STUDY PROTOCOL

Title: Oxygen versus PAP for treatment of sleep apnea in chronic heart failure

Brief title: OPTIMAL-HF

NCT number: NCT01807897

Unique Protocol ID: CLIN-008-12S

Funding source: Department of Veterans Affairs

Protocol date: 8/4/2017

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OVERVIEW

The proposed study is a randomized, parallel group clinical trial comparing three months of therapy with of continuous positive airway pressure (CPAP) or nocturnal supplemental oxygen (NSO) to optimized medical therapy for treatment of sleep apnea in patients with chronic heart failure. This study will be conducted over 4 years and participants will be recruited from among patients seen at the VA Boston and VA Connecticut Healthcare Systems for a diagnosis of heart failure. A total of approximately 500 patients will be recruited to undergo portable sleep monitoring in order to randomize 39 patients to each active treatment group (CPAP or NSO) and 20 subjects to optimized medical therapy alone (HSLE). Participation of an individual subject will be approximately 1 week for subjects not meeting criteria for randomization, and 3.5 months for subjects randomized. Participants will be age 18 and over, of either sex, and will have chronic heart failure with left ventricular ejection fraction <45%. No children or other special classes of individuals will be enrolled. All enrolled subjects will be veterans.

(1) RATIONALE

(a) Statement of the Problem

Chronic heart failure (HF) is a highly prevalent disease associated with physical disability, extensive health care utilization and high rates of mortality, which have persisted despite recent advances in pharmacologic therapy. The prevalence of HF in the US is estimated at 5.7 million individuals, with an annual incidence of 10 per 1000 population over the age of 65 and a lifetime risk of HF of approximately 20%. Heart failure is a major cause of health care utilization, accounting for over 3 million doctor visits and over 1.1 million hospitalizations in 2006. According to the VA Chronic Heart Failure Quality Enhancement Research Initiative 2009 Strategic Plan, VA outpatient encounters for HF reached 900,000 in FY09 and VA hospitalizations were over 96,000. HF is reported to be the most common medical discharge diagnosis for veterans treated within the VA system. Heart failure also carries a high mortality risk, with 1-year mortality of approximately 20% and 5-year mortality of 42- 54%, with HF listed as a contributing cause of death on 12% of US death certificates in 2005 and as the underlying cause in almost 59,000. Sleep apnea is a common comorbid condition in patients with chronic HF. Multiple studies demonstrate that moderate to severe sleep apnea (AHI >15 per hour) is present in 50-60% of patients with chronic HF with reduced left ventricular ejection fraction (LVEF), with a slight preponderance of central over obstructive sleep apnea. Moreover, sleep apnea portends a markedly worse prognosis in patients with chronic HF, with a 2- to 3-fold increased hazard ratio for mortality in those with either central or obstructive sleep apnea. There are currently three recommended treatments for sleep apnea with a prominent central component, but the relative benefits of these therapies have never been directly compared.

(b) Hypotheses

We hypothesize that the two recommended treatments for sleep apnea with a

component of central sleep apnea, continuous positive airway pressure (CPAP) and nocturnal supplemental oxygen (NSO), are each superior to medical management alone in their effect on LVEF and exercise capacity.

(c) Specific Objectives

Our primary goals are to establish the efficacies of continuous positive airway pressure (CPAP)) and nocturnal supplemental oxygen (NSO) compared to a control group receiving usual care plus healthy lifestyle and sleep education (HLSE). Because past studies were suggestive of a more beneficial effect of CPAP or NSO compared to HLSE, we will randomize more subjects to the two experimental treatment groups. Specifically, we will allocate patients into CPAP,NSO, or HLSE randomly according to a 2:2:1 ratio. This strategy also improves statistical power for the secondary comparisons between CPAP and NSO.

(2)BACKGROUND AND SIGNIFICANCE

(a) Background

Heart failure prevalence, morbidity and mortality. Chronic heart failure (HF) is a highly prevalent disease associated with physical disability, extensive health care utilization and high rates of mortality, which have persisted despite recent advances in pharmacologic therapy. The prevalence of HF in the US is estimated at 5.7 million individuals, with an annual incidence of 10 per 1000 population over the age of 65 and a lifetime risk of HF of approximately 20% (1). Heart failure is a major cause of health care utilization, accounting for over 3 million doctor visits and over 1.1 million hospitalizations in 2006 (1). According to the VA Chronic Heart Failure Quality Enhancement Research Initiative 2009 Strategic Plan, VA outpatient encounters for HF reached 900,000 in FY09 and VA hospitalizations were over 96,000 (2). HF is reported to be the most common medical discharge diagnosis for veterans treated within the VA system (3). Heart failure also carries a high mortality risk, with 1-year mortality of approximately 20% and 5-year mortality of 42-54%, with HF listed as a contributing cause of death on 12% of US death certificates in 2005 and as the underlying cause in almost 59,000 (1).

Prevalence of sleep apnea in patients with chronic HF. Sleep apnea is a common comorbid condition in patients with chronic HF. It is characterized by recurrent episodes of decreased (hypopnea) or absent (apnea) airflow during sleep, resulting in intermittent hypoxemia and sleep fragmentation. These respiratory events can result from either collapse of the upper airway (obstructive sleep apnea) or ventilatory control instability (central sleep apnea). Multiple studies of patients with chronic HF with reduced left ventricular ejection fraction (LVEF), selected independent of sleep complaints, provide remarkably consistent estimates of the prevalence of sleep apnea. Sleep apnea of at least mild severity (apnea-hypopnea index [AHI], defined as the frequency of apneas plus hypopneas per hour of sleep, >5 per hour) is present in >70% of patients with chronic HF, while moderate to severe sleep apnea (AHI >15 per hour) is present in 50-60% (4-10), with a slight preponderance of central over obstructive sleep apnea. In the three largest studies, totaling over 1300 patients, the prevalence of moderate to severe central sleep apnea was 28-32% overall (6, 9,10).

There is a clear sex difference, with a prevalence of moderate to severe central sleep apnea of 15-26% in women and 31-45% in men (6, 9, 10). Another important finding of these and other studies is that sleep apnea in chronic HF typically lacks the daytime sleepiness characteristic of sleep apnea in the general population (4, 7-9, 11, 12) and central sleep apnea in particular is less strongly associated with obesity (4, 9, 10). This may explain why as few as 2% of patients with newly diagnosed HF are evaluated for the presence of sleep apnea within a year of HF diagnosis (13).

Impact of sleep apnea on HF incidence and mortality. At the baseline examination of the Sleep Heart Health Study, a multi-center prospective epidemiologic study of the cardiovascular consequences of sleep apnea, moderate to severe sleep apnea was associated with a 2.4-fold increased odds of prevalent HF (14). While HF-related ventilatory instability may cause sleep apnea, the relation of sleep apnea to HF is clearly bidirectional. We have recently demonstrated that sleep apnea is an independent predictor of incident HF: in the Sleep Heart Health Study, severe sleep apnea was associated with a 58% increased risk of incident HF over 8 years of follow-up in middle-aged and older men (15). In a dog model, it has been demonstrated that 1-3 months of exposure to obstructive sleep apnea results in sustained daytime hypertension (16), reduced left ventricular ejection fraction and eccentric left ventricular hypertrophy (17). We have demonstrated a similar pattern of reduced ejection fraction and eccentric left ventricular hypertrophy associated with sleep apnea in 2058 Sleep Heart Health Study participants (18). Moreover, sleep apnea portends a markedly worse prognosis in patients with chronic HF. In studies of sleep apnea and mortality in chronic HF, the adjusted hazard ratio for mortality was 2.8 in those with obstructive sleep apnea (19) and 2.1 in those with central sleep apnea (20), when compared to HF patients without sleep apnea.

Mechanisms of the effect of sleep apnea on HF. The adverse effects of sleep apnea on cardiac function are multifactorial and have been recently summarized in an American Heart Association/American College of Cardiology Scientific Statement (21). These include sympathetic nervous system hyperactivity, oxidative stress, reduced myocardial oxygen delivery, activation of inflammatory pathways, and (in the case of obstructive sleep apnea) increased left ventricular transmural pressure resulting from large negative swings in intrathoracic pressure when breathing against an occluded glottis. While the relative contributions of these factors is uncertain, it is likely that the repetitive cycles of hypoxemia and resaturation that characterize sleep apnea play a central role in its impact on chronic HF, contributing to sympathetic activation, systemic inflammation and oxidative stress.

Role of hypoxemia in sleep apnea-related sympathetic activation. Multiple studies over more than two decades demonstrate increased sympathetic activity in patients with either obstructive or central sleep apnea, which may contribute to progression of myocardial dysfunction by both direct adverse effects on myocardial remodeling and through elevation of diurnal and especially nocturnal blood pressure. Hypoxemia increases sympathetic nerve activity in humans, and this effect is particularly great in the presence of hypercapnia, as occurs in sleep apnea (22). In sleeping patients with HF, muscle sympathetic nerve activity (MSNA) is higher during periods of central sleep apnea than during periods of stable breathing (23). MSNA increases across the duration of each central apnea, reaching values 50% above the already elevated baseline MSNA in these patients (23). Intermittent hypoxia results in sustained

hypertension in rodent models, an effect that is mediated by the sympathetic nervous system (24). In canine models of sleep apnea, the acute hypertensive response to obstructive apneas is considerably diminished by supplemental oxygen (25), and while obstructive apneas result in sustained hypertension, acoustic arousals of a similar frequency do not (16). Thus, it appears that hypoxemia is the major stimulus to sympathetic activation and consequent hypertension in patients with sleep apnea. Hypertension is recognized as a major risk factor for the development of chronic HF (26), and sleep apnea is strongly associated with hypertension in both cross-sectional (27,28) and longitudinal observational studies (29). Among middle-aged adults participating in the Wisconsin Sleep Cohort Study, mild to moderate sleep apnea was associated with more than a 2-fold increased risk of incident hypertension over approximately 8 years of follow-up, after adjusting for potential confounding factors such as body habitus (29). Moreover, while sleep is usually associated with a decrease in blood pressure, failure of the blood pressure to fall at night (blood pressure 'non-dipping') is more common in individuals with sleep apnea (30), and is an important predictor of left ventricular hypertrophy (31). In addition to its effects on blood pressure, long-term activation of the sympathetic nervous system is known to have direct deleterious effects on the failing heart, via vasoconstriction, induction of cardiac hypertrophy, increased heart rate and reduced myocardial oxygen delivery (26).

Role of hypoxemia in sleep apnea-related systemic inflammation and oxidative stress. Inflammatory markers are elevated in patients with chronic HF and may play an important role in the progression of disease (32). Systemic inflammation is also present in sleep apnea, and intermittent hypoxemia appears to be central to its pathogenesis. Intermittent hypoxia induces the expression of transcription factors including hypoxia-inducible factor-1 (HIF-1) and nuclear factor kappa B (NF-kB), which play key roles in upregulating expression of inflammatory cytokines including TNF-α and IL-6 (33). Induction of NF-kB in heart and aorta has been demonstrated in a mouse model of intermittent hypoxemia (34), and elevated monocyte NF-kB activity in human subjects with sleep apnea is normalized by treatment of the sleep apnea with continuous positive airway pressure (34). In a rat model of sleep apnea, it has been demonstrated that, compared to tracheotomy alone, repetitive upper airway obstruction and repetitive hypoxia-resaturation each increase NF-kB expression and markers of endothelial dysfunction, while airway obstruction with supplemental oxygen to prevent hypoxemia does not (35). Our preliminary data (Section 2.3) indicate that in patients with moderate to severe sleep apnea, hypoxemia is much more strongly correlated with inflammatory markers than is apnea-hypopnea index. Oxidative stress also appears to play a role in the pathogenesis of HF (36). Repetitive episodes of hypoxia-resaturation promote the production of reactive oxygen species in animal models, and sleep apnea is associated with increased systemic markers of oxidative stress and increased production of reactive oxygen species by neutrophils and monocytes (37). Inflammation and oxidative stress have also been directly demonstrated in vascular endothelial biopsies in patients with obstructive sleep apnea and resolves with treatment of the sleep apnea (38).

As both central and obstructive sleep apnea are associated with intermittent hypoxemia, these considerations suggest that prevention of nocturnal hypoxemia, even if it does not treat sleep apnea per se, might mitigate the adverse effects of sleep apnea on the heart. This may be particularly true of central sleep apnea, in which large swings in intra-thoracic pressure are not a potential pathophysiologic factor.

Positive airway pressure treatment of sleep apnea in patients with chronic HF.
The mainstay of therapy for obstructive sleep apnea for over 25 years has been continuous positive airway pressure (CPAP). The major effect of CPAP is to prevent a drop in upper airway pressure during inspiration, thereby preventing airway collapse. CPAP has also been used in the treatment of central sleep apnea. Although the mechanism of improvement in central sleep apnea with CPAP is uncertain, short-term studies demonstrate that in many chronic HF patients with central sleep apnea, CPAP therapy results in fewer central apneas, improved nocturnal oxygenation, and improved LVEF (39, 40). Moreover, while CPAP resulted in an 8% increase in mean LVEF in HF patients with central sleep apnea, no improvement was seen in HF patients without sleep apnea, suggesting that the improvement in LVEF is a result of treating the central sleep apnea, and not a non-specific effect of CPAP on chronic HF (40). A recent meta-analysis of 7 controlled CPAP treatment trials for CSA in patients with HF, presented in an American Academy of Sleep Medicine (AASM) Practice Parameters paper published this year, estimates the meta-analyzed mean effect of CPAP on LVEF to be 6.5% (41). Although this effect is substantial, it should be interpreted with caution. All but one of these studies was a small, single-center, unregistered clinical trial, with an average sample size of 20 subjects, raising concern for possible publication bias. The seventh study, the multicenter Canadian Positive Airway Pressure (CANPAP) trial found that, compared to usual care, CPAP therapy for central sleep apnea in chronic HF resulted in a much smaller mean improvement in LVEF of only 2.2% (42). Moreover, although CPAP improved mean LVEF, there was no difference in transplant-free survival and a trend towards increased short-term mortality (42). Subgroup analyses indicated that those participants whose sleep apnea was suppressed by CPAP had a better disease-free survival than the usual care group, while those whose sleep apnea was not suppressed had a worse outcome (43). Although the ability to suppress sleep apnea with CPAP may simply be a positive prognostic indicator in chronic HF with central sleep apnea, the finding that CPAP therapy acutely lowers stroke volume and ejection fraction in patients with HF and obstructive sleep apnea (44) suggests a plausible explanation for increased short-term mortality in the CPAP-treated group. Despite the initial reduction in stroke volume and LVEF, after 4 weeks of chronic CPAP therapy both measures increased to above baseline levels (44).

Until recently, adaptive servo-ventilation (ASV) had emerged as a preferred form of positive pressure ventilation for central sleep apnea. It differs from CPAP in providing a higher pressure during inspiration than during expiration but, unlike standard bi-level positive airway pressure devices, it monitors respiration and varies the inspiratory pressure support level to maintain ventilation above 90% of the preceding baseline value. The AASM Practice Parameters paper includes a meta-analysis of 6 ASV treatment trials, and estimates the meta-analyzed mean effect of ASV on LVEF to be 6.2% (41). Again, this value should be interpreted with caution, as all were small, unregistered clinical trials with a mean sample size of 23.7 subjects. In three head-to-head comparisons of ASV with CPAP, ASV appears more effective than CPAP for treating central sleep apnea in patients with chronic HF, with more complete suppression of sleep apnea and greater improvements in LVEF (45-47). In these 3 studies, the increase in LVEF over 3-6 months of treatment with ASV was 4.0-9.1%, compared to changes of -2.4- 1.9% for CPAP. Four other uncontrolled studies of ASV treatment for 2 weeks to 12 months in patients with HF and central sleep apnea also showed improvements in LVEF of 4.6-7.9% (49-52).

Two studies have reported significantly improved exercise capacity following 6 months of ASV treatment for central sleep apnea, with increases in maximal oxygen consumption on cardiopulmonary exercise testing of 1.4-2.7 ml/kg/min (47, 50). The long-term safety and effectiveness of ASV for sleep apnea in chronic HF patients was until recently unknown; however, a preliminary report from a randomized clinical trial of over 1300 patients with heart failure, LVEF <45%, and predominantly central sleep apnea found a significant increase in mortality in the ASV-treated group, from 7.5% annual mortality in those treated with usual cardiac care, to 10% annually in those treated with ASV, and revised labeling of this product as contraindicated in this patient population is planned (http://www.resmed.com/us/en/serve-hf.html - accessed 5/24/2015).

Despite the effectiveness of positive airway pressure for treatment of obstructive sleep apnea, many patients find it uncomfortable and are unwilling to use it, with reported utilization for >4 hours per night in fewer than two-thirds of patients in most reports, with adherence generally worse in asymptomatic or mildly symptomatic patients (51). As sleep apnea in HF patients is often asymptomatic, adherence to positive airway pressure therapy is likely to be particularly problematic. In the CANPAP trial, even among patients completing the study, average nightly use of CPAP after 1 year was only 3.6 hours (42).

Oxygen as an alternative therapeutic option in sleep apnea. Despite evidence that hypoxemia plays a major role in the cardiovascular consequences of sleep apnea, there has been little research into the potential benefits of supplemental oxygen to treat this condition. Supplemental oxygen delivered by nasal cannula during sleep is very well tolerated; our preliminary experience indicates substantially greater adherence to nocturnal supplemental oxygen than to CPAP for treatment of sleep apnea in patients screened for sleep apnea in a Cardiology clinic (Section 2.7). In patients with obstructive sleep apnea, several studies have demonstrated that supplemental oxygen at 1-4 liters per minute delivered by nasal cannula improves hypoxemia but does not reduce the AHI. In one study of patients with moderate to severe obstructive sleep apnea, oxygen was delivered at 2 lpm in those with a nadir oxyhemoglobin saturation below 80% at baseline, and at 1 lpm in those with a higher nadir saturation. This was sufficient to increase the mean nadir saturation from 70% to 90%, and reduced the frequency of 4% desaturation events by 89% (52). In another study of patients with moderate to severe obstructive sleep apnea, supplemental oxygen at 3 lpm improved nocturnal oxyhemoglobin saturation but had no significant impact on other measures of sleep quality (53). In a sample of 46 patients who underwent ambulatory blood pressure monitoring, blood pressure was modestly but not significantly reduced in the group receiving supplemental oxygen compared to those receiving placebo CPAP, with an effect approximately half as large as therapeutic CPAP (54).

In contrast to its effect in obstructive sleep apnea, supplemental oxygen in patients with central sleep apnea not only improves oxygenation, but often leads to a reduction in the frequency of apneas and hypopneas, with the reported reduction in AHI typically 40-75% (55-59). Two controlled studies have examined the effect of nocturnal supplemental oxygen on cardiac function (58, 59). These studies showed improvements in LVEF of 5.5-9.7% following 3 to 12 months of treatment, with increases in LVEF of only 1.3% among controls in each study. A third, uncontrolled trial was included with these in the AASM Practice Parameters paper meta-analysis, which estimated the effect of nocturnal supplemental oxygen on LVEF to be 5.0% (41); again, all were small, single-center, unregistered clinical trials, with an average sample

size of only 26.7. Two studies have reported that nocturnal oxygen improves exercise capacity, with increases in maximal oxygen consumption on cardiopulmonary exercise testing of 2.3-5 ml/kg/min (55, 58). Little is known regarding the effect of oxygen treatment for sleep apnea on long-term cardiovascular risk.

(b) Significance

HF is a common disease with high morbidity, mortality and health care utilization. Sleep apnea is highly prevalent in patients with chronic HF and is associated with a doubling of mortality risk, although it is commonly asymptomatic and usually goes undiagnosed. There are currently three approved therapies for sleep apnea in patients with HF, although as noted above ASV will soon be contraindicated in this patient population. The present study will for the first time directly compare the two remaining treatments, evaluating their effects on ventricular function, exercise capacity, and other markers of risk for progression of HF. This study will also lay the foundation for a long-term study comparing the effects on morbidity and mortality of these therapies for treatment of sleep apnea in patients with chronic HF.

(c) Relevance to Veterans Health

Heart failure is reported to be the most common medical discharge diagnosis for veterans treated within the VA system (3). Heart failure also carries a high mortality risk, with 1-year mortality of approximately 20% and 5-year mortality of 42-54%. Sleep apnea is a common co-morbid condition associated with increased HF mortality. Identifying the optimal treatment regimen for sleep apnea in patients with HF is therefore of great relevance to Veterans health.

(3) Work Proposed

Overview

The proposed study is a randomized, parallel group clinical trial comparing three months of therapy with continuous positive airway pressure (CPAP) or nocturnal supplemental oxygen (NSO) to optimized medical therapy for treatment of sleep apnea in patients with chronic heart failure. This study will be conducted over 4 years and participants will be recruited from among patients seen at the VA Boston and VA Connecticut Healthcare Systems for a diagnosis of heart failure. A total of approximately 500 patients will be recruited to undergo portable sleep monitoring in order to randomize 39 patients to each active treatment group (CPAP or NSO) and 20 subjects to optimized medical therapy alone. Participation of an individual subject will be approximately 1 week for subjects not meeting criteria for randomization, and 3.5 months for subjects randomized. Participants will be age 18 and over, of either gender, and will have chronic heart failure with left ventricular ejection fraction ≤45%. No children or other special classes of individuals will be enrolled. All enrolled subjects will be veterans.

Study procedures will include:

- Screening Questionnaires
- Portable Sleep Monitoring
- Baseline (Randomization) Visit, including:
  - Resting Blood Pressure and Pulse
  - Blood draw
  - Anthropometry
  - Heart Failure and Quality of Life Health Questionnaires

- 24 Hour Blood Pressure
- Echocardiogram
- Cardiopulmonary Testing

- Randomization to treatment with one of the following three treatments:
  - Healthy Lifestyle and Sleep Education alone (HLSE)
  - HLSE plus PAP (HLSE-P)
  - HLSE plus nighttime supplemental oxygen (HLSE-O)
- Titration Visit for patients randomized to HLSE-P
- Interim Telephone Contacts
- Final Study Visit with repeat of Baseline Visit procedures

Inclusion criteria for sleep apnea screening:

- Age ≥18 years
- Physician diagnosis of chronic HF, American Heart Association Stage C-D
- LVEF ≤45%
- No change in active cardiac medications for 4 weeks prior to randomization
- Ability to provide informed consent

For continuing to randomization, the following additional inclusion criterion applies:

- Moderate to severe sleep apnea with a prominent central component, defined as an apnea-hypopnea index ≥15 events per hour, with a central apnea-hypopnea index >5 events per hour
- LVEF ≤45% indicated at baseline echo test.

Exclusion criteria:

- Hospitalization for acute decompensated HF within previous 30 days
  - The patient may be screened for inclusion in the study and administered an HST at this time, but will not be eligible to complete a baseline visit until the 30 day window has passed
- Hospitalization for myocardial infarction or cardiac surgery within previous 30 days
  - The patient may be screened for inclusion in the study and administered an HST at this time, but will not be eligible to complete a baseline visit until the 30 day window has passed
- Presence of a left ventricular assist device
- History of heart transplantation
- Poorly controlled hypertension (>175/>110), **OR** severe renal failure requiring dialysis, **OR** prior stroke with functional impairment **OR** other severe, or uncontrolled medical problems that may impair ability to participate in study exams based on medical history and review of medical records.
- Severe chronic primary insomnia, with reported usual sleep duration <4 hours
- Severe daytime sleepiness, defined as Epworth Sleepiness Scale score ≥18 or report of falling asleep driving during the previous year, unless determined by a study physician to be at low risk for motor vehicle accident
- Awake resting oxyhemoglobin saturation <89%
- Pregnancy
- Smoking by subject or other person in the subject's bedroom, or other open flame in bedroom

- Current use of a positive airway pressure device (including continuous or bi-level positive airway pressure or adaptive servo-ventilation) or supplemental oxygen therapy

Study Design

The proposed study is a randomized, parallel group study comparing three months of therapy with optimized medical therapy plus continuous positive airway pressure (CPAP) or nocturnal supplemental oxygen (NSO), respectively, to optimized medical therapy alone for patients with comorbid sleep apnea and chronic HF with reduced ejection fraction. The primary study outcomes are: (1) left ventricular ejection fraction (LVEF) measured by echocardiography, which is identified by the American College of Cardiology and American Heart Association as the single most useful test in the evaluation of patients with HF (26) and which has been shown in several studies to increase significantly over 4 to 12 weeks of therapy with CPAP or NSO in patients with heart failure and central sleep apnea (41), and (2) peak oxygen consumption on cardiopulmonary exercise testing (peak VO2), a valid and reproducible measure of functional capacity that has also been reported to increase following ASV or NSO (47, 50, 58, 59). The primary analysis will compare each of the active treatment arms to the optimized care control group.

Sample selection

The target population is veterans with American Heart Association Stage C or D chronic HF with reduced ejection fraction and comorbid sleep apnea. Patients will be recruited from among those patients enrolled in the VA Boston or VA Connecticut Healthcare Systems who carry a diagnosis of chronic HF. Potential participants will be identified via the computerized patient record system, by searching on the diagnosis of HF using diagnostic codes 428.0-428.9. Medical records will be screened to confirm the diagnosis of HF and document reduced LVEF by echocardiogram, nuclear gated blood pool scan, or ventriculogram.

Recruitment

Subjects will be recruited by mailings to patients seen for a diagnosis of heart failure at any time within 3 years of the start of this study, as well as through the inpatient cardiology service. This recruitment approach will be supplemented, if needed, by direct contact in clinic. After initial contact, interested participants will have initial screening for eligibility. Potentially eligible patients will be invited to complete a screening visit, at which informed consent will be obtained and the patient will be instructed in the use of a portable sleep monitoring device. Participants who screen positive for moderate to severe sleep apnea with a prominent central component will proceed to the baseline visit and randomization to treatment.

Initial Screening

The primary approach to recruitment will be through mailing to all patients with a diagnosis of heart failure, identified through the computerized medical record or via the Xcelera echocardiogram database. All mailings will contain a cover letter explaining the purpose of the mailing and containing the key elements of informed consent. The letter will contain the Epworth Sleepiness Scale and several additional questions, including age and contact information. The Epworth Sleepiness Scale, the most widely used tool for self-report assessment of sleepiness, asks the subject to rate the likelihood of falling

asleep in a number of common situations. It has good internal reliability and test-retest reliability. This scale will be used to identify patients with sleepiness so severe that it would preclude safe participation in the study (Epworth Sleepiness Scale score ≥18). Low sleepiness scores will not preclude participation, as sleep apnea is often asymptomatic in HF patients.

A stamped and addressed return envelope will be provided to return the questionnaire. A toll-free number will also be provided to allow patients to respond by telephone, should they prefer. All participants responding to the questionnaire by mail or telephone will be screened for eligibility, and potentially eligible subjects invited to attend a Screening Visit. In addition, the mailing will include an "opt-out" postcard for patients who do not wish to be further contacted. Patients who do not respond to the mailing either by responding to the questionnaire or returning an opt-out postcard will be contacted by telephone approximately 2 weeks after the mailing and invited to participate.

Should response to the mailed questionnaires be inadequate we will pursue direct face-to-face recruitment from various Cardiology Clinics at the VA by trained research staff. This will entail study staff pre-screening the charts of patients visiting the clinic that day and approaching them after their visit to describe the study and ask them if they would be interested in participating. Prior to contacting each patient, the cardiologist from each collaborating cardiology clinic will review the rosters of potentially eligible patients and will indicate his/her assent to contact each patient. If needed, study staff will post recruitment flyers for the study in heavy traffic areas around the hospital as well as in the Cardiology clinics. No personally identifiable data will be retained for patients who do not opt to participate.

Additionally, study staff will recruit patients from the in-patient Cardiology service, with the assent of the Cardiology team. Study staff will pre-screen charts prior to approaching patients face-to-face. However, patients screened through the in-patient Cardiology service will not be have a baseline visit scheduled until they have been without a major cardiac incident for 30 days, as approved by the IRB.

Screening visit

At the Screening Visit, written informed consent will be obtained, adherence to treatment guidelines for chronic HF will be assessed, and participants will be instructed in the performance of home portable sleep monitoring.

Informed Consent Procedures. The informed consent process will be undertaken by investigators and study staff who have current training in human subjects protections and are credentialed by the VA to conduct the informed consent process. They will explain the study to the potential participants and answer any questions that they may have about the protocol. They will make it clear that participating in research is always voluntary and that not participating will in no way affect their further evaluation or care. All participants will be informed that they may withdraw their consent at any point throughout the study. Participants will then be asked to sign the IRB-approved written consent form.

Assessment of adherence to heart failure treatment guidelines

At the screening visit, adherence to current medical treatment guidelines for heart failure will be assessed using a standardized checklist based on the 2009 American College of Cardiology/ American Heart Association Guideline Update for Evaluation and Management of Chronic Heart Failure in the Adult (33), and reviewed by a study

physician to ensure adherence to these guidelines. Particular attention will be paid to the use of angiotensin converting enzyme inhibitor (or angiotensin receptor blocker) and beta blocker in all patients unless contraindicated. Where adherence to these recommendations is not met, the treating physician will be contacted by a study physician to discuss the rationale for current therapeutic choices and, if appropriate, the patient will be referred to the Heart Failure Clinic for optimization of care prior to the baseline visit.

Portable Sleep Monitoring

At the Screening Visit, after written informed consent is obtained, subjects will be instructed in the use of the Embletta Gold portable monitor (Embla Systems, Inc., Broomfield, CO). This battery-operated device can store data at 200 Hz, with 125 MB of storage capacity allowing storage of data from up to 24 hours of recording. The device contains the critical sensors which are recommended by the American Academy of Sleep Medicine (AASM) as validated sensors for measuring sleep apnea (60): airflow via a nasal cannula/pressure transducer system and oronasal thermocouple; respiratory effort via thoracic and abdominal inductance plethysmography; and oxyhemoglobin saturation via finger pulse oximetry (NONIN OEM board). In addition, signals are captured for body position and a 3-lead ECG.

Subjects will be taught how to self-apply the sensors in their own homes. Application of sensors will be demonstrated by a trained staff member. Subjects will be asked to demonstrate their understanding of sensor placement and will be provided with simple pictorial and written instructions. Subjects will be asked to apply the sensors before bedtime and remove them upon awakening. A 24-hour phone service will be available to provide assistance should questions arise once the participant is home. Patients are instructed to depress the event marker button 3 times in succession at the time of lights off, and again upon arising in the morning. They are also asked to complete a simple sleep diary, indicating bed time, rise time, and any long periods of wakefulness during the night of the study. When units are returned to the clinic site (by mail or direct drop-off), the data will be downloaded to local computers, reviewed by the Research Coordinator, and saved to a secure drive for review by a trained research polysomnography technician based at the VA Connecticut, who will score the studies and grade them for quality. Studies will be scored following AASM guidelines for standard hypopnea and apnea definitions based on respiratory effort, flow sensors and oximetry (60). Studies that do not meet minimal quality grades (4 hours of scorable record) will be repeated.

Patients who have had a recent sleep study demonstrating the presence of sleep apnea meeting criteria for inclusion in this study, but not yet treated, may proceed to randomization without repeating the portable sleep study.

Baseline (randomization) visit

Participants with at least moderate sleep apnea with a prominent central component (AHI >15, with central AHI >5) on portable sleep monitoring will proceed to the baseline study visit. Participants will be instructed to arrive between 7 and 9 AM on the day of the baseline visit, and asked to eat only a light breakfast on the day of the visit. The visit will begin with a blood draw, after which participants will proceed with the remaining baseline measurements and be instructed in use of the ambulatory blood pressure monitor.

These baseline measures will be followed by randomization to one of the three

treatment arms and training in the assigned intervention. The entire baseline visit is expected to take approximately 4 hours.

Fasting venipuncture and assays. Phlebotomy will be performed using standard techniques by trained staff following a written protocol, for withdrawal of 20 cc of blood. The phlebotomist will draw two 10 ml EDTA plasma tubes for this protocol. Pre-labeled, bar coded tubes will be used for specimen tracking. After venipuncture, the blood tubes will be incubated at room temperature for 30 minutes before being spun in a centrifuge, aliquoted and frozen. Samples will be placed into an at least -20◦C ± 10◦C freezer within 90 minutes from venipuncture time. The samples will be transferred into the final freezer (-80◦C) within 24 hours.

Serum PIIINP will be measured in Dr. Jacob's laboratory using a commercially available radioimmunoassay (UniQ PIIINP RIA, Orion Diagnostica). This is a quantitative radioimmunoassay of intact aminoterminal propeptide of type III procollagen in human serum, which will be used to detect changes in connective tissue metabolism. Plasma NT-proBNP will also be measured in Dr. Jacob's lab, using a commercially available ELISA kit (Alpco Diagnostics, Salem, NH). Serum isoprostanes will be measured in Dr. Jacob's laboratory using a commercially available ELISA (Cayman Chemical, Ann Arbor, MI). TNFα and IL-6 will also be measuredin Dr. Jacob's laboratory , using a commercially available ELISA (R & D Systems Inc., Minneapolis, MN) for TNFα and an Access Chemluminescent Immunoassay (Beckman Coulter, Fullerton, CA) for IL-6. Hs-CRP will be measured in the clinical laboratory at the VA Boston Healthcare System.

Echocardiogram. Standard transthoracic 2-dimensional and Doppler echocardiography will be performed using a Philips IE33 cardiac ultrasound (Philips Healthcare, Andover, MA) to estimate cardiac dimensions, mass, and systolic and diastolic function. All images will be captured in 3-beat loops for patients in sinus rhythm, 5-beat loops for those in atrial fibrillation. M-mode measurements of LV dimensions will be performed and analyzed according to the American Society of Echocardiography recommendations (61). LVEF will be measured using the modified Simpson's method. The interventricular septum thickness (IVST), posterior LV wall thickness (LVPWT), and left ventricular internal diastolic diameter (LVIDD) will be measured at end-diastole, and left ventricular mass calculated as $0.8*(1.04*[(LVIDD+IVST+LVPWT)^3–(LVIDD)^3]+0.6)$. We will determine standard measures of diastolic function including E and A wave velocities, deceleration time, and pulmonary venous flow velocities, as well as utilize tissue Doppler imaging to detect abnormalities of diastolic function. Pulmonary artery systolic pressure will also be estimated utilizing Doppler measurements. For individuals with unclear images, or who have required contrast in the past, contrast will be used.

Cardiopulmonary Exercise Testing. Treadmill exercise testing in association with air-gas-exchange, generally considered to be an optimal gauge of functional capacity, will be supervised by Dr. Daniel Forman (co-investigator), who has used this technique extensively in both clinical and clinical-research applications. All patients will be assessed by a cardiologist for clinical stability immediately before the exercise stimulus. An intravenous catheter will be placed in advance of the procedure per routine as a routine safety precaution. A motor-driven treadmill will be used and exercise will follow a modified Balke protocol. A bicycle ergometer will be used for those participants who are unable to walk on a treadmill but are capable of bicycle exercise (e.g., due to balance problems). A lightweight disposable pneumotach

device will be positioned in the participant's mouth during the exercise VO2 peak, VO2 at anaerobic threshold and VE/VCO2 will be measured using a metabolic cart. During exercise, electrocardiogram waveforms and hemodynamics (maximum heart rate and blood pressure) will be monitored. Patients will exercise to their symptomatic limits, with encouragement to achieve a respiratory exchange ratio >1.0 (consistent with high physiological workload). However, if there are any signs of medical instability, the cardiologist will end the test before the symptomatic endpoint is achieved. In any instances of submaximal workload, analysis would focus on VO2 at anaerobic threshold, VE/VCO2 and other indices that do not depend on peak exercise performance.

Questionnaires

- Medical Outcomes Study SF36 Health-related Quality of Life Questionnaire. Each subject will complete the SF36 at their baseline and 3 month follow-up appointment. This questionnaire is a multi-purpose, short-form health survey that is widely used in research to estimate specific disease burden and to compare disease-specific benchmarks with general population norms. The questionnaire consists of 36 questions and provides an 8-scale profile of functional health and well-being scores (62).
- Kansas City Cardiomyopathy Questionnaire. Each subject will complete this questionnaire at their baseline and 3 month follow-up appointment. This questionnaire is widely used to evaluate quality of life in heart failure patients. It consists of 23 items which assess the level of impact of physical symptoms in this population such as shortness of breath, fatigue, peripheral edema, and difficulty sleeping. It also assesses the impact of psychological symptoms like anxiety and depression, as well as social functioning (63).
- CHAMPS Physical activity questionnaire for older adults (64). Each subject will compete this questionnaire at their baseline and 3 month follow-up appointment. This questionnaire is used to assess physical activity in our population.
- Health Questionnaire. Each subject will complete this questionnaire at their baseline and 3 month follow-up appointment. This questionnaire is used to collect data about medical history, and general but important health indicators, e.g., alcohol use, sleep quality, and restless leg symptoms.

Ambulatory Blood Pressure Monitoring. Participants will be instructed in the use of an Ambulatory Blood Pressure monitor. The device consists of a blood pressure cuff that is connected by rubber tubing to a small pressure monitoring device that weighs only 9 oz and fits easily in a shirt pocket. The device will be programmed to measure BP at 20 minute intervals during the day and 30 minute intervals at night (11 PM to 7 AM) for the subsequent 24 hours. A pre-paid addressed box will be provided for mail return of the device.

Randomization. After completing testing at the baseline visit, and being instructed in the use of the ambulatory blood pressure monitor, participants will be randomly assigned in a 1:2:2 ratio to one of three treatment groups: **H**ealthy **L**ifestyle and **S**leep **E**ducation alone (HLSE); HLSE plus Continuous Positive Airway Pressure (CPAP); or HLSE plus nocturnal supplemental oxygen (NSO). Randomization will be performed using permuted blocks, stratified by recruitment site. A SAS program will be used to generate two separate lists of randomization assignments for the two strata. These lists will be

placed into a single data table in a Microsoft SQL Server 2008 database to serve as a lookup table. When a new participant record is created in the database, a trigger is fired on the SQL Server randomization data table that looks up the corresponding stratum using predominant sleep apnea type, picks the next assignment from that stratum, updates the lookup table with the Study ID randomized and the date/time of randomization. Due to the nature of the treatments, blinding of subjects to treatment arm is not possible. The ultrasonographers and physicians overseeing and scoring the echocardiograms and cardiopulmonary exercise tests will be blind to treatment assignment.

Treatment

Healthy Lifestyle and Sleep Education (HLSE Group)

Research Staff at each site will provide counseling on sleep hygiene and general heart healthy lifestyle using a slide show developed for this purpose. The presentation will suggest non-pharmacologic approaches to improve the regularity and duration of sleep, aiming for 7-8 hours of sleep per night. General lifestyle advice relevant to sleep apnea will also be provided, including a recommendation for weight loss and regular exercise as tolerated, per American College of Cardiology/American Heart Association guidelines (26), and avoidance of smoking, excessive alcohol consumption, and use of illicit drugs. The importance of adherence to prescribed medical regimens will also be emphasized. The slides and written materials will be provided to participants at the baseline visit and reviewed at the one-week telephone contact. All participants will have had clinical management reviewed by a study physician to ensure adherence to current HF treatment guidelines, as described above.

Healthy Lifestyle and Sleep Education plus CPAP (CPAP Group)

In addition to HLSE, this intervention includes sleep apnea treatment with continuous positive airway pressure (CPAP). The CPAP device to be employed in this study is the AutoSet Med S9 (Resmed, San Diego, CA). Participants will be educated on the use of the CPAP device, targeting self-efficacy and cognitions related to CPAP. Participants will have an opportunity to try various mask interfaces in order to optimize fit. Verbal and written directions on the use of these materials will be provided, with instructions reinforced at interim telephone follow-up calls.

Participants randomized to the CPAP Group will then be scheduled for CPAP titration in the Sleep Laboratory of the VA Boston or VA Connecticut Healthcare System. All technicians in both Sleep Laboratories are Registered Polysomnography Technicians who are credentialed for human subjects research and have experience in the administration and titration of CPAP. CPAP titration will be performed overnight on a single night in the Sleep Laboratory. Participants will undergo polysomnography with a typical montage according to current American Academy of Sleep Medicine recommendations, including electroencephalogram, electro-oculogram, chin electromyogram, respiratory inductance plethysmography, finger pulse oximetry, leg electromyogram, and electrocardiogram. Airflow and mask pressure will be monitored and recorded from the CPAP device. Participants will be habituated to the preferred mask prior to study initiation. The CPAP device will be set to deliver pressure starting at 4 cm H2O pressure. The CPAP pressure will be increased in increments of 1 cm H2O, at intervals of no less than 10 minutes, in order to eliminate both obstructive and central apneas, with a maximum CPAP pressure of 20 cm H2O.

The Research Coordinator will maintain contact with participants by telephone during

the first 7 days of CPAP treatment to assist with any troubleshooting. The CPAP device is capable of wireless transmission of utilization and efficacy data. At the end of the first week of CPAP use, and again at weeks 2, 4 and 8 (in advance of each scheduled interim telephone contact), the utilization data will be reviewed by the Research Coordinator who will judge their acceptability based on usage for at least 4 hours/night for at least 5 nights and absence of excessive mask leak. If adherence does not meet these targets, the Research Coordinator will discuss with the participant in an attempt to overcome barriers to adherence.

Healthy Lifestyle and Sleep Education plus Nocturnal Supplemental Oxygen (NSO Group)

In addition to HLSE, this intervention includes nightly treatment with nocturnal supplemental oxygen (NSO). Oxygen therapy will be initiated at 2 lpm via nasal cannula, with routine clinical follow-up using overnight oximetry to assess adequacy of this flow rate. If needed, oxygen will be increased in 1 lpm increments as needed to (1) maintain baseline saturation >90%, and (2) to reduce the frequency of 3% oxyhemoglobin desaturation events to <5 per hour (independent of baseline saturation level). As oxygen at 2 lpm via nasal cannula has been shown to reduce the number of 4% desaturations during sleep in patients with sleep apnea by 89%, we anticipate that most participants will be adequately treated at 2-4 lpm. Oxygen is provided by a stationery oxygen concentrator. Adherence with oxygen use is measured by hours of machine use over the intervention period.

Interim telephone contact

Following initiation of therapy, study staff will make telephone contact with each participant at weeks 1, 2, 4 and 8 to identify any early problems with treatment adherence and to ascertain any adverse events. In particular, sleepiness will be re-assessed using the Epworth Sleepiness Scale and Dr. Gottlieb or Dr. Yaggi will contact any patient whose Epworth Sleepiness Scale score is ≥16 or who provides a response of 2 or 3 on the item regarding drowsy driving. At week one the Healthy Lifestyle Education will be presented to each group over the phone in conjunction with education materials set home with patient at baseline visit.

Final study visit

After 12 weeks of intervention, participants will return for a final study visit at which time all procedures performed at the baseline visit will be repeated, including phlebotomy, echocardiography, cardiopulmonary exercise testing, and questionnaire administration. Participants will be asked to complete, while wearing the assigned therapy24-hour ambulatory blood pressure monitoring.

Following completion of study procedures, each participant will be encouraged to accept referral to a sleep specialist within the VA to discuss treatment of sleep apnea.

Statistical analysis

This study is a randomized clinical trial with three parallel treatment groups, designed to compare the active treatment groups (CPAP and NSO) to the optimal medical management comparator (HLSE). Baseline data will be summarized using standard descriptive statistics for demographic and baseline clinical characteristics by treatment group. Based on our experience with the HeartBEAT Study, the rate of dropouts during the course of the three-month trial is expected to be low and we do not expect dropouts

to be differential with respect to treatment group assignment. The main analysis will include all subjects completing the follow-up examination. For the purposes of a sensitivity analysis, a result of "no change" will be imputed for all drop- outs, and compared to the main analysis.

The analysis for each of the primary outcome measures (LVEF and peak VO2) will consist of a one-factor analysis of variance comparing the mean changes from baseline in LVEF (or VO2). As we postulate similar benefits from CPAP and NSO, we will specify two contrasts: CPAP vs. HLSE and NSO vs. HLSE as our primary analyses. In a secondary analysis, we will also compare the effects of CPAP to NSO for the purpose of hypothesis generation for subsequent larger studies. This analysis is a simple analysis of variance, with data transformation or adoption of rank-based inference if approximate normality is not present. While the randomization should achieve approximate balance on potentially confounding conditions, analysis of covariance models that employ adjustments for recruitment site, age, sex, sleep apnea severity, comorbid illness, smoking and alcohol use will be fit to potentially improve the efficiency of the treatment effect estimates. Should a significant difference between treatment and comparator be identified, further exploratory analyses will assess the relation of adherence to therapy to change in outcome measures.

In order to compare the effectiveness of the assigned interventions in controlling sleep apnea over the course of the study, an additional exploratory analysis will compare the change in AHI, change in time in periodic breathing, and change in time at SpO2 <90% between the baseline and final portable sleep monitoring studies. This analysis will utilize a one-factor analysis of variance. Further exploratory analyses will assess the relation of effectiveness of control of sleep apnea to changes in the primary outcome measures.

This study provides an opportunity to evaluate multiple intermediate measures that might shed light on the mechanism of benefit of CPAP or NSO. These analyses are considered exploratory in nature. As each of the secondary outcome measures is continuous, analysis of these variables will be treated in a similar fashion to the analysis of the primary study endpoints. For analysis of blood pressure, the 24-hour mean blood pressure and the ratio of mean nighttime to mean daytime blood pressure will also be analyzed.

Mean hours of use of therapy over the 3-month intervention period between CPAP and NSO groups will be compared using a one-factor analysis of variance, with appropriate modification as needed for deviation from normality. The number of adverse events and serious adverse events in each per study arm will be tabulated and categorized according to their severity, expectedness and relationship to the study intervention.

Sample size and power

Our primary goals are to establish the efficacies of CPAP and NSO compared to HLSE. Because past studies were suggestive of a more beneficial effect of CPAP or NSO compared to HLSE, we propose to randomize more subjects to the two experimental treatment groups. That is, we propose to allocate patients into CPAP, NSO or HLSE randomly according to a 2:2:1 ratio. This strategy also improves statistical power for the secondary comparisons between CPAP and NSO.

The sample size for this study was chosen to provide adequate power to detect a significant difference in LVEF between each treatment group and the control group (Aim

1). We have used effect estimates based on the meta-analyzed mean effect sizes for CPAP and NSO included in the AASM Practice Parameters paper (41) of 6.4%, and 5.0% for CPAP and NSO, respectively, and an estimated SD of change in LVEF of 4.8% based on previous reports of the effect of either ASV, CPAP or NSO (40, 42, 45-47) on LVEF in patients with sleep apnea. We use the Bonferroni method to account for 2 main comparisons and perform the test comparing each treatment to control at a 2.5% significance level. Using a two-sided two-sample t-test, an evaluable sample size of 34 in the NSO (or CPAP) group and 17 in the HLSE group will achieve 90% power to detect a difference of 5.0% with a significance level of 2.5% assuming a standard deviation of 4.8% in each group, and 98% power to detect a difference in LVEF of 6.4%; there will be 80% power to detect a difference as small as 4.4% between either active treatment group and the HLSE group.

Changes in peak V02 (Aim 2) will be compared in a similar fashion as changes in LVEF. An evaluable sample size of 34 in CPAP or NSO group and 17 in HLSE group will have 80% power to detect a difference of 0.92 standard deviations with a significance level of 2.5% using a two-sided two-sample t-test. Only one study of treatment of central sleep apnea in HF reports the SD of change in peak VO2, which was 2.5 ml/kg/min (58). The reported change in peak VO2 with treatment of central sleep apnea with NSO was 1.4-5 ml/kg/min, with a median of 2.5 ml/kg/min (47, 50, 55, 58). The power for this Aim therefore appears adequate.

For the exploratory comparison of CPAP and NSO, the sample sizes of 34 evaluable subjects per group will provide 80% power to detect a difference of 3.3% in change in LVEF, assuming a SD of change of 4.8% and a two-sided significance level of 5%.

As comparisons for secondary outcomes (Aim 4) are exploratory in nature, they will be performed at 5% significance level without multiple comparison adjustment. For comparisons in a continuous outcome between each treatment group and the control group, an evaluable sample size of 34 in CPAP or NSO group and 17 in HLSE group achieve 80% power to detect a difference of 0.84 standard deviations with a significance level of 5% using a two-sided two-sample t-test.

The proposed sample size of 39 in each active treatment group and 20 in the HLSE group includes a 15% increase over the needed number of evaluable subjects, to allow for expected rates on non-completion of the protocol.

Reasons for stopping assigned treatment

As there is clinical equipoise with respect to the long-term benefits of treatment of sleep apnea in chronic HF, and the duration of the intervention is short at 3 months, there is no plan to discontinue assigned treatment due to therapeutic failure related to cardiac disease. However, as treatment of sleep apnea may be expected to improve sleepiness, any participant who develops unsafe levels of sleepiness that in the opinion of the PI place him or her at increased risk of motor vehicle accidents or other safety risks, will be treated for their sleep apnea off protocol. While serious adverse effects of either CPAP or supplemental oxygen are not anticipated, should any serious adverse events occur that in the opinion of the PI are treatment related, the treatment will be discontinued.

Human Subjects Potential Risks

The study procedures do not place the subjects at risk of harm or discomfort greater than those encountered in routine medical care. The vein puncture for blood drawing is

associated with temporary pain at the time of needle insertion and may result in bruising at the needle insertion site. Rarely, fainting occurs with a blood draw. Portable sleep monitoring and ambulatory blood pressure monitoring may lead to minor sleep disturbance and some subjects may experience mild skin irritation from the sensors or electrodes used. Use of the blood pressure cuff may cause mild discomfort as the cuff is inflated. When the blood pressure cuff is worn for 24 hours, there may be some soreness in the arm. The administration of questionnaires may be stressful, although none ask sensitive information. The echocardiogram may cause transient discomfort as the ultrasound probe is pressed against the chest and upper abdomen. Cardiopulmonary exercise testing may cause shortness of breath, fatigue, muscle discomfort, and very rarely (<1:1,000) may be associated with heart attack or death. The intravenous (IV) catheter that will be placed for the exercise has a small chance of causing bruising or infection. Standard precautions will be followed in cleaning and sterilizing the area. If contrast is needed for the echocardiogram, there is a small chance of allergic reaction. There is a rare chance (1:10,000) that patients may be allergic to the microscopic bubble contrast (lipid shell and gas), thus allergies will be confirmed via patient medical charts and verbally with the patient prior to the injection of the contrast agent. Special efforts will be taken to reduce risks by watching each subject for 30 minutes after the echo contrast agent.

The study treatments are generally considered quite safe. CPAP is an FDA-approved therapy for the treatment of sleep apnea. Its use can be associated with a number of minor side effects, including nasal congestion, runny nose, dry nose or mouth, skin irritation from the mask or headgear, aerophagia or discomfort from the mask or air pressure. Rarely, sinus problems may get worse while using CPAP and mild nose bleeds may occur. Polysomnography will be performed for the purpose of CPAP titration in patients randomized to this therapy. This procedure is inconvenient, as it requires an overnight stay in the Sleep Laboratory, but poses no major risks. There may be some discomfort from placement of the sensors on the scalp and face, and wearing the sensors may cause sleep disruption. Occasionally there is discomfort or redness at the site of sensor placement. Rarely (<1:100) the skin irritation may require treatment with a topical steroid. Supplemental oxygen delivered through the nose may be associated with minor side effects such as discomfort from the nasal prongs, dry nose, nasal stuffiness, mild nose bleeds or skin irritation. The use of a saline nasal spray can help prevent dryness and nosebleeds. Although oxygen at the levels prescribed in this study is not known to be harmful, oxygen can increase the risk of fire. It is possible that patients randomized to optimized medical care alone or with NSO may not be effectively treated for their sleep apnea for the 3 months of the study. Untreated sleep apnea may place subjects at increased risk of motor vehicle and other accidents; however, in a study of 1105 patients with sleep apnea randomly assigned to CPAP or sham CPAP for 6 months (the Apnea Positive Pressure Long-term Efficacy Study), we had no episodes of motor vehicle accidents due to sleepiness using safety education and monitoring procedures similar to those of present study.

Protection against risks

All study personnel will be fully trained and credentialed in Human Subjects Protections. All research data will be collected on standardized research forms with de-identified ID numbers, without personal identifiers. Any data collected from medical records will be entered onto case report forms with only study ID numbers, excluding personal

identifiers. Only study personnel will have access to research data, which is kept either in locked cabinets, in password-protected computers in locked offices, or on secure password-protected drives located behind the VA firewall or at the Center for Clinical Investigation at Brigham & Women's Hospital. All personal data will be stored separately from de-identified research data, and will be stored in password-protected files behind the VA firewall or in locked cabinets within the VA. Blood and specimens will be stored using de-identified bar codes at the VA Boston and shipped to Dr Jacob's laboratory, the VA Boston clinical lab for testing. Once the assays have been run on the samples, any leftovers will be destroyed.

Risks from cardiopulmonary exercise testing will be minimized by close physician supervision of testing, which will be performed by trained technicians in the Cardiopulmonary Exercise Laboratories at the VA Boston and VA Connecticut HCS sites, with emergency equipment readily available. Although patients will be encouraged to exercise to their symptomatic limits, if there are any signs of medical instability, the cardiologist will end the test before the symptomatic endpoint is achieved.

Phlebotomy will be performed by trained phlebotomists.

All CPAP devices will be equipped with heated humidifiers to minimize drying, and attention will be paid at set-up to identifying a best-fit mask to minimize mask discomfort and air leaks. Subjects will be contacted at weeks 1, 2, 4 and 8 to identify any early problems with treatment and to ascertain any adverse events, in particular the onset of dangerous levels of sleepiness. Participants will be extensively counseled at the baseline visit on safety measures related to excessive sleepiness. Participants randomized to NSO will be counseled on risks of fire from use of oxygen near open flames, including cigarettes.

Potential Benefits of the proposed Research to Human Subjects and Others
There are a number of potential benefits to participants. All participants who undergo sleep apnea screening will be provided information on the results of their sleep studies, which may be useful in further health management. Participants randomized to CPAP or oxygen may experience direct benefit related to treatment of underlying sleep apnea. There are also potentially important benefits to others, if the study identifies a well-tolerated alternative to positive pressure ventilation to reduce cardiac risk in the many patients with chronic heart failure and sleep apnea. As the risks to individual participants are small, and the potential benefit large, the risks of participation in the study are justified.

Importance of the knowledge to be gained
The societal benefits to the study include the generation of pivotal data for designing a definitive study that will for the first time address the relative effectiveness of alternative approaches to treatment of a very common comorbid illness (sleep apnea) in patients with heart failure. The approaches proposed may significantly reduce the costs and burden of current diagnostic and treatment approaches and improve access to treatment for a high risk population. The study may also provide important insights into the mechanism of the adverse cardiac effects of intermittent hypoxemia and sleep apnea, thereby stimulating research into additional novel therapies.

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