

Obstructive Sleep Apnea Treatment to Improve Cardiac Rehabilitation

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STUDY PROTOCOL

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Overview

The proposed study is a randomized, parallel group study comparing three months of therapy with continuous positive airway pressure (CPAP) to an educational control for patients with comorbid obstructive sleep apnea and coronary heart disease undergoing a structured cardiac rehabilitation program. The study will be conducted over 2 years and participants will be recruited from among patients seen at the VA Boston Healthcare Systems with a diagnosis of coronary heart disease and referred to the Cardiac Rehabilitation Program. A total of approximately 150 patients will be recruited in order to randomize 25 patients to each group (CPAP or Control). Participation of an individual subject will be approximately 1 week for subjects not meeting criteria for randomization, and 8-10 weeks for subjects randomized. Participants will be age 18 and over, of either gender, have a diagnosis of coronary heart disease, and be referred to the Cardiac Rehabilitation Program at the VA Boston Healthcare System. No children or other special classes of individuals will be enrolled. All enrolled subjects will be veterans.

(1) RATIONALE

(a) Statement of the Problem:

Coronary heart disease is the leading cause of death in the United States and a major cause of disability. Cardiac rehabilitation programs that include an exercise training intervention have been shown to reduce cardiac mortality by approximately 25%, with improved exercise tolerance and peak oxygen consumption, and a concomitant improvement in functional status and quality of life. Unfortunately, many patients entering cardiac rehabilitation programs do not complete them, and the increase in exercise capacity among completers is variable. Although psychosocial factors are important predictors of successful cardiac rehabilitation, one common but often undiagnosed barrier to successful rehabilitation is the presence of obstructive sleep apnea (OSA), which is highly prevalent in patients with coronary heart disease. Obstructive sleep apnea is a common condition in adults, associated with recurrent airway collapse during sleep resulting in intermittent hypoxemia and sleep fragmentation. Two studies of OSA in patients undergoing cardiac rehabilitation suggest prevalence in excess of 50%. While OSA is strongly associated with obesity, studies of exercise training in patients with OSA demonstrate a poorer response to exercise independent of body habitus. The sleepiness and fatigue caused by OSA may contribute to impaired motivation to exercise, although intermittent hypoxia itself has been shown to decrease ventilatory efficiency in healthy adults. Patients with OSA have reduced exercise tolerance compared to obese controls, and treatment of OSA with continuous positive airway pressure (CPAP) results in increased peak oxygen consumption on symptom-limited exercise testing and an increase in constant load exercise time. These studies suggest that treatment of OSA might substantially improve the response to exercise training as part of cardiac rehabilitation, although

these were uncontrolled case series in general patients with OSA, not in the setting of cardiac rehabilitation.

(b) Hypothesis

We hypothesize that identification and treatment of obstructive sleep apnea (OSA) in patients with comorbid OSA and coronary heart disease undergoing cardiac rehabilitation will improve their response to rehabilitation.

(c) Specific Objectives

The goal of the proposed study is to evaluate the impact of OSA treatment on the effectiveness of cardiac rehabilitation. This goal will be met through a parallel-group, randomized, clinical trial in patients with coronary heart disease referred for cardiac rehabilitation that screen positive for OSA on home sleep testing. These patients will be randomized to treatment with OSA with CPAP or to an educational control intervention for a three month treatment period.

(2) BACKGROUND AND SIGNIFICANCE

(a) Background

Coronary heart disease remains the leading cause of death in the United States, and is a major cause of disability. Cardiac rehabilitation programs that include an exercise training intervention have been shown to reduce the rate of recurrent myocardial infarction by approximately 20% and cardiac mortality by approximately 25% (1). Following 3 months of exercise training three times per week, exercise tolerance increases by 30-50% and peak oxygen consumption by 15-20%, with a concomitant improvement in activities of daily living (2). The cardioprotective effects of exercise training are thought to relate to the salutary effects of shear stress on endothelial function, reduced systemic inflammation, reductions in adiposity and blood pressure, and improved glucose homeostasis (1), while improved exercise tolerance and functional capacity from aerobic conditioning relate to cardiac, skeletal muscle and vascular adaptations (2). Despite the well documented beneficial effects of cardiac rehabilitation on cardiac morbidity and mortality, a minority of eligible patients undergoes cardiac rehabilitation, and many patients who do enroll in cardiac rehabilitation programs do not complete the program, typically 36 sessions over 12 weeks (3). While psychosocial and demographic factors appear to be important predictors of referral to and participation in cardiac rehabilitation programs, comorbid illnesses are also predictive (4).

Obstructive sleep apnea (OSA) is a common chronic adult illness characterized by recurrent collapse of the pharyngeal airway during sleep causing episodes of decreased (hypopnea) or absent (apnea) airflow, resulting in intermittent hypoxemia and sleep fragmentation. OSA is a highly prevalent condition among US Veterans and is associated with excessive daytime sleepiness, diabetes, hypertension, incident coronary heart disease and stroke, and increased mortality and health care utilization. The general population prevalence of OSA is estimated at 9% of women and 24% of men aged 30-60 years (5), with estimates of even higher prevalence in the veteran

population (6,7). Prevalence of OSA is even higher in patients with coronary heart disease. Two studies of OSA prevalence in patients undergoing cardiac rehabilitation suggest prevalence in excess of 50% (8, 9).

While these studies did not evaluate the impact of OSA on the effectiveness of cardiac rehabilitation, a number of studies have evaluated the impact of OSA on exercise tolerance and response to exercise training programs outside the context of coronary heart disease. Patients with OSA have reduced exercise tolerance compared to obese controls (10), and a poorer cardiac response to exercise as measured by cardiac output and stroke volume as a function of workload (11). In a one-year study of a diet and exercise intervention, OSA was associated with a smaller reduction in cardiovascular risk factors, including body mass index, waist circumference, and visceral adiposity, and smaller improvements in HDL cholesterol and glucose homeostasis, compared with obese controls without OSA (12). Sleepiness and fatigue, cardinal symptoms of OSA, are commonly cited by OSA patients as a reason they are unable to exercise, and may be an important mediator of poor response to exercise training; however, intermittent hypoxia has itself been shown to decrease ventilatory efficiency in healthy adults (13), which might also limit exercise capacity in OSA. Treatment of OSA with CPAP results in improved cardiac response to exercise (11) and increased peak oxygen consumption on exercise testing of 1.8 to 3.2 ml/kg/min even in the absence of a structured exercise training program (14,15). Perhaps even more relevant to functional capacity, a 40% increase in constant load exercise time was noted after one month of CPAP treatment (16). These studies suggest that OSA may be an unrecognized barrier to effective cardiac rehabilitation.

(b) Significance

Coronary heart disease is a common disease with high morbidity, mortality, and health care utilization. Obstructive sleep apnea (OSA) is highly prevalent in patients with coronary heart disease. The present study will for the time directly evaluates the impact of CPAP treatment in patients with comorbid coronary heart disease and OSA that undergo cardiac rehabilitation. If a beneficial effect is confirmed, this could have a direct impact on clinical practice, leading to routine screening for and treatment of OSA to improve the effectiveness of cardiac rehabilitation.

(c) Relevance

Coronary heart disease remains a leading cause of morbidity and mortality among veterans treated in the VA Health Care System (17, 18). Cardiac rehabilitation programs that include an exercise training intervention have been shown to reduce cardiac mortality by approximately 25% (1), with improved exercise tolerance and peak oxygen consumption, and a concomitant improvement in functional status and quality of life. Sleep apnea is a common co-morbid condition in patient with coronary heart disease and may be a barrier to effective cardiac rehabilitation. Determining the impact of sleep apnea treatment in patients with comorbid coronary heart disease and OSA, who undergo cardiac rehabilitation is therefore of great relevance to Veterans Health.

(3) Work Protocol

Overview

The proposed study is a randomized, parallel group study comparing three months of therapy with continuous positive airway pressure (CPAP) to an educational control for patients with comorbid obstructive sleep apnea and coronary heart disease undergoing a structured cardiac rehabilitation program. The study will be conducted over 2 years and participants will be recruited from among patients seen at the VA Boston Healthcare Systems with a diagnosis of coronary heart disease and referred to the Cardiac Rehabilitation Program. A total of approximately 150 patients will be recruited in order to randomize 25 patients to each group (CPAP or Control). Participation of an individual subject will be approximately 1 week for subjects not meeting criteria for randomization, and 8-10 weeks for subjects randomized. Participants will be age 18 and over, of either gender, have a diagnosis of coronary heart disease, and be referred to the Cardiac Rehabilitation Program at the VA Boston Healthcare System. No children or other special classes of individuals will be enrolled. All enrolled subjects will be veterans.

Study procedures will include:

- Screening Questionnaires (Epworth Sleepiness Scale)
- Portable Sleep Monitoring
- Baseline (Randomization) Visit, including:
 - Anthropometry
 - Randomization to treatment with one of the following two treatments:
 - Healthy Lifestyle and Sleep Education alone (HLSE)
 - HLSE plus CPAP (CPAP)
- Interim Telephone Contacts
- Final Study Visit
 - Anthropometry
 - Epworth Sleepiness Scale
 - 7 day actigraphy recording

Inclusion criteria for sleep apnea screening:

- Age \geq 18 years
- Physician diagnosis of ischemic heart disease, with prior myocardial infarction or coronary revascularization procedure
- Referral to the Cardiac Rehabilitation Program
- Epworth Sleepiness Scale $<$ 18
- Ability to provide informed consent

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

- Moderate to severe obstructive sleep apnea, defined as an apnea-hypopnea index \geq 15 events per hour, with $>$ 50% of events being obstructive apneas or hypopneas

Exclusion criteria:

- Poorly controlled hypertension (>170/>110), poorly controlled diabetes (HbA1c > 9.0), severe renal failure with estimated glomerular filtration rate <30 ml/min, prior stroke with functional impairment or other severe, uncontrolled medical problems that may impair ability to participate in the study exams, based on medical history and review of medical records
- Severe daytime sleepiness, defined as Epworth Sleepiness Scale score 18 or higher or a report of falling asleep driving during the previous year
- Awake resting oxyhemoglobin saturation <89%
- Pregnancy
- Current use of a positive airway pressure device (including continuous or bi-level positive airway)

Study Design

The proposed study is a randomized, parallel group study comparing 8 weeks of therapy with continuous positive airway pressure (CPAP) to an educational control for patients with comorbid obstructive sleep apnea and coronary heart disease undergoing a structured cardiac rehabilitation program. The primary study outcome measure, to be made at baseline and at end of the treatment period, is change in walking distance and speed as measured by 6 minute walk test, a valid and reproducible measure of functional capacity. The primary analysis will compare the active treatment group to the control group. Secondary outcome measures include measures of functional status and health related quality of life, and adherence to cardiac rehabilitation.

Sample Selection

The target population is veterans with stable coronary heart disease referred for cardiac rehabilitation at the VA Boston Healthcare System and comorbid sleep apnea. Patients will be recruited from among those patients enrolled in the VA Boston Healthcare System who carry a diagnosis of coronary heart disease and are referred for cardiac rehabilitation. Potential participants will be identified via the computerized patient record system, by confirming a diagnosis of coronary heart disease and an active referral to the Cardiac Rehabilitation Program. We propose to recruit approximately 75 patients per year for home sleep testing, in order to identify 25 per year for inclusion in the randomized clinical trial. Given the low participant burden of home sleep testing, and the potential health benefit, we believe this is a reasonable recruitment target.

Recruitment

Subjects will be recruited by mailings to patients seen at the VA Boston Healthcare System for a diagnosis of coronary heart disease referred to the Cardiac Rehabilitation Program. This recruitment approach will be supplemented, if needed, by direct contact during an inpatient hospitalization or at the time of presentation for intake evaluation into the Cardiac Rehabilitation Program. After initial contact, interested participants will have initial screening for eligibility. Potentially eligible patients will be invited to 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. This screening visit may take

place on the day of Cardiac Rehabilitation intake evaluation. Participants who screen positive for moderate to severe obstructive sleep apnea 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 coronary heart disease referred to the Cardiac Rehabilitation Program at the VA Boston Healthcare System. 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).

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.

Subjects may also be recruited directly at the time of the Cardiac Rehabilitation Program intake evaluation or during inpatient hospitalizations at the West Roxbury VA Medical Center by trained research staff. This will entail study staff pre-screening the charts for eligible patients admitted to the inpatient medical services for recent ischemic cardiac event, percutaneous coronary intervention, or coronary artery bypass, or referred for Cardiac Rehabilitation and scheduled for initial intake evaluation. These patients will be approached by trained research staff during their hospitalization or at their Cardiac Rehabilitation intake visit, to describe the study and ask them if they would be interested in participating. Prior to contacting each patient, the primary medical team (in the case of inpatients) or Cardiac Rehabilitation staff will be informed of the study and potential eligibility of the patient to participate. The primary medical team or Cardiac Rehabilitation staff will request permission from the patient for a member of the research staff to discuss participating in the study. Patients who provide permission for the research staff to speak with them will be screened for eligibility, and potentially eligible subjects invited to attend a Screening Visit. This will also ensure no disruption in the ongoing care and management of the patient.

No personally identifiable data will be retained for patients who do not opt to participate.

Screening Visit

At the Screening Visit, written informed consent will be obtained and participants will be instructed in the performance of home portable sleep testing. Participants will also be given the Epworth Sleepiness Scale if it has not already been completed in response to a recruitment letter.

Informed Consent Procedures

The informed consent process will be undertaken by investigators and study staff who have current training in human subject 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.

Portable Sleep Monitoring

At the Screening Visit, after written informed consent is obtained, subjects will be instructed in the use of the portable sleep apnea monitor (Embletta Gold or Embletta MPR, 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 (19,20): 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. 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 the Home Sleep Testing Coordinator. 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 a VA server for scoring by the Home Sleep Testing Coordinator or other polysomnography technician and review by Dr. Gottlieb.

Studies will be scored following AASM guidelines for standard hypopnea and apnea definitions based on respiratory effort, flow sensors and oximetry (20). Apneas will be identified based on absence of airflow for at least 10 seconds, and scored as obstructive if there is continued respiratory effort during the event and as central if there

is no respiratory effort during the event. Identification of hypopneas will require: (1) a fall in peak signal excursion of $\geq 30\%$ from the pre-event baseline, using nasal pressure as the preferred sensor; (2) an event duration of at least 10 seconds; and (3) an associated $\geq 3\%$ fall in oxyhemoglobin saturation from the pre-event baseline. 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 obstructive sleep apnea (AHI >15 , with $>50\%$ obstructive events) on home sleep testing will proceed to the baseline study visit. The entire baseline visit is expected to take approximately 15 minutes.

Anthropometry

- Height and weight
- Waist, hip, and neck circumference

Cardiac Rehab Assessment Measures

Information from the participant's initial assessment for Cardiac Rehabilitation will be pulled from the Cardiac Rehabilitation exercise evaluation note in CPRS. Measures of particular interest include strength, balance, and range of motion assessments as well as results from the 6 min walk test. Participants' responses to World Health Organization Disability Assessment Scale II (WHODAS II) (21) will also be recorded.

Randomization

After completing the baseline visit, participants will be randomly assigned in a 1:1 ratio to one of two treatment groups: **Healthy Lifestyle** and **Sleep Education** alone (HLSE) or HLSE plus **Continuous Positive Airway Pressure** (CPAP). A SAS program will be used to generate a list of randomization assignments, which will be placed into a 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 picks the next assignment, updates the lookup table with the Study ID randomized and the date and time of randomization. Due to the nature of the treatments, blinding of subjects to treatment arm is not possible. The Home Sleep Testing Coordinator or other polysomnography technician will be unblinded to group assignment and will administer and troubleshoot the CPAP intervention. The research assistant, research coordinator, exercise physiology staff and physicians overseeing the study will be blind to treatment assignment.

Treatment

Healthy Lifestyle and Sleep Education (HLSE Group)

The Research Coordinator 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, and avoidance of smoking, excessive alcohol consumption, and use of illicit drugs. The importance of adherence to prescribed medical regimens will also be emphasized.

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). Participants will be educated on the use of the CPAP device by the Home Sleep Testing Coordinator or other polysomnography technician, 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 given an auto-titrating CPAP device with pressure range initially set at 4-20 cm H₂O pressure. The CPAP device is capable of wireless transmission of utilization and efficacy data. At the end of the first week of CPAP use, the utilization data will be reviewed by the Home Sleep Testing 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. At this time, the pressure profile will be reviewed and the 90th percentile pressure (i.e., the pressure that is exceeded only 10% of the time) will be identified and the CPAP device wirelessly reset to a pressure range of this 90th percentile pressure \pm 3 cm H₂O. The Coordinator will review utilization data again at weeks 2, 4 and 6. If adherence does not meet the above target, the Coordinator will call the participant to discuss ways to overcome barriers to adherence. This approach has been used successfully for evaluating CPAP utilization in the recently completed HeartBEAT Study.

Interim telephone contact

Following initiation of therapy, study staff will make telephone contact with each participant at weeks 2, 4 and 6 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 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.

Final study visit

After 8 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 anthropometry and the Epworth Sleepiness Scale. Measurements taken at the end of participation in the Cardiac Rehabilitation program, including 6 minute walk test results and responses to the WHODAS II questionnaire, will also be recorded.

Participants will also be asked to wear an Actigraph GT3X monitor for a period of 7 days (except when swimming or bathing). This will be used to assess the level of activity performed by the participant at home following completion of the Cardiac Rehabilitation program.

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

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 dropouts, and compared to the main analysis.

The analysis for the primary outcome measure will consist of a one-factor analysis of variance comparing the mean changes from baseline in six minute walk distance. The primary analysis is a simple analysis of variance, with data transformation or adoption of rank-based inference if approximate normality is not present. A p value <0.05 will be considered statistically significant. While the randomization should achieve approximate balance on potentially confounding conditions, analysis of covariance models that employ adjustments for 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 CPAP therapy to change in outcome measures.

Each of the secondary outcome measures is continuous; therefore, analysis of these variables will be treated in a similar fashion to the analysis of the primary study endpoints.

Sample size and power

Our primary goal is to determine the impact of identification and treatment of obstructive sleep apnea in patients with coronary heart disease undergoing cardiac rehabilitation. Patients will be allocated into the two groups, HLSE or HLSE plus CPAP, randomly according to a 1:1 ratio.

There are no published data on the effect of CPAP therapy on 6-minute walk distance in patients with coronary heart disease; however, in a recent report from a general sample of patients with OSA, treatment with CPAP was associated with a mean 114 m improvement in 6-minute walk distance after 4 weeks, compared to a control group not treated with CPAP (22). This is well above the minimal clinically important difference of 23 m in 6-minute walk distance reported for patients with stable coronary heart disease (23). The standard deviation in 6-minute walk distance in patients with stable coronary

heart disease has been estimated at 104 m (24), similar to the 90 m estimated for healthy adults (25). Assuming a modest correlation of 0.4 between repeated measures of the 6-minute walk test, the sample size of 25 subjects in each group will have 80% power to detect a difference between groups of 57 m in 6-minute walk distance, half of the difference reported for the effect of OSA treatment (22).

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. Portable sleep monitoring may lead to minor sleep disturbance and some subjects may experience mild skin irritation from the sensors or electrodes used. The administration of questionnaires may be stressful, although none ask sensitive information.

The study treatment is generally considered quite safe. CPAP is a FDA-approved therapy for the treatment of sleep apnea. The 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. These side effects will be minimized by using a humidifier built into the device and by using the most appropriate pressure.

It is possible that patients randomized to HLSE alone may not effectively be treated for their sleep apnea for the 8 weeks 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. Research staff members that are no longer involved during the course of the study will have their access terminated. 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. Records will be destroyed in accordance with the VA Record retention schedule.

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 2, 4 and 6 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.

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 may experience direct benefit related to treatment of underlying obstructive sleep apnea. There are also potentially important benefits to others, if the study confirms improved response to cardiac rehabilitation in those treated with CPAP.

Importance of the knowledge to be gained

The societal benefits to the study include an understanding of the extent to which treatment of obstructive sleep apnea, a highly prevalent comorbid condition in patients with coronary heart disease, will improve response to cardiac rehabilitation. If an improvement is demonstrated, this should lead to a change in practice patterns for the millions of adults who are enrolled in cardiac rehabilitation programs, with routine screening for and treatment of sleep apnea at the initiation of cardiac rehabilitation.

Data Safety and Monitoring

As described above, frequent contact will be maintained with participants throughout their participation in this study, with contact at 2, 4 and 6 weeks after randomization to ascertain sleepiness, hospitalizations, illnesses or other adverse events. The PI and staff will meet on a weekly basis to review study progress and adverse events. The PI will, on a weekly basis, review all data collected to assure that no physiological findings warrant immediate intervention. If so, the participant will be contacted and advised of the findings and offered assistance with appropriate referrals. Data from the Cardiopulmonary Exercise Testing procedures will be reviewed by a cardiologist-investigator and any unusual or adverse findings will be communicated to the participant's primary care physician or Cardiologist. Adverse events (classified by severity and unexpected/expected) will be defined and reported to the IRB in accordance with the rules regulating each severity class (expected vs unexpected, serious vs. other, related vs. unrelated). No Data and Safety Monitoring Board is envisioned.

Resources

Research Space

This study will be conducted at the Boston VA hospitals. The clinical resources of the VA Boston Healthcare System for recruitment of patients with coronary heart disease undergoing cardiac rehabilitation are large and growing. Almost 1000 patients per year are treated at the VA Boston HCS with diagnoses for which cardiac rehabilitation would be indicated. Currently, 180 patients per year are being enrolled in cardiac rehabilitation, and this number is expected to increase as additional staff has recently been added to meet the demand for cardiac rehabilitation services.

The Cardiopulmonary Exercise Laboratory is located in the Clinical Studies Unit of the Jamaica Plain campus of the VA Boston Healthcare System, sharing the 11C wing with the Cardio/Pulmonary Rehabilitation Exercise Suite. Dr. Gottlieb has office space on the same floor, and research staff offices are one floor above in the Clinical Studies Unit. The close proximity of these research and clinical facilities will facilitate coordination of this research project with the cardiac rehabilitation program.

Other Research Resources

In addition to these patient resources, there is a rich academic and intellectual environment at the VA Boston HCS, with close collaborations developed over the past 3 years between Dr. Gottlieb and members of the Cardiology section, including Dr. Forman. Dr. Gottlieb has collaborated with the chief of Cardiology, Dr. Deepak Bhatt, on the NHLBI-funded HeartBEAT Study. Drs. Gottlieb and Forman, along with Dr. Bhatt, Dr. Joseph (head of the Heart Failure Program), and Dr. Aragam (head of the Echocardiography Lab) have recently received Merit Review funding to initiate a study of sleep apnea treatment in patients with chronic heart failure. Dr. Forman has an interest in the relation of sleep to quality of life and functional status in heart failure, and has developed a state-of-the-art cardiopulmonary exercise program for both clinical and research purposes. These expanding collaborations and shared interests provide an excellent environment for the successful conduct of the proposed research.

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