), CRT was associated with a significant reduction in AHI (19.2 ± 10.3 to 4.6 ± 4.4 events/hour, p <0.001) and improved nocturnal oxygen saturation. There was no change in these parameters in those without CSA. These results were replicated by Oldenburg et al, who also found that day time capillary pCO_2 was lower in those with CSA and this rose following CRT, suggesting a normalisation of the hypercapnic ventilatory response(80). Meta-analysis of all studies examining the impact of CRT on CSA found a significant reduction in AHI (mean reduction 13.05 events/hour; CI 16.74 to 9.36; p<0.00001) (202). Whether this reduction in AHI confers an additional survival advantage, or is merely a marker of improved cardiac function, is unknown.

Phrenic Nerve Stimulation

A novel therapy under evaluation for the treatment of CSA is phrenic nerve stimulation (PNS). This involves the implantation of a pacemaker-like device with a lead anastomosing with the phrenic nerve via the brachiocephalic or pericardiophrenic vein. Upon detection of apnoea or hypopnoea, the device paces the phrenic nerve at a rate and output appropriate to stimulate diaphragmatic contraction and breathing. In a study of 16 patients with HF and moderate-to-severe CSA over two nights (one night with device turned on in random order), Ponikowski et al showed that PNS resulted in a marked reduction in AHI (median (inter-quartile range) 45 (39– 59) vs. 23 (12–27) events/hour, p =0.002) alongside significant reductions in oxygen desaturation index and arousal index (203). Abraham et al performed a prospective feasibility study enrolling 57 patients with CSA (204). They confirmed a significant reduction in AHI with PNS at 3 months (49.5±14.6 episodes/h vs. 22.4 ±13.6 events/h; p < 0.0001) that was maintained at 12 months (49.9±15.1 vs. 27.5±18.3 events/h, P<0.001) (205). The procedural complication rate was 26% at 6 months, mostly due to early lead displacement.

A subsequent trial recruited 151 patients with CSA (AHI>20/hour) to implantation of a PNS device and then randomised 1:1 to device on or off (206). After 6 months, 51% of those

with the PNS device active had a reduction in AHI of >50%, compared with 11% of those with an inactive device. There were also improvements in sleep efficiency, ESSs and MLwHF scores in those actively treated. 9% of patients suffered a device-related complication, most commonly lead displacement, and 34% were affected by uncomfortable phrenic pacing which was resolved with programming in all but 1 case.

No trial powered to detect an improvement in survival or hospitalisation with PNS therapy is currently planned. Whilst PNS technology offers unique insights in the pathophysiology of CSA in HF, until we have data on clinical outcomes it cannot be recommended for the treatment of CSA in HF.

1.2.10 Why look for sleep-disordered breathing in patients with heart failure?

The publication of the SERVE-HF trial during the period of this research significantly changed the way physicians approached SDB in HF (57). Prior to publication of these results, it was common practice in many parts of the world (but not the UK) to treat CSA in HF with ASV, and thus diagnosis was worthwhile for this purpose. The publication of SERVE-HF has caused a re-evaluation of the significance of SDB in HF.

Given the uncertainty over the management of both OSA and CSA in those with HF, it should be questioned whether investigating patients for this condition is, in fact, a useful exercise.

The detection of moderate-to-severe OSA in those with HF should precipitate inquiry in to excess somnolence, usually defined as an Epworth Sleepiness Score >10. If this is present, treatment with CPAP should be considered as it may lead to significant improvement in symptoms (167). The current evidence for improved prognosis in those with OSA and HF treated with CPAP is observational only, so whether treating OSA in the absence of excess somnolence is indicated remains subject to debate (171).

Based on current data, positive pressure therapy for CSA cannot be recommended but further research is underway which will illuminate the debate further, including the ADVENT-HF trial (197). New technologies, such as phrenic nerve stimulators, may prove to be of benefit but are still under investigation.

Even without randomised evidence of improved prognosis with treatment of SDB in HF, both OSA and CSA are associated with poor outcomes in HF and may be useful markers of deteriorating heart failure (55). The presence of significant SDB should alert the clinician to the severity of the HF syndrome in the affected patient and may direct appropriately focussed care. The ApneaScan algorithm does not affect the performance or battery life of the device and, should it prove to be an accurate measure of SDB, may be a useful screening test for SDB and improve patient care.

1.3 Hypotheses

In this research, I test 3 hypotheses:

1) That the ApneaScan algorithm can accurately detect moderate-to-severe SDB (Apnoea-hypopnoea index ≥15 events per hour) in patients with heart failure with reduced ejection fraction (HFREF).

2) That there is minimal night-to-night variability in severity of SDB as assessed by ApneaScan in patients with stable chronic heart failure

3) That those with heart failure and moderate-to-severe SDB, as assessed by ApneaScan, have a higher rate of adverse cardiovascular events than those without significant SDB.

Chapter 2: General Methods

A detailed description of each study method is included in the individual study chapters. This chapter presents the general methods applicable to all areas of this work.

2.1 Ethical Approval and Subject Recruitment

2.1.1 Ethical approval

Ethical approval for all aspects of this research was obtained via the Integrated Research Application System (IRAS) with the guidance of the research and development department (Patrik Pettersson and Ginette Hoare) at the Royal Brompton Hospital, London. The ApneaScan validation and prognosis study was presented to the Bromley Research Ethics committee (REC) in January 2014 (REC Reference numbers 14/LO/0077). Following amendments to the patient information leaflets, REC approval was granted on 26th February 2014. A further substantial amendment, permitting recruitment of patients having pacemaker generator changes and retrospective recruitment of patients who had received compatible devices within the past year for the validation and prognosis study, was submitted to and approved by the REC on 13/3/14. A minor amendment to the validation study protocol, expanding patient recruitment to St George's Hospital, London, was granted on 30/9/14. The requisite annual reports were supplied to the REC.

2.1.2 Research Registration

The studies were registered with www.clinicaltrials.gov (reference number NCT02204865) and the UK clinical research network (UKCRN, reference number 16260). Monthly recruitment data were uploaded to the UKCRN database.

2.1.3 Subject Recruitment

Patients were eligible for the ApneaScan validation and prognosis study if they met the following criteria:

- Age 18 years or over
- HFREF (ejection fraction <40%)
- Implanted with or due to receive an ICD, CRT-P or CRT-D device made by Boston Scientific plc. (Marlborough, Ma, USA) incorporating the ApneaScan™ function
- Able to give written informed consent

Exclusion criteria were:

- Known diagnosis of SDB on non-invasive ventilation therapy
- Haemodynamic instability
- For those receiving Incepta™ or Invive™ devices, ApneaScan™ can only record data if the respiratory rate response sensor is on. Therefore patients in whom activation of the rate response function of the pacemaker was undesirable for clinical reasons were excluded. On Autogen™ and Visionist™ devices, it is possible for ApneaScan™ to record without the pacemaker rate response via the "passive" setting.

Patients were recruited in person from scheduled pacing lists and cardiology clinics at the Royal Brompton and Harefield Hospitals, London. Patients were also identified from device databases at the Royal Brompton, Harefield and St George's Hospitals and invited to take part in the study by letter. In total, 173 patients were screened from retrospective pacemaker databases of whom 85 met the inclusion criteria and were contacted by letter. Approximately 400 patients were screened from prospective pacing lists of whom approximately 130 met inclusion criteria and were invited to take part in person. All recruitment was performed in accordance with Good Clinical Practice and REC guidance.

2.1.4 Sample Size Calculation

The data from the study by Shalaby and colleagues was used to estimate sample size for the validation study, with the assistance of Mr Winston Banya, statistician at the Royal Brompton Hospital (152). In the Shalaby study of an automated pacemaker algorithm for the diagnosis of SDB, the mean difference in AHI between the algorithm and polysomnography was 2.4 events/hour with a coefficient of variance of 34.2 events/hour (SD of the difference 17.1 events/hour). For an alpha value of 0.05 and a power of 90% with a non-inferiority limit of 10 events/hour to prove non-inferiority of ApneaScan against sleep polygraphy, a sample size of 60 was estimated to be sufficient. Allowing for 20% attrition, a recruitment target of 72 was set.

For the prognosis arm of the study, data from Bitter and colleagues was used for the likely incidence of ICD therapies, and data from Javaheri and colleagues for mortality (55,113). In the Bitter study, approximately 40% of those with CSA and 20% of those without received appropriate ICD shocks at 20 months. In the Javaheri study, mortality at 20 months was approximately 30% in those with significant SDB vs 15% in those without. As many of those who received shocks would also have died during follow-up, we may estimate an incidence of the combined endpoint of ICD shocks, mortality or cardiovascular hospital admission at 20 months of 50% in those with significant SDB and 25% of those without significant SDB. To achieve 80% power with alpha 0.05, an estimated sample size of 116 patients would be required to differentiate groups by the combined endpoint. A 90% power would require 154 subjects.

2.2 Patient Assessment

2.2.1 Questionnaires

Epworth Sleepiness Scale

The Epworth sleepiness scale (ESS) was published in 1991 by Dr Murray Johns as a simple questionnaire to detect and quantify daytime somnolence (141). It asks the subject to

estimate the likelihood of falling asleep in 8 different every-day scenarios on a scale of 0 to 3 (Appendix 1). It was shown to be simple to use, highly reproducible and closely correlated with severity of OSA and its treatment (134). For these reasons it is the most commonly used screening questionnaire for daytime somnolence in the investigation of SDB. Comparison with other sleepiness questionnaires has shown the ESS to have the best specificity (67%) but relatively lower sensitivity (54%) for the diagnosis of moderate-to-severe OSA at the standard cut-off of ≥11 out of 24 (207).

Minnesota Living with Heart Failure Questionnaire (MLwHFQ)

The MLwHF questionnaire (Appendix 2) is a validated method of assessing the impact of HF symptoms on a subject's quality of life (208). It asks the subject to rate the impact of 21 symptoms and consequences of HF on their ability to live as they wanted in the past 4 weeks. Each question is rated between 0 (no impact) and 5 (severe impact). Meta-analysis has shown the MLwHF questionnaire to be valid and responsive to changes in NYHA class, 6-minute walk test and physical and social functioning assessments (209). It is widely used in HF research.

2.2.2 The New York Heart Failure Classification

The functional status of subjects was classified according to the New York Heart Association (NYHA) grade. This is the most commonly used way of assessing a patient's functional status based on reported exercise capacity and has been in use for over 50 years (210). It is graded from I to IV as follows:

I. No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation or dyspnoea.
II. Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation or dyspnoea.
III. Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation or dyspnoea.

IV. Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.

Whilst this is simple to use and understand, research has shown that it may correlate poorly with objective exercise tolerance and is subject to marked inter-observer variability (211). There is also significant variation between physicians' interpretation of a patients' NYHA class and patients' interpretation of their own symptoms (212).

2.2.3 Echocardiography

All subjects underwent baseline echocardiography. Echocardiography involves the use of ultrasound to visualise cardiac structure and function in real time. The addition of Doppler physics allows assessment of blood flow and myocardial wall motion. All echocardiography was performed by British Society of Echocardiography (BSE) accredited physiologists in accordance with BSE guidance. Left ventricular ejection fraction was measured by Simpson's biplane method.

2.2.4 B-Type Natriuretic Peptide (BNP) Assay

BNP is a peptide released from the ventricular myocardium in response to wall stress and distension. It counteracts the effects of the renin-angiotensin-aldosterone system and promotes diuresis, natriuresis and vasodilatation. It is a sensitive and specific marker of left ventricular dysfunction, is a prognostic marker and may be used to monitor a patient's condition and tailor therapy (213). BNP assay is supported by international guidelines for the assessment of possible HF (13). All assays were done in the laboratories of the Royal Brompton, Harefield and St George's Hospitals.

2.2.5 Sleep Polygraphy

Sleep polygraphy ("sleep studies") were performed using the Embletta Gold system (ResMed, San Diego, USA; see Chapter 1, Figure 7). This system uses elasticated effort belts

around the chest and abdomen, a pulse oximeter probe on a fingertip and nasal cannulae to measure nasal airflow. Home polygraphy generally, and the Embletta system specifically, have been shown to perform well when compared against polysomnography (142,214). The Embletta system is commonly used for the diagnosis of SDB. Subjects had the polygraphy study at home. The device was posted or delivered to the subject's house with instructions. The subject fitted and wore the device on the appointed night and then brought the device to the pacing appointment, at which ApneaScan data were retrieved from the pacemaker.

The sleep studies were analysed by the author according to the 2012 American Academy of Sleep Medicine (AASM) criteria (58), with the following definitions:

- Hypopnoea - a reduction in airflow of ≥30% from baseline for ≥10 seconds accompanied by a ≥3% fall in oxygen saturation.
- Apnoea - a reduction in airflow of ≥90% from baseline for ≥10 seconds.
- Apnoea-Hypopnoea Index (AHI) – the mean number of apnoeas and hypopnoeas per hour of sleep.
- Respiratory Disturbance Index (RDI) – the mean number of episodes in which nasal airflow falls by ≥30% from baseline for ≥10 seconds, irrespective of desaturations, per hour of sleep.
- Oxygen Desaturation Index (ODI) – the mean number of episodes in which arterial oxygen saturations fall by ≥3% from baseline for ≥10 seconds per hour of sleep.
- Auto AHI – Analysis by the automatic 'respiration analyser' function on RemLogic-E software (version 3.2, ResMed, San Diego). This function requires a desaturation of ≥4% for ≥10 seconds for the recognition of a hypopnoea (as per the 2007 AASM guidelines (215)).

Sleep studied were set-up to record from midnight to 5am, to correspond with the default recording time of the ApneaScan™ algorithm. If the timing of the ApneaScan™ recording

was altered (to coincide with the subject's usual sleep pattern), the timing of the sleep study was adjusted to the same times.

2.2.6 ApneaScan™ Download

The ApneaScan™ graph was downloaded from the device via the standard programmer or via the Latitude™ remote monitoring device. The latter is a box connected to either a static or mobile phone line that allows patient-initiated or hospital-initiated download of data via a secure internet link. The Latitude™ box can connect with the pacemaker if it is within a 2-metre radius and most patients keep the Latitude box near the bedside. The pacemaker interrogation data can be seen on specified hospital computers via a secure login. As it is a new algorithm, older generation Latitude™-compatible devices do not transmit ApneaScan™ data.

The ApneaScan™ graph is found under the "Events" tab on the programmer or Latitude™ screen and the graph is incorporated in the printable "Heart Failure Management Report" and the "Combined Follow-up Report". The ApneaScan™ RDI was recorded on the night of the sleep study for direct comparison. As the ApneaScan™ algorithm does not record an RDI if the quality of the signal is poor, there are frequently several missing data points on the ApneaScan™ graph.

2.2.7 Acquisition and classification of outcome data

At a minimum of 1 year post-enrolment, data were collected for the combined outcome of all-cause mortality, unplanned cardiovascular hospital admission, ventricular arrhythmia requiring acute therapy, heart transplantation or implantation of a ventricular assist device. Acute therapy for ventricular arrhythmia was defined as appropriate ICD shocks or anti-tachycardia pacing, external cardioversion or hospitalisation for ventricular arrhythmia requiring oral or intravenous therapy. We also assessed burden of atrial fibrillation. These data were collected by review of the patient electronic notes (EPR), pacing notes (Pacenet™) and contacting the patient and the patient's General Practitioner.

The cause of any hospital admissions was classified as the primary discharge diagnosis on the discharge summary.

2.3 Statistical analysis

Detailed statistical analysis will be presented in the 'methods' section in each individual chapter. Quantitative variables are expressed as mean and standard deviation or median and interquartile range for normally and non-normally distributed data, respectively. Normality of distribution was assessed using the Shapiro-Wilk test. Differences between groups were analysed using the Student t-test for continuous data and chi-square test for categorical data. Agreement between ApneaScan™ and sleep polygraphy was assessed by the intra-class correlation coefficient, Bland-Altman plots and receiver operator characteristics curves. Intra-class correlation was also used to assess night-to-night variability in SDB. Kaplan Meier plots were used to assess outcomes over time. SPSS™ version 24 computer software (IBM Corporation, New York) was used to perform statistical calculations. Statistical significance was taken as $p<0.05$ for all results.

Chapter 3: Accuracy of the ApneaScan™ algorithm for the diagnosis of sleep-disordered breathing in heart failure

3.1 Introduction

Sleep-disordered breathing (SDB) affects over half of patients with heart failure (HF) and remains significantly under-diagnosed (51,56,62). Making a diagnosis of SDB in patients with HF may facilitate better management. Observational data suggests improved survival in those with HF and OSA treated with CPAP (171). In small randomised trials, CPAP treatment for those with OSA and HF resulted in improved ventricular dimensions and ejection fraction (167,168). Following the results of the CANPAP and SERVE-HF trials, management of CSA in HF is uncertain – CPAP did not improve overall mortality and ASV was associated with higher mortality in this group (57,186). However, CSA is a marker of poor prognosis in HF and its presence may help the clinician identify patients at higher risk requiring more intensive therapy (52,55). In addition, CSA is frequently severe in those admitted to hospital with decompensated HF and remote monitoring of CSA may enable early up-titration of HF therapy to ameliorate the decompensation and prevent the need for admission. (61).

The major barrier to diagnosing SDB is the availability of polysomnography or sleep polygraphy testing. These tests are often only available in specialist centres. The increasing prevalence of HF, the high prevalence of SDB in HF and the low sensitivity of standard predictors of SDB such as high Epworth sleepiness scores and obesity in those with HF means that centres would have to perform large numbers of tests in the HF population with significant resource implications.

Increasing numbers of patients with HF are receiving implanted cardiac devices. In the 2013-14 financial year, the implant rate for all pacemaker, ICD and CRT devices in the UK was 837 per million population, of which 72 were ICDs, 151 CRT devices and 614 simple pacemakers (154). The rate of complex (ICD and CRT) device implantation has

approximately doubled in the past 10 years, but remains below the overall western European average (of 141 ICDs and 119 CRT devices per million population per year). The publication of the most recent NICE guidelines for complex device therapy in HF expands the indications for ICD and CRT devices and it is expected that rates of implantation will increase accordingly (40).

Pacemakers have the ability to monitor depth and frequency of breathing, via changes in transthoracic impedance, and use this to inform the minute ventilation monitor which can be programmed to increase the cardiac pacing rate in response to exercise in those with chronotropic incompetence. Over the past decade, there has been interest in whether the same technology can be programmed to detect and quantify SDB. Early feasibility research by Shalaby and colleagues and Defaye and colleagues indicated that changes in transthoracic impedance could be used to detect and quantify SDB (151,152) and the DREAM study, investigating an automated algorithm on simple brady-pacemakers, demonstrated good sensitivity and specificity for the detection of SDB in a non-HF population (153).

ApneaScan™ is a novel algorithm available on certain ICD and CRT devices manufactured by Boston Scientific corporation (Natick, Ma). ApneaScan™ uses changes in transthoracic impedance to diagnose and quantify SDB and provides an automated read-out at device interrogation. The algorithm does not significantly decrease battery longevity and may be a useful screening tool to alert clinicians to the presence of significant SDB. No published study has yet investigated the accuracy of this algorithm for the diagnosis of SDB in a HF population.

This chapter tests hypothesis 1 of the thesis – that the ApneaScan™ algorithm can accurately diagnose moderate-to-severe SDB in patients with HFREF. As there is debate over the optimal measure of SDB, ApneaScan™ data are compared with polygraphic Apnoea-Hypopnoea Index, Respiratory Disturbance Index and Oxygen Desaturation Index.

3.2 Methods

3.2.1 Eligibility and baseline tests

Patients were eligible for recruitment if they fulfilled all the following criteria:

- Impaired LV systolic function (ejection fraction ≤40%)
- No known diagnosis of SDB
- With or due to receive an ICD or CRT device with ApneaScan function.

Patients were recruited from the Royal Brompton, Harefield and St George's Hospitals, London. Catheter laboratory lists, pacing clinic lists and the PaceNet patient database were screened by the author to identify patients meeting eligibility criteria.

At the time of recruitment, patients underwent the following tests and questionnaires:

- Echocardiography (performed by British Society of Echocardiography-accredited echocardiographers)
- Serum B-type natriuretic peptide (BNP) assay (measured in the biochemistry laboratories of the respective hospitals)
- Electrocardiography
- Epworth sleepiness score
- Minnesota Living with Heart Failure Questionnaire
- Routine clinical examination and history-taking

3.2.2 Sleep polygraphy study and ApneaScan™ assessment

Participants underwent a home sleep polygraphy study (Embletta™, ResMed, San Diego), which records nasal airflow, chest and abdominal excursion and arterial oxygen saturation. The ApneaScan™ data were then downloaded from the ICD or CRT device either in person via the programmer in the pacing clinic, or remotely via the Latitude™ system. Following implantation of a new device or generator change, a minimum of 4 weeks was required

prior to assessment to allow resolution of any haematoma which may interfere with transthoracic impedance measurements. The sleep polygraphy study is a common means of evaluating SDB and is the measure against which ApneaScan™ is evaluated. The mean AHI, RDI and ODI from the sleep polygraphy study (PG-AHI, PG-RDI and PG-ODI) were compared with the ApneaScan™ RDI (AP-RDI) on the same night. ApneaScan records between midnight and 5am by default, although this can be altered according to sleep patterns. The sleep polygraphy study was set up to record over the same time period. If the transthoracic impedance signal is poor, ApneaScan™ will not record a value for the night (and leave a blank space on the ApneaScan™ graph at download). The sleep polygraphy study was analysed by me, blinded to the ApneaScan™-RDI, according to the 2012 American Academy of Sleep Medicine guidelines (see section 2.2.6) (58).

3.2.3 Statistical analysis

Quantitative variables are expressed as mean and standard deviation if normally distributed, and median and interquartile range for those not-normally distributed. Student's t-test was used to assess differences in continuous data between groups if normally distributed; the Mann-Whitney test if the data were non-normally distributed. Chi squared test (Fisher's exact) was used for comparing categorical data. Pearson's correlation coefficient was used to assess correlation between ApneaScan™ and polygraphy measures (expressed as value, 95% confidence interval and p value). A Bland Altman plot was used to visualise agreement between the tests including mean difference and coefficient of variation. A receiver operator characteristic (ROC) curve was used to represent the utility of ApneaScan™ to detect moderate to severe SDB at different RDI cut-offs, including the optimal cut-off defined as the best trade-off between sensitivity and specificity (the greatest sum of the two measures). A p-value of <0.05 was taken as statistically significant. Statistical analysis was performed using SPSS™ v24 software (IBM, Armonck, New York).

3.2.4 Contribution by the candidate

All patients for this arm of the study were screened and recruited by me. I collected baseline data, arranged echocardiography and blood tests as required and organised the sleep polygraphy studies either by posting the Embletta™ device to the subject with instructions, or by delivering and demonstrating the Embletta™ myself either at the hospital or the patient's home. I analysed the polygraphy studies myself using Embla Rem-Logic™ software, blinded to the ApneaScan™ reading. I retrieved the ApneaScan™ data with the help of the pacing physiologists at the respective hospitals. I performed the data analysis myself.

3.3 Results

3.3.1 Subject enrolment

Ninety-five patients were enrolled in this study between January 2014 and December 2015. 32 patients were subsequently excluded. The reasons for exclusion are presented in Figure 1. Sixty-three patients completed the sleep study and ApneaScan™ download. In 9 (14%), no ApneaScan™ data was recorded by the device on the study night. Fifty-four therefore had complete ApneaScan and polygraphy data. In 12 subjects (22%), the oxygen saturation probe recorded incomplete data (most frequently due to overnight detachment); in these cases, the PG-AHI was assumed to equal the PG-RDI for the period of missing saturation data.

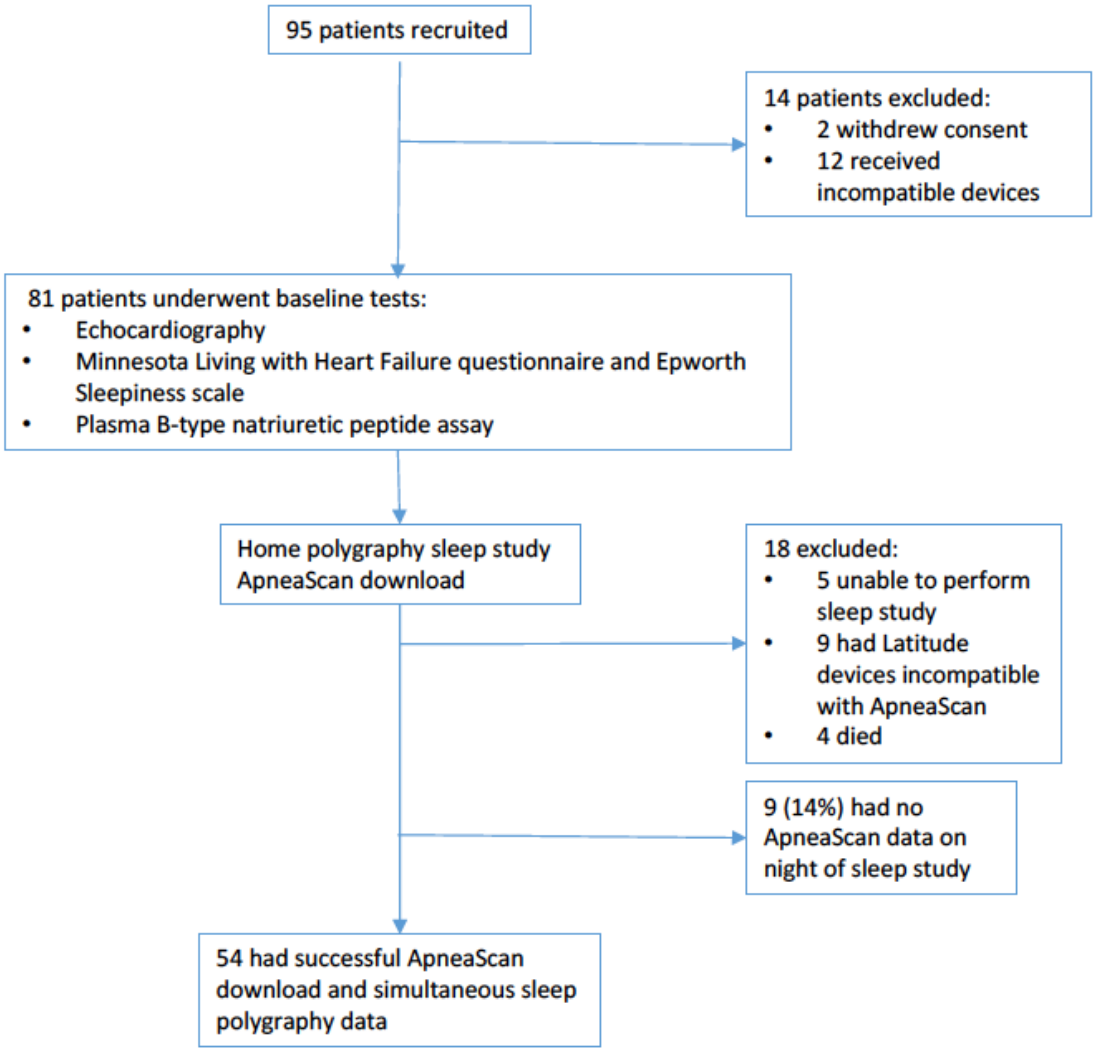


Figure 1. Flow chart of subject recruitment and exclusion

3.3.2 Baseline characteristics of patients recruited to the study

The baseline data on the 95 patients enrolled in the study and the 54 completing the study are presented in Table 1. There were no significant differences in the baseline characteristics of the patients enrolled in and completing the study, other than more missing NYHA data, more non-Boston Scientific devices and a longer median time from

device implant to enrolment in the 95-patient enrolment group (these patients were excluded).

Patient characteristic	All enrolled patients (n=95)	Patients completing study (n=54)	P value
Age	67±13 years	68±13 years	0.65
Sex	71 (76%) Male	41 (76%) Male	1.00
Aetiology of heart failure:			
- Ischaemic heart disease	49 (52%)	23 (43%)	0.31
- Dilated cardiomyopathy	32 (34%)	23 (43%)	0.29
- Valvular heart disease	7 (7%)	3 (5%)	0.75
- Sarcoidosis	4 (4%)	4 (7%)	0.46
- Congenital heart disease	3 (3%)	1 (2%)	1.00
Ejection fraction	30±8%	28±9%	0.16
B-type natriuretic peptide Median, (IQR)	321 (158-667) ng/l	357 (145-730) ng/l	0.93
NYHA class			
- I	3 (3%)	2 (4%)	1.00
- II	46 (49%)	33 (61%)	0.39
- III	30 (32%)	19 (35%)	0.72
- IV	1 (1%)	0 (0%)	1.00
- Not recorded	15 (15%)	0	<0.01
Heart failure pharmacotherapy			
- ACEi/ARB	82 (86%)	51 (94%)	0.17
- Betablocker	77 (81%)	43 (80%)	0.83
- Aldosterone antagonist	52 (55%)	35 (65%)	0.30
- Ivabradine	7 (7%)	5 (9%)	0.76
- Loop diuretic	64 (67%)	39 (72%)	0.58
- Thiazide	5 (5%)	3 (6%)	1.00
Epworth sleepiness score (Median (IQR)**;** out of 24)	5 (4-10)	7 (4-10)	0.81
Minnesota living with heart failure score (Median (IQR)**;** out of 105)	36 (17-52)	34 (15-48)	0.53
Body mass index:	27±5 kg/m^2	27±4 kg/m^2	1.00
Device implanted			
- ICD	16 (17%)	11 (19%) ICD	0.66
- CRTD	52 (55%)	37 (68%) CRTD	0.12
- CRTP	12 (13%)	7 (13%) CRTP	1.00
- Non-Boston Scientific device	15 (16%)	0	<0.01
Heart rhythm			
- AF/AT	20 (21%)	11 (20%)	1.00
Implanting Hospital:			
Royal Brompton	63 (66%)	31 (57%)	0.29
Harefield	20 (21%)	17 (31%)	0.17
St George's	12 (13%)	6 (11%)	1.00

Patient characteristic	All enrolled patients (n=95)	Patients completing study (n=54)	P value
Time from device implant to recruitment (median (IQR))	3 (1-227) days	4 (1-90.5) days	0.04
Generator position:			
Pre-pectoral	49 (52%)	29 (54%)	0.87
Sub-pectoral	35 (37%)	21 (39%)	0.86
Not Documented	11 (11%)	4 (7%)	0.57

Table 1. Baseline characteristics of the 95 patients enrolled in the study and 54 completing the ApneaScan™ download and sleep study. NYHA – New York Heart Association; ACEi – Angiotensin converting enzyme inhibitor; ARB – Angiotensin receptor blocker; BB – beta blocker; AA – Aldosterone antagonist; CRTD – cardiac resynchronisation therapy defibrillator; CRTP – cardiac resynchronisation therapy pacemaker; ICD – implantable cardioverter-defibrillator; AF/AT – atrial fibrillation/flutter/tachycardia.

3.3.3 Detailed characteristics of patients completing the sleep study and ApneaScan download

The baseline characteristics of the 54 patients successfully completing the sleep study and ApneaScan download are presented in Table 2. The severity and type of SDB was determined by the sleep polygraphy study.

Characteristic	All patients (n=54)	Mild or no SDB (n=32)	Moderate-to-severe OSA (n=7)	Moderate-to-severe CSA (n=15)	P value: (Mild or no SDB vs. OSA; vs CSA; OSA vs CSA)
Age	68±13 years	69±13 years	65±11 years	69±13 years	0.46; 1.00; 0.49
Sex	41 (76%) Male	23 (72%) Male	5 (71%) Male	13 (87%) Male	1.00; 0.46; 0.56
Aetiology of heart failure:					
- Ischaemic heart disease	23 (43%)	12 (40%)	1 (14%)	10 (67%)	0.39; 0.12; 0.06
- Dilated cardiomyopathy	23 (43%)	15 (45%)	3 (44%)	5 (33%)	1.00; 0.53; 1.00
- Valvular heart disease	3 (5%)	2 (6%)	1 (14%)	0 (0%)	0.46; 1.00; 0.35
- Sarcoidosis	4 (7%)	2 (6%)	2 (28%)	0 (0%)	0.14; 1.00; 0.09
- Congenital heart disease	1 (2%)	1 (3%)	0 (0%)	0 (0%)	1.00; 1.00; 1.00
Ejection fraction	28±9%	29±10%	25±11%	27±9%	0.35; 0.51; 0.67
B-type natriuretic peptide ng/l (Median, IQR)	357 (145-356)	376 (105-544)	866 (425-1196)	225 (128-623)	0.08; 0.93; 0.22

Characteristic	All patients (n=54)	Mild or no SDB (n=32)	Moderate-to-severe OSA (n=7)	Moderate-to-severe CSA (n=15)	P value: (Mild or no SDB vs. OSA; vs CSA; OSA vs CSA)
NYHA class					
- I	2 (4%)	2 (6%)	0 (0%)	0 (0%)	1.00; 1.00; 1.00
- II	33 (61%)	20 (63%)	5 (71%)	8 (53%)	1.00; 0.75; 0.65
- III	19 (35%)	10 (31%)	2 (29%)	7 (47%)	1.00; 0.34; 0.65
Heart failure pharmacotherapy					
- ACEi or ARB	51 (94%)	31 (97%)	6 (86%)	14 (93%)	0.33; 0.54; 1.00
- BB	43 (80%)	26 (81%)	6 (86%)	13 (87%)	1.00; 1.00; 1.00
- AA	35 (65%)	18 (56%)	5 (71%)	12 (80%)	0.68; 0.19; 1.00
- Ivabradine	5 (9%)	4 (13%)	1 (14%)	0 (0%)	1.00; 0.29; 0.31
- loop diuretic	39 (72%)	23 (72%)	4 (57%)	10 (67%)	0.65; 0.74; 1.00
- thiazide	3 (6%)	1 (3%)	0 (0%)	2 (13%)	1.00; 0.24; 1.00
SDB characteristics:					
- Mean AP-RDI	35±4/hour	29±12/hour	45±11/hour	44±11/hour	
- Mean PG-AHI	17±15/hour	7±4/hour	30±19/hour	31±12/hour	
- Mean PG-RDI	20±15/hour	12±7/hour	33±19/hour	34±13/hour	
- Mean PG-ODI	16±14/hour	8±4/hour	31±17/hour	29±12/hour	
Epworth sleepiness score (median [IQR])	7 (4-10)	7 (4-10)	5 (4-7)	8 (4-13)	0.44; 0.31; 0.18
Minnesota living with heart failure score (median [IQR])	33 (15-48)	36 (14-48)	24 (15-39)	37 (21-58)	0.56; 0.46; 0.30
Body mass index (kg/m^2):	27±4	26±3	29±5	29±3	0.04; <0.01; 1.00
Device implanted:					
- CRTD	37 (68%)	24 (75%)	5 (71%)	8 (53%)	1.00; 0.18; 0.65
- CRTP	7 (13%)	4 (13%)	0 (0%)	3 (20%)	1.00; 0.66; 0.52
- ICD	11 (19%)	4 (13%)	2 (29%)	4 (27%)	0.29; 0.25; 1.00
Heart rhythm:					
- Atrial Fibrillation	11 (20%)	3 (9%)	3 (43%)	5 (33%)	0.06; 0.09; 1.00
- Sinus Rhythm	43 (80%)	29 (91%)	4 (57%)	10 (67%)	
Implanting Hospital:					
Royal Brompton	31 (57%)	19 (59%)	5 (71%)	8 (54%)	0.69; 0.76; 0.65
Harefield	17 (31%)	11 (34%)	2 (29%)	5 (33%)	1.00; 1.00; 1.00
St George's	6 (11%)	2 (6%)	0 (0%)	2 (13%)	1.00; 0.58; 1.00
Time from device implant to recruitment (median (IQR))	4 (1-90.5) days	20 (1-128) days	1 (1-4) days	1 (1-3) days	0.23; 0.08; 1.00
Generator position:					
Pre-pectoral	29 (54%)	21 (65%)	6 (86%)	5 (33%)	0.40; 0.06; 0.06
Sub-pectoral	21 (39%)	12 (38%)	1 (14%)	8 (53%)	0.39; 0.36; 0.16
Not Documented	4 (7%)	2 (6%)	0 (0%)	2 (13%)	1.00; 0.58; 1.00

Table 2. Characteristics of patients completing the sleep study and ApneaScan download. NYHA – New York Heart Association; ACEi – Angiotensin converting enzyme inhibitor; ARB – Angiotensin receptor blocker; BB – beta blocker; AA – Aldosterone antagonist; AP-RDI – ApneaScan Respiratory-Disturbance Index; PG-AHI – Polygraphy Apnoea-Hypopnoea Index; PG-RDI – Polygraphy Respiratory-Disturbance Index; PG-ODI – Polygraphy Oxygen-Desaturation Index; CRTD – cardiac resynchronisation therapy defibrillator; CRTP – cardiac resynchronisation therapy pacemaker; ICD – implantable cardioverter-defibrillator.

Of the 54 subjects completing the sleep study and ApneaScan download, 22 (41%) had previously-undiagnosed moderate-to-severe SDB. Ten of these subjects (19%) had severe SDB (PG-AHI≥30). Fifteen subjects (28%) had moderate-to-severe CSA and 7 (13%) had moderate-to-severe OSA. The median AHI by polygraphy (PG-AHI) was 10.7/hour, IQR 16.75/hour.

Of the 54 subjects, 76% were male and the mean age was 68±13 years. The most common aetiologies of HF were ischaemic heart disease and dilated cardiomyopathy (43% of subjects each). The majority of patients had severe LV systolic dysfunction with a mean EF of 28±9% and a median plasma BNP of 357 (IQR 145-356) ng/l. Most patients were in NYHA class II (61%) or III (35%) and the majority of patients were on disease-modifying HF pharmacotherapy with ACE inhibitors or angiotensin receptor blockers (94%), beta blockers (80%) and aldosterone antagonists (65%), as well as a loop diuretic (72%). 68% of devices implanted were CRTDs, 13% CRTPs and 19% single or dual chamber ICDs.

The median Epworth sleepiness score was within the normal range at 5 (IQR 4-10) points and there was no significant difference in the score between those with moderate-to-severe SDB (either predominant CSA or OSA) and those without. 13 out of 39 subjects (33%) with moderate-to-severe SDB had ESSs ≤10 and only 4 out of 15 (27%) subjects with an ESSs ≥11 had moderate-to-severe SDB. Those with moderate-to-severe CSA had higher median Minnesota Living with Heart Failure scores than those with moderate-to-severe OSA, but this did not reach statistical significance (37 (21-58) vs 24 (15-39) out of 105, p=0.30). There was no overall difference in Minnesota Living with Heart Failure score between those with moderate-to-severe SDB and those without (p=0.83). There was no

statistical association between ejection fraction and the severity or type of SDB. There was a trend towards higher BNP levels in those with OSA than either those with CSA or without SDB, but this was not statistically significant (p=0.29 for those with mild-or-no SDB vs. moderate-to-severe SDB).

In keeping with previous research on the HF population, most patients were overweight rather than obese. BMI was higher by a mean of 3 units in those with both OSA and CSA than those without, possibly reflecting higher total body water in those with more severe HF. Eighty percent of patients had underlying sinus rhythm whilst 20% were in atrial fibrillation (AF). Higher rates of AF were seen in those with moderate-to-severe SDB than those without (8 (36%) vs 3 (9%), p=0.04). This did not reach statistical significance when OSA and CSA are compared against insignificant SDB separately (p=0.06 and p=0.09 respectively).

There was a non-significant trend towards higher rates of pre-pectoral implants in those with OSA and sub-pectoral in those with CSA. There was no significant difference between those with significant SDB and those without in time from implantation of device to recruitment and sleep polygraphy study. It was not possible to determine exact time from diagnosis of HF as most patients were referred in from other hospitals and reliable data were not available, but time from device implantation may be a surrogate marker on the HF timeline.

As RDI does not require desaturation to record an event, the mean polygraphic RDI (PG-RDI) was higher than PG-AHI (20.3±15.2/hour vs 16.8±15.1/hour). The mean polygraphic oxygen desaturation index (PG-ODI) was similar to the mean PG-AHI at 16.2±13.9/hour.

The mean ApneaScan™ RDI (AP-RDI) was substantially higher than the mean PG-AHI and mean PG-RDI at 35.3±13.9/hour (a mean difference of 18.5 and 15.0 events per hour respectively). AP-RDI was significantly higher in those with moderate-to-severe SDB by polygraphy than in those without.

3.3.4 Correlation between ApneaScan™ and polygraphic Apnoea-Hypopnoea Index

There was a close and statistically significant correlation between ApneaScan™-Respiratory Disturbance Index (AP-RDI) and sleep polygraphy-Apnoea-Hypopnoea Index (PG-AHI) (r=0.73, 95% CI 0.61-0.87, p<0.01). This equates to an r^2 value of 53%, suggesting that around half of the variation seen in AP-RDI is related to true variation in severity of SDB as assessed by polygraphy. This is represented as a scatter plot and Bland-Altman plot in Figures 2 and 3.

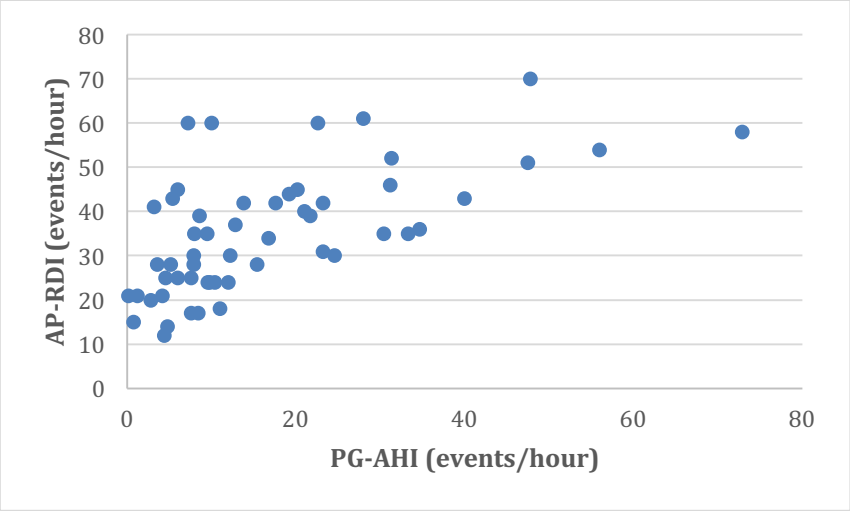
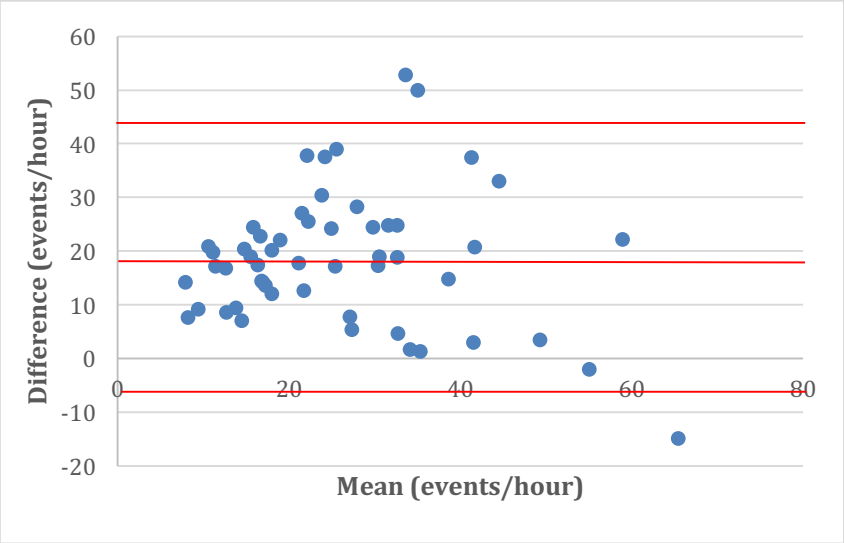


Figure 2. Scatter plot of ApneaScan™ Respiratory Disturbance Index (AP-RDI) against polygraphy Apnoea-Hypopnoea Index (PG-AHI). Each dot represents simultaneous data from a single subject.



Mean difference 18.5 events/hour, Coefficient of variation 0.68

Figure 3. Bland Altman plot of the mean of ApneaScan™-Respiratory Disturbance Index (AP-RDI) and polygraphy-Apnoea-Hypopnoea Index (PG-AHI) against the difference. Red lines indicate mean and 2 standard deviations limit. Mean difference 18.5 events/hour, SD 12.5, coefficient of variation 0.68.

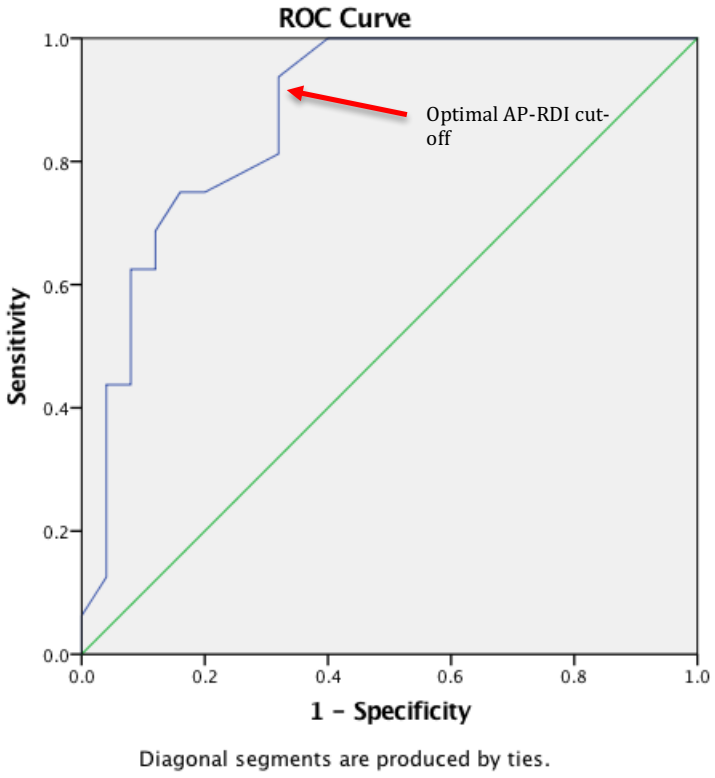
Correlation between AP-RDI and PG-AHI was closer in those with predominant OSA (n=7) than in those with predominant CSA (n=15, r=0.86, 0.61-0.95, p<0.01 vs. r=0.70, 0.42-0.85, p<0.01). The correlation was also closer in those with predominant apnoeic events (n=14) as opposed to predominant hypopnoeic events (n=40, r=0.87, 0.61-0.96, p<0.01 vs. r=0.65, 0.33-0.81, p<0.01). Correlation was closer in those with sub-pectoral (n=29) rather than pre-pectoral generators (n=21, r=0.81, .57-0.92, p<0.01 vs. r=0.72, 0.38-0.88, p<0.01). These sub-group analyses must be interpreted in the context of lower patient numbers.

Correlation between AP-RDI and PG-AHI was statistically significant in those with moderate-to-severe SDB on the polygraphy study (n=22) but not in those with mild-or-no SDB (n=32, r=0.69, 0.26-0.87, p<0.01 vs. r=0.28, 0.47-0.65, p=0.18).

On the ROC curve (Fig. 4), the optimal ApneaScan™ (AP-RDI) cut-off for the diagnosis of moderate-to-severe SDB by polygraphy (PG-AHI≥15/hr) was 30.5 events per hour. This yielded a sensitivity of 95%, a specificity of 69%, a positive predictive value of 68% and a

negative predictive value of 95%. The area under the ROC curve was 0.84 (0.75-0.95, p<0.001).

At the manufacturer-specified ApneaScan cut-off of 32 events per hour for the diagnosis of 'significant' SDB (PG-AHI≥15/hour), sensitivity was 87%, specificity 76%, positive predictive value 76% and negative predictive value 88%.



Area under the curve 0.84, p<0.01

Figure 4. Receiver Operator Characteristic (ROC) curve for the detection of moderate to severe SDB (polygraphy Apnoea-Hypopnoea Index ≥15/hour) by ApneaScan™. Optimal ApneaScan™ cut-off 30.5 events/hour. Area under the curve 0.84 (95% CI 0.74-0.95, p<0.01).

At the cut-off of 30.5 events/hour to distinguish between no-or-mild SDB and moderate-to-severe SDB, ApneaScan correctly classified more than 90% of those with none, moderate or severe SDB by polygraphy. However, 9 out of 22 cases (41%) of those with mild SDB had a 'false positive' AP-RDI above 30.5/hour (Fig. 5).

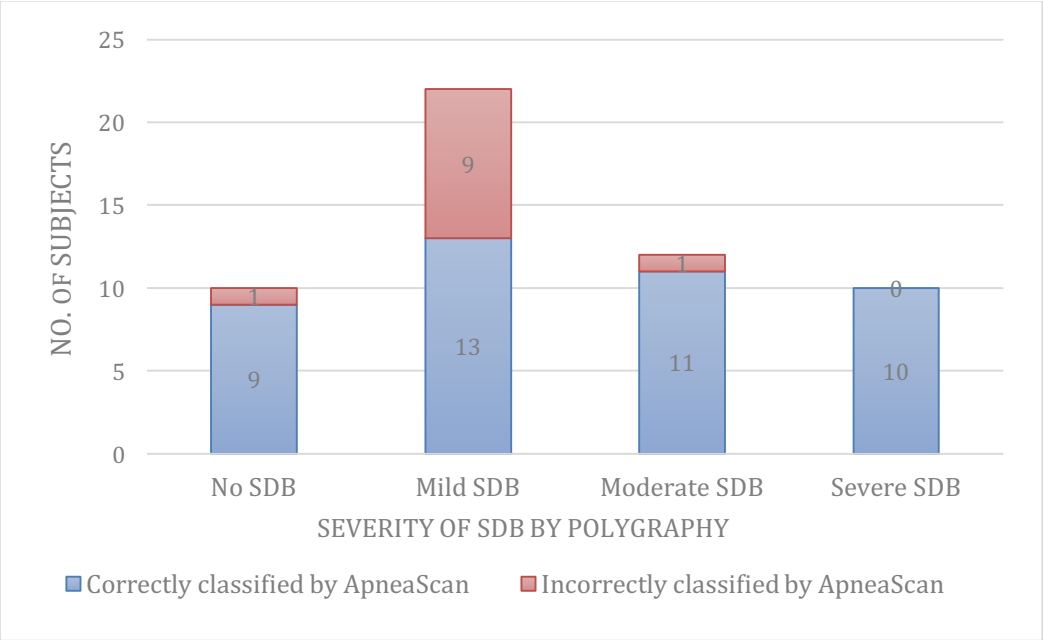
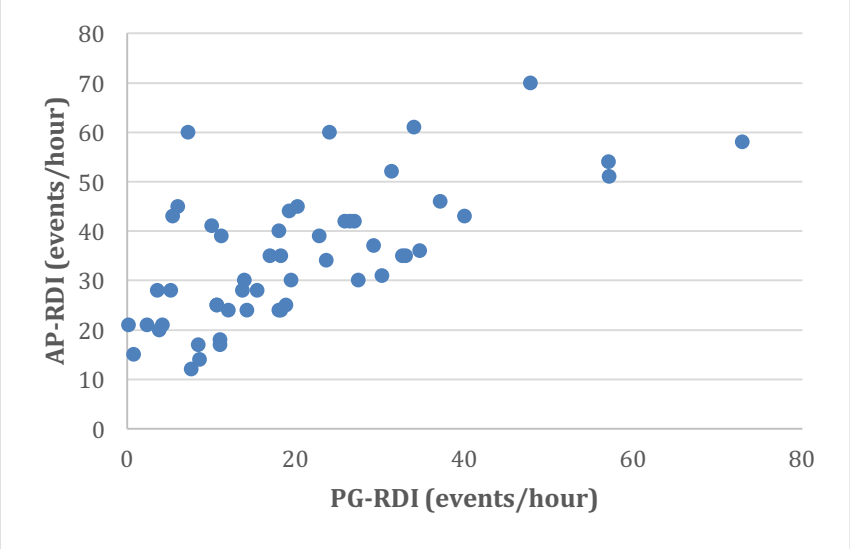


Figure 5. Histogram illustrating the performance of ApneaScan at different severities of SDB (by sleep polygraphy) using an AP-RDI cut-off of 30.5 events/hour to distinguish between no-or-mild SDB and moderate-to-severe SDB. Severity of SDB classified according to the AASM guidelines.

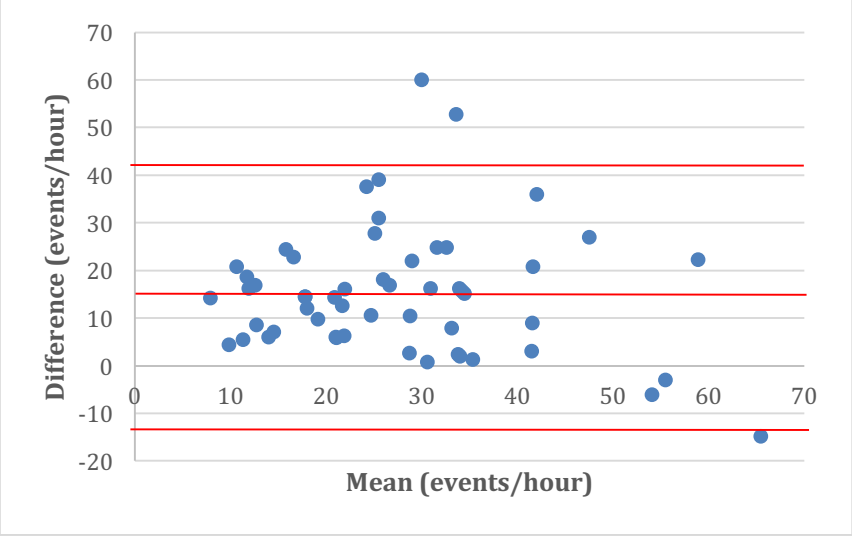
3.3.5 Correlation between ApneaScan™ and polygraphic Respiratory-Disturbance Index

There was a close correlation between ApneaScan™-RDI and polygraphic-RDI (r=0.73, 95% CI 0.54-0.85, p<0.01; Figs. 6 and 7). r^2 was 53%.



r=0.73, p<0.01

Figure 6. Scatter plot of ApneaScan™-Respiratory Disturbance Index (AP-RDI) against polygraphy Respiratory Disturbance Index (PG-RDI). Each dot represents simultaneous data from a single subject.



Mean difference 15.3 events/hour, Coefficient of variation 0.88.

Figure 7. Bland Altman plot of mean of ApneaScan™-Respiratory Disturbance Index (AP-RDI) and polygraphy-Respiratory Disturbance Index (PG-RDI) against the difference. Red lines indicate mean and 2 standard deviations limit. Mean difference 15.3 events/hour, SD 13.4, coefficient of variation 0.88.

On the ROC curve, the optimal ApneaScan™-RDI cut-off for the diagnosis of moderate-to-severely elevated polygraphy Respiratory Disturbance Index (≥15/hour) was 29 events/hour, yielding a sensitivity of 87% and a specificity of 71% (Fig. 8).

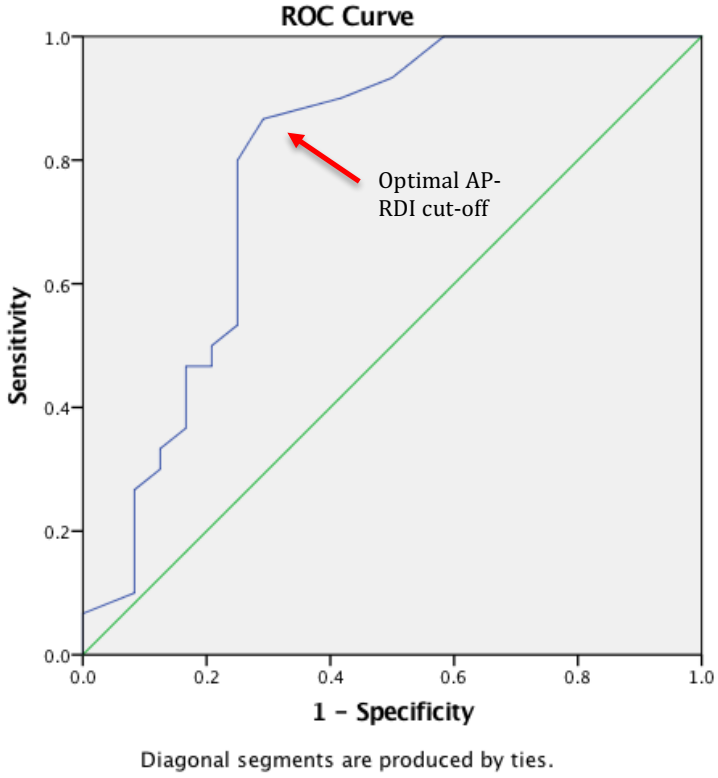
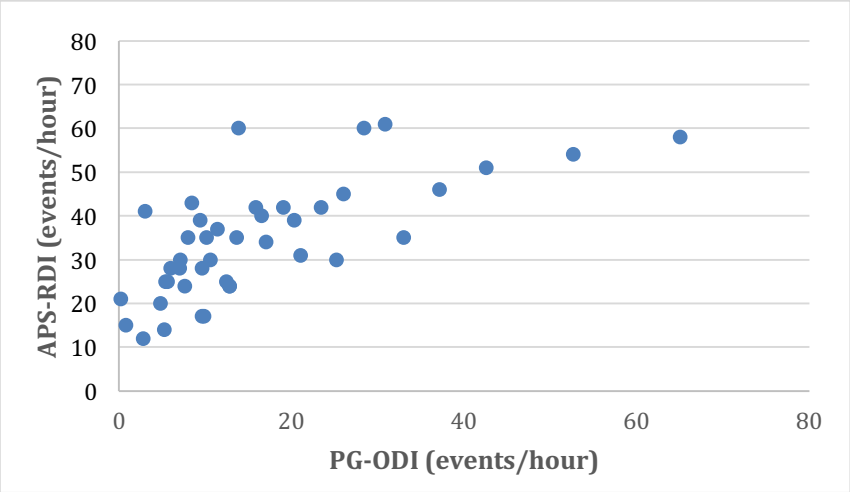


Figure 8. Receiver Operator Characteristic (ROC) curve for the detection of moderate-to-severely elevated polygraphic-Respiratory Disturbance Index (polygraphy-RDI≥15/hour) by ApneaScan™. Optimal ApneaScan™ cut-off 29.0 events/hour. Area under the curve 0.79 (95% CI 0.66-0.92, p<0.01).

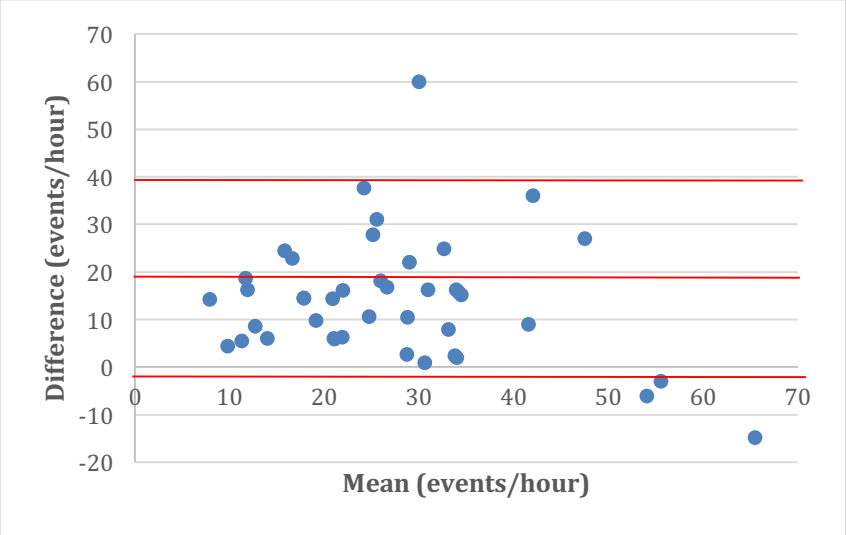
3.3.6 Correlation between ApneaScan and polygraphic Oxygen Desaturation Index

There was also a close correlation between ApneaScan™-Respiratory Disturbance Index (AP-RDI) and polygraphic Oxygen Desaturation Index (PG-ODI) (r=0.82 0.67-0.91, p<0.01, Figs. 9 and 10). r^2 was 67%.



r=0.82, p<0.01

Figure 9. Scatter plot of ApneaScan™ Respiratory-Disturbance Index (AP-RDI) against polygraphy Oxygen Desaturation Index (PG-ODI). Each dot represents simultaneous data from a single subject.



Mean difference 18.2 events/hour, coefficient of variation 0.57

Figure 10. Bland Altman plot of mean of ApneaScan™-Respiratory Disturbance Index (AP-RDI) and polygraphy-Oxygen Desaturation Index (PG-ODI) against the difference. Red lines indicate mean and 2 standard deviations limit. Mean difference 18.2 events/hour, SD 10.4, coefficient of variation 0.57.

On the ROC curve, the optimal ApneaScan™-RDI cut-off for the detection of moderate-to-severely elevated ODI was 30.5 events/hour, yielding a sensitivity of 94% and a specificity of 68% (Fig. 11).

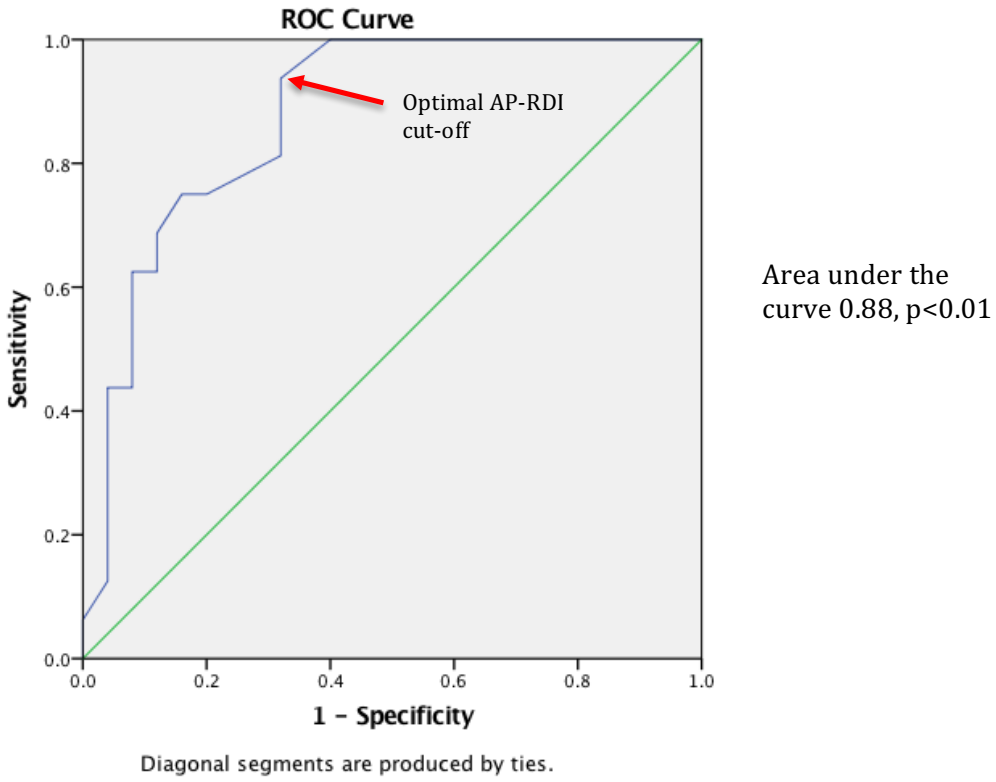


Fig. 11. Receiver Operator Characteristic (ROC) curve for the detection of moderate-to-severely elevated Oxygen Desaturation Index (polygraphy-ODI ≥15/hour) by ApneaScan™. Optimal ApneaScan™ cut-off 30.5 events/hour. Area under the curve 0.88 (95% CI 0.77-0.98, p<0.01).

3.3.7 Correlation between ApneaScan and sleep polygraphy – subgroup analysis

The question arises as to whether there are characteristics of SDB in particular subjects which affect the ability of ApneaScan™ to correctly identify apnoeas and hypopnoeas, when compared against sleep polygraphy. To investigate this, subjects were divided in to those with mild-or-no SDB vs. moderate-to-severe SDB, those with predominant CSA vs. OSA and those with predominant apnoeas vs. hypopnoeas. The intra-class correlation coefficients between ApneaScan™ and polygraphy indices for the different subgroups are presented in Table 3.

ApneaScan™ correlated most closely with all polygraphy indices in those with moderate-to-severe SDB, OSA rather than CSA and predominant apnoeas rather than hypopnoeas.

	AP-RDI v PG-AHI	**AP-RDI v PG-RDI**	**AP-RDI v PG-ODI**
All patients	r=0.73 (0.61-0.87, p<0.01) n=54	r=0.73, (0.54-0.85, p<0.01) n=54	r=0.82 (0.67-0.91, p<0.01) n=42
Mild or no SDB	r=0.28 (0.47-0.65, p=0.18) n=32	r=0.49 (-0.05-0.75, p<0.05) n=32	r=0.47 (-0.17-0.76, p=0.06) n=26
Moderate to severe SDB	r=0.69 (0.26-0.87, p<0.01) n=22	r=0.75 (0.38-0.90, p<0.01) n= 22	r=0.76 (0.30-0.92, p<0.01) n=16
Predominant CSA	r=0.70 (0.42-0.85, p<0.01) n=36	r=0.71 (0.43-0.85, p<0.01) n=36	r=0.76 (0.46-0.90, p<0.01) n=25
Predominant OSA	r=0.86 (0.61-0.95, p<0.01) n=18	r=0.87 (0.66-0.95, p<0.01) n=18	r=0.86 (0.65-0.96, p<0.01) n=17
Predominant hypopnoeas	r=0.65 (0.33-0.81, p<0.01) n=40	r=0.68 (0.39-0.83, p<0.01) n=39	r=0.75 (0.47-0.88, p<0.01) n=29
Predominant apnoeas	r=0.87 (0.61-0.96, p<0.01) n=14	r=0.87 (0.60-0.96, p<0.01) n=15	r=0.89 (0.62-0.97, p<0.01) n=13

Table 3. Intra-class correlation coefficient between ApneaScan™-Respiratory Disturbance Index (AP-RDI) and polygraphy-Apnoea-Hypopnoea Index (PG-AHI), polygraphy-Respiratory Disturbance Index (PG-RDI) and polygraphy-Oxygen Desaturation Index (PG-ODI). Data are further divided according to the characteristics of the subject's SDB. Data presented as intra-class correlation coefficient (r), 95% confidence interval and p value. n=number of subjects in each group.

For the diagnosis of moderate-to-severe SDB (≥15 events/hour) by polygraphic-AHI, -RDI or –ODI, ApneaScan™ had a consistently high sensitivity and negative predictive value at the optimal cut-off point (Table 4). Specificity and positive predictive value were weaker, though this was less marked when comparing AP-RDI with PG-RDI.

	AP-RDI vs PG-AHI	**AP-RDI vs PG-RDI**	**AP-RDI vs PG-ODI**
Area under ROC curve	0.84 (0.74-0.95, p<0.01)	0.79 (0.66-0.92, p<0.01)	0.88 (0.77-0.98, p<0.01)
Optimal AP-RDI cut-off for the diagnosis of moderate-to-severe SDB (≥15 polygraphic events/hour)	30.5	29.0	30.5
Sensitivity	95%	87%	94%
Specificity	69%	71%	68%
Positive predictive value	68%	82%	58%
Negative predictive value	95%	81%	94%

Table 4. Comparison of the receiver operator characteristic (ROC) curves analysing ApneaScan™ for the diagnosis of moderate to severe SDB (PG-AHI, PG-RDI or PG-ODI≥15 events/hour). Data are presented as value (95% confidence interval, p value) or percentage.

The mean difference between ApneaScan™-RDI and Polygraphy-AHI was 18.4 events/hour. It is not previously known if there are patient characteristics which predispose to greater or poorer accuracy of ApneaScan™ compared against sleep polygraphy. To investigate this, I divided patients in to those with closer correlation between ApneaScan™ and polygraphy (difference ≤ 18.4 events/hour) and those with lower correlation (difference≥18.4 events/hour). I then assessed mean BMI, weight, height, EF, plasma BNP and PG-AHI in the two groups to identify if there were characteristics which predisposed to closer or wider correlation, which may then be taken in to account when reviewing data in a clinical setting.

None of the physical characteristics were found to be predictive (Table 5). There was a trend towards more severe SDB in those with closer correlation, but this did not reach statistical significance (20.5±17.8 v 13.0±10.9, p=0.07). Body mass index, weight, height, ejection fraction and B-type natriuretic peptide concentration did not differ significantly between the groups and are thus not independent predictors of ApneaScan accuracy, based on these data.

Characteristic:	**Those with difference > mean (>18.4/hour)**	**Those with difference ≤ mean (≤18.4/hour)**	**P value**
BMI	26.3±4.6	27.3±4.1	0.49
Weight	80.6±20.2	78.7±15.9	0.75
Height	173.2±9.0	168.9±9.1	0.16
EF	30.4±9.2	26.1±9.4	0.11
BNP	421±377	720±750	0.15
PG AHI	13.0±10.9	20.5±17.8	0.07

Table 5. Comparison of the characteristics of those with closer correlation between ApneaScan™-RDI and polygraphy-AHI (difference less than the mean difference of 18.4/hour) and those with poorer correlation (difference greater than the mean difference). Data presented as mean±SD. BMI – body mass index, EF – ejection fraction, BNP – B-type natriuretic peptide, PG-AHI – Polygraphic Apnoea-Hypopnoea Index.

3.3.8 The effect of CPAP therapy on ApneaScan-Respiratory Disturbance Index

Seven subjects in this study had previously-undiagnosed moderate-to-severe OSA and were referred for consideration of CPAP therapy. Of these 7, 4 declined CPAP therapy due to lack of daytime somnolence and 2 were unable to tolerate CPAP and discontinued therapy within a few nights; it was not possible to retrieve ApneaScan data for these nights. Only one patient continues on CPAP therapy with a reported improvement in symptoms of somnolence and lethargy. The ApneaScan graph during initiation of CPAP therapy is

presented as Figure 12. There appears to be a decrease in AP-RDI from pre-treatment to post-treatment levels. However, the most marked change is the high frequency of missing data after the commencement of CPAP. It could be postulated that the electromagnetic and muscular noise associated with CPAP therapy interferes with the quality of the ApneaScan signal and leads to rejection of data by the algorithm.

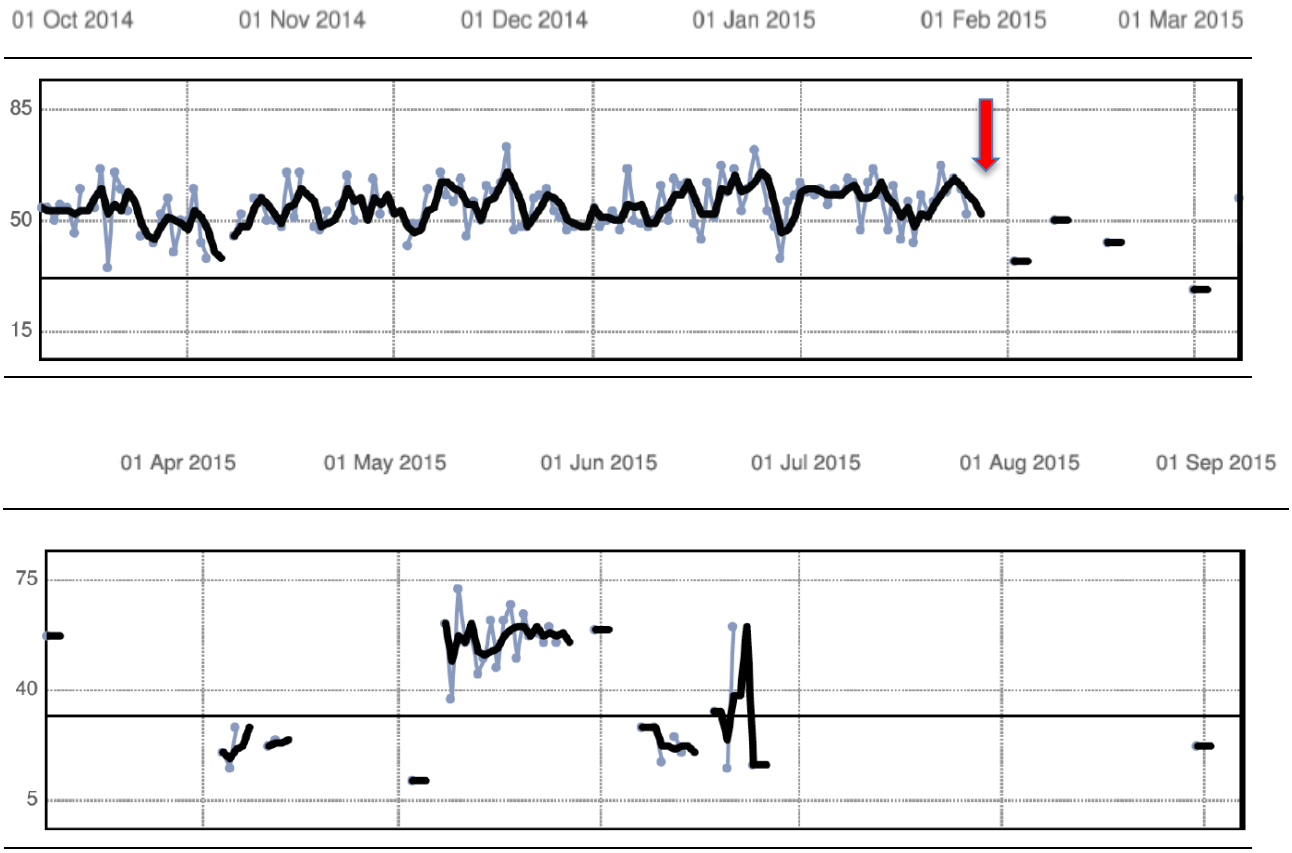


Figure 12. ApneaScan-RDI graph downloaded from the Latitude™ remote monitoring system for a single patient with severe OSA. CPAP treatment was started on 29th January 2015 (arrow).

3.3.9 Characteristics of subjects in whom ApneaScan™ did not record

Nine subjects in this study had no ApneaScan™ data recorded on the night of the sleep study, despite the respiratory sensor being 'on' or 'passive'. Some patients only have a few data points per month. The question arises as to whether there are certain factors which

impair the performance of the algorithm and lead to automatic rejection of data. A comparison of the 9 patients with no data and the remainder of the cohort with data is presented in Table 6.

Characteristic	**Missing data group (n=9)**	**Complete data group (n=54)**	**P Value**
Age	69±12 years	68±13 years	0.83
Height	172±5 cm	171±9 cm	0.75
Weight	81±14 Kg	80±18 Kg	0.87
BMI	27±4 Kg/M^2	27±4 Kg/M^2	1.00
Ejection Fraction	32±8%	28±9%	0.22
BNP	307 (247-696) umol/l	357 (145-356) umol/l	0.96
Generator position - Pre-pectoral - Sub-pectoral - Not Documented	 6 (67%) 3 (33%) 0	 29 (54%) 21 (39%) 4 (7%)	 0.72 1.00 1.00
Mean PG-AHI	14±11/hour	17±15/hour	0.57
Lung disease	0	Unknown	
Type of device - CRTD - CRTP - ICD	 6 (67%) 3 (33%) 0	 37 (68%) 7 (13%) 11 (19%)	 1.00 0.15 0.34
Time from implant	838 (147-1988) days	4 (1-90.5) days	0.06
RV lead impedance	591±288 Ohms	567±220 Ohms	0.77

Table 6. A comparison of the characteristics of those patients with complete ApneaScan data at the point of the sleep study and those in whom ApneaScan failed to record.

There was no difference between the complete and missing data groups with regard to the characteristics listed in Table 6. There was a trend towards longer time from implant in those with missing data but this did not reach statistical significance and should be interpreted with caution in the context of a low sample size. If this is borne out in a larger sample, one explanation may be that pocket fibrosis affects the performance of ApneaScan™. None of the patients with missing data had chronic lung disease, but one of the nine had dextrocardia and one had congenitally-corrected transposition of the great arteries and a heart that is significantly deviated to the right of the sternum on chest radiograph. Both of these conditions may increase the distance between the RV lead and

the generator and thus affect the signal quality and degree of interference, resulting in rejection of the data by the algorithm.

3.4 Discussion

3.4.1 The accuracy of ApneaScan™ for the diagnosis of moderate-to-severe SDB in patients with heart failure

The main finding of this study is that, at a cut-off of 30.5 events per hour, ApneaScan™ is a sensitive means of screening for moderate-to-severe SDB in patients with HF, with a high negative predictive value of 95%. In this population, ApneaScan™ could be used as a good 'rule out' test for moderate-to severe SDB (but not mild SDB).

If a firm diagnosis of SDB is sought, readings above 30.5 events/hour should be confirmed with formal sleep studies as the specificity and positive predictive value at this threshold for the diagnosis of moderate-to-severe SDB are relatively low (69% and 68% respectively). An ApneaScan™-RDI of ≥30.5/hour may not, therefore, reliably mean a polygraphic-AHI ≥15/hour. This is especially true in those with mild SDB, amongst whom 41% had a 'false positive' AP-RDI in this cohort. Further investigation of high readings may also be important as ApneaScan™ cannot differentiate between OSA and CSA and management of these two conditions is very different. Furthermore, based on these data, 5% of 'true positives' would be missed by ApneaScan™, so any patient in whom there is a high suspicion of SDB should be considered for a sleep study even if the ApneaScan™ reading is less than 30.5/hour. This may include patients with daytime somnolence, those who report fragmented sleep or those in whom a partner has observed erratic sleep-breathing patterns. A suggested investigation pathway for patients with HF and devices with ApneaScan is presented in Figure 12.

It must be stated that, although the number of subjects in this study is greater than in most previously published studies of pacemaker algorithms for the diagnosis of SDB, I did not reach the pre-specified recruitment number of 72, based on the power calculation (please see section 2.1.4). This must be borne in mind when interpreting the results. Please see section 3.4.4 for further limitations of the study.

In current practice, SDB is usually diagnosed on the basis of a single night sleep study. With ApneaScan™, continuous monitoring of the RDI is possible and the last 3 months of data are available at each device interrogation. There is no consensus as to whether possible significant SDB should be diagnosed based on individual readings above the 30.5 events/hour threshold or whether the diagnosis should be reserved for those with a mean or median value above the threshold. The implications of these two approaches for treatment and prognosis are not known. In the flow diagram, mean ApneaScan™ values are suggested as a more accurate measure of the true severity of SDB, but it should be noted that this is not based on evidence, guidelines or current practice. The night-to-night variability of SDB as quantified by ApneaScan™ is explored in Chapter 4.

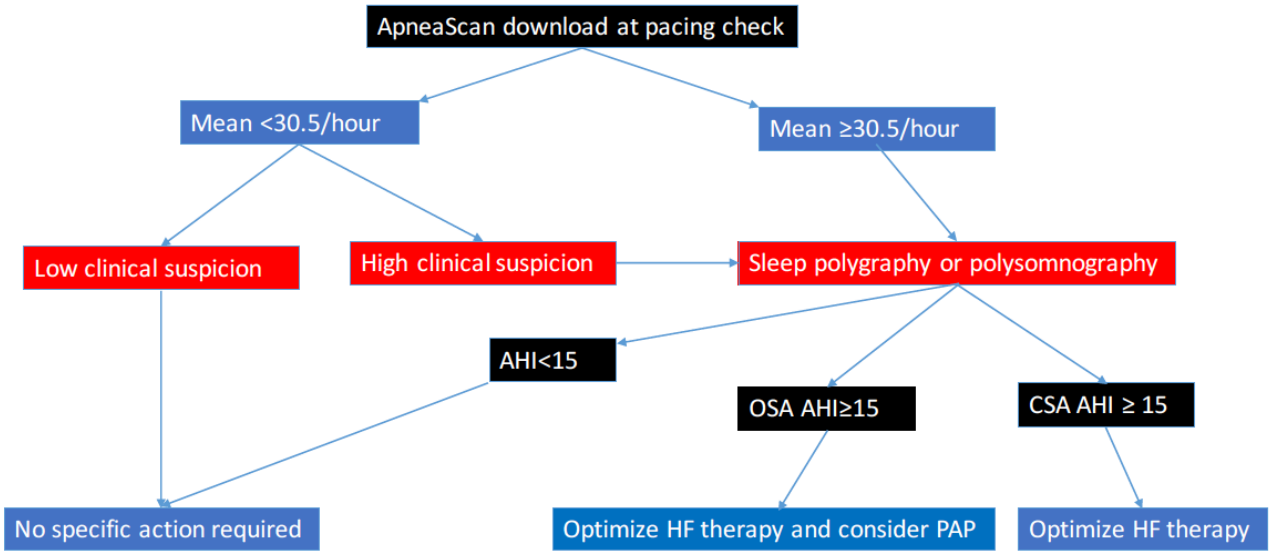


Fig 13. Suggested flowchart for the investigation of SDB in patients with HF and implanted devices with ApneaScan™ function. AHI – Apnoea-Hypopnoea Index, OSA – obstructive sleep apnoea, CSA – central sleep apnoea, HF – heart failure, PAP – positive airway pressure. 'High clinical suspicion' refers to those in whom there is excessive daytime somnolence, snoring, fragmented sleep or observed erratic sleep-breathing patterns. 'Low clinical suspicion' refers to those without any of these features.

Given the emerging evidence that ODI correlates more closely with adverse outcomes than AHI, it is clinically useful that ApneaScan™ correlates closely with ODI in this population and has a similarly strong sensitivity and negative predictive value at an ApneaScan™ threshold of 30.5 events/hour (147). The lower specificity and positive predictive value necessitate further investigation as with AHI. The close correlation between ODI and AHI in this population is presented in Appendix 3.

As ApneaScan™ records a respiratory disturbance index, irrespective of oxygen desaturation, it is interesting that correlation with polygraphic-RDI is not greater than with PG-AHI and PG-ODI. The most likely explanation is that, in a HF population in whom there is frequently a degree of nocturnal pulmonary oedema and limited physiological reserve, almost all apnoeic-hypopnoeic events are accompanied by desaturation and therefore fulfil

diagnostic criteria for AHI, ODI and RDI. This may be particularly so with the 2012 AASM guidelines which necessitate only a ≥3% desaturation for an AHI event, as opposed to the ≥4% required in the 2007 guidelines (216). This is borne out by the very high correlation between PG-AHI, PG-ODI and PG-RDI in this population, presented in Appendix 3.

3.4.2 Possible explanations for the over-reading of SDB events by ApneaScan™

The question then arises as to why ApneaScan™ over-reads apnoeic-hypopnoeic events compared to sleep polygraphy, even when compared against PG-RDI. Some of the difference is accounted for by the fact that ApneaScan™ measures apnoeic-hypopnoeic events irrespective of oxygen desaturation, whereas an AHI and ODI event requires desaturation to be recorded. However, as discussed above, very few apnoeic-hypopnoeic events occur without desaturation and the mean difference between AP-RDI and PG-RDI is only marginally smaller than when AP-RDI is compared against PG-AHI or PG-ODI (15.3, 18.4 and 18.2/hour respectively). There must, therefore, be other factors leading to the over-identification of events by ApneaScan.

It is known that various factors affect transthoracic impedance and may lead to misdiagnosis of events by ApneaScan™. These factors include position, movement, myopotentials and cardiac contraction (148). In addition, rostral shift of fluid overnight in patients with HF increases the volume of extracellular fluid in the lungs and thus reduces transthoracic impedance (54). Other patient factors may also affect transthoracic impedance or quality of the electrical signal. These may include obesity, underlying lung disease and frequency of abdominal breathing.

However, in this study, patient BMI, weight, height, BNP concentration, PG-AHI and ejection fraction did not predict the correlation between ApneaScan™ and PG-AHI. There was, however, a trend towards greater correlation in those with greater BNP concentration and lower ejection fraction, as well as a greater PG-AHI. This is likely to be due to the greater correlation between ApneaScan™ and polygraphy in those with moderate-to-severe SDB. Sub-pectoral generator position was also associated with closer correlation between AP-

RDI and PG-AHI than pre-pectoral, which is likely to be due to greater proximity to the lung, less fat and muscle between the generator and lung and possibly less movement of the generator in the pocket resulting in reduced noise on the transthoracic electrical signal.

That ApneaScan™ is more accurate in those with moderate-to-severe SDB is unsurprising, as apnoeic-hypopnoeic events are more marked in more severe SDB and the more frequent the apnoeic-hypopnoeic events, the less the impact of occasional misdiagnoses. Similarly, respiratory-disturbance events in OSA are more abrupt than in CSA and apnoeas are more absolute than hypopnoeas, which leads to greater correlation between polygraphy and ApneaScan™ in these circumstances.

ApneaScan™ is programmed to record an event when the amplitude of the transthoracic impedance wave falls by ≥27% for ≥10 seconds. It may be that this threshold could be adjusted to improve correlation and specificity, although inevitably at the expense of sensitivity and negative predictive value. Boston Scientific did not wish to release details of their own testing of the algorithm and the rationale for the selection of this threshold for the detection of an event. Increasing the fall in the transthoracic impedance wave amplitude required for the diagnosis of an event (to 30%, 40% or 50% for example) would increase the specificity and positive predictive value of the algorithm, but at the expense of sensitivity and negative predictive value. As ApneaScan™ is a screening algorithm, rather than a diagnostic algorithm, it is more important that there are few false negatives and this may be why a relatively low threshold was chosen.

Investigation of the characteristics of the 9 patients without ApneaScan™ data did not determine a consistent cause, but it was interesting that two of the patients had RV leads placed relatively to the right of the chest due to congenital heart disease, which may have affected the quality of the signal. The loss of data is regrettable but is in keeping with other pacemaker algorithms measuring transthoracic impedance.

Other device algorithms have used changes in transthoracic impedance to monitor measures of health. As transthoracic impedance decreases with increased pulmonary fluid,

this has been used as an 'early warning' of HF decompensation and incorporated in to remote monitoring systems (217). Two algorithms have been developed which monitor this - OptiVol™ (Medtronic, Minn., USA) and CorVue™ (St Jude, Minn., USA). Evidence for efficacy of these algorithms is variable, with some studies reporting sensitivity for the identification of HF decompensation requiring hospital admission as low as 20.7% and other as high as 76% (156,218), possibly reflecting different populations studied, blinding, enrolment timeframe and definition of events. In the SENSE-HF study, there was a marked improvement in sensitivity as time from device implant increased, which may be due to reduction in pocket haematoma or oedema (156). In this study, there was no significant change in ApneaScan™ measures over the first month post-implant (see Chapter 4) but the study was not powered to detect this. A fundamental difficulty with using pacing devices to monitor changes in transthoracic impedance, either acutely due to breathing or chronically due to oedema, is that only a single vector is measured between the RV lead tip and the generator, which may not reflect other areas of the chest. Some research has suggested that this vector can be representative of markers of general pulmonary congestion, but conclusive evidence of clinical utility in preventing HF events is lacking (155,217,219).

3.4.3 Comparison of ApneaScan™ with previous pacemaker algorithms for the detection of sleep-disordered breathing

Three previous studies have examined pacemaker algorithms using transthoracic impedance to assess SDB, although none have examined a HF population specifically. This is also the only study to examine an algorithm on ICD and CRT devices.

An early feasibility study by Defaye and colleagues in 2004 examined the transthoracic impedance measurements over 1 night from 46 patients with pacemakers for bradycardia with simultaneous polysomnography. They recorded an event when transthoracic impedance fell by ≥50% for ≥10 seconds (151). The area under the ROC curve was 0.75

with an optimal cut-off for the diagnosis of severe SDB of 30.6 events/hour, producing a sensitivity and specificity of 75% and 94% respectively.

Two years later, Shalaby and colleagues performed a similar study using a purpose-designed automated computer analysis programme to determine the pacemaker RDI and compared against simultaneous polysomnography (152). The algorithm recorded an event when the transthoracic impedance amplitude fell by ≥30% for ≥10 seconds. In 60 patients with pacemakers for bradycardia, the Pearson's correlation coefficient between pacemaker-RDI and PG-AHI was 0.80. The area under the ROC curve was 0.85 and the optimal cut-off for the diagnosis of moderate-to-severe SDB by the pacemaker algorithm was 37 events/hour, producing sensitivity and specificity of 82% and 88% respectively.

More recently, the DREAM study assessed a comercially available algorithm on Sorin brady pacemakers (Clamart, France) which uses transthoracic impedance to generate an overnight RDI in a similar manner to ApneaScan™ (153). Polysomnography and pacemaker RDI data were collected on 36 patients of whom 5 (14%) had no suitable pacemaker data at download. The pacemaker algorithm recognised an event if the amplitude of the transthoracic impedance wave fell by ≥50% for ≥10 seconds (as opposed to 27% in ApneaScan™). Based on these 31 patients, the area under the ROC curve was 0.90 and, in contrast to previous studies, the optimal cut-off for the pacemaker algorithm to detect severe SDB was lower at 20 events/hour, yielding a sensitivity of 88.9% and specificity of 84.6%.

The performance of ApneaScan™ is broadly in keeping with these previous studies. Compared with polygraphy-AHI, the area under the ROC curve was 0.84 with an optimal cut-off for the diagnosis of moderate-to-severe SDB of 30.5 events/hour, producing a sensitivity of 95% and specificity of 69%. The differences in optimal cut-off and, as a consequence sensitivity and specificity, between this and the previous studies are largely explained by the different amplitude thresholds employed (50% vs. 30%. vs. 27%) and the decision to test the accuracy in diagnosing moderate-to-severe SDB rather than only severe

SDB. The frequency of missing data from the ApneaScan algorithm (14%) is the same as in the DREAM study.

With the threshold for the detection of moderate-to-severe SDB set at 30.5 events/hour, ApneaScan™ is a sensitive means of screening for SDB with a strong negative predictive value. It may therefore be a useful screening tool to identify those at low risk of significant SDB who do not require sleep studies. Those with a mean ApneaScan-RDI above 30.5 events/hour, or those in whom the diagnosis is likely despite a lower ApneaScan™-RDI, should be investigated with a sleep study to guide further management. Using this algorithm could prevent unecessary sleep studies, help focus resources and aid physicians in the management of patients with HF.

3.4.4 Limitations of the study

This study did not reach its pre-specified sample size, largely due to the high rate of exclusion and absent data from the ApneaScan™ algorithm (54 subjects with complete data vs. 60 determined from the power calculation). Despite this, the study is the largest of a commercially available pacemaker algorithm for the diagnosis of SDB. The published DREAM study, for example, had complete data on only 31 patients (153). In order to confidently assess the ApneaScan algorithm, further recruitment would be required which was not possible due to time restraints.

In this study, I did not directly assess the performance of the ApneaScan™ algorithm against measured transthoracic impedance changes or apnoeic events. This was a clinical study assessing the utility of the algorithm in practice. This means that I cannot comment on the relationship between ApneaScan™-identified events and true changes in transthoracic impedance. I requested details of in-house testing from Boston Scientific but this was declined. The ApneaScan™ data available at download does not permit detailed adjudication of individual apnoeic events against sleep polygraphy. The technology is similar in principle to that used in the previous studies of pacemaker algorithms for the diagnosis of SDB, which demonstrated good agreement between pacemaker-identified

changes in transthoracic impedance and individual apnoeic-hypopnoeic events, but further details are not available (151,152).

The use of sleep polygraphy as opposed to full polysomnography may lead to some error, as SDB measures are averaged over the whole recording time rather than only the time spent sleeping. Previous studies have, however, shown good correlation between the techniques (142). Sleep polygraphy is also a commonly used 'real-world' diagnostic test for SDB, with full polysomnography largely restricted to specialist units or for complex diagnostic cases.

Some polygraphy studies were affected by poor quality data, most frequently due to the finger saturation probe or the nasal cannulae becoming displaced. In the case of displaced nasal cannulae, PG-AHI and PG-RDI events were estimated from chest and abdominal excursion and oxygen desaturation (for AHI), with additional information from the Embletta™ X-Flow function if required (this function on Embla Rem-Logic™ software automatically estimates nasal airflow from chest and abdominal movement). In the 22% of subjects with incomplete oxygen saturation data, the ODI and AHI were assumed to equal the RDI for the duration of incomplete data. Whilst this introduces inaccuracy, correlation between the three measures in this study is very high and therefore the uncertainty is likely to be acceptable.

In 14% of patients, no ApneaScan™ data were recorded on the study night. Whilst this loss of data is regrettable, it is in keeping with the DREAM study on a similar algorithm (153). In addition, 34% of patients enrolled in the study did not complete either the sleep polygraphy study, ApneaScan™ download or both. The most common reasons were patients receiving devices without ApneaScan function after consenting and problems downloading ApneaScan™ data via older generation Latitude™ systems. Whilst this is unlikely to have introduced bias, and no important differences in baseline characteristics were identified between those enrolling in and completing the study (Table 1), it cannot be excluded. Similarly, some of the frailer patients refused or withdrew consent which may have biased outcomes. The non-completion rate is higher than that predicted in the power

calculation, but the total completing the study only marginally below the target of 60 subjects.

Despite these limitation, so far as we are aware this is the largest study of a commercially-available algorithm on complex devices for the diagnosis of SDB in a HF population. It is a 'real world' study with important and clinically useful data on the use of the ApneaScan™ algorithm in the management of patients with HF.

3.5 Conclusions

SDB is common in patients with HF and implanted cardiac devices, often in the absence of obesity or daytime somnolence. Although 6 patients short of the pre-specified sample size, these data suggest an optimal ApneaScan™-RDI cut-off of 30.5 events/hour, at which threshold ApneaScan™ is a sensitive screening test for moderate-to-severe SDB in patients with HF with a strong negative predictive value. This cut-off differs only slightly from the Boston Scientific-suggested value of 32 events/hour for the detection of significant SDB. Values above 30.5/hour require investigation, if a firm diagnosis is sought, with a sleep study but ApneaScan™ may be a useful 'rule out' test preventing unnecessary sleep studies in those at low likelihood of SDB (i.e. those with ApneaScan™-RDI <30.5/hour).

Incorporating data from this algorithm into patient management may facilitate diagnosis of SDB via appropriate selection of patients requiring sleep studies, as well as possibly assessing response to therapy and predicting HF decompensation. ApneaScan™, which is freely available at every device download, may become a useful tool for the clinician caring for patients with HF and implanted devices.

Chapter 4: Variability in the severity of sleep-disordered breathing over 28 nights as assessed by the ApneaScan™ algorithm in patients with stable heart failure

4.1 Introduction

Sleep-disordered breathing (SDB) is usually diagnosed on the basis of a single night polysomnography or polygraphy study, with repeat studies done only if the clinical condition changes or to assess response to treatment. Although most previous studies have demonstrated a low variability in severity and type of SDB in patients with HF, these were only done over 2 or 4 nights and questions remain regarding the variability over a greater number of nights. This is pertinent in the HF population in whom changes in fluid status over days, weeks or months may significantly influence SDB. In addition, there is thought to be a "first night effect" in patients wearing monitoring devices, whereby sleep is not representative of the person's norm (220).

The majority of studies investigating variability in SDB have been done in the non-HF population. The degree of variability of SDB in the HF population over longer time periods is not known. Making an accurate diagnosis of SDB in HF is important as CPAP therapy may be offered to those with moderate-to-severe OSA, with possible improvement in symptoms and HF outcomes, and those with CSA represent a high-risk group who may benefit from more intensive therapy. In addition, making an true diagnosis is important as the SERVE-HF trial demonstrated increased mortality in those with HF and significant CSA treated with adaptive servo-ventilation compared with optimal medical therapy and the CANPAP trial found no mortality benefit for CPAP in CSA (57,186). If there is significant night-to-night variability in type and severity of SDB in those with HF, repeated sleep studies would be necessary to reach a reliable diagnosis, with significant implications for health service resources, particularly with the rising prevalence of HF. There is currently no consensus as to whether repeat tests are necessary and, if so, how many and how far apart.

The ApneaScan™ algorithm on Boston Scientific ICD and CRT devices uses changes in transthoracic impedance with respiration to determine a respiratory disturbance index (AP-RDI), which correlates with polygraphic apnoea-hypopnoea index (PG-AHI – please see chapter 3). Data collected over the preceding 3 months are available at each device download, with a single point on the graph representing the mean RDI over one night. This presents a unique opportunity to study changes in RDI over more nights than has previously been possible with formal sleep studies.

Selected patients with HF, intra-cardiac electro-mechanical dyssynchrony and CSA demonstrate significant improvement in AHI following implantation of a CRT device (201). There are little published data on the speed and persistence of this effect and this may also be assessed by ApneaScan™.

The aim of this study is to determine the variability in AP-RDI over 28 consecutive nights to determine short-term variability, and over 92 consecutive nights to assess longer-term variability, in patients with HF and ICD or CRT devices with ApneaScan™ function. A sub-study will investigate the rate of change in AP-RDI in those with CSA following implantation of a CRT device.

4.2 Methods

4.2.1 Eligibility and baseline tests

Patients were eligible for recruitment if they fulfilled all of the following criteria:

- Impaired LV systolic function (ejection fraction ≤40%)
- No known diagnosis of SDB
- With or due to receive an ICD or CRT device with ApneaScan™ function.

Patients were recruited from the Royal Brompton, Harefield and St George's Hospitals, London. At the time of recruitment, patients underwent the following tests and questionnaires:

- Echocardiography (performed by British Society of Echocardiography-accredited echocardiographers)
- Plasma B-type natriuretic peptide (BNP) assay (measured in the biochemistry laboratories of the respective hospitals)
- Electrocardiography
- Epworth sleepiness score
- Minnesota Living with Heart Failure Questionnaire
- Routine clinical examination and history-taking

Patients were excluded from this study for the following reasons:

- <21 data points in the last 28 nights on ApneaScan™ (28-night group) or <63 data points over 92 nights (92-night group).
- Unsuccessful ApneaScan™ download

4.2.2 ApneaScan™ data acquisition and analysis

Patients for this study were drawn from the ApneaScan™ validation and prognosis studies (presented in chapters 3 and 5). For the 92-patient group, the Latitude™ system was used to obtain the data, as 92-night data were not available for most subjects in the pacing notes. Only patients with ICD and CRTD devices are on the Latitude™ system; patients with CRTP devices were therefore excluded from the 92-night group. Data from patients implanted at St George's hospital, those who had been transferred to other hospitals for follow-up after the 1 month pacing check, and those in whom there were problems with obtaining Latitude™ data were also unavailable for the 92-night group (Fig. 3). The 92-night group consisted of different patients from the 28-night group due to these logistics of obtaining data. Sixteen patients were common to both groups, the remaining 24 patients in the 28-night group and 31 in the 92-night group were unique to that group.

The ApneaScan™ graph was printed at the time of device interrogation, at least 4 weeks following device implantation or generator change, either from the programmer or from the Latitude™ remote monitoring system. An example of an ApneaScan™ graph is shown in figure 1. For the 28-night group, the AP-RDI for the last 28 nights prior to device interrogation was recorded by scanning each graph on to a computer and using a scale to record the RDI per night. For those in the 92-night group, the most recent 92-night data download was analysed using the nightly figures provided on the Latitude™ platform.

In order to assess the change in AP-RDI following CRT, the nightly AP-RDI was recorded for the first 28 nights following implant in those with moderate-to-severe CSA or OSA by polygraphy (PG-AHI≥15/hour) receiving a CRT device *de novo.*

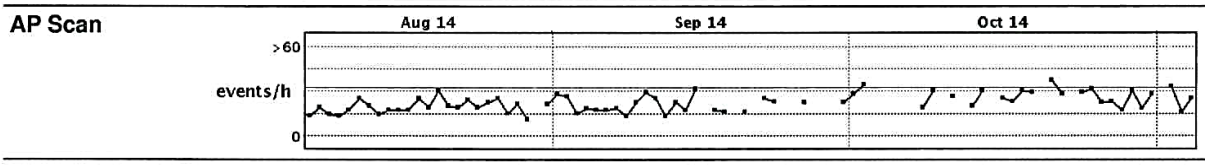


Figure 1. The ApneaScan™ graph as displayed on a device programmer or print-out. Each dot represents the mean AP-RDI (events/hour) for a single night. A line at 32 events/hour is provided by the manufacturer.

4.2.3 Statistical analysis

Quantitative variables are expressed as mean and standard deviation if normally-distributed and median and interquartile range if non-normally distributed. Student t-test was used to assess differences in continuous data between groups. Chi squared test (Fisher's exact) was used for comparing categorical data. Consistency of AP-RDI was assessed using the intra-class correlation coefficient with 0.75 or greater taken as demonstrating good correlation. Statistics were analysed using SPSS™ v24 (IBM, Armonck, New York).

4.2.4 Contribution by the candidate

I was responsible for screening and recruiting the patients. I obtained the baseline data and the ApneaScan™ data both from the pacing clinic and the Latitude™ system. I collated the results and performed the statistical analysis.

4.3 Results

4.3.1 Subject enrolment

Patients for the 28-night group were drawn from the "Accuracy of the ApneaScan™ algorithm for the diagnosis of sleep-disordered breathing in heart failure" study (please see chapter 3). Of the 95 patients enrolled in the *accuracy* study, 35 had adequate ApneaScan™ and polygraphy data and were included in the 28-night group. For the 92-night group, subjects were drawn from the "Accuracy of the ApneaScan™ algorithm for the diagnosis of sleep-disordered breathing in heart failure" study and the "Prognostic implications of sleep-disordered breathing in heart failure as diagnosed by ApneaScan™" study (chapters 3 and 5). Of the 161 patients enrolled in these studies, 47 met criteria and were included in the analysis.

The enrolment flow chart and baseline characteristics are presented in figures 2 and 3 and table 1.

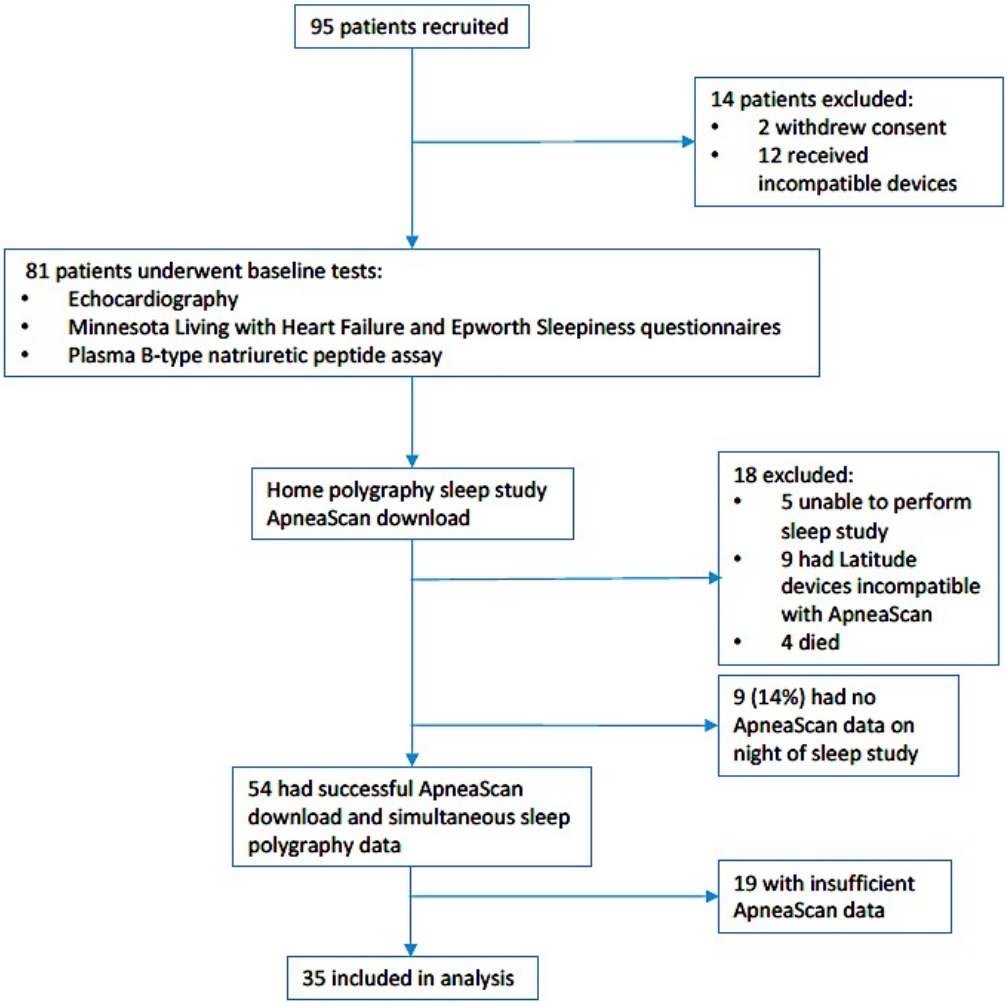


Figure 2. Flow chart of patient recruitment and exclusion for the 28-night study group.

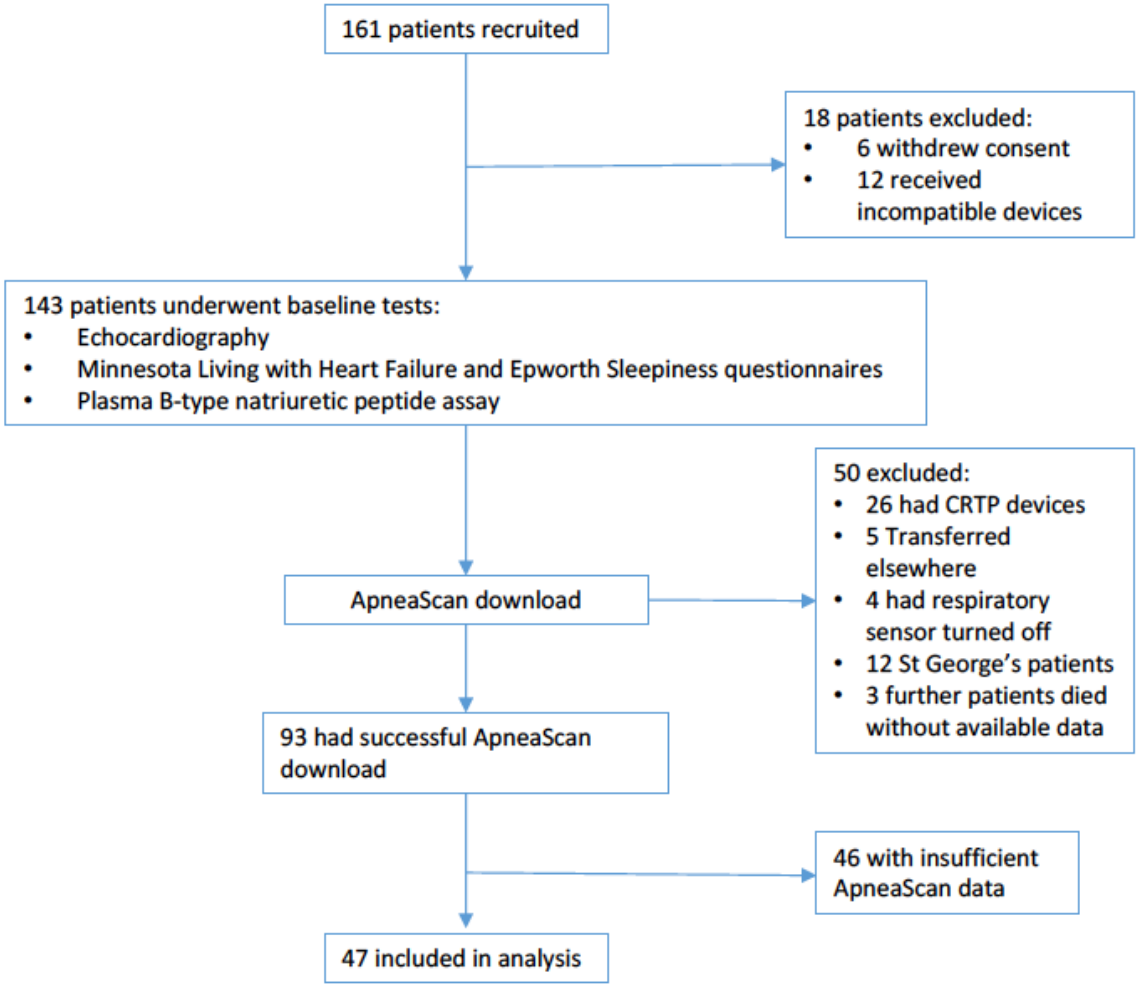


Figure 3. Flow chart of patient recruitment and exclusion for the 92-night study group.

Characteristic	Mean ± standard deviation (%)		P value
	28-Night Study Group (n=35)	**92-Night Study Group (n=47)**	
Age	71±11 years	65±13 years	0.03
Sex	80% Male	83% Male	0.54
Aetiology of Heart Failure; Ischaemic Heart Disease Dilated Cardiomyopathy Valvular Congenital Sarcoidosis Not documented	 17(48%) 14 (40%) 1 (3%) 1(3%) 2 (6%) 0 (0%)	 18 (38%) 20 (43%) 3 (6%) 1 (2%) 4 (9%) 1 (2%)	 0.38 1.00 0.63 1.00 1.00 1.00
Ejection fraction	28±10%	31±12%	0.23
B-type natriuretic peptide concentration (median (IQR))	337 (217-626) umol/l	310 (103-455) umol/l	0.51
NYHA class	I – 0 (0%) II - 19 (54%) III - 16 (46%)	I – 7 (15%) II – 25 (53%) III – 13 (28%)	0.02 1.00 0.11
Heart failure pharmacotherapy: **ACEi/ARB** **betablocker** **aldosterone antagonist** **ivabradine** **loop diuretic** **thiazide**	 33 (94%) 28 (80%) 22 (63%) 5 (14%) 26 (74%) 2 (9%)	 44 (94%) 40 (85%) 22 (47%) 4 (9%) 26 (55%) 2 (4%)	 1.00 0.57 0.26 0.49 0.10 1.00
Minnesota living with heart failure score	35±23	33±26	0.72
Epworth sleepiness score (median (IQR))	5 (4-9)	6 (3-11)	0.20
Body mass index **(kg/m²)**	26±4	27±6	0.40
Device implanted	10 (29%) ICD 21 (60%) CRTD 4 (11%) CRTP	13 (28%) ICD 34 (72%) CRTD 0 (0%) CRTP	1.00 0.34 0.03
Implanting hospital - **Royal Brompton** - **Harefield** - **St George's**	 21 (60%) 11 (31%) 3 (9%)	 36 (77%) 11 (23%) 0	 0.15 0.46 0.07

Table 1. Baseline characteristics of patients completing the study. ACEi/ARB – ACE Inhibitor/Angiotensin Receptor Blocker; ICD – Implantable Cardioverter-Defibrillator; CRTD/P – Cardiac Resynchronisation Therapy-Pacemaker/Defibrillator.

4.3.2 Variability of ApneaScan™-RDI over 28 nights

35 subjects had sufficient ApneaScan™ data and were included in the analysis. 23 subjects were studied 4-6 weeks after implantation of a new device, 5 subjects 4-6 weeks after a generator change and 7 subjects were studied several months-to-years after device implantation.

For these 35 subjects over 28 consecutive nights, the mean AP-RDI was 34.2±11.5/hour. The mean coefficient of variation per subject over 28 nights was 18.7±7%. The mean intra-class correlation coefficient per subject was 0.99 (95% CI 0.98-0.99, P<0.001), suggesting minimal variability in AP-RDI.

Of those with a mean AP-RDI greater than the optimal cut-off for the diagnosis of moderate-to-severe SDB (30.5 events/hour, n=22), a mean of 3.5±4.4 out of the 28 nights (12.5±15.7%) were at an AP-RDI of <30.5/hour, which may lead to false negative results if a sleep study was performed on these nights. Thirteen out of 22 subjects (59%) with a mean AP-RDI>30.5/hour had at least one night out of 28 at a AP-RDI below 30.5/hour. The frequency of these 'false-negative' nights was greatest in those with a mean AP-RDI between 30.5 and 40.5/hour (mean of 6.9±3.6 out of 28 nights, n=10) and rare in those with a mean AP-RDI > 40.5/hour (0.4±0.9 out of 28 nights, n=12). For those with a mean AP-RDI<30.5, 14% of nights were at an AP-RDI>30.5, which may lead to a false-positive result (Table 2).

Mean AP-RDI (events/hour)	Number of subjects with ≥1 night out of 28 with AP-RDI<30.5/hour	Number of subjects with ≥1 night out of 28 with AP-RDI≥30.5/hour	Mean number of nights in 'incorrect' range* per subject (out of 28 nights)	Likelihood of obtaining a non-representative** AP-RDI based on a single-night study
<30.5 (n=13)	13 (100%)	11 (85%)	3.9±3.6	14.0%
30.5-40.4 (n=10)	10 (100%)	10 (100%)	6.9±3.6	24.6%
≥40.5 (n=12)	3 (25%)	12 (100%)	0.4±0.9	1.4%

Table 2. Frequency of AP-RDI readings outside the subject's mean, divided in to those with a mean AP-RDI of <30.5, 30.5-40.4 and ≥40.5/hour.
* 'Incorrect' range refers to AP-RDI>30.5 in those with a mean AP-RDI<30.5, or <30.5 in those with a mean AP-RDI≥30.5.
** 'Non-representative' refers to an AP-RDI>30.5 in those with a mean AP-RDI<30.5, or <30.5 in those with a mean AP-RDI≥30.5.

There was no difference in night-to-night consistency between those with moderate-to-severe OSA and moderate-to-severe CSA, nor between those with moderate-to-severe SDB or those without as assessed by sleep polygraphy. The mean AP-RDI for different groups with coefficient of variation and ICC is presented in Table 3.

Group	Mean AP-RDI ± SD (events/hour)	Coefficient of Variation	Intra-class correlation coefficient ± 95%CI
All subjects (n=35)	34.2±11.5	18.7%	0.99 (0.98-0.99, p<0.001)
Moderate-to-severe CSA (n=11)	38.9±9.7	17.3%	0.99 (0.97-1.00, p<0.001)
Moderate-to-severe OSA (n=5)	45.4±7.2	17.0%	0.95 (0.82-1.00, p<0.001)
Moderate-to-severe SDB (n=16)	41.0±9.2	17.5%	0.98 (0.95-1.00, p<0.001)
Mild-or-no SDB (n=19)	30.3±10.1	20.2%	0.99 (0.98-1.00, p<0.001)

Table 3. Mean AP-RDI of different groups, categorised according to the result of the sleep polygraphy study, with mean and standard deviation (SD) of AP-RDI readings over 28 nights (expressed as value±standard deviation, coefficient of variation and intra-class correlation coefficient (ICC)). P=NS for differences in coefficient of variation and ICC between groups.

4.3.3 Variability of ApneaScan™-RDI over 92 nights

47 subjects were studied over 92 consecutive nights. All had had the device implanted or box changed over 1 month before the start of data collection. Compared to the 28-night group, the 92-night group were younger (mean age 65±13 vs. 71±11 years, p=0.03) and had a higher proportion of patients with NYHA I symptoms (7 (15%) vs. 0, p=0.02). There were no other significant baseline differences between the groups.

For these 47 subjects over 92 consecutive nights, the mean AP-RDI was 34.6±8.4/hour. The mean coefficient of variation per subject over 92 nights was 25.5±7.4%. The mean intra-class correlation coefficient per subject was 0.99 (95% CI 0.99-0.99, P<0.001), suggesting minimal variability in AP-RDI.

To detect trends in AP-RDI over the 92 night period, the mean AP-RDI in week 1 was compared with the mean AP-RDI in week 13. In week 1, mean AP-RDI was 33.0±15.0/hour and in week 13 it was 34.3±13.8/hour (p=0.66). There was therefore no significant difference in mean AP-RDI between weeks 1 and 13.

Despite this overall equivalence, 7 out of 24 patients (29%) with a mean AP-RDI below the ApneaScan™ threshold of 30.5/hour in week 1 had a mean AP-RDI greater than 30.5 in week 13, suggesting increased severity of SDB possibly related to progression of HF. The mean change in these 7 subjects was from 24.4±6.1 to 37.8±5.1 (p<0.001). For these 7 patients, there was no difference in the type of device they received (5 (71%) CRTD, 2 (29%) ICD) compared with those with no increase in AP-RDI (p=1.00) and there was no significant difference in mean ejection fraction at enrolment (25.3±8.7 vs 32.1±13.1 p=0.22). All 7 subjects were taking beta blockers and ACE inhibitors, 3 (43%) were taking aldosterone antagonists and 5 (71%) were on a loop diuretic (p=0.57, 1.00, 1.00 and 0.44 compared with the remaining 40 subjects respectively). Six of these subjects had had sleep studies as part of the *validation* study. One had mild CSA, 2 had mild OSA and 3 had no SDB at baseline.

Two subjects out of 23 (9%) with an AP-RDI>30.5 in week 1 had a mean AP-RDI<30.5 in week 13, but this was not statistically significant (36.7±5.9 vs 27.7±0.3, p=0.16). One of these patients had mild CSA and received a CRTD, the other did not have a sleep study and received an ICD.

Of those with a mean AP-RDI<30.5/hour over 92 nights (n=19), a total of 244 out of 1639 nights with available data were at an AP-RDI≥30.5 (14.9% of nights), which may lead to a 'false positive' diagnosis if a study was done on one of these nights. Of those with a mean AP-RDI≥30.5/hour (n=28), a total of 299 out of 2083 nights with available data were at an AP-RDI<30.5 (14.4%), which may lead to 'false negative' diagnoses. As might be expected, the highest number of nights outwith the mean group occurred in those with a mean AP-RDI closest to the 30.5/hour cut-off (Table 4).

Mean AP-RDI (events/hour)	**Number of subjects with ≥1 night out of 92 with AP-RDI<30.5/hour**	**Number of subjects with ≥1 night out of 92 with AP-RDI≥30.5/hour**	**Mean number of nights in 'incorrect' range* per subject (out of 92 nights)**	**Likelihood of obtaining a non-representative** AP-RDI based on a single-night study**
<30.5 (n=19)	19 (100%)	18 (95%)	12.8±12.5	14.9%
30.5-40.4 (n=12)	12 (100%)	12 (100%)	19.3±13.8	25.9%
≥40.5 (n=16)	11 (69%)	16 (100%)	5.3±7.0	7.1%

Table 4. Frequency of AP-RDI readings outside the subject's mean, divided in to those with a mean AP-RDI of <30.5, 30.5-40.4 and ≥40.5/hour.
* 'Incorrect' range refers to AP-RDI>30.5 in those with a mean AP-RDI<30.5, or <30.5 in those with a mean AP-RDI≥30.5.

4.3.4 Comparison between 28- and 92-night groups

Only 16 subjects were included in both the 28- and the 92-night groups, so comparison between the whole groups is influenced by the inclusion of different subjects. Sub-group analysis of the 16 patients common to both groups was also undertaken. There was no

difference in intra-class correlation coefficient between the 28- and 92-night groups (0.99 (95% CI 0.98-0.99) vs. 0.99 (95% CI 0.99-0.99), p=1.00) or in mean AP-RDI (34.2±11.5 vs. 34.6±8.4/hour, p=0.86). There was no significant difference between groups in the likelihood of a non-representative sleep study based on a single study for those with an AP-RDI<40.5. For those with and AP-RDI≥40.5, there was a borderline-significant greater likelihood of a false negative result in the 92-night group compared with the 28-night group (Table 5).

Mean AP-RDI (events/hour)	**Probability of a single night being in the 'incorrect' range – 28 night group**	**Probability of a single night being in the 'incorrect' range – 92 night group**	**P value**
<30.5	14.0±13.0% (n=13)	14.9±14.2% (n=19)	0.86
30.5-40.4	24.6±13.0% (n=10)	25.9±18.5% (n=12)	0.85
≥40.5	1.4±3.1% (n=12)	7.1±9.4% (n=16)	0.05

Table 5. Probability of obtaining a non-representative AP-RDI if a single night study is undertaken – comparison of 28- and 92- night groups.

As differences between the whole 28- and 92-night groups may be in part due to the difference between subjects, I also separately analysed the data from the 16 patients common to both groups. Baseline characteristics of these 16 patients are presented in Table 6.

Characteristic	Mean ± standard deviation (%) n=16
Age	73±6 years
Sex	15 (81%) Male
Aetiology of Heart Failure: - **Ischaemic Heart Disease** - **Dilated Cardiomyopathy** - **Valvular** - **Congenital** - **Sarcoidosis** - **Not documented**	 8 (50%) 7 (41%) 0 1 (9%) 0 0
Ejection fraction	28±10%
B-type natriuretic peptide concentration (median (IQR))	295 (217-496) umol/l
NYHA class	II – 10 (63%) III – 6 (37%)
Heart failure pharmacotherapy: - **ACEi/ARB** - **betablocker** - **aldosterone antagonist ivabradine** - **loop diuretic** - **thiazide**	 16 (100%) 12 (75%) 7 (44%) 10 (63%) 1 (6%)
Minnesota living with heart failure score	30±19
Epworth sleepiness score (median (IQR))	5 (3-9)
Body mass index **(kg/m²)**	25.6±3.3
Device implanted	3 (19%) ICD 13 (81%) CRTD

Table 6. Baseline characteristics of the 16 patients common to both the 28- and 92-night groups

A comparison of data from the first 28-nights and the subsequent 92-night ApneaScan analysis is presented in Table 7. The data samples are separate (i.e. none of the 28-night values were included in the 92-night data).

Mean AP-RDI (events/hour)	Number of subjects with ≥1 night with AP-RDI<30.5/hour		Number of subjects with ≥1 night with AP-RDI≥30.5/hour		Mean number of nights in 'incorrect' range* per subject		Likelihood of obtaining a non-representative** AP-RDI based on a single-night study		
Sample group (nights):	**28**	**92**	**28**	**92**	**28**	**92**	**28**	**92**	**P value**
Subjects with mean AP-RDI<30.5:	7 of 7 (100%)	7 of 7 (100%)	5 of 7 (71%)	7 of 7 (100%)	1.9±2.0	13.3±13.4	7.3%	15.3%	0.25
Subjects with mean AP-RDI 30.5-40.4:	5 of 5 (100%)	4 of 4 (100%)	5 of 5 (100%)	4 of 4 (100%)	7.0±3.7	23.5±20.3	26.1%	34.4%	0.22
Subjects with mean AP-RDI≥40.5:	1 of 4 (25%)	3 of 5 (60%)	4 of 4 (100%)	5 of 5 (100%)	0.75±1.5	7.8±9.2	3.7%	9.4%	0.41

Table 7. Comparison of data from the 16 patients common to both the 28- and 92-night groups. Frequency of AP-RDI readings outside the subject's mean, divided in to those with a mean AP-RDI of <30.5, 30.5-40.4 and ≥40.5/hour. Differences between the groups were adjusted for number of nights to determine statistical significance.
* 'Incorrect' range refers to AP-RDI>30.5 in those with a mean AP-RDI<30.5, or <30.5 in those with a mean AP-RDI≥30.5.

There was no significant difference in the mean AP-RDI over 28 nights compared with 92 nights (31.9±12.3/hour vs 33.2±14.6/hour p=0.78). There was a trend towards higher coefficient of variation in the 92-night group, but this did not meet statistical significance (20.3±5.7% vs 25.6±9.0%, p=0.06). None of the subjects with a mean AP-RDI≥30.5 over 28-nights had a mean AP-RDI<30.5 over 92-nights or vice versa. There was a trend towards a higher likelihood of mis-diagnosing the severity of SDB based on a single sample-night in the 92-night sample, but this did not reach statistical significance. This may represent greater changes in SDB over the longer sample time.

4.3.5 Change in ApneaScan™-RDI in the first 28 nights following implantation of a cardiac resynchronisation therapy device

6 patients with moderate-to-severe CSA and 2 patients with moderate-to-severe OSA received *de novo* CRT devices and were included in this analysis. There was no significant change in AP-RDI in either group over the 28 nights (Figure 3). Over the first 28 nights

following CRT device implantation, the mean AP-RDI in the moderate-to-severe CSA group changed from 31±9 to 33± 5/hour (p=0.64). In the 2 patients with moderate-to-severe OSA, the mean AP-RDI changed from 50±14 to 53±11/hour (p=0.83).

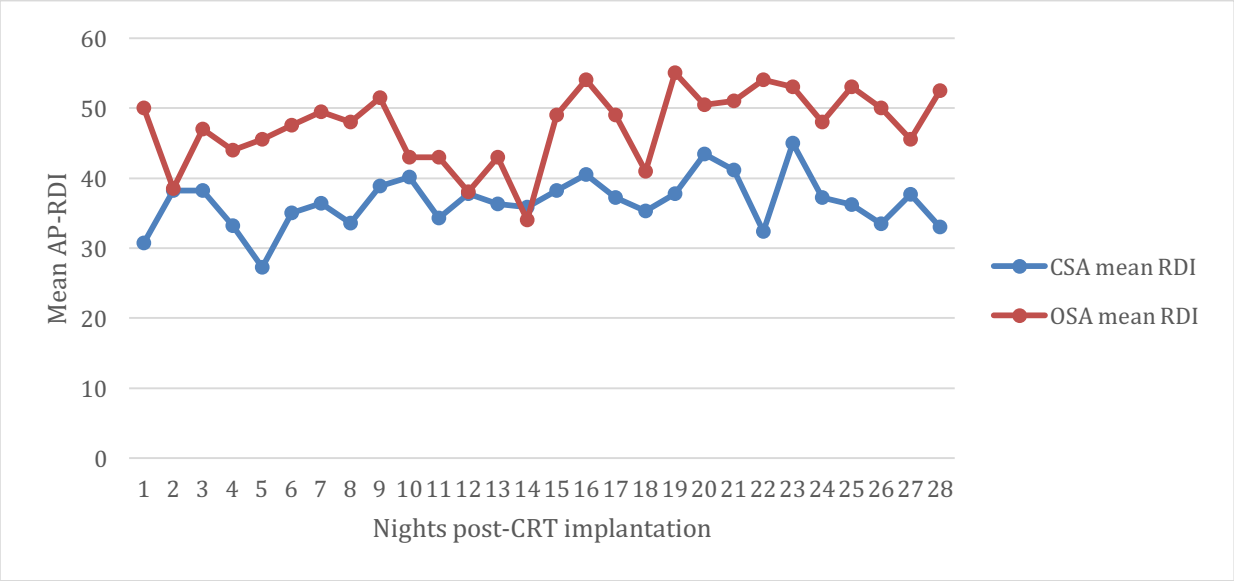


Fig. 4a The mean AP-RDI for the first 28 nights following implantation of a CRT device for 6 patients with moderate-to-severe CSA and 2 with moderate-to-severe OSA as diagnosed by polygraphy. There was no significant change in mean AP-RDI in either group over the 28 nights.

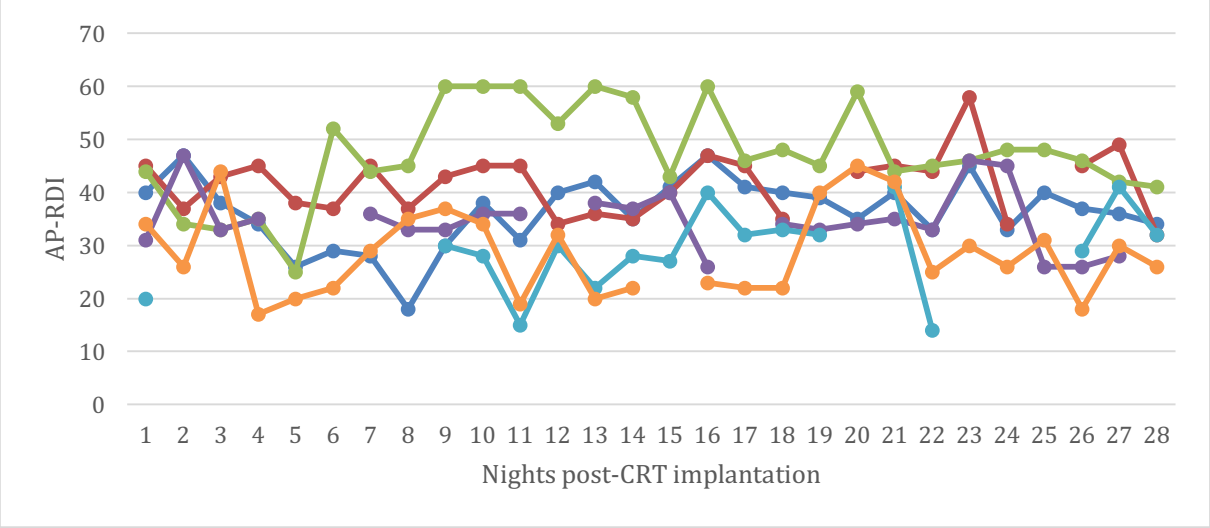


Fig. 4b. AP-RDI for the 6 subjects with moderate-to-severe CSA by polygraphy over the first 28 nights following implantation of the CRT device. Missing data points are nights on which no AP-RDI value was recorded by the device.

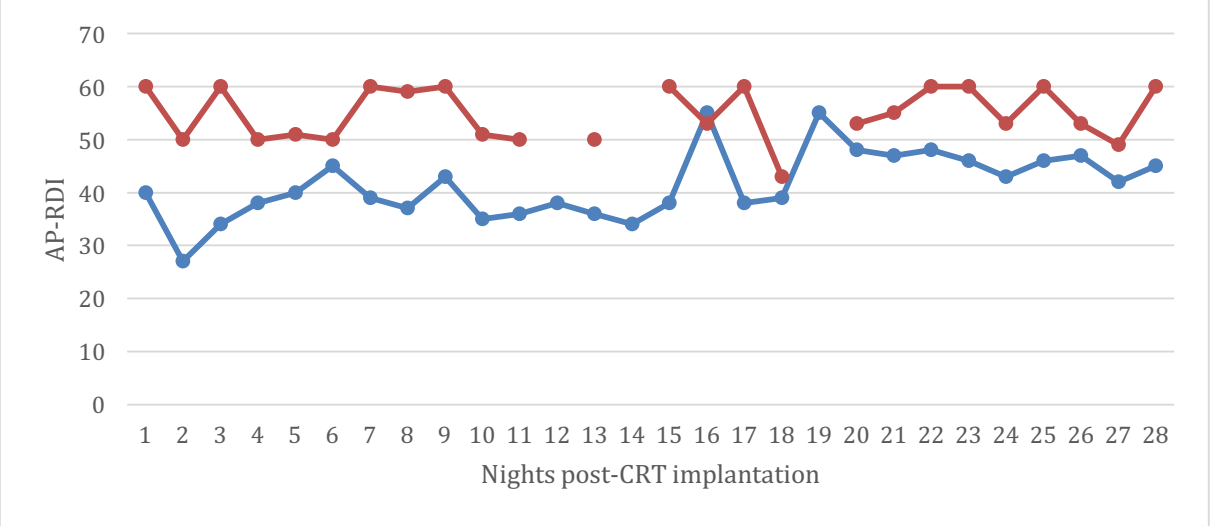


Fig. 4c. AP-RDI for the 2 subjects with moderate-to-severe OSA by polygraphy over the first 28 nights following implantation of the CRT device. Missing data points are nights on which no AP-RDI value was recorded by the device.

4.4 Discussion

4.4.1 Variability in AP-RDI over 28 nights

These data are the first to use a transthoracic impedance sensor to quantify the severity of SDB in subjects with HF over a longer time-period than previously investigated. Night-to-night variability over 28 nights was small (coefficient of variation 18.7%) and did not vary significantly depending on the type or severity of SDB. The likelihood of misclassifying SDB as 'mild' based on a single-night recording was as high as 24.6% in those with a 'borderline' raised mean AP-RDI of 30.5 to 40.5/hour, but very low (1.4%) in those with greater mean AP-RDI. This reflects regression to the mean, but does demonstrate high confidence in sleep study results away from the 30.5/hour AP-RDI or 15/hour sleep polygraphy cut off for the diagnosis of moderate-to-severe SDB.

In 2002, Quan and colleagues published data from the Sleep Heart Health Study on 91 patients without HF at baseline who underwent two home sleep polygraphy studies a mean

of 77±18 days apart (221). They found an intra-class correlation coefficient between the two studies of 0.77 to 0.81, depending on the measure used, and concluded good correlation between repeat studies in this population. In 79% of cases, the classification of SDB was consistent between the two nights. Le Bon and co-workers found a similar consistency in 243 subjects suspected to have OSA and noted a significant "first night effect", suggesting that a second sleep study is mandatory to achieve accurate diagnosis (222). The second night detected up to 25% more cases of SDB compared with the first. These results were consistent with those of Meyer and colleagues, who found significant OSA in 6 of 11 subjects tested for a second time having had no significant SDB on a previous sleep study but with high clinical suspicion of SDB (223). In a study monitoring ODI over 7 nights in 35 patients, Fietze and co-workers found that the probability of placing a subject in the wrong SDB category (none-or-mild vs. moderate-or-severe) if only one night data are sampled was 14.4% (224). They conclude that ODI is relatively consistent and a single night study is likely to be representative of the mean.

For patients with HF, in whom CSA comprises a significantly higher proportion of SDB compared with the general population, the evidence is more limited. Vazir and colleagues collected home sleep polygraphy data over 4 consecutive nights on 19 subjects with stable NYHA II to III HF and LVEF<45% (225). They found minimal variation in severity of SDB (ICC 0.94, 95% CI 0.76 to 0.97 for AHI). However, 42% of patients changed predominant type of SDB (OSA to CSA or vice versa) for at least one night and 37% changed from a moderate-to-severe category to a none-or-mild category or vice versa for at least one night. Oldenburg and colleagues performed sleep polygraphy on two consecutive nights in 50 patients with symptomatic HF and LVEF<40% (226). They found a very high correlation between the two nights (ICC 0.95) and a mean variation in AHI of only 1.4±5.0 events/hour. 17 of 19 patients with AHI>10/hour had the same classification of SDB over the two nights. The initial sleep study was most closely reproduced in those with more severe SDB. Maestri and co-workers performed sleep polygraphy on two consecutive nights in 56 patients with severe symptomatic LV dysfunction (227). The 95% limit of variation was ±10.6 events/hour. In those with moderate-to-severe SDB, 82% of subjects were classified

consistently by both studies. They conclude that, whilst there is significant night-to-night variability, the majority of cases are correctly classified by a single sleep polygraphy study.

More recently, McDonald and colleagues used a non-contact motion sensor, that collects data on sleep-breathing patterns using radiowaves, to monitor SDB in patients with HF for up to 2 years (149). They found a significant degree of variability, with a mean coefficient of variation of 57% and around half of patients changed SDB category (from none-or-mild to moderate-to-severe or vice-versa). The greater variation may be explained by the long follow-up period, which is likely to produce more variability in SDB as the HF syndrome varies with time.

The findings of this study are in keeping with this previous research and extend confidence in the validity of a single night sleep study in those with HF. Both this study and that of Oldenburg demonstrate that those with more 'borderline' moderate SDB are more likely to change classification over repeated tests and thus repeated sleep studies may be warranted prior to embarking on long-term therapy. In those with suitable devices, comparison of the AP-RDI on the night of the diagnostic sleep study with the mean AP-RDI over longer time periods may help determine how representative the sample night was of the mean and thus reduce the risk of misdiagnosis. In addition, as ApneaScan™ has a high negative predictive power (94% - please see chapter 3), a mean AP-RDI of <30.5/hour following the initiation of treatment for OSA would suggest a high likelihood of therapeutic success and may reduce the need for repeated sleep studies. Due to the lesser positive predictive value of an AP-RDI >30.5, confirmation with further sleep studies would be mandatory in this group.

As guidelines and research have been based predominantly on a diagnosis of SDB made on a single-night sleep study, the implications of the 'first-night effect' and the possibility of making a more secure diagnosis over longer time periods using ApneaScan™ are not known. This algorithm may help secure a more reliable diagnosis and thus help tailor care and selection for research trials.

As the severity of both OSA and CSA vary with the HF status of the patient, and the severity of both are increased at the time of HF decompensation, it is reassuring that in this group of patients with severe LV systolic dysfunction the variability of AP-RDI was minimal. Whether AP-RDI increases reliably in the days or weeks prior to decompensation, and could thus be used as a remote monitoring tool, is an appealing concept that requires investigation.

AP-RDI was significantly greater than PG-AHI on the sleep study night (by a mean of 18.5/hour – please see chapter 3). The question therefore arises as to the consistency of this difference. The low variability in AP-RDI in this study, and the close similarity between the consistency of AP-RDI in this study and PG-AHI in previous studies, suggests that this relationship is relatively consistent but further investigation with more polygraphy studies would be required to prove this.

4.4.2 Variability in AP-RDI over 92 nights

There was also minimal variability in AP-RDI in the 47 patients studied over 92 consecutive nights (coefficient of variation 25.5±7.4%, ICC 0.99 (95% CI 0.99-0.99, P<0.001)). Coefficient of variation was higher than in the 28-night group, as may be expected with a longer monitoring period. There was no significant overall change in AP-RDI over the 92 nights, suggesting that the severity of SDB in a HF population is relatively stable over both a shorter (1 month) and longer (3 month) time period. However, 29% of patients with a low AP-RDI (<30.5/hour) progressed to a significantly higher AP-RDI (mean 37.8±5.1/hour) over the 13 weeks. Whether this has implications for clinical outcomes in this group, and hence could be incorporated in to remote monitoring algorithms, is beyond the scope of this research to determine. There was no clear difference in the group with increasing AP-RDI in terms of device received, medical therapy or measures of heart function at baseline compared with those without increasing AP-RDI. Only 2 subjects (9%) changed from a high AP-RDI to a lower AP-RDI over the 3 months and the change was not statistically significant.

The likelihood of obtaining a non-representative AP-RDI based on a single night sample was very similar between the 28- and 92-night groups, other than in those with a mean AP-RDI≥40.5, amongst whom there was a greater chance (of borderline significance) of an unrepresentative reading in the 92-patient group (7.2±9.4% vs 1.4±3.1%, p=0.05). This trend persisted when only the 16 patients common to both groups were studied, but was not statistically significant (3.7 v 9.4%, p=0.41). It could be postulated that this is due to greater variation in AP-RDI in those with severe SDB over the 3 month time-frame, but this cannot be concluded from these data.

4.4.3 Change in AP-RDI over the first 28 nights following implantation of a CRT device

In the small sub-study of only 8 patients, AP-RDI did not change in those with moderate-to-severe CSA or OSA from nights 1 to 28 following biventricular pacing. This is at odds with previous research demonstrating a significant decrease in PG-AHI in those with significant CSA (but not OSA) following CRT implantation (202).

This may be due to the small sample size although, in the study by Sinha and colleagues, PG-AHI fell in every patient with HF and CSA following CRT (201). A second possibility is that ApneaScan™ is not accurate enough to detect more subtle changes in SDB, although the relatively consistent values obtained over 28 nights would argue against this.

A third possibility is that the greatest decrease in AHI occurs between the pre-CRT phase and the first post-CRT night, and that subsequent decreases in AHI are minimal. Most published sleep polygraphy data only documents the AHI before and at one time point (months) after CRT, so the timing and rate of change cannot be determined accurately. In addition, existing polygraphy data before and after CRT may be influenced by the 'first night effect', leading to inaccuracy.

It is also notable that there was no improvement in AP-RDI between week 1 and week 13 in the 92-night variability group, despite 72% of the cohort receiving CRT therapy and the majority of subjects likely to have some degree of CSA.

Only one study has examined acute changes in SDB with CRT (228). In this study, 12 patients with HF who already had a CRT device underwent polysomnography on 3 consecutive nights with CRT turned on for nights 1 and 3 and off on night 2 (with back-up RV pacing at 40bpm if required). They found a significantly lower frequency of central apnoeic-hypopnoeic events when CRT was on rather than off (6.9±1.7 vs. 14.3±2.9 events/hour, $p<0.01$). This may explain the lack of change seen in our post-CRT population with CSA.

Lastly, it is possible that the widespread use of disease-modifying drugs and careful diuretic management in our population results in relatively-optimised CSA, so that the additional effect of CRT is not as great as in previous studies (most of which do not report details of medical therapy). However, the study by Oldenburg and colleagues does specify pharmacotherapy (which was similar to our own population), and they did find a decrease in central AHI with CRT (80).

The consistency of AP-RDI over the first 28 nights suggests that any pocket haematoma has little effect on transthoracic impedance as measured by the device and that the ApneaScan™ data is as reliable immediately after implantation as it is months later.

To determine the timing and rate of change in CSA, a study would have to use the same technique to monitor SDB over many nights before and after CRT implantation. It is unlikely that many patients would consent to repeated polygraphy or polysomnography studies, but alternative non-contact technologies such as Sleepminder™ (ResMed, San Diego) could be used for this purpose (145,229)

4.4.4 Limitations of the study

Although there is good correlation between ApneaScan™ and sleep polygraphy, ApneaScan™ over-estimates the frequency of apnoeic-hypopnoeic events (see chapter 3) and thus the variability as determined by ApneaScan™ may differ from that determined by sleep polygraphy. In addition, ApneaScan™ is not able to determine changes in type of SDB (OSA or CSA) with time. In the sub-study examining the change in SDB following CRT, numbers of subjects are too small to draw confident conclusions and a measurement of SDB prior to implantation of the device would have been informative.

However, the numbers enrolled in this study are greater than in all-but-one previous studies and this is the first study to monitor SDB over almost 5000 person-nights, providing useful data on variability of SDB in a HF population.

4.5 Conclusions

Night-to-night variability in SDB, as assessed by ApneaScan™, is minimal in patients with HF and a single-night sleep study would provide a reliable diagnosis in most cases. Those with an AHI closer to the borders between severity groups (particularly around the 15/hour cut-off for PAP treatment of OSA) may benefit from repeated studies to establish a more secure diagnosis before deciding on treatment. Variability is similar over 28- and 92-nights, suggesting both short-term and longer-term stability in the severity of SDB.

In this small study, no change in the severity of CSA (as assessed by ApneaScan™) was seen in the first month following CRT implantation. Further research including pre-implantation measurements and a larger sample size is required to investigate further.

Chapter 5: Prognostic implications of sleep-disordered breathing in heart failure as diagnosed by ApneaScan™

5.1 Introduction

The presence of either obstructive or central sleep apnoea is associated with poor outcomes in patients with heart failure. Rates of death and malignant ventricular arrhythmias are greater in those with significant SDB compared to those without. In one study of patients with HF (EF<45%), the presence of CSA (mean AHI 34/hour) was associated with half the mean duration of survival compared to those without SDB (45 vs 90 months, p=0.02) (113). Bitter and colleagues found a significantly shorter time to first monitored or treated ventricular arrhythmia in those with CSA or OSA and an ICD device compared with those without SDB (55). Another observational study of 10,701 patients in a sleep clinic (most of whom had no cardiovascular disease at enrolment) found OSA to be a significant predictor of sudden cardiac death, the greatest risk being in those with the most severe OSA (230). The various pathophysiological mechanisms implicated are discussed in section 1.2. In addition, SDB is associated with increased risk of developing atrial fibrillation (111,231,232).

SDB is usually diagnosed with a single sleep study, which may not be representative of the subject's usual sleep pattern (222). The ApneaScan™ algorithm on Boston Scientific ICD and CRT devices uses changes in transthoracic impedance with breathing to diagnose and quantify SDB. Data can be collected over long time-periods, thus avoiding the 'first night' effect. The ApneaScan™ algorithm is a sensitive means of screening for SDB in patients with HF (chapter 3). Whether the severity of SDB, as diagnosed by ApneaScan™, correlates with adverse HF outcomes is not known. If so, ApneaScan™ may be a useful means of risk-stratifying patients with HF and aid clinicians in their care.

The aim of this study is to determine whether the presence of moderate-to-severe SDB, as assessed by ApneaScan™, correlates with clinical outcomes.

5.2 Methods

5.2.1 Eligibility and data acquisition

Patients were eligible for recruitment if they fulfilled all the following criteria:

- Impaired LV systolic function (ejection fraction ≤40% at the time of device implant)
- No known diagnosis of SDB
- With or due to receive an ICD or CRT device with ApneaScan™ function.

Patients were recruited from the Royal Brompton, Harefield and St George's Hospitals, London. At the time of recruitment, patients underwent the following tests and questionnaires:

- Echocardiography (performed by British Society of Echocardiography-accredited echocardiographers)
- Plasma B-type natriuretic peptide (BNP) assay (measured in the biochemistry laboratories of the respective hospitals)
- Electrocardiography
- Epworth sleepiness score
- Minnesota Living with Heart Failure Questionnaire
- Routine clinical examination and history-taking

Patients then underwent download of the ApneaScan™ data from the device via a programmer in person or via the Latitude™ remote monitoring system. The ApneaScan™ respiratory-disturbance index (AP-RDI) was recorded on the night before the download. If no data were recorded on the night before, the next available night was recorded. Patients were then followed-up at least 1 year after this date with a telephone call to the patient and GP, as well as review of hospital and pacing clinic notes. All admissions and events were reviewed by me, blinded to the AP-RDI, to determine the primary cause.

Patients were classified as having significant SDB if the AP-RDI was greater than 30.5 events/hour on the study night, as this is the optimal cut-off for moderate-to-severe SDB by sleep polygraphy (chapter 3). This figure is also close to the manufacturer-recommended cut-off at 32 events/hour.

5.2.2 Endpoints

The primary endpoint was time to first event, classified as any of:

- All-cause mortality
- Non-elective cardiovascular hospitalisation
- Ventricular tachycardia or fibrillation managed with ICD or external therapy (including anti-tachycardia pacing, internal or external cardioversion and IV antiarrhythmic drugs)

The secondary endpoint was burden of atrial tachyarrhythmia at follow-up, divided in to:

- no AF/AT (mean of <1% AF/AT per day at device download over the whole follow up period)
- paroxysmal or persistent AF/AT (1-99% burden)
- permanent AF/AT. (>99% AF/AT burden)

5.2.3 Statistical analysis

Quantitative variables are expressed as mean and standard deviation if normally distributed and median and interquartile range if non-normally distributed. The Student's t-test was used to assess differences in continuous data between groups when normally distributed and the Mann-Whitney test when not. Chi squared test (Fisher's exact) was used for comparing categorical data. A Kaplan-Meier plot and log rank test was used to assess differences in outcomes between groups. The association between a variable and outcomes was assessed with Cox multivariate regression analysis. A p-value of <0.05 was

taken as statistically significant. Statistical analysis was performed using SPSS™ v24 software (IBM, Armonck, New York).

5.2.4 Contribution by the candidate

The patients for this arm of the study were screened and recruited by me with help from Rebecca Lucas, research nurse at the Royal Brompton Hospital. I completed the background data and obtained the ApneaScan™ readings. The follow-up phone calls and letters were done by Rebecca Lucas. I collated the data and performed the data analysis and statistics.

5.3 Results

5.3.1 Recruitment

130 patients were recruited to the study, of whom 72 had complete ApneaScan™ and follow-up data. The remaining 58 subjects were excluded. The flow chart and reasons for exclusion are presented in Figure 1. 14 patients received devices without ApneaScan™ function after consenting, 3 died and 5 withdrew consent before device download. After download, 14 had no ApneaScan™ data points despite the algorithm being active, 15 were lost to follow-up and 7 had the ApneaScan™ function turned off (on Incepta™ devices, ApneaScan™ only records data if the rate response function is active, which is inappropriate in some patients). Patients were followed up at a median of 532 (IQR 386-736) days following recruitment (median 541 (IQR 451-707) days for those with insignificant SDB and 532 (IQR 422-786) days for those with significant SDB, p=0.76).

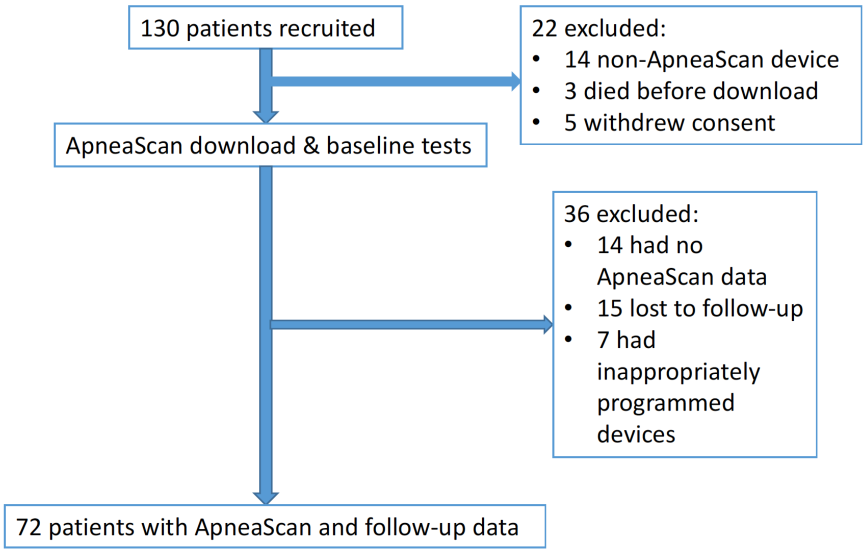


Figure 1. Flow chart of patient recruitment and exclusion.

5.3.2 Baseline characteristics

Baseline characteristics of the 72 patients with complete ApneaScan™ and follow-up data are presented in Table 1. Those with significant SDB by ApneaScan™ (AP-RDI≥30.5/hour) had a significantly lower rate of loop diuretic use than those with insignificant SDB. There were no other statistically-significant differences in baseline characteristics between the groups (other than AP-RDI).

Characteristic	**All patients (n=72)**	**Insignificant SDB by ApneaScan** (AP-RDI<30.5/hour) **(n=29)**	**Significant SDB by ApneaScan** (AP-RDI≥30.5/hour) **(n=43)**	**p value** (insignificant vs. significant SDB groups)
Age	65±15 years	67±13 years	64±15 years	p=0.38
Aetiology of Heart Failure				
DCM	31 (43%)	10 (35%)	19 (44%)	p=0.47
IHD	24 (33%)	13 (45%)	13 (31%)	p=0.22
Sarcoidosis	5 (7%)	1 (3%)	4 (9%)	p=0.64
Valvular	8 (11%)	4 (14%)	4 (9%)	p=0.71
Congenital	4 (6%)	1 (3%)	3 (7%)	p=0.64
Ejection fraction	33±13%	30±12%	35±13%	p=0.10
B-type natriuretic peptide concentration Median (IQR)	309 (105-626) ng/l	283 (113-730) ng/l	322 (98-470) ng/l	p=0.74
NYHA class				
- I	8 (11%)	1 (3%)	7 (16%)	p=0.13
- II	40 (56%)	16 (55%)	25 (58%)	p=0.81
- III	24 (33%)	12 (42%)	11 (26%)	p=0.20
ApneaScan-RDI	35±13 events/hour	22±5 events/hour	43±10 events/hour	p<0.01*
Heart failure pharmacotherapy Beta-blocker	57 (79%)	23 (79%)	34 (79%)	p=1.00
ACEi/ARB	63 (88%)	26 (90%)	37 (86%)	p=0.73
MRA	43 (60%)	16 (55%)	27 (63%)	p=0.63
Ivabradine	6 (8%)	5 (17%)	2 (5%)	*p=0.11*
loop diuretic	41 (57%)	21 (72%)	20 (47%)	**p=0.05***
Minnesota living with heart failure score	33±25	35±25	31±26	p=0.52
Epworth sleepiness score median (IQR)	6 (3-10)	7 (4-12)	5 (3-8)	p=0.40
Body mass index	26±5 kg/m²	25.2±4.2 kg/m²	26.8±4.8 kg/m²	P=0.15
Device implanted	42 (58%)	19 (66%)	24 (56%)	p=0.47
- CRTD	15 (21%)	4 (14%)	11 (25%)	p=0.26 (p=1.00 for all CRT)
- CRTP	15 (21%)	6 (20%)	8 (19%)	p=1.00
- ICD				
Heart rhythm at recruitment				
- AF/AT	14 (19%)	6 (21%)	8 (19%)	P=1.00
- SR	58 (81%)	23 (79%)	35 (81%)	
Implanting Hospital:				
- Brompton	55 (76%)	21 (72%)	34 (91%)	0.58
- Harefield	17 (24%)	8 (18%)	9 (9%)	

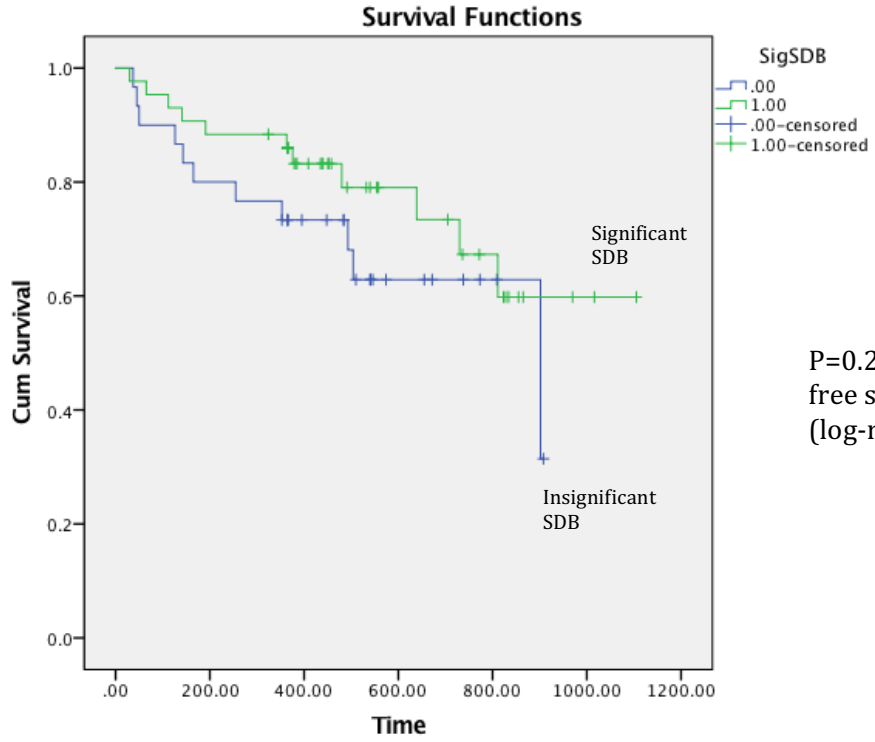
Device Indication:				
- Primary Prevention	47 (65%)	18 (62%)	29 (68%)	0.80
- Secondary Prevention	10 (14%)	7 (24%)	3 (7%)	0.08
- CRTP	15 (21%)	4 (14%)	11 (25%)	0.26
Time from device implant to follow-up (median, IQR)	468 (365-502)	420 (365-498)	438 (382-500)	0.32

Table 1. Baseline characteristics of patients completing the study, divided in to those with insignificant SDB by ApneaScan™ (AP-RDI<30.5/hour) and those with significant SDB (AP-RDI≥30.5). SDB – sleep-disordered breathing; DCM – dilated cardiomyopathy; IHD – ischaemic heart disease; ACEi/ARB – ACE inhibitor/angiotensin receptor blocker; MRA – mineralocorticoid receptor antagonist; CRTD – cardiac resynchronisation therapy with defibrillator; CRTP – cardiac resynchronisation therapy pacemaker; ICD – implantable cardioverter-defibrillator; AF/AT – atrial fibrillation or flutter/atrial tachycardia; SR – sinus rhythm. Primary/secondary prevention refers to whether the defibrillator was implanted following a cardiac arrest (secondary prevention) or not (primary prevention).

5.3.3 Primary endpoint

At a median follow-up of 532 (IQR 386-736) days following recruitment, the composite primary endpoint occurred in 11 out of 29 patients (38%) with insignificant SDB by ApneaScan™ and 11 out of 43 patients (26%) with significant SDB (p=0.30). Mean event-free survival was 660±344 days (95% CI 535-785 days) in the insignificant SDB group and 854±413 days (95% CI 730-978 days) in the significant SDB group (p=0.25 by log rank test) (Figure 2). For every 10 patient-years, 2.0 patients with insignificant SDB and 1.5 patients with significant SDB had an event**.**

There was a trend towards a higher proportion of subjects in the insignificant SDB group having defibrillators implanted for the secondary prevention of sudden cardiac death compared with the significant SDB group (7 (24%) vs 3 (7%), p=0.08). There was also a trend towards a higher frequency of the primary outcome amongst those with secondary prevention devices than those with primary prevention or CRTP devices (5 of 11 subjects (45%) with a device for secondary prevention had a primary endpoint event vs. 17 of 61 (28%) patients with secondary prevention or CRTP devices, p=0.30).



Number at risk:						
Sig:	43	37	23	13	8	1
Insig:	29	22	15	5	2	2

P=0.25 for event-free survival time (log-rank test)

Figure 2. Event-free survival of patients divided in to those with insignificant SDB by ApneaScan™ (AP-RDI<30.5, blue line) and those with significant SDB by ApneaScan™ (AP-RDI≥30.5, green line). Y-axis: fraction of group free or primary outcome; X-axis: time from enrolment in days.

AP-RDI, age, LV ejection fraction, plasma B-type Natriuretic Peptide (BNP) concentration and furosemide dose were analysed independently in a Cox univariate regression analysis to determine if any of these potential risk factors were associated with the primary outcome. None of these factors were found to be significantly associated with the combined primary outcome (Table 2).

Risk Factor:	**Hazard Ratio**	**95% CI**	**P value**
AP-RDI	0.98	0.94-1.01	0.15
Age	0.99	0.96-1.02	0.41
LV EF	1.00	0.96-1.03	0.64
BNP	1.00	1.00-1.00	0.86
Furosemide dose	1.00	1.00-1.01	0.20

Table 2. Results of univariate Cox survival analysis for the primary endpoint for 5 possible risk factors. None were found to be independently associated with the combined primary endpoint. For patients on bumetanide, the equivalent furosemide dose was calculated by the approximation that 1mg bumetanide is equivalent to 40mg furosemide.

In the insignificant SDB group, the most common end-point was ICD therapies (8 out of 11 events), whereas in the significant SDB group, the predominant endpoint was CV hospitalisation (8 out of 11 events). There were significantly more ICD therapies in the insignificant SDB group (Table 3), although only 2 of these occurred amongst the 8 patients with ICD/CRTD devices for secondary prevention.

Insignificant SDB group (n=29)	**Significant SDB group (n=43)**	**p value**
3 CV hospitalisations	8 CV hospitalisations	P=0.50
8 ICD therapies	1 ICD therapy	**p<0.01**
0 deaths	2 deaths (HF)	p=0.51

Table 3. Nature of first event in those with insignificant or significant SDB by ApneaScan™ (AP-RDI threshold 30.5/hour). CV – cardiovascular, ICD – implantable cardioverter-defibrillator, HF – heart failure.

5.3.4 Secondary endpoint

At the final follow-up, 6 (21%) patients with insignificant SDB had paroxysmal, persistent or permanent AF or AT (no change from enrolment). In the significant SDB group, 10 (23%) patients had AF or AT at follow-up (2 new patients had developed an atrial tachyarrhythmia, p=0.51) (Table 4). The presence of significant SDB by ApneaScan™ did not correlate significantly with the prevalence or incidence of atrial tachyarrhythmias in this cohort.

	Insignificant SDB (n=29)	**Significant SDB (n=43)**	**P value**
AF/AT at enrolment	6 (21%)	8 (19%)	1.00
AF/AT at follow-up	6 (21%)	10 (23%)	1.00
New cases of AF/AT	0 (0%)	2 (5%)	0.51
New cases of AF/AT per 10 patient-years	0	0.28	1.00

Table 4. Number of subjects in atrial fibrillation/flutter/tachycardia, divided in to those with significant and insignificant SDB by ApneaScan™ (AP-RDI <30.5 or ≥30.5 respectively). SDB – sleep-disordered breathing. Atrial fibrillation/flutter/tachycardia (AF/AT) includes those with paroxysmal, persistent or permanent arrhythmia (burden≥1% on pacing download).

5.3.5 Analysis of outcomes by Sleep polygraphy result

46 patients in this cohort also had a sleep polygraphy study as part of the ApneaScan™ validation arm of the study (please see chapter 3). Analysis of the combined primary endpoint in these patients was undertaken with patients classified according to the sleep polygraphy result, rather than by ApneaScan™. Patients were divided in to those with mild or no SDB (AHI by AASM 2012 criteria <15/hour on the study night, n=28), or moderate-to-severe SDB (AHI≥15/hour, n=18). 10 out of 46 patients (22%) were classified differently by sleep polygraphy compared with ApneaScan (9 with AHI<15 by polygraphy had AP-RDI>30.5).

Mean follow-up duration for those with none-or-mild SDB by polygraphy (AHI <15) was 528±268 days and for those with moderate-to-severe SDB (AHI≥15) was 568±320 days

(p=0.64). The composite primary endpoint occurred in 8 of 28 patients (29%) with none-or-mild SDB by polygraphy and 7 of 18 patients (39%) with moderate-to-severe SDB (p=0.75). Mean time to first event was 748±360 days in those with none-to-mild SDB and 823±382 days in those with moderate-to-severe SDB (p=0.50). Event-free survival is presented as a Kaplan-Meier curve in Figure 3. There was no statistically significant difference in event-free survival between those with moderate-to-severe SDB and those with mild-or-no SDB by polygraphy.

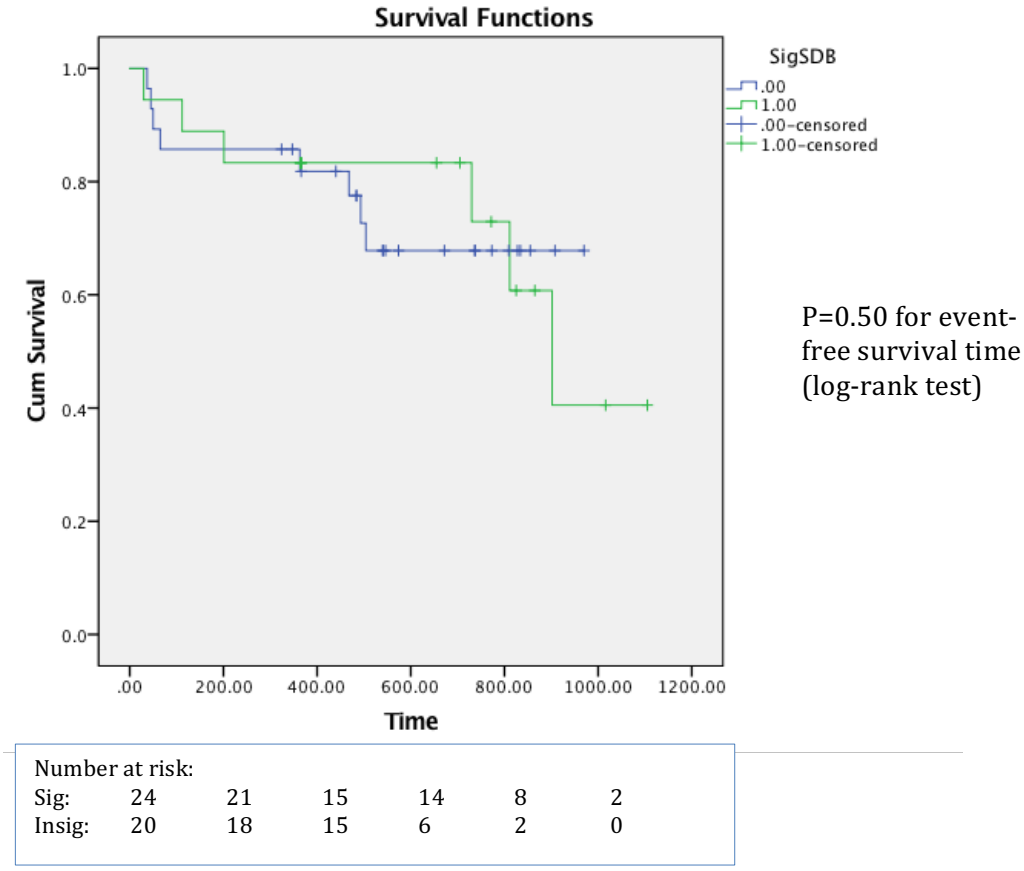


Figure 3. Event-free survival of patients divided in to those with none-or-mild SDB by sleep polygraphy (PG-AHI<15, green line) and those with moderate-to-severe SDB by polygraphy (PG-AHI ≥15, blue line). Y-axis: fraction of group free or primary outcome; X-axis: time from enrolment in days.

5.4 Discussion

5.4.1 Primary endpoint – incidence of adverse cardiovascular events

This study found no difference in rates of the composite primary endpoint between those with significant and non-significant SDB, as stratified by the ApneaScan™ algorithm. This contrasts with previous studies demonstrating worse outcomes in those with SDB. It must be stressed that this study was under-powered to detect a difference and further recruitment is taking place to address this more definitively (166 patients currently recruited and awaiting follow-up). It was not possible to complete follow-up for the whole cohort within the time constraints of the MD(Res) period.

In a study of 88 patients with at least moderate LV systolic dysfunction (EF<45%), Javaheri and colleagues demonstrated half the median survival in those with CSA (AHI>5) compared to those without SDB (45 vs 90 months, HR 2.14, p=0.02) (113). There are several possible reasons for the difference in outcomes compared with this study. The mean follow-up in the Javaheri study was 51 months compared with 22 months in this study, which may have 'allowed' the deleterious effects of SDB to manifest as clinical outcomes. At 20 months, however, mortality in the SDB group in Javaheri's study was approximately 30% compared with 15% in the no-SDB group. Mortality rates are significantly lower in our cohort (7%) at the same time point, which reduces the power of this study to detect mortality differences.

The SDB patients in Javaheri's cohort all had predominant CSA, which is thought to be particularly associated with poor outcomes in the HF population, and were all male, which is also associated with worse outcomes (64). In addition, the mean AHI in the CSA group was 34/hour (defined by the 2007 AASM criteria – the AHI would have been greater according to the 2012 AASM criteria adopted for this study (216)). The mean AHI by polygraphy in the significant SDB group in this study (defined by the 2012 AASM criteria) was only 23/hour. The type of SDB was also different, with 72% having predominant CSA

in this study as opposed to 100% of the Javaheri cohort. Those with OSA are known to have a lower rate of defibrillator therapies (55).

Javaheri does not report the number of patients in his study with CRT or ICD devices. CRT is known to dramatically reduce the AHI in those with CSA (a mean reduction of 75% in one study), as well as having beneficial effects on cardiovascular function (43,201). As 80% of the significant SDB group in this study received CRT, it could be postulated that this ameliorated many of the detrimental effects of the of the severe HF syndrome associated with CSA. There was also a difference in medical management of patients in this study compared with the Javaheri study – only 11% of patients in the CSA group received beta blockers (vs. 79% in this study) and the frequency of MRA use is not recorded (presumably lower, compared with 60% in this study). Both beta blockers and MRAs are known to improve survival in patients with advanced HF (21,24). In addition, 75% of patients in the Javaheri study had HF of ischaemic aetiology, compared with 36% in this cohort. Ischaemic HF carries a more severe prognosis than DCM and the rates of ICD therapies are thought to be lower in those with DCM (233,234). These important differences may explain the parity in outcomes between those with and without significant SDB as assessed by ApneaScan™ and by polygraphy in this study.

Bitter and colleagues investigated the rates of monitored and treated ventricular arrhythmias in 283 patients with HF and CRTD devices (55). Patients were classified according to a single polygraphy study performed 6 months after implantation of the device. Over a mean of 48 months follow-up, they reported significantly shorter times to first monitored or treated ventricular arrhythmia in those with moderate-to-severe CSA and OSA compared with those without significant SDB. 34.1% of the cohort received an appropriate ICD therapy during follow-up. The probability of receiving a therapy was greater in those with moderate-to-severe CSA (HR 3.41, 95% CI 2.10–5.54, $p<0.001$) and OSA (HR 2.10, 95% CI 1.17–3.78, $P<0.01$) compared to those without significant SDB.

The baseline characteristics of the patients in the Bitter study are similar to those in this research, however there are some differences that may explain the variance in outcomes.

Bitter performed sleep polygraphy 6 months after implantation of the device, as opposed to around 1 month in this study. As CRT is known to greatly reduce the AHI in CSA, those with persistently elevated CSA-AHI may be a particularly high-risk group with greater frequency of ventricular arrhythmia. Whilst not specified in the paper, programming of ICD therapies at the time of Bitter's study was generally more aggressive than the present. Common practice prior to publication of the MADIT-RIT study in 2012 was to programme a treatment zone at lower ventricular rates (such as 170 bpm) (41). The MADIT-RIT study demonstrated that superior outcomes could be achieved with a significantly lower rate of inappropriate shocks, in those with ICDs for primary prevention of sudden cardiac death, when the zones for detection and treatment of ventricular tachyarrhythmias are programmed at higher rates and/or with longer detection periods. Thus, the frequency of ICD therapies are lower now than they might have been five years ago. This is supported by the relatively higher rate of ICD therapies in Bitter's cohort – 47% of those with moderate-to-severe SDB and 24% of those with mild-or-no SDB received an ICD therapy at a mean of 26 months post-device implantation. The shorter follow-up in our group does not explain the lower incidence of ICD therapies. Only 9 of 72 patients (12.5%) received an ICD therapy during the approximately 1.5 years of mean follow-up in this study. Taking data from the Kaplan-Meier curves, approximately 40% of Bitter's cohort with moderate-to-severe SDB and 20% of those without had received an ICD therapy at the same time point.

Although the frequency of ICD therapies was lower than anticipated in this group, mortality and hospitalisation rates were similar to previous research in device populations. In this study, 3 out of 72 patients (4%) died during a mean of approximately 1.5 years of follow-up and 11 (15%) had a cardiovascular hospitalisation. In the MADIT-CRT trial, mortality at a mean of 4.2 years was approximately 7% in both those with CRTD or ICD therapy (235). The HF hospitalisation rate in MADIT-CRT was 23% in those with CRTDs and 14% in those with ICDs only. In the RAFT study, at 40 months of follow-up, 33% of those with CRTDs had died or been hospitalised for HF compared to 40% of those with an ICD alone (236). Allowing for the longer follow-up in these studies, the rates are broadly similar to the population in this research.

It is interesting that the first event in those with insignificant SDB was most frequently appropriate ICD therapy, whereas the most frequent first event in those with significant SDB was cardiovascular hospitalisation. The higher incidence of ICD therapies in those without significant SDB by ApneaScan™ reached statistical significance but must be interpreted with caution in the context of the low number of events. It could be postulated that those with more severe SDB (particularly CSA) have worse pump function (which exacerbates the sympathetic overdrive that underpins the pathophysiology of CSA) and this predisposes to more cardiovascular hospitalisations for HF. More research with a larger population size is currently on-going in our department to investigate this.

5.4.2 Interpretations and implications of the data

That there was no difference in outcomes between those with significant and non-significant SDB by ApneaScan™ may be due to inadequate discriminatory power of the algorithm, or because there is genuinely no difference in outcomes in this cohort. Of the 46 patients who had a sleep polygraphy study, 9 of 25 (36%) classified as having significant SDB by ApneaScan™ had none-or-mild SDB by polygraphy. Thus, some of those classified as having significant SDB by ApneaScan probably did not in fact have significant SDB. These false-positives may have 'diluted' the frequency of events in the significant SDB group. However, when these 46 patients were classified according to sleep polygrapy result, there was still no statistically-significant difference between the groups, suggesting that the observed similarity between groups is genuine. It must be stressed, however, that the number of patients and events is too low to draw conclusions on this.

Although not statistically significant, a higher proportion of patients in the insignificant SDB group had ischaemic heart disease and are thus at a higher risk of ventricular tachyarrhythmias compared with those with DCM (233). A higher proportion of subjects in the insignificant SDB group also received defibrillators for the secondary prevention of sudden cardiac death, although this did not reach statistical significance either. It might be expected that these patients are at the highest risk of ventricular arrhythmia which may

have lead to a high rate of events in the insignificant SDB group. However, only 2 of the 8 patients experiencing an ICD therapy in the insignificant SDB group had a device for secondary prevention, so the higher secondary prevention population is unlikely to have influenced the outcome.

Patients in this study found to have moderate-to-severe OSA (n=7) were referred for consideration of CPAP therapy and three started on this treatment (although only one continued the therapy long-term). There is evidence that the use of CPAP improves some measures of cardiac function and observational data that it may decrease mortality (171,172). This may have contributed to the lower-than-expected event rate in this group.

Whether the parity in outcomes between the two groups in this study is due to underperformance of the algorithm, or due to a genuine attenuation of the deleterious effects of SDB with modern HF treatment, cannot be determined based on these under-powered data. A larger study is required, especially with the low event rate in this population, and recruitment is ongoing in our department to address this.

5.4.2 Secondary endpoint – prevalence of atrial tachyarrhythmia

This study found no statistically significant difference in the prevalence of atrial tachyarrhythmias between those with significant and insignificant SDB by ApneaScan, either at baseline or at the point of follow-up. There was also no difference in the incidence of new atrial tachyarrhythmias during the follow-up period between the two groups. This contrasts with previous studies which found higher rates of AF in those with significant SDB and HF. It must be stressed that this study was under-powered to detect a difference and further recruitment is on-going.

Much data exists demonstrating an association between AF and OSA. Gami and colleagues reviewed 463 patients with current or previous atrial fibrillation and used the Berlin questionnaire to diagnose OSA (with sleep polygraphy performed on 44 subjects to

validate the questionnaire) (111). The questionnaire had a sensitivity of 86% and a specificity of 89% for the diagnosis of OSA (AHI≥5). They diagnosed OSA in 49% of those with current or previous AF compared with 32% of those in the general cardiology clinic with no history of AF (p=0.004). Gami and colleagues also performed a retrospective community cohort study of 3542 subjects who underwent polysomnography, without AF at baseline (237). After a mean follow-up of 4.7 years, the incidence of AF was 4.3% in those with OSA compared with 2.1% without OSA (HR 2.18, 95% CI 1.34 to 3.54, p=0.002).

There is also evidence of an association between CSA and AF in those with normal LV function. One study of patients with AF and normal LV systolic function found CSA in 31% and OSA in 43% of subjects (112). Another study recruiting patients without known cardiovascular disease found a significantly higher prevalence of AF in those with idiopathic CSA compared with subjects with OSA or normal sleep-breathing (27%, 1.7%, and 3.3%, respectively, P<0.001) (238). Ng and colleagues performed a meta-analysis of 6 studies comprising 3995 patients following ablation procedures for AF and demonstrated that those with OSA had a 25% greater risk of recurrent AF following ablation than those without (RR 1.25, 95% CI 1.08 to 1.45, p=0.003).

In those with heart failure, Javaheri and colleagues demonstrated an association between CSA and AF (60). In a cohort of 81 patients with moderate-to-severe LV systolic dysfunction (mean EF 25%), AF was found in 22% of patients with CSA and 5% of those without. In the SchlaHF registry, comprising 6876 patients with moderate-to-severe LV systolic dysfunction, the presence of AF was an independent risk factor for the development of SDB (OR: 1.19; 95% CI 1.06 to 1.34) (52).

In this study, however, the presence of SDB as diagnosed by ApneaScan was not associated with higher prevalence or incidence of AF. The prevalence of AF in those with SDB (23% at follow-up) is similar to previous studies. However, the prevalence of AF in those without SDB in this study (21% at follow-up) is significantly higher than the 5% observed in the Javaheri cohort. ApneaScan has a strong negative predictive power (94% - see chapter 3) and therefore this group is likely to be genuinely free of significant SDB. The reason for this

high prevalence of AF in those without SDB is unclear. Mean EF is similar in this study to that of Javaheri, as is BMI and age. A possible explanation is that, as this is a cohort of patients with complex devices, they may represent a group with more chronic HF, and this may have resulted in more dilated atria and thus higher rates of AF. Atrial size is not reported in Javaheri's paper. The lack of association may also merely be a product of the small study size (see 'study limitations' below).

5.4.3 Study limitations

The major limitation of this study is the population size, especially in light of the low event rate. On-going research in the department is continuing to recruit for this arm of the study to achieve the pre-specified sample size (172 patients currently recruited, against an estimated pre-study sample size requirement of 116). [Re-presented power calculation deleted].

In this study, however, the event rate was lower than anticipated at 20 months (32%) with no difference between those with significant SDB and those without. This was largely driven by the low incidence of ICD therapies. I aim to publish these data once follow-up of adequate numbers has been achieved.

The large number of patients excluded from this study after recruitment is disappointing (45% of the cohort). The majority of these exclusions were unavoidable and recruitment became more efficient once we started recruiting only after device implantation (to prevent recruitment of those who went on to receive devices without ApneaScan™ function or those in whom ApneaScan could not be turned on for pacing reasons). As we made these changes to our recruitment process, there will be a lower rate of exclusion when the final data are produced.

ApneaScan™ records up to 3 months of data at a time. It could therefore be argued that a more representative picture of the true severity of SDB could be achieved by taking the average of several nights' results, rather than just one. However, evidence from chapter 4 of

this thesis suggests that night-to-night variability is limited and the use of a single night reading is consistent with previous research in this area. Therefore, the use of a single night reading is unlikely to have influenced the outcome.

5.5 Conclusions

In this cohort, the presence of significant SDB, as diagnosed by either ApneaScan™ or sleep polygraphy, did not correlate with adverse cardiovascular events over a median of 532 days follow-up. The presence of significant SDB, as diagnosed by ApneaScan™, also did not correlate with the prevalence or incidence of atrial tachyarrhythmias. This is in contrast to previous research and there are several reasons why this may have been the case. This study was under-powered for the primary endpoint and further recruitment is taking place which will allow definitive conclusions on the influence of SDB, as diagnosed by ApneaScan™, on cardiovascular outcomes in the future.

Chapter 6: Conclusions and future directions

6.1 General Conclusions

6.1.1 Validity of the ApneaScan™ algorithm for the diagnosis of SDB in HF: implications for clinical practice

In this study, ApneaScan™ was shown to correlate closely with sleep polygraphy for the diagnosis of moderate-to-severe SDB in patients with HF. ApneaScan™ over-estimates the RDI compared with polygraphy, but when adjusted with a cut-off of 30.5 events/hour, it is a useful screening tool with a high negative predictive power of 94% for moderate-to-severe SDB. It may therefore be a clinically useful 'rule-out' test for significant SDB, although readings above 30.5 events/hour should be investigated with formal sleep studies as specificity and positive predictive power are lower. The prevalence of undiagnosed SDB in this population with implanted cardiac devices is high and daytime somnolence is not a useful predictor, so ApneaScan™ may help focus testing on those with the highest pre-test probability and thus prevent unnecessary sleep studies with benefit for hospital resources.

An algorithm for the diagnosis of SDB in those with HF incorporating the ApneaScan™ algorithm is presented in chapter 3 (Fig. 11). Given the high prevalence of undiagnosed SDB in those with HF, it could be argued that sleep studies (or overnight pulse oximetry as an initial test) should be performed in all patients with an AP-RDI ≥30.5/hour, and those in whom there is suspicion of SDB despite a lower AP-RDI. In this study, 28% of subjects screened had previously undiagnosed moderate-to-severe CSA and 13% moderate-to-severe OSA.

The question then arises as to how to manage SDB once discovered in these patients. Our understanding of the management of SDB in HF is incomplete and has changed significantly in recent years following the publication of the SERVE-HF trial (57). Based on current data, positive airway pressure is contra-indicated for the management of CSA. Further data from

the ADVENT-HF trial (NCT01128816) may inform the debate further. Phrenic nerve stimulators remain an interesting concept which requires clinical outcome data to prove benefit. At the present time, optimal medical therapy, with consideration of CRT for those meeting criteria, should be the approach to those with CSA and HF.

The management of OSA in HF is also incompletely understood. Randomised data suggest improvements in physiological parameters and observational data shows improved survival in those with HF and OSA treated with CPAP, but there is no randomised outcome data. The ADVENT-HF trial has recruited patients with OSA (or CSA) and HF to treatment with ASV or not and may provide the first randomised controlled data on mortality with PAP treatment for OSA in HF.

In the population without HF, CPAP therapy for OSA is recommended by European and British guidelines for the treatment of excessive daytime somnolence and hypertension (139,239). In the HF population, daytime somnolence is less frequently reported - a third of those with moderate-to-severe SDB in this cohort had low Epworth Sleepiness Scores (<11) - and hypertension is rare, especially once optimal pharmacological treatment has been established. Whether CPAP therapy for OSA should be prescribed purely for its beneficial effects on cardiovascular physiology is open to debate. The SAVE trial found no reduction in cardiovascular events in those with moderate-to-severe OSA (but not HF) treated with CPAP (164). It should be remembered that ASV therapy for CSA was shown to improve cardiac function and measures of HF but was still associated with increased mortality in the SERVE-HF trial. It is of some reassurance that the treatment of CSA with CPAP in the CANPAP trial, whilst not improving mortality, was at least not associated with increased mortality (186). However, the study was not powered to detect this and was terminated early.

In the absence of randomised outcome data, caution must be advised when considering PAP for those with OSA and HF in the absence of excessive daytime somnolence. Even in those with excessive daytime somnolence, the effects of PAP on the heart must be carefully

considered. The results of ADVENT-HF may illuminate this debate and potentially extend the indications for PAP in those with SDB and HF.

Despite the uncertainty of how to manage SDB in HF, making the diagnosis - with the aid of ApneaScan - remains a useful exercise. A high ApneaScan™ reading should alert the clinician to the possibility of SDB and to subsequent enquiry about daytime somnolence, with possible intervention to prevent the patient falling asleep while driving. Multiple studies have shown that those with HF and SDB have significantly greater rates of adverse cardiovascular events, including death, compared to those without. Those with SDB should receive the most intensive management of their HF. Also, the severity of CSA is markedly increased in those admitted to hospital with decompensated HF, which raises the possibility that monitoring CSA may allow early warning of deterioration with an opportunity for timely intervention (61). This concept requires further investigation, especially as trials of remote monitoring for HF have not consistently shown improved outcomes (156,157).

6.1.2 Variability in SDB in those with HF: implications for clinical practice

Night-to-night variability of SDB in this group of patients with HF, as assessed by ApneaScan over 28 or 92 nights, was low. This has significant implications for the investigation of SDB as it increases confidence in the validity of the current practice of diagnosing SDB on the basis of a single sleep study. This study is the first to assess SDB over so many consecutive nights in those with HF. Those with an RDI closer to the ApneaScan cut-off for moderate-to-severe SDB (30.5/hour) were, unsurprisingly, more likely to change groups in to the mild-range intermittently during 30 nights of follow-up and therefore may benefit from multiple sleep studies to determine the true mean AHI prior to embarking on treatment. It should be noted that the AHI threshold of 15 events/hour for treatment is, of course, arbitrary and the optimal threshold for treatment is not definitively proven, especially in the HF population. Whether AHI is, in fact, the optimal measure of SDB or whether clinicians should take multiple other factors in to

account, such as ODI or total time with arterial oxygen saturation below 90%, before deciding on treatment is also subject to debate.

The consistency of ApneaScan readings means that it may be useful clinically in determining whether the night of a sleep study is representative of the patient's mean AHI or whether the results of a single-night sleep study are affected by a 'first-night' effect. This would focus repeat studies only on those in whom the AP-RDI was far from the mean on the night of the study. In addition, ApneaScan may be useful to determine response to treatment of OSA with CPAP therapy, reducing the need for regular sleep studies in those in whom AP-RDI is successfully suppressed. This is particularly true given the high negative predictive power of the algorithm. The caveat to this is that the effect of positive airway pressure on the accuracy of the algorithm has not been determined and should be compared against polygraphy before the algorithm alone can be relied upon. In this study, ApneaScan™ data was poorly-recorded in a single subject following the initiation of CPAP therapy, so the utility of ApneaScan™ in this group is uncertain.

There is no consensus on how frequently the severity of SDB should be assessed. This may be particularly important in less stable HF patients in whom both CSA and OSA may vary significantly over weeks and months as the severity of the HF syndrome and total body water varies. ApneaScan™ allows assessment of SDB at every download and, with Latitude™ remote monitoring technology, SDB can be reviewed at any time without the need for multiple sleep studies. The caveat remains that AP-RDI over-estimates the 'true' AHI and, where appropriate for decision-making, should be confirmed with sleep polygraphy.

6.1.3 Prognostic significance of SDB in HF as assessed by ApneaScan™: implications for clinical practice

In this cohort, moderate-to-severe SDB as diagnosed by ApneaScan™ (AP-RDI>30.5/hour) or sleep polygraphy (PG-AHI>15/hour) was not associated with an increased risk of adverse cardiovascular outcomes, in contrast to previous publications. There are several

possible reasons for this, as discussed in chapter 5, and the cohort size was inadequate to draw firm conclusions. Recruitment and data collection for this arm of the study is on-going and total recruitment numbers have now reached our power calculation target. When these data are collected in the next year we will be able to draw appropriate conclusions. I will present and publish these data at that time.

Although the severity of SDB, as diagnosed by either sleep polygraphy or ApneaScan™, was not associated with the risk of adverse events in this cohort, the possibility remains that ApneaScan™ could prove to be a useful risk-stratification tool in an appropriately powered study. This is particularly true as the association of SDB (diagnosed by polygraphy or polysomnography) with adverse events is well-proven in the literature. If sleep polygraphy was able to risk-stratify patients but ApneaScan™ was not in this cohort confidence in the algorithm would be diminished. I will seek to publish the final data on the prognostic significance of an elevated AP-RDI once the data have been fully collected.

6.1.4 Final comments

This is the first study to demonstrate that ApneaScan™ is a useful screening tool for SDB in those with HF and implanted cardiac devices. Our understanding of SDB in HF is incomplete and future research will increase our confidence in diagnosing and managing this prevalent and potentially harmful condition. SDB remains significantly under-diagnosed in this population and ApneaScan™ may aid clinicians caring for these complex patients to improve our diagnosis and management of SDB in HF.

6.2 Future directions

Recruitment for the prognostic arm of this study is on-going and currently stands at 155 patients. We will complete recruitment at 180 patients (which exceeds the pre-specified population size of 154 to give 90% power). The larger number recruited may partially counter the lower-than-expected event rate in our population and may allow us to conclude whether SDB as assessed by ApneaScan™ correlates with prognosis in this

population. The 1 year follow-up data from this cohort will not be available in time to be included in this thesis, due to the submission deadline, but will be published elsewhere.

The publication of the SERVE-HF trial during this research period changed the way we think about managing CSA (57). Whilst CSA is still a useful marker of severity of HF, and changes in CSA may act as an early warning of decompensation, treatment with positive pressure ventilation appears to either have no overall effect (CPAP) or increases mortality (ASV). The implications of this for treatment of CSA and future research in to CSA are still being digested. The ADVENT-HF trial is ongoing and may add to our understanding. This trial has recruited subjects with HF and either CSA or OSA with randomisation to ASV or medical therapy only. When analysed in 2015, no safety signal was noted with ASV therapy but final results on outcomes are awaited. Should the ADVENT-HF trial show benefit in treating OSA with ASV, thought will have to be directed at whether the result can be extrapolated to the simpler, cheaper and more readily-available CPAP therapy.

The *Remede*™ phrenic nerve stimulator (Respicardia, Minnetonka, MN, USA) appears to effectively reduce AHI in CSA in those with HF and recent research suggests that the reduction in AHI seen with this device persists over 4 years (205,240,241). Whether this device influences clinical outcomes is unknown and, following the results of SERVE-HF, surrogate markers can no longer be accepted as proof of clinical benefit in treating CSA. The *Remede*™ system may provide particular insight as it reduces the AHI in CSA without positive airway pressure, thereby allowing differentiation between the possible (beneficial) effects of CSA and the possible (deleterious) effects of positive airway pressure. We are not aware of any on-going trial powered for mortality outcomes with this device, and this would be required prior to widespread acceptance of the benefit of this technology.

Given the unexpected results of the SERVE-HF trial, a suitably-powered randomised trial of morbidity and mortality with CPAP for the treatment of OSA in HF would be enlightening. However, CPAP is an older technology provided by several different manufacturers and therefore there is limited financial incentive for industry to fund such a trial.

An interesting and relatively simple study to perform would be to review changes in AP-RDI in those with CSA in the days to weeks leading up to a hospital admission with decompensated HF, when CSA-AHI is known to be high. This may indicate whether AP-RDI could be used as an 'early warning' signal for HF decompensation, particularly in those with CSA. Current evidence for the clinical benefit of remote monitoring algorithms is variable and it would be interesting to determine whether monitoring CSA could add to this.

CRT significantly reduces AHI in CSA. As an exaggerated hypercapnic ventilatory response drives the respiratory pattern in CSA, it would be interesting to determine whether this abnormal response is ameliorated by CRT implantation. A pilot for this study, using the Read re-breathe method to assess the hypercapnic ventilatory response, has been undertaken in our department.

There remain many uncertainties in the management of SDB in HF, not least whether treating CSA is appropriate and, if so, by what means. The relationship between sleep-disordered breathing and heart failure is complex and our approach to diagnosing and managing these conditions is changing rapidly as new evidence is published. ApneaScan™ is a useful tool that can alert clinicians to the presence of SDB and may be of benefit in improving diagnosis and outcomes in patients with sleep-disordered breathing.

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Appendix 1

Epworth Sleepiness Scale

Name: _____ Today's date: _____

Your age (Yrs): _____ Your sex (Male = M, Female = F): _____

How likely are you to doze off or fall asleep in the following situations, in contrast to feeling just tired?

This refers to your usual way of life in recent times.

Even if you haven't done some of these things recently try to work out how they would have affected you.

Use the following scale to choose the **most appropriate number** for each situation:

0 = would **never** doze
1 = **slight chance** of dozing
2 = **moderate chance** of dozing
3 = **high chance** of dozing

It is important that you answer each question as best you can.

Situation	**Chance of Dozing (0-3)**
Sitting and reading _____	___
Watching TV _____	___
Sitting, inactive in a public place (e.g. a theatre or a meeting) _____	___
As a passenger in a car for an hour without a break _____	___
Lying down to rest in the afternoon when circumstances permit _____	___
Sitting and talking to someone _____	___
Sitting quietly after a lunch without alcohol _____	___
In a car, while stopped for a few minutes in the traffic _____	

THANK YOU FOR YOUR COOPERATION

Appendix 2

MINNESOTA LIVING WITH HEART FAILURE® QUESTIONNAIRE

The following questions ask how much your heart failure (heart condition) affected your life during the past month (4 weeks). After each question, circle the 0, 1, 2, 3, 4 or 5 to show how much your life was affected. If a question does not apply to you, circle the 0 after that question.

Did your heart failure prevent you from living as you wanted during the past month (4 weeks) by -	**No**			**Very Little**					**Very Much**
1. causing swelling in your ankles or legs?	0			1	2	3	4	5	
2. making you sit or lie down to rest during the day?	0			1	2	3	4	5	
3. making your walking about or climbing stairs difficult?	0			1	2	3	4	5	
4. making your working around the house or yard difficult?	0			1	2	3	4	5	
5. making your going places away from home difficult?	0			1	2	3	4	5	
6. making your sleeping well at night difficult?	0			1	2	3	4	5	
7. making your relating to or doing things with your friends or family difficult?	0			1	2	3	4	5	
8. making your working to earn a living difficult?	0			1	2	3	4	5	
9. making your recreational pastimes, sports or hobbies difficult?	0			1	2	3	4	5	
10. making your sexual activities difficult?	0			1	2	3	4	5	
11. making you eat less of the foods you like?	0			1	2	3	4	5	
12. making you short of breath?	0			1	2	3	4	5	
13. making you tired, fatigued, or low on energy?	0			1	2	3	4	5	
14. making you stay in a hospital?	0			1	2	3	4	5	
15. costing you money for medical care?	0			1	2	3	4	5	
16. giving you side effects from treatments?	0			1	2	3	4	5	
17. making you feel you are a burden to your family or friends?	0			1	2	3	4	5	
18. making you feel a loss of self-control in your life?	0			1	2	3	4	5	
19. making you worry?	0			1	2	3	4	5	
20. making it difficult for you to concentrate or remember things?	0			1	2	3	4	5	
21. making you feel depressed?	0			1	2	3	4	5	

Appendix 3 - Comparison of polygraphic AHI, -RDI and -ODI in this population

Background

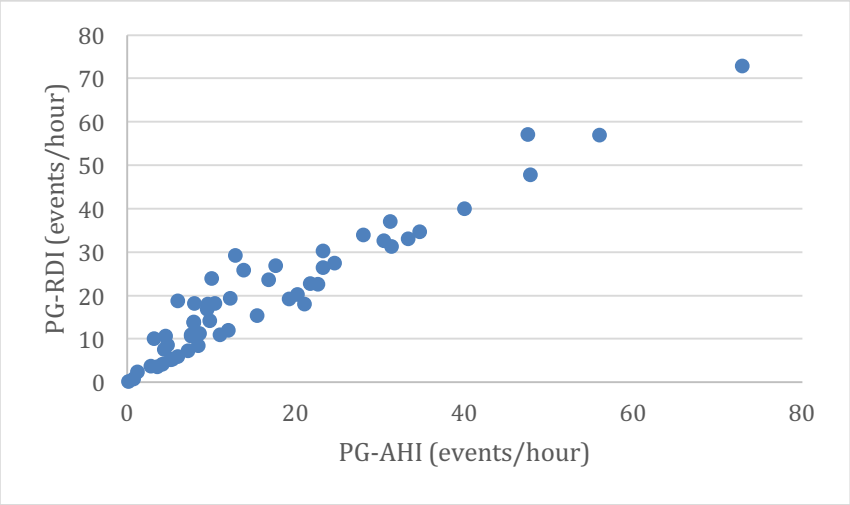
There is uncertainty which polygraphic measure should be used to assess the severity of sleep-disordered breathing. Apnoea-Hypopnoea Index (AHI) has been the most frequently reported measure and is employed in the AASM guidelines (58). However, many centres screen for SDB using simple overnight pulse oximetry and there is growing evidence that total nocturnal hypoxaemic time correlates most closely with clinical outcomes (107,143,146). Automated devices now exist which monitor respiratory movements during sleep using electromagnetic waves, producing a Respiratory Disturbance Index (145). It is not known how closely these measures correlate in those with advanced heart failure.

Methods

Single-night sleep polygraphy studies on the 54 patients completing the ApneaScan validation study were analysed by a single researcher to generate an Apnoea-Hypopnoea Index, Respiratory-Disturbance Index and Oxygen Desaturation Index, according the 2012 AASM guidelines (58). Intra-class correlation between the various measures was calculated using SPSS v 24 (Armonck, NY). Please see chapter 3 section 3.2 for detailed methods.

Results

There was very close correlation between PG-AHI and both PG-RDI and PG-ODI, and between PG-RDI and PG-ODI (Figures 1 to 3).



r=0.98 (0.96-0.99, p<0.001)

Figure 1a. Scatter plot of polygraphic Apnoea-Hypopnoea Index (PG-AHI) against polygraphic Respiratory Disturbance Index (PG-RDI). Each data point represents a single sleep study on a different patient.

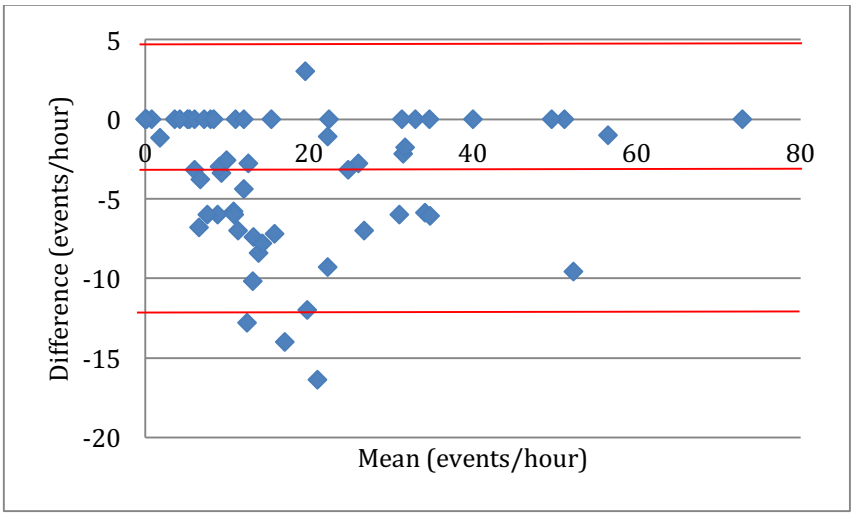
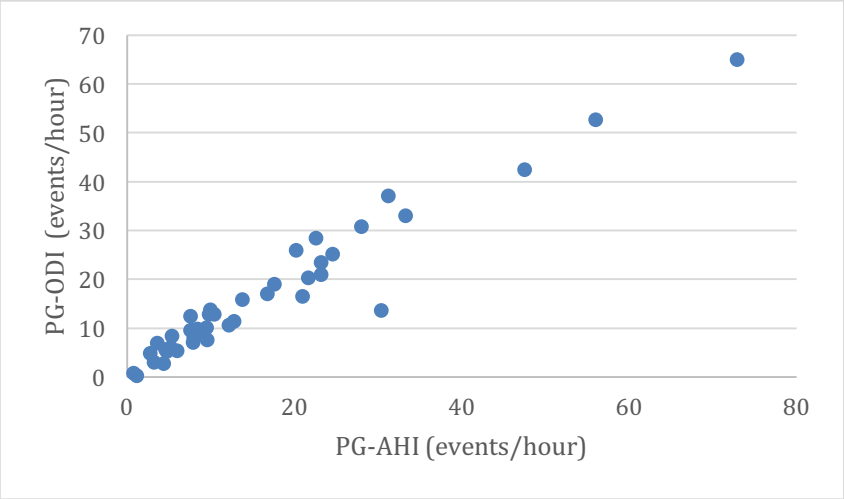


Figure 1b . Bland Altman plot of the mean vs. the difference of PG-AHI and PG-RDI. Red lines represent the mean and 2 standard deviation limit. Mean difference (AHI-RDI) was -3.7 events/hour, SD 4.3, coefficient of variation 1.2.



r=0.98 (0.97-0.99, p<0.001)

Figure 2a. Scatter plot of polygraphic Apnoea-Hypopnoea Index (PG-AHI) against polygraphic Oxygen Desaturation Index (PG-ODI). Each data point represents a single sleep study on a different patient.

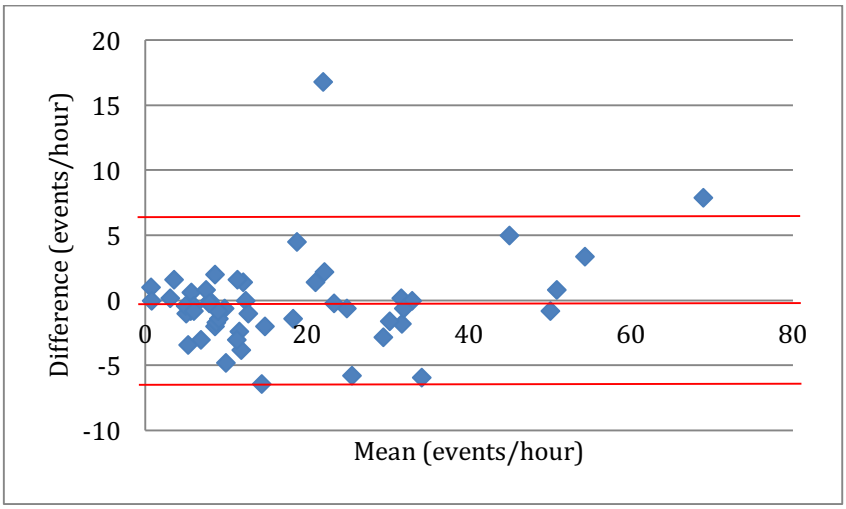
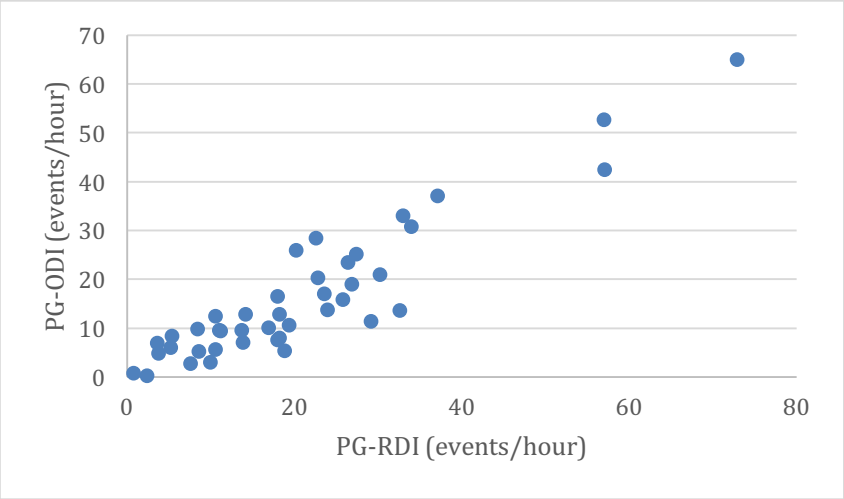


Figure 2b. Bland Altman plot of the mean vs. the difference of PG-AHI and PG-ODI. Red lines represent the mean and 2 standard deviation limit. Mean difference (AHI-ODI) was -0.2 events/hour, SD 3.5, coefficient of variation 17.5.



r=0.96 (0.92-0.99, p<0.001)

Figure 3a. Scatter plot of polygraphic Respiratory Disturbance Index (PG-RDI) against polygraphic Oxygen Desaturation Index (PG-ODI). Each data point represents a single sleep study on a different patient.

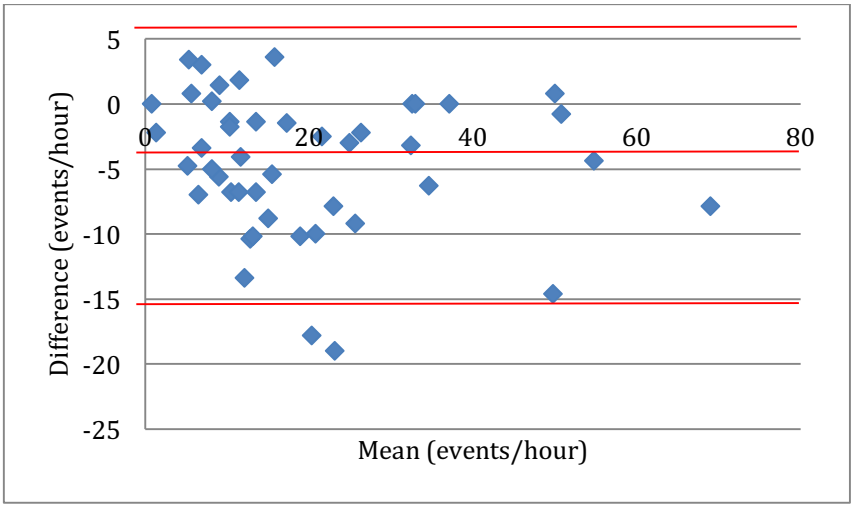


Figure 3b. Bland Altman plot of the mean vs. the difference of PG-RDI and PG-ODI. Red lines represent the mean and 2 standard deviation limit. Mean difference (RDI-ODI) was -4.5 events/hour, SD 5.3, coefficient of variation 1.2.

Discussion

In this population, there was very close correlation between polygraphy AHI, -RDI and –ODI, suggesting that these measures are equivalent for the reporting of SDB events. This is supported by data presented in chapter 3 section 3.3 which found similar correlation

between ApneaScan-RDI and the 3 polygraphy indices, and similar mean and median PG-AHI, -RDI and ODI in this population.

These data imply that few apnoeas or hypopnoeas occur in this population without an associated arterial oxygen desaturation of ≥3% from baseline. The most likely reason for this is that patients with advanced HF often have a degree of pulmonary oedema at night and limited physiological reserve, so that the majority of respiratory disturbances result in a desaturation. This is especially true when the 2012 AASM criteria are applied to analyse the sleep study, as these only require a ≥3% desaturation from baseline to diagnose a hypopnoea, as opposed to the ≥4% required in the preceding guidelines. Research has shown that this significantly increases the number of events diagnosed in the same sleep study (216,242).

In conclusion, polygraphic-AHI, -RDI and -ODI appear to be equivalent measures for monitoring the severity of SDB in this population of patients with advanced HF. Further research will determine whether any of these are the most appropriate measure of SDB, or whether total hypoxaemic time will become accepted as the 'gold-standard' measure. It is important to emphasise that these measures only describe the number of events per hour and not the nature of these events (central versus obstructive), nor the severity of events (duration and degree of hypoxaemia) and this differentiation is essential to guide positive pressure therapy.

Appendix 4. Publications arising from this research

Abstract of a poster presented at the meeting of the Heart Failure Association of the European Society of Cardiology, Seville, May 2015:

Accuracy of the pacemaker-derived ApneaScanTM algorithm for the diagnosis of sleep disordered breathing in heart failure.

Dr S Pearse, Dr R Sharma, Dr T Wong, Prof M Morrell, Prof A Simonds, Dr R Lane, Dr M Mason, Prof M Polkey, Prof M Cowie, Dr A Vazir. Royal Brompton and Harefield NHS Trust and Imperial College London

Purpose

Sleep disordered breathing (SDB) is highly prevalent in patients with heart failure and its presence is associated with a worse prognosis. Treatment with continuous positive pressure is beneficial for those with obstructive sleep apnoea (OSA), however the treatment of central sleep apnoea (CSA) is under investigation. Many centres do not have routine access to sleep polygraphy or polysomnography and SDB is frequently underdiagnosed. A novel pacemaker algorithm (ApneaScanTM, Boston Scientific, Marlborough, MA) uses variation in transthoracic impedance with breathing to quantify apnoeas and hypopnoeas. It is available on ICD and CRT devices. The aim of this study is to assess the accuracy of this algorithm compared to standard multichannel sleep polygraphy.

Methods

Patients with symptomatic heart failure, ejection fraction <40%, not on nocturnal non-invasive ventilation and with compatible pacing or ICD devices underwent home sleep polygraphy (EmblettaTM, Embla, Canada) at least 6 weeks following device implantation or

box change, followed by download of ApneaScan data from the pacemaker. The data for the study night was compared using correlation coefficients and a Bland Altman plot.

Results

18 patients (mean ±SD: age 68 ±14 years, 78% male, NYHA 2.1±0.5, BNP 469±417ng/l, EF 26.8±9.5%) underwent home polygraphy and pacemaker download. Mean apnoea-hypopnoea index by polygraphy (PG-AHI), analysed according to the American Academy of Sleep Medicine 2012 criteria, was 16.0±17.8 events/hr. Mean ApneaScan-derived AHI (APS-AHI) was 31.1±11.4/hr. The APS-AHI demonstrated good correlation with PG-AHI overall ($r= 0.79$, $p<0.01$). ApneaScan performed well in those with moderate to severe SDB defined as AHI>15/hr, ($r=0.93$, $p<0.01$) but was less accurate in those with mild or no SDB ($r=0.28$, $p=0.37$). The accuracy of ApneaScan was not significantly different between those with CSA and OSA. ApneaScan over-estimated SDB by a mean difference 15.94±11.39 in this cohort. In detecting those with moderate to severe SDB (AHI>15/hr) the sensitivity was 100% with specificity 8%; positive predictive value 35% and negative predictive value 100%.

Conclusions

The ApneaScan algorithm is a sensitive but non-specific means of diagnosing SDB, with a strong negative predictive value. The algorithm over-estimates severity of SDB but is more accurate in those with moderate to severe SDB. The APS-AHI may prove a useful tool for screening for SDB in patients with chronic heart failure.

Abstract of a poster presented at the Heart Failure Association of the European Society of Cardiology meeting, Florence, May 2016:

Validity of the ApneaScan™ algorithm in implantable devices for the diagnosis of sleep-disordered breathing in heart failure

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Royal Brompton and Harefield NHS Trust and Imperial College, London

Purpose

Sleep-disordered breathing (SDB) affects over half of patients with heart failure (HF). Both obstructive sleep apnoea (OSA) and central sleep apnoea (CSA) are associated with a poor prognosis and are under-diagnosed in the HF population. Current evidence demonstrates benefits for positive airway pressure therapy in those with OSA and HF, whilst optimal management of CSA is unclear. A novel pacemaker algorithm (ApneaScan™, Boston Scientific, Marlborough, Ma.) has been developed to diagnose and quantify SDB. There are no published data on the accuracy of this algorithm compared with sleep polygraphy.

Methods

Patients with systolic heart failure and an ejection fraction <40%, not on nocturnal non-invasive ventilation and with compatible pacing or ICD devices underwent home sleep polygraphy (Embletta™, Embla, Canada) at least 4 weeks following device implantation or box change, with concurrent download of ApneaScan™ data from the pacemaker. The data for the study night were compared with the download using correlation coefficients, Bland Altman plots and a receiver operating characteristic curve (ROC).

Results

60 patients (mean±SD: age 69.1±11.9 years, male 71%, NYHA 2.4±0.5, BNP 496±466ng/l, EF 29.3±9.4%) underwent home sleep polygraphy and pacemaker download. 10 patients (17%) had no recorded data from the algorithm. Mean apnoea-hypopnoea index by polygraphy (PG-AHI) was 16.3±15.0/hour and by ApneaScan (AP-AHI) 34.8±13.8/hour. The intraclass correlation coefficient (r) for all patients was 0.78 (0.61-0.88, $p<0.01$)). ApneaScan™ was more accurate in those with OSA (r=0.86, 0.53-0.95, $p<0.01$) than CSA (r=0.74, 0.48-0.83, $p<0.01$). It was accurate in those with moderate to severe SDB (AHI>15/h, r=0.79, 0.42-0.92, $p<0.01$), but inaccurate in those with mild or no SDB (AHI ≤ 15/h)(r=0.22, -0.60-0.62, p=0.25). Correlation was closer in those with predominantly apnoeic events (r=0.83, 0.37-0.955, $p<0.01$) compared with hypopnoeic events (r=0.62, 0.27-0.81, $p<0.01$). On the ROC curve, the optimal ApneaScan cut-off for the diagnosis of moderate to severe SDB was 30.5/hour, yielding a sensitivity of 89%, specificity 68%, positive predictive value 62% and negative predictive value 91%. The area under the ROC curve was 0.84.

Conclusion

ApneaScan™ over-estimates the severity of SDB compared with sleep polygraphy. At the cut-off of 30.5 events per hour, ApneaScan™ is a sensitive screening test for moderate to severe SDB with a high negative predictive value. The algorithm may be a useful means of screening for SDB in those with HF and an implanted device – particularly for those with apnoeic episodes; a value above 30.5/hour should be confirmed with a sleep study.

Abstract of a review article published in the European Journal of Heart Failure (Editor's choice article, April 2016. One of the top 10 cited articles in the journal 2016):

European Journal of Heart Failure (2016) 18, 353–361
doi:10.1002/ejhf.492

REVIEW

Sleep-disordered breathing in heart failure

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Received 9 April 2015; revised 4 January 2016; accepted 5 January 2016; online publish-ahead-of-print 11 February 2016

Sleep-disordered breathing—comprising obstructive sleep apnoea (OSA), central sleep apnoea (CSA), or a combination of the two—is found in over half of heart failure (HF) patients and may have harmful effects on cardiac function, with swings in intrathoracic pressure (and therefore preload and afterload), blood pressure, sympathetic activity, and repetitive hypoxaemia. It is associated with reduced health-related quality of life, higher healthcare utilization, and a poor prognosis. Whilst continuous positive airway pressure (CPAP) is the treatment of choice for patients with daytime sleepiness due to OSA, the optimal management of CSA remains uncertain. There is much circumstantial evidence that the treatment of OSA in HF patients with CPAP can improve symptoms, cardiac function, biomarkers of cardiovascular disease, and quality of life, but the quality of evidence for an improvement in mortality is weak. For systolic HF patients with CSA, the CANPAP trial did not demonstrate an overall survival or hospitalization advantage for CPAP. A minute ventilation-targeted positive airway therapy, adaptive servoventilation (ASV), can control CSA and improves several surrogate markers of cardiovascular outcome, but in the recently published SERVE-HF randomized trial, ASV was associated with significantly increased mortality and no improvement in HF hospitalization or quality of life. Further research is needed to clarify the therapeutic rationale for the treatment of CSA in HF. Cardiologists should have a high index of suspicion for sleep-disordered breathing in those with HF, and work closely with sleep physicians to optimize patient management.

Keywords Heart failure • Sleep-disordered breathing • Diagnosis • Treatment

Pearse SG, Cowie MR. Sleep-disordered breathing in heart failure. Eur J Heart Fail 2016, 18: 353–361.

Abstract of a poster presented at the CardioSleep Conference, Paris, April 2015:

Variation in severity of sleep-disordered breathing over 30 nights diagnosed by a pacemaker algorithm in patients with heart failure

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Rationale

Sleep-disordered breathing is usually diagnosed on the basis of a single night polygraphy or polysomnography study. Previous research on patients with heart failure (HF) has shown that night-to-night variation in apnoea-hypopnoea index (AHI) is minimal over 4 consecutive nights. No study has examined longer-term variation in AHI. This study aims to determine variation in AHI over 30 nights using an automatic pacemaker algorithm which assesses variations in transthoracic impedance with breathing to quantify SDB.

Methods

Patients with an implantable cardioverter-defibrillator (ICD) or biventricular pacemaker/ICD with ApneaScan™ function (Boston Scientific, Natick, Ma) were followed up at least 6 weeks following device implantation. They underwent home sleep polygraphy, pacemaker download with recording of the AHI over the last 30 nights, echocardiography and routine blood analysis. Data was analysed as mean ± standard deviation for normally distributed data. Night-to-night variation was assessed with intra-class correlation coefficient (ICC).

Results

Eighteen patients (83% male, mean ±SD: age 69 ±11 years, BNP 437±312ng/l, EF 25±8%) participated in the study. Mean pacemaker-derived AHI (PM-AHI) over 30 nights was

35±10/hr. Mean polygraphic AHI (PG-AHI) on one night was 18±19/hr. Night-to-night AHI demonstrated good consistently overall (ICC 0.91, CI 0.76-0.99, p<0.01). Consistency was similar for those with both predominant obstructive (ICC 0.92, CI 0.70-0.99, p<0.01) and central sleep apnoea (ICC 0.95, CI 0.89-0.99, p<0.01) on polygraphy. Similarly, those with mild SDB on polygraphy (AHI<15/hr) displayed a similar consistency in AHI (ICC 0.96, CI 0.89-0.99, p<0.01) as those with moderate to severe SDB (AHI ≥15/hr; ICC 0.96, CI 0.87-1.0, p<0.01). The ICC was consistently high when patients were divided according to left ventricular ejection fraction and B-type natriuretic factor concentration (ICC > 0.9 for all).

Despite this low variation from night-to-night, 2 patients with severe SDB (mean PM-AHI>30) had at least one AHI of <15/hr, which may lead to missed diagnoses.

Conclusions

Night-to-night variation is minimal in patients with HF, so a single night polygraphy study should be adequate to diagnose SDB. However, 'atypical' nights do occur and this should be remembered when investigating for this condition.

Review article published in European Cardiology Review, December 2015:

Sleep-disordered Breathing in Heart Failure

Simon G Pearse, Martin R Cowie, Rakesh Sharma and Ali Vazir

Royal Brompton and Harefield NHS Trust and Imperial College London, London, United Kingdom

Abstract

Sleep-disordered breathing affects over half of patients with heart failure (HF) and is associated with a poor prognosis. It is an under-diagnosed condition and may be a missed therapeutic target. Obstructive sleep apnoea is caused by collapse of the pharynx, exacerbated by rostral fluid shift during sleep. The consequent negative intrathoracic pressure, hypoxaemia, sympathetic nervous system activation and arousals have deleterious cardiovascular effects. Treatment with continuous positive airway pressure may confer symptomatic and prognostic benefit in this group. In central sleep apnoea, the abnormality is with regulation of breathing in the brainstem, often causing a waxing-waning Cheyne Stokes respiration pattern. Non-invasive ventilation has not been shown to improve prognosis in these patients and the recently published SERVE-HF trial found increased mortality in those treated with adaptive servoventilation. The management of sleep-disordered breathing in patients with HF is evolving rapidly with significant implications for clinicians involved in their care.

Keywords

Sleep-disordered breathing, heart failure, sleep apnoea, CPAP, ASV

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Pearse SG, Cowie MR, Sharma R, Vazir A. Sleep disordered breathing in heart failure. European Cardiology Review 2015;10(2):89-94.

Abstract of an article under review at Europace journal:

Diagnosing sleep-disordered breathing in patients with heart failure using a pacemaker algorithm

SG Pearse[1], MR Cowie[1,3], MI Polkey[1,2], R Sharma[1], AK Simonds[1,3], T Wong[1], R Lane[1], M Mason[1], L Anderson[4], N Shanmugam[4], R Lucas[1], A Vazir[1]

Abstract

Aims

Sleep-disordered breathing (SDB) is highly prevalent and frequently undiagnosed in patients with heart failure (HF). The ApneaScan algorithm on Boston Scientific ICD and CRT devices quantifies SDB through changes in transthoracic impedance with respiration, but there are no published data on its validity. This study assesses the accuracy of the algorithm compared with sleep polygraphy for the diagnosis of moderate-to-severe SDB (AHI≥15/hour) in patients with HF.

Methods and results

63 subjects with compatible CRT or ICD devices, ejection fraction ≤40% and no prior diagnosis of SDB underwent home sleep polygraphy and simultaneous download of ApneaScan data. In 9 subjects (14%), no ApneaScan data recorded on the study night. Mean age was 68±13 years, mean BMI 27±4 kg/m^2 and 73% were male. The mean AHI by polygraphy was 16.8±15.1/hour and the mean ApneaScan respiratory disturbance index 35.3±13.9/hour. 22 subjects (41%) had undiagnosed moderate-to-severe SDB. The area under the ROC curve was 0.84 for the diagnosis of moderate-to-severe SDB (AHI≥15 by polygraphy). The optimal ApneaScan cut-off for this diagnosis was 30.5/hour, when

sensitivity was 95%, and specificity 69%, positive predictive value 68% and negative predictive value 95%.

Conclusion

ApneaScan over-estimates the severity of SDB, but at a cut-off of 30.5 events/hour it is a sensitive means of screening for moderate-to-severe SDB in patients with HF, with a high negative predictive value. The prevalence of undiagnosed SDB in patients with HF and ICD or CRT devices is high and ApneaScan may be a useful tool to prioritise those for formal sleep studies.

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