The Clinical Advantage

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Introduction
by Dr. David White, Chief Medical Officer

Welcome to the first edition of Philips Respironics’ newsletter The Clinical Advantage. This is a newsletter dedicated to keeping you up to date with clinical information and new clinical literature regarding sleep apnea.

Obstructive sleep apnea (OSA) has been the engine that has driven the remarkable growth of the sleep field over the last 25 years. Although the medical community and the general public have been interested in the performance and quality-of-life problems that result from sleep apnea, the real concern has been the potential relationship between OSA and the cardiovascular system. This goes back as far as the book “The Sleep Apnea Syndromes” (published in 1978 and edited by Christian Guilleminault and Bill Dement) which contained the proceedings of the Kroc Foundation meeting organized to discuss the newly identified disorder; OSA.

In that book, the possibility that sleep apnea might lead to adverse cardiovascular events was raised as a real possibility. Since that time, the sleep research community has steadily toiled to determine if such a relationship actually exists using both clinical and basic science approaches. However, this question has not been answered to the satisfaction of many clinicians and scientists.

That obstructive apnea can contribute to the development of systemic hypertension seems relatively clear despite the fact that treatment of the OSA does not always lead to improvements in blood pressure even in hypertensive patients. Whether sleep apnea leads to hard end point adverse events such as myocardial infarctions, strokes, or the development of congestive heart failure is still the subject of considerable debate.

The devices discussed in these journal articles have not been cleared by FDA for the uses described.

(continued on next page)
In this first Philips Respironics newsletter, Michael Arzt summarizes the current state of the literature regarding the association between OSA and cardiovascular disease and points out many of the areas where controversy still remains. Case studies are also presented which develop several of these themes further. However, this controversy will not end until adequately powered, randomized, controlled, clinical trials are conducted addressing this issue. At last, several such studies are underway. SAVE was designed to determine the relationship between OSA and strokes or heart attacks by conducting a secondary prevention study (with CPAP) in patients with both OSA and known coronary or cerebrovascular disease. ADVENT HF will answer the question of whether a reduction in, or elimination of, OSA or Cheyne-Stokes Respiration (CSR) with an auto servo ventilation device leads to improved survival in patients with congestive heart failure. The recently funded National Institutes of Health (NIH) studies being conducted by Drs. Redline and Yaggi are not designed to assess hard cardiovascular end points, but will both quantify treatment (CPAP) effects on intermediate markers of vascular disease and serve to power larger studies with more definitive outcomes. Finally, Dr. Bassetti is conducting a study in Europe to assess the relationship between OSA and stroke using both intermediate and hard outcomes (see pages 9-11 for more trial information).

While we are years away from the completion of any of the more definitive trials we must make clinical decisions on a daily basis regarding the care of patients with sleep apnea. Although this may seem frustrating, it is the nature of science and clinical care. Physicians frequently must act on incomplete information and have for hundreds of years. At least we, in the sleep field, anticipate that some of the answers are on the way.

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Sleep-disordered breathing and cardiovascular disease – a vicious cycle?

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Introduction
The prevalence of moderate to severe sleep-disordered breathing (SDB) in patients with hypertension refractory to medical therapy, atrial fibrillation, coronary artery disease, heart failure and stroke ranges between 40 and 60 percent. A growing body of evidence suggests that OSA is often associated with the development of various cardiac disorders. In addition, when non-ischemic or ischemic cardiomyopathy has developed, impaired cardiac function itself may contribute to the development of both obstructive and central SA by inducing ventilator control instability and rostral fluidshift induced upper airway narrowing during sleep. There are effective means to interrupt this cycle: Treatment of heart failure improves SDB as well as treatment of SDB with different modes of positive airway pressure (PAP) may attenuates surrogates of cardiac outcome such as hypertension and impairment cardiac function. It is yet unclear whether the improvement of such surrogates of treating sleep disordered breathing do translate into prevention of cardiovascular events and mortality. Considering the high prevalence of SDB in patients with cardiovascular disease, the potential of improving SDB-related symptoms in such patients justifies high awareness, suspicion, and adequate diagnosis and treatment of SDB in such patients.
How is untreated OSA associated with progression of cardiac disease?

Acute increase of cardiac afterload and non-dipping

Untreated OSA is thought to precede and potentially contribute to the development of heart failure (HF) through several acute and long-term effects. OSA is characterized by respiratory efforts against the occluded pharynx. Its immediate pathophysiological consequences include intermittent hypoxia, arousals from sleep and repetitive surges of sympathetic activity leading to an increase in heart rate as well as arterial blood pressure. The repetitive respiratory efforts against an occluded pharynx result in multiple peaks of exaggerated intrathoracic pressure that, in addition to surges in blood pressure, increase cardiac afterload.[1-2]

In severe OSA cycles of apnea, arousals and sympathetic surge occur 300-500 times per night.[1, 3] In such patients frequently the physiologic fall of systolic blood pressure during sleep of at least 10% of the daytime pressure is absent (non-dipping)[4] or the nightly pressures even exceed the awake levels up to 40 mm Hg.[5] Severity of OSA correlates with the extent of non-dipping.[6] Importantly, non-dipping is also frequent in normotensive patients with obstructive SA (50%).[6, 7]

Hypertension

The weight of evidence has led the Joint National Committee on the Detection and Management of Hypertension to identify OSA as an important identifiable cause of hypertension.[8-9] In addition, to the acute effects of OSA on diurnal and nocturnal blood pressure that are “visible” in daily routine in sleep clinics, data from epidemiological studies and randomized controlled trials of continuous positive airway pressure (CPAP) in patients with severe OSA support the above statement. Data suggest that OSA is an important secondary cause of systemic hypertension.[10-12]

This modest association of OSA evident in epidemiological studies is supported by numerous interventional studies demonstrating amelioration of hypertension with CPAP therapy in patients with OSA.[16] The overall effect on mean blood pressure in this meta analysis is -2.2 mmHg.[17]

The major limitation of many included in this meta analysis of randomized trials was that patients in all trials were not hypertensive at baseline. The largest effects of treating OSA with CPAP on blood pressure can be observed in patients with more severe OSA, difficult-to-control hypertension, and those with better CPAP compliance.[9, 19] In such patient groups, falls in mean blood pressure up to 10 mmHg can be detected.[18, 20] A decrease in mean arterial pressure of 10 mm Hg could potentially reduce the risk of coronary artery disease and stroke by 37% and 56%, respectively.[18, 20-21]

Left ventricular hypertrophy

Systemic hypertension is the most common risk factor for cardiac hypertrophy and failure in longitudinal studies.[22] Interestingly, left ventricular hypertrophy is more closely linked to hypertension during sleep than during wakefulness.[23]

Several investigators found a highly significant correlation between the interventricular septum thickness and the severity of untreated OSA.[24-25] Moreover, in patients with severe OSA the left ventricular hypertrophy was partially reversed after six months of treating the OSA with CPAP in an uncontrolled trial.[24]

Endothelial dysfunction and atherosclerosis

Atherosclerosis is a complex condition in which an artery wall thickens as a result of lipid deposition in the vascular wall. Oxidative stress[26] and inflammation mediators like C-reactive protein and interleukins[27] as well as endothelial dysfunction[28, 29][30] play an important role in atherosclerotic plaque and thrombus formation.[31, 32]

Untreated OSA-related repetitive hypoxia may be considered to be a culprit triggering and accelerating development of atherosclerosis.[27, 30, 33-34] Levels of oxygen radicals in neutrophile granulocytes and monocytes[26] as well as C-reactive protein, IL-6 and IL-18[27] have been found to be elevated in patients with untreated OSA compared to normal subjects. Activated leukocytes develop adhesion molecules required to adhere to vascular walls for plaque formation. In addition, circulating nitric oxide levels are decreased in patients with untreated OSA.[28-29] As a consequence endothelium dependent nitric oxide-mediated vasodilatation is impaired in patients with untreated OSA.[30] In the absence of any comorbidities, including obesity, OSA alone impairs endothelial repair capacity and promotes endothelial apoptosis.[35] This data may support a causal relationship with untreated OSA. It has also been demonstrated that treatment of OSA with CPAP reduces endothelial dysfunction paralleled by an increased endothelial repair capacity.[36-37]
Coronary artery disease, myocardial infarction and heart failure
Observational studies from sleep clinic samples and community-based cohort studies complement the evidence that untreated OSA promotes risk factors for myocardial infarction and stroke, such as hypertension, diabetic metabolism, endothelial dysfunction and atherosclerosis as well as platelet aggregation and atrial fibrillation. They strongly suggest that OSA precedes cardio- and cerebrovascular events. Marin et al.[34] reported data from a non-randomized prospective observational study involving a sleep clinic population, and a community sample of healthy subjects without OSA followed up for a mean of 10 years. They found that compared to healthy subjects, those with untreated severe OSA (i.e. apnea-hypopnea index [AHI] of > 30 per hour of sleep) had a 3-fold higher rate of fatal and non-fatal cardiovascular events, including ischemic heart disease and stroke, after controlling for confounding variables. The diurnal variation in the onset of myocardial infarction in patients with OSA is strikingly different from the diurnal variation in patients without OSA. Patients with OSA have an approximately four-fold higher probability of nocturnal onset of myocardial infarction.[41] Such findings parallel those of a nocturnal peak of platelet aggregation in patients with OSA which is partially reversible by CPAP.[42] These results suggest that OSA may not only be a risk factor but also a trigger for myocardial infarction.

Systemic hypertension and coronary artery disease are the most common risk factors for heart failure.[22] SDB in a heart failure population is approximately twice as common compared to individuals without heart failure.[13] Central SA occurs in approximately 30% of patients with heart failure.[43-46] and OSA in 11-38%.[44-47] Lately the investigators of the Sleep Heart Health Study demonstrated for the first time that untreated severe OSA increases the risk of incident heart failure in men by 58%.[49]

Cardiovascular disease promotes sleep disordered breathing
Epidemiology
Recently, Chami, et al. published the possibility that incident cardiovascular disease (CVD) may cause or worsen sleep-disordered breathing (50). Compared with participants without incident CVD, those with incident CVD experienced larger increases in both mean obstructive and central apnea indices, by 1.75 events per hour (95% confidence interval, 0.10 to 1.75; P=0.04) and by 1.07 events per hour (95% confidence interval, 0.40 to 1.74; P=0.001), respectively within a five year follow-up period. This association is most pronounced in subjects with body mass index ≥30 and apnea-hypopnea index ≥5 events per hour at baseline. These findings suggest that the association between SDB and cardiovascular disease may be bidirectional.

Central and obstructive sleep apnea in heart failure
In contrast to OSA, central SA is caused by intermittent cessation of inspiratory drive due to a fall in PaCO₂ below the apnea threshold.[51] Therefore, respiratory effort during apnea is absent. Heart failure clearly predisposes the patient to central SA e.g. by provoking hypocapnia partly as a result of pulmonary irritant receptor stimulation by pulmonary congestion.[52] Increasing LVEF in HF patients by medication, cardiac resynchronisation therapy[53] or normalising LVEF by heart transplantation partially or completely suppresses central SA.[54] Like OSA, central SA in heart failure patients could cause progression of heart failure. Central SA has been identified as an independent predictor of mortality in patients with heart failure independent of cardiac function and other known risk factors for mortality.[45, 55-56] In contrast to OSA however, central SA does not cause generation of negative intrathoracic pressure swings. Thus the impact of central SA on left ventricular preload and afterload is less than in OSA.

Central SA with Cheyne Stokes respiration has to be regarded as a consequence of heart failure secondary to left ventricular systolic dysfunction.[43] Heart failure promotes ventilator control instability as a result of pulmonary congestion, increased chemosensitivity for CO₂ and circulatory delay.[57-58] This ventilatory control instability may contribute to the pathogenesis of obstructive as well as central SA.[59-62] A recent study of patients with heart failure and proven SDB indicates that, during sleep, fluid from the lower extremities shifts to the neck, causing obstruction of the upper airway and worsening their SDB.[63] This fluid shift was directly related to the degree of leg edema and sitting time and inversely related to the degree of physical activity.[63] As heart failure is predisposing to leg and pulmonary edema as well as a reduced physical activity it may contribute to the pathogenesis of obstructive and central SA. Despite their differing pathologies, approximately 10% of patients with heart failure have both types of SA, and the predominant type can shift from obstructive to central in association with a fall in PaCO₂ and an increase in circulation time (worsening of cardiac function), or vice versa.[64-65]

Treatment of SDB – does it reduce cardiovascular risk?
Evidence from observational studies suggests a possible reduction of the occurrence of fatal and non-fatal cardiovascular events when treating severe OSA with CPAP[34, 65] To date, there are no randomized trials that have proven this effect. Similarly, the effect of CPAP therapy on central sleep apnea in patients with HF is still unclear. The CANPAP study...
trial with chronic heart failure patients with central SA was designed to answer this question.\cite{66} Indeed a post hoc analysis\cite{67} revealed significantly better transplant-free survival (hazard ratio 0.371, P = .043) in subjects whose AHI had been suppressed below 15 events/h, compared with those with AHI >15 on CPAP and the control group. Such data are complemented by an observational study of heart failure patients with severe SDB which was predominantly central in nature.\cite{56} Chronic heart failure patients with central apnea and who adhered to positive airway pressure treatment had a significantly better survival rate than those who did not. Positive airway pressure treatment was targeted to optimally suppress respiratory events. Patients were switched to bi-level PAP or adaptive servo-ventilation (ASV) when CPAP was not effective. Such data are promising, however, randomized controlled trials confirming such findings are pending.

Advanced PAP technologies for patients with untreated CA and HF are more showing promising results with respect to normalizing ventilation and improving sleep quality. Small clinical studies suggest that ASV may improve quality of life and neuroendocrine function in some patients with central SA and heart failure.\cite{68, 69} However, it is unclear whether such effects will translate in improved cardiac outcome. ASV is currently subjected to large-scale, long-term randomized trials (e.g. SERVE-HF and ADVENT-HF) in order to evaluate its effects on cardiovascular outcomes in heart failure with central SA.

**Diagnosis of sleep disordered breathing**

The primary indication to treat central and OSAS is to improve SA-related symptoms. Therefore, awareness for symptoms including loud snoring with breathing pauses, unproductive sleep, hypersomnolence, morning headaches, xerostomia, nocturia, nocturnal dyspnea and angina should be increased. Importantly women and men do present differently. For example, women with SDB suffer more frequently from insomnia and depression. In patients exhibiting the above symptoms, diagnosis of SDB should be considered.

Since OSA is recognized as a common and reversible cause of resistant hypertension among renal parenchymal disease, primary aldosteronism and renal artery stenosis, screening for OSA as a secondary cause of hypertension is recommended.\cite{70} The same applies for patients with non-dipping of arterial blood pressure at night. The guidelines for diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology, Heart Failure Society of America, American College of Cardiology and American Heart Association recommend that patients with chronic heart failure be asked questions about their sleep and if SA is suspected, documented by polysomnography and appropriate CPAP should be considered.\cite{71}

**References**


Auto servo-ventilation therapy in a patient with central sleep apnea

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This case was presented at the ESC-Congress 2009 in Barcelona

Summary

Introduction: Central sleep apnea is frequently seen in association with congestive heart failure and implies a poor prognosis.

Case report: We report the successful therapy of a patient with non-ischemic cardiomyopathy and central sleep apnea (which was not adequately suppressed by Continuous Positive Airway Pressure (CPAP)), using Auto Servoventilation (ASV; BiPAP autoSV, Respironics).

The Apnea Hypopnea Index (AHI) was significantly reduced when using ASV (from 57 to 6/h)

Discussion: The present case suggests that ASV may be an important option for heart failure patients with central sleep apnea.

Introduction

Central sleep apnea (CSA) is characterized by repetitive cessation of ventilation during sleep resulting from a loss of ventilatory drive. A central apnea is a ≥10-seconds pause in ventilation with no respiratory efforts. Five or more of these events per hour of sleep is considered abnormal. Causes of CSA are not well understood, however, CSA is more common in patients with heart failure and the presence of CSA with heart failure implies a poor prognosis.

ASV is a new form of positive airway pressure therapy that can be used for patients with periodic breathing or central apneas. ASV provides positive expiratory airway pressure and inspiratory pressure support which is servocontrolled based on the detection of CSA. The present case report demonstrates the potential for ASV to provide hemodynamic benefits in heart failure patients when the AHI is effectively suppressed.

Case report

In May 2009, a 72-year-old overweight man (109 kg, 180 cm) with non-ischemic cardiomyopathy was admitted to our hospital for diuretic therapy. Cardiomyopathy had been diagnosed four years previously by echocardiography and heart catheterization. He had not been hospitalized for congestive heart failure in the years since diagnosis and was classified as New York Heart Association class II (NYHA: an international classification of disease severity in patients with heart failure). Upon admission in May 2009 his cardiac status was assessed as NYHA class III and he complained of nocturnal dyspnea, edema, and fatigue. His heart failure medication was optimal and consisted of Angiotensin-Converting Enzyme inhibitors, betablockers, diuretics, and an aldosterone antagonist. An electrocardiogram revealed a normal sinus-rhythm and there was no other reason for decompensation of pre-existing chronic heart failure such as infection, renal failure, volume overload, or lack of adherence to medication.

The patient did not report subjective daytime sleepiness; however, snoring and gasping were witnessed by his partner, and also confirmed by nighttime hospital staff. Consecutive polysomnography showed severe CSA with an AHI of 57 (Figure 2a) and, accordingly, nasal CPAP was applied at a pressure of 10 cm H2O. Sleep study and cardiac function...
tests were repeated four weeks after the application of CPAP and showed a reduction of the AHI to 30/h. At this time, the patient had a non-productive cough and was able to walk only a short distance without stopping because of dyspnea.

The patient was initiated on ASV therapy (BiPAP autoSV settings were: EPAP 8 cm H₂O, IPAPmin 9 cm H₂O and IPAPmax 16 cm H₂O) and within three months his AHI had improved to 6/h (Figure 2b). The patient’s cardiac symptoms improved and he returned to a normal level of activity, with no dyspnea on exertion and no nocturia. The patient demonstrated high compliance with the BiPAP autoSV device (5.2 h/night) over the three month treatment period.

Discussion
The present case demonstrates the successful therapy of a patient with non-ischemic cardiomyopathy and central sleep apnea (which was not adequately suppressed by CPAP) using ASV (BiPAP autoSV, Respironics). Notably, the patient was already on optimal pharmacological treatment. Following ASV initiation, AHI improved (from 57 to 6/h) as well as cardiac symptoms and cardiac function (LVEF from 33% to 40%) as demonstrated by 3D echocardiography (iE33, Philips).

Of course this is an individual case that cannot be generalized. However, there have been a number of studies reporting the treatment of CSA with ASV and the results of the present case are in accordance with the outcome of these studies. In these studies ASV has been shown to be successful in reducing all types of sleep apnea, especially central sleep apnea.

Possible reasons why ASV may be more effective than CPAP include an increased effectiveness in reducing the AHI and better patient compliance.

Taken together, a high prevalence of CSA in heart failure and its adverse impact on mortality suggest that polysomnography should be considered in the evaluation of heart failure patients. Our observation suggests that ASV may be an important option and mechanical adjunct to optimised drug therapy for heart failure, at least in individual cases, although studies investigating the reduction of mortality by ASV are still needed.

References
Clinical trials focusing on sleep apnea and heart failure

**Principal Investigator(s):** Douglas Bradley, M.D

**Title of Study:** A Multi-Centre, Randomized Study to Assess the Effects of Adaptive Servo Ventilation (ASV) on Survival and Frequency of Hospital Admissions in Patients with Heart Failure (HF) and Sleep Apnea (SA)—The ADVENT-HF Trial

**Objective of the Study:** Sleep Apnea (SA) is a disorder that causes pauses in breathing during sleep that expose the heart to oxygen deprivation. It is common in patients with heart failure (HF) where it is associated with increased risk of hospitalizations and death. It is not known however whether treating SA reduces these risks. This study is looking at whether a respiratory device known as Adaptive Servo Ventilation (ASV) can reduce the rate of cardiovascular hospitalizations and death in subjects with HF and SA. Study subjects will randomly receive either their regular medications OR their regular medications plus ASV. They will be followed for approximately five years, and information relevant to their health will be collected and compared.

**Primary Outcome Measures:**
The time to the composite outcome of death or first hospital admission for a cardiovascular cause. The study will end once 540 primary endpoints have occurred. Enrollment is expected to take three years with a minimum follow-up of two years thus the last patient is expected to complete the study by April 2015.

**Potential impact of positive finding:** The findings from this study will add to our understanding of the interactions between cardiovascular disorders and treatment of various forms of sleep apnea with ASV and the effect that ASV treatment has on this patient population.

ClinicalTrials.gov Identifier: NCT01128816
Supported by: Canadian Institute of Health Research & Respironics

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**Principal Investigator(s):** Henry Yaggi, MD and Dawn M. Bravata, MD

**Title of Study:** The Diagnosis and Treatment of Sleep Apnea in Cerebrovascular Disease

**Objective of the study:** This study seeks to evaluate a diagnostic and therapeutic intervention strategy among veterans with cerebrovascular disease, hypertension and obesity that consists of using unattended sleep studies to diagnose sleep apnea and CPAP to treat sleep apnea. It is hypothesized that the intervention strategy will:
1. reduce hypertension at the end of the one-year study period;
2. reduce daytime sleepiness;
3. result in improved cognitive function;
4. result in improved quality of life and(4) will increase the rate and treatment of diagnosed sleep apnea.

**Outcomes:** The primary outcome measure is the proportion of patients with a diagnosis of sleep apnea in both arms (where the denominator is all patients randomized to each arm). The secondary outcome is blood pressure. The blood pressure outcome for this study is the mean 24-hour ambulatory systolic pressure obtained at one-year post enrollment.

**Potential impact of positive finding:** The findings from this study will add to our understanding of the interactions between cerebrovascular disease and OSA and the effect that treatment has on this patient population.

ClinicalTrials.gov Identifier: NCT00807417
Major Investigator: Claudio Bassetti, MD

Title of Study: Sleep Disordered Breathing in Transient Ischemic Attack (TIA)/Ischemic Stroke and Continuous Positive Airway Pressure (CPAP) Treatment Efficacy: An open, prospective multicentre trial with a randomized arm – SAS CARE study.

Objective of the Study: The study aims to observe the short term effect (3-month, SAS CARE 1) of sleep disordered breathing (SDB) on cardiovascular parameters, heart rate variability, endothelial function and surrogate markers of atherosclerosis after ischemic stroke or transient ischaemic attack (acute cerebrovascular ischemic events (AIE). The long-term effect (SAS CARE 2) of Continuous Positive Airway Pressure (CPAP) on clinical vascular outcome, cardiovascular parameters, evolution of surrogate of atherosclerosis, heart rate variability and endothelial function after ACE will be observed over 12-24 months. The effect of CPAP therapy on cardio- and cerebrovascular events will be evaluated in patients with moderate-severe obstructive SDB (AHI>20) without sleepiness.

Outcomes: The SAS CARE 1 study is planned to verify whether or not sleep disordered breathing has a detrimental 3 months effect on cardiovascular functions and markers after acute cerebrovascular events. The SAS CARE 2 study is designed to address whether or not the treatment of sleep disordered breathing with CPAP reduces the combined rate of mortality, stroke, cardiovascular events (myocardial infarction/revascularisation/instable angina/hospitalisation for heart insufficiency) over a 24-month period in patients after acute cerebrovascular events.

Preliminary Results: Today 41 patients have been included in SAS CARE 1, 32 in SAS CARE 2. Seven patients have already been randomised to CPAP/non CPAP. Current recruitment status corresponds to expectations and let us anticipate by December 2011 the inclusion of n=100 in SAS CARE 1, n=100 in SAS CARE 2 (with n=30 randomized patients).

When the study might be completed: Summer 2014

Potential impact of positive finding: The SAS CARE study will contribute to our understanding of the clinical implications of SDB in patients with AIE and the feasibility/efficacy of CPAP treatment in selected patients with AIE and SDB.

ClinicalTrials.gov Identifier: NCT01097967
Supported by: Swiss National Research Foundation, Swissheart, Respironics Inc., Resmed Inc.
Clinical trials on sleep apnea and cardiovascular disease

**Principal Investigator(s):** Susan Redline, MD, MPH and Murray Mittleman, MD, DrPH  
**Title of Study:** A Planning Study: Sleep Apnea Intervention for Cardiovascular Disease Reduction

**Objective of the Study:** We propose to conduct a planning study to evaluate alternative study design features that address the potential for Obstructive Sleep Apnea (OSA) treatment to reduce cardiovascular disease (CVD) and to identify those features that would strengthen a later, large-scale Phase 3 randomized controlled trial (RCT). For this pilot study, we will recruit approximately 225 patients presenting to a sleep clinic with moderate to severe OSA and with CVD risk factors or established CVD. After a two week run-in period, we aim to randomize 180 participants to one of four arms, two of which use active continuous positive airway pressure (CPAP) and two of which are control conditions. All include conservative medical therapy (CMT). The active groups are: 1) active CPAP treatment delivered using standard respiratory therapist (RT) adherence education and support and 2) active CPAP treatment administered using adherence education and support delivered by a RT and enhanced by behavioural promotion intervention. The control arms are: 1) sham-CPAP and 2) CMT alone.

**Outcomes:** The primary outcome measure is to determine the effectiveness of continuous positive airway pressure therapy on cardiovascular disease, using mean 24 hour systolic blood pressure as the trial’s primary endpoint. This is a 12 month study to evaluate alternative ways to address the potential for OSA treatment to reduce heart disease and to identify those features that would strengthen a later, large-scale randomized controlled trial.

**Potential impact of positive finding:** The findings from this study will add to our understanding of the interactions between cardiovascular disorders and treatment of various forms of sleep apnea.

ClinicalTrials.gov Identifier: NCT 01261390

Continuous positive airway pressure treatment of obstructive sleep apnea to prevent cardiovascular disease

**Principal Investigator:** R. D. McEvoV, MD  
**Co-Principal Investigator:** C. Anderson, MBBS, PhD

The Sleep Apnea cardiovascular Endpoints (SAVE) is an international, academic multi-center randomized-controlled trial of continuous positive airway pressure (CPAP) therapy in patients with co-existing high cardiovascular risk and obstructive sleep apnea (OSA).

The aim of the trial is to see whether patients who, by random assignment, have CPAP added to their usual medical care will have fewer future cardiovascular events (i.e. heart attacks, acute heart failure episodes, strokes and transient ischemic attacks, sudden death) than patients assigned to continue with their usual care alone. Patients with severe daytime sleepiness or night-time oxygen desaturation are excluded from enrolment.

To conclusively answer the question of whether or not OSA treatment reduces cardiovascular risk, it is estimated that approximately 5000 patients will need to be followed for an average of four years.

To date approximately 1100 patients have been enrolled in SAVE from sites in Australia, New Zealand, China and India. In 2011 it is planned to expand the international recruitment network to centers in Brazil, the United Kingdom and the United States. It is anticipated that the study will be concluded in another five to six years.

ClinicalTrials.gov Identifier: NCT 00738179  