Official title: Effects of CPAP on Diet, Physical Activity, and Cardiovascular Risk

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Specific Aims:

Obstructive sleep apnea (OSA) has a variety of adverse cardiometabolic consequences. This disorder is characterized by recurrent episodes of partial or complete loss of airflow during sleep, resulting in low blood oxygen levels, frequent nocturnal arousals, and sleep architecture disruption. The associated daytime hypersomnolence experienced by some can lead to reduced physical activity and exercise. Estimated prevalence of OSA is as high 28% of the population (1), and the clinical entity “OSA syndrome” (OSAS), defined as OSA in conjunction with excessive daytime sleepiness is estimated to occur in as much as 1 of 20 adults (1). Almost all cross-sectional clinic-based studies as well as population-based observational studies have found an association between excess body weight and OSA, and it was reported that 70% of OSA patients are overweight or obese (2). Increased weight gain and BMI are associated with increased odds of OSA. This is critical, since the overall prevalence of overweight and obesity is ~68% and 34%, respectively, in the U.S (3). As such, there is a large proportion of the US population at risk of OSAS and its co-morbidities.

Whether obesity is strictly a cause of OSAS, or if a bidirectional relationship exists between obesity and OSAS has recently come into question (4). Newly diagnosed patients have a greater propensity for recent weight gain compared to controls (5). Metabolic, hormonal, and/or behavioral changes associated with OSAS may place patients in a condition favoring positive energy balance, which can lead to further weight gain or difficulty losing weight. Continuous positive airway pressure (CPAP) is effective in alleviating breathing and sleep abnormalities in OSAS, although it is unclear whether these improvements lead to weight loss. The proposed study will look closely at energy expenditure (EE) and energy intake (EI) with OSAS treatment to determine how CPAP affects these parameters. This will help determine if CPAP can improve weight control in obese OSAS patients, and if it can be used to promote weight loss and ameliorate obesity-related co-morbidities.

The proposal is to investigate the effects of 2 mo of CPAP on EE and EI in obese patients with OSAS. The proposal is a combined ambulatory and laboratory-based study. Free-living measures of physical activity (via waist-actigraphy), food intake (via 3-d food log), sampling of blood for appetite-regulating hormones (leptin, ghrelin, adiponectin, glucagon-like peptide-1 [GLP-1]), lipid profile, and inflammatory markers, and body composition measurements will be obtained at baseline and after 2 mo of CPAP treatment. At the start and conclusion of each treatment phase, patients will enter the laboratory for measures of polysomnographic sleep, hunger levels, and food intake (via ad libitum test meals). The objective of the proposed study is to determine how CPAP treatment affects energy balance in obese OSAS patients. The central hypothesis is that CPAP treatment will improve sleep architecture, which will be associated with improved EE, EI, cardiovascular health, and body composition. We have shown that adverse changes in sleep are associated with alterations in both EE and EI (6, 7). Specifically, reduced sleep duration is associated with increased nocturnal and 24-h EE (6). Moreover, we observed that rapid eye movement (REM) sleep is inversely related to hunger, and that both REM sleep and slow wave sleep (SWS) are inversely related to intake of fat and carbohydrate (7).

Aim 1 (Cardiovascular health): To determine the effects of 2 mo of CPAP compared to pre-treatment baseline on body composition in obese OSAS patients.

Hypothesis 1: CPAP will reduce blood pressure, fasting glucose, total cholesterol, inflammatory markers, and percent body fat relative to baseline.

Aim 2 (Energy intake): To determine the effects of 2 mo of CPAP compared to pre-treatment baseline on hunger, food intake, and the hormonal regulation of food intake in obese OSAS patients.

Hypothesis 2: Hunger levels and ad libitum food intake will be lower in patients after CPAP vs. baseline.

Hypothesis 43: Abnormally high leptin levels will be reduced in CPAP vs. baseline. Levels of ghrelin (hunger signal) will be reduced, and glucagon-like peptide-1 (GLP-1; satiety signal) increased, after CPAP vs. baseline.

Research Strategy

Significance

Importance of the problem to public health: Obstructive sleep apnea (OSA) is a disorder characterized by recurrent episodes of partial or complete loss of airflow during sleep, due to narrowing or closure of the upper airway. The prevalence of OSA is stated to be as high as 28% of the population (1). This is critical, since there are many cardiometabolic consequences of sleep-disordered breathing-related hypoxia, including hypertension (8), coronary artery disease (9), stroke (1), systemic inflammation (2), dyslipidemia (10), insulin resistance (2), and increased overall mortality (11). Upper airway collapse results in repeated arousals during the night and fragmentation of sleep, and subsequently, significant reductions in slow wave sleep (SWS) and rapid eye movement (REM) sleep are observed in OSA patients (12). A consequence of these reductions in restorative sleep is excessive daytime sleepiness (EDS), which, when present with OSA, defines the clinical entity OSA syndrome (OSAS). OSAS is estimated to occur in up to 5% of the adult population, with another 5% having undiagnosed OSAS (1).

Obesity is considered a leading risk factor for the development of OSA. Indeed, ~70% of OSA patients are obese, and OSA occurs in ~45% of obese individuals (2). Rising rates of overweight and obesity suggest that OSAS prevalence will also be on the rise in the near future. An improved understanding of how OSA and its treatment affect energy balance is therefore important from a global public health perspective.

Obesity is mainly the result of an imbalance between energy intake (EI) and energy expenditure (EE), wherein EI is increased relative to EE, or EE is reduced relative to EI. Interestingly, not only is obesity a risk factor for OSA development, but OSA itself seems to play a role in further weight gain (4). It has been reported that newly diagnosed OSA patients have a history of

significant weight gain over the year prior to diagnosis (5), and the presence of OSA attenuates the effects of a weight loss intervention otherwise effective in non-OSA obese controls (13). Reasons for this are still uncertain, but OSA may predispose to positive energy balance. In terms of EE, EDS in OSAS is associated with reduced daytime physical activity (PA) (14). Conversely, increased 24-h EE has been reported in patients vs. controls (15). While it may seem that the increase in daily EE would prevent the development of a positive energy balance in OSA, it was proposed that the metabolic costs of sleep disruption are likely to trigger a set of compensatory neuroendocrine adaptations aimed at increasing hunger, reducing satiety, and stimulating food intake (16). In this way, it is possible that increased EE is overcompensated for by increased food intake. Indeed, evidence suggests a dysregulation of appetite-regulating hormones in OSA. Abnormally high levels of leptin (satiety signal) have been documented in OSA, suggesting a leptin resistance to levels beyond what is already seen in obesity (17). The appetite-stimulatory hormone ghrelin is also observed to be higher in OSA patients compared to non-OSA obese controls (17), suggesting that high EI may be present in OSA patients. EI has not been systematically studied in OSAS, but severity of sleep-disordered breathing was associated with increased preference for calorie-rich foods high in fat and carbohydrate in children (18).

The gold standard in OSA treatment is continuous positive airway pressure (CPAP). CPAP applies mild pressure through a nose mask to prevent occlusion of the upper airway during sleep (19). Clinical studies in OSA have demonstrated improvements in a variety of outcomes in response to CPAP. By eliminating recurrent episodes of nocturnal hypoxia, CPAP reduces sleep fragmentation and arousals (12) and increases the expression of SWS and REM sleep (15, 20). Daytime hypersomnolence is also alleviated by CPAP (21). An effect on some energy balance-related parameters has also been demonstrated, as CPAP was shown to reduce sleeping EE (15), and to normalize leptin and ghrelin to levels seen in obese non-OSA controls (17). This suggests that treating OSAS with CPAP may lead to improvements in appetite and food intake. Whether long-term CPAP treatment results in weight loss in obese OSA patients is still unclear, as weight loss has been shown to occur in some (22-24), but not other CPAP intervention studies (25-27).

Ramifications of proposed study for public health: Results of the proposed study will determine how CPAP treatment in obese OSAS patients affects energy expenditure and intake, as well as body composition and cardiovascular health. This information is significant because it will clarify the factors which contribute to the increased propensity for weight gain and cardiovascular disease in these patients, as well as determining which aspects of energy balance regulation are improved by CPAP treatment. CPAP is considered the first-line treatment for OSAS, and weight loss has also been promoted as the best nonmedical method for reducing the symptoms and overall prevalence of this disorder (1). Understanding how the components of energy balance and cardiovascular risk are affected by CPAP will allow practitioners and clinicians to more efficiently guide overall treatment approaches to optimize weight loss and symptom amelioration in these patients. This could include efforts to promote weight loss and improve respiratory function, sleep quality, and daytime functioning in this population by promoting CPAP in conjunction with other weight loss approaches to encourage optimal outcomes.

Research Design:

Study participants: Men and women, age 18-65 y, will be included in the study. Participants will be overweight, with a BMI ≥ 25 kg/m2. However, in order to exclude patients who are at the highest risk patients with an AHI > 50 will be excluded from participation (45). Patients will not currently, or have previously been treated with CPAP. Once a diagnosis of OSAS is made and a CPAP prescription is given, but before the start of CPAP treatment, we will meet with potential participants to inform them of the study details. Those interested will begin the screening phase, followed by enrollment if they are eligible and interested in participation. A second group of participants who are diagnosed with OSA but do not choose to undergo CPAP will be studied, as a control group.

Participants will be excluded if they are currently taking any anti-psychotic medications, or hypnotics and other drugs to treat insomnia. Individuals with uncontrolled severe (stage 2) hypertension (blood pressure > 160/100 mmHg) or anemia will be excluded. Participants with uncontrolled severe hypertension will be considered as individuals with known severe hypertension who are not actively receiving medical or drug treatment to manage this disorder. Anemia will be defined from medical history. Habitual drivers, commercial drivers and individuals with any recent near-miss or prior car crashes due to excessive daytime sleepiness (i.e. high-risk drivers) will be excluded. Premenopausal women will be studied in the laboratory during the follicular phase of their menstrual cycle, to exclude the possible confounding effects of sex hormones on outcome parameters like sleep, EE, hunger, and food intake. Participants will be excluded if they have a history of coronary artery disease, transient ischemic attack, or stroke.

Study Design Overview: This study will investigate the effects of CPAP on EE and EI in obese patients with moderate-to-severe OSA and EDS. Following pre-experimental baseline measures, including a 1-d inpatient testing period at the CTSA at Columbia University Medical Center, participants will be instructed to use CPAP at home each night throughout the 2 mo treatment phases. After the 2 mo treatment phase, participants will undergo a repeat of baseline procedures including assessments and the 1-d inpatient testing period. Procedures for the non-CPAP control participants will be the same, with the exception that they will not be using CPAP during the 2-mo period.

Experimental Procedures: Anthropometric measures including height, weight, neck- and waist circumferences, and body composition via air displacement plethysmography will be taken at baseline before the start of CPAP treatment. A urine pregnancy test to confirm the absence of pregnancy will be administered to female participants before scanning. Height and weight will be used to calculate BMI. In addition, a baseline fasting blood sample of 12 ml will be obtained to assay for levels of appetite-regulating hormones (leptin, ghrelin, GLP-1), lipid profile, fasting glucose, and inflammatory markers (c-reactive protein [CRP], tumor necrosis factor-α [TNF- α], interleukin-6 [IL-6]). Blood pressure will also be measured at this time via sphygmomanometer. Questionnaires filled out during this baseline period will include the ESS, a questionnaire measuring daytime sleepiness (50), and the Functional Outcomes of Sleep Questionnaire (FOSQ), to assess quality of life in disorders of excessive sleepiness (51). The ESS is an

established metric that asks patients to rate their chances of dozing/falling asleep in 8 different situations. A score > 10 is indicative of pathological sleepiness, and the measure has frequently been used to characterize EDS in OSAS sufferers. The FOSQ is a 30-item questionnaire addressing the impact of sleepiness on multiple everyday activities (51). Ambulatory measures of PA, food intake, and sleep will be taken during a baseline 1-wk period before the start of the intervention. Free-living PA will be measured with a waist-mounted accelerometer (ActiLife 5, ActiGraph, Pensacola, FL) (52). A sleep-wake log will be filled out daily for 1 wk, for subjective estimates of sleep continuity measures, including total sleep time (TST), sleep efficiency (SE), and sleep onset latency (SOL). Patients will be asked to wear the accelerometer on their wrist at night, to provide objective measures of sleep quality and continuity (53), including TST, SE, and SOL. Food intake will be measured with a 3-d food log (54), filled out on 2 weekdays and 1 weekend day.

During the baseline assessment before treatment, patients will enter the laboratory at the CTSA at Columbia University for a 1-d period. Patients will arrive at ~0900 h and will remain in the laboratory for the following 24h. Patients will fill out questionnaires assessing their level of sleepiness during their wake episode throughout the laboratory day. A Likert scale will assess current energy level each hour spent awake (“How energetic do you feel right now?”; “How sluggish do you feel right now?”) and a Likert scale will assess current feelings of hunger (“How hungry do you feel right now?”), satiety (“How satisfied do you feel right now?”; “How full do you feel right now?”), and appetite/food preferences (“How much would you like to eat something sweet right now?”; (“How much would you like to eat something salty right now?”; (“How much would you like to eat something savory right now?”; How much would you like to eat fruits/vegetables right now?”).

Ad libitum EI will be measured during the laboratory day for each treatment phase. During the laboratory day, participants will self-select their food intake. Participants will have access to a specified food budget for the day (up to $55.50) to purchase foods and beverages of their choice. Participants will be escorted by study personnel to local markets where they will be able to purchase foods they want to eat during the day. Participants will also have the opportunity to purchase food from take-out restaurants throughout the day. The only restrictions that will be imposed are that nutrient information must be available for the items purchased and that beverages must be nonalcoholic. Participants will not be able to keep any food not consumed during the experimental day. Participants will not be allowed to take any purchased foods home with them. Energy and macronutrient intakes will be calculated using Diet Analysis Plus Software using the weight (pre – post intake) and nutritional information of the food consumed.

Patients will have a fixed sleep episode from 2300-0700 h during the in-laboratory testing day, which will be identical in both phases. At the baseline visit, no CPAP will be used during the sleep episode. At the 2-mo post-treatment follow-up, CPAP will be used. Overnight sleep will be recorded via PSG during the sleep episode in the laboratory using a portable sleep system. The recording montage will include electroencephalogram, electrooculogram, electromyogram, electrocardiogram, nasal and oral airflow via thermistor, and oxygen saturation via pulse oximetry, and 30-sec epochs of sleep will be scored for sleep staging (Stage 1, Stage 2, SWS,

REM sleep), wakefulness, arousals, and respiratory events according to standard criteria (67). Patients will be discharged after awakening from the laboratory sleep episode.

Upon completion of the baseline 1-d inpatient visit, patients will return home for the 2 mo treatment phase where they will be using CPAP each night. Patients will be instructed to begin to CPAP at home each night throughout the 2 mo treatment phases. Nightly duration of CPAP use will be objectively monitored with a memory chip, and compliance will be defined as the use of the CPAP machine for at least 4 h/night for ≥ 70% of the nights (i.e. 64 nights) (55). Participants will also complete a daily CPAP compliance form, in which they will document the duration of CPAP use for the prior night. We will also do random checks of compliance during the 2 mo period. Only compliant patients will undergo the in-lab testing at the end of the intervention period. During the final week of the intervention phase, free-living ambulatory measures of PA (waist-actigraphy), food intake (3-d food log), and subjective (sleep-wake log) and objective (wrist-actigraphy) sleep will be taken, as described above. In-lab testing will be done with the CPAP equipment. At the conclusion of the 2-mo treatment phase, all study procedures and measurements will be repeated. This will include questionnaires, fasting blood sample, anthropometry including BodPod, and the 1-d inpatient period. Procedures for the non-CPAP patients will be same during ambulatory and lab visits. The non-CPAP patients will not use any CPAP during the intervening 2-mo period.

Statistical Procedures:

Sample size estimates are for paired-samples, two-tailed level of significance at 0.05 and 80% power, and are based on prior studies showing a significant effect of CPAP vs. baseline on outcomes of interest. We hypothesize that reduced sleepiness in response to active CPAP treatment will result in increased free-living PA compared to sham. We expect to be able to detect an effect size of 1.195 for decreased Stanford Sleepiness Scores (37) with 8 patients. The main outcomes hunger and EI, have not previously been investigated in response to CPAP. However, we have previously demonstrated a relationship between REM sleep and SWS with hunger and food intake (7). We expect to be able to detect an effect size of 1.01 for REM sleep increases (43) and 1.64 for SWS increases (43) with 10 and 6 patients, respectively. We expect to be able to detect an effect size of 0.736 for decreased leptin with 17 patients (62). To have power to detect changes in leptin, we will recruit 25 patients, assuming a 30% drop-out rate.

Change-from-baseline will be calculated for single-measure parameters that are assessed at the pre-experimental baseline, and after the 2-mo experimental phase (including ESS, FOSQ, PA, blood samples, body composition, blood pressure). Paired-samples t-tests will be used to compare single-measure parameters that are assessed during laboratory phase 1 and laboratory phase 2. These will include polysomnographic sleep measures (sleep stages and indices of sleep-disordered breathing), and total energy and macronutrient intakes. Repeated or continuously measured parameters taken during laboratory phase 1 and laboratory phase 2 will be analyzed with two-way repeated measures ANOVA (factors: condition x time). These will include hourly measures of sleepiness (SSS), and appetite-satiety ratings. Non-parametric equivalent tests will be used if data are deemed to be not normally distributed. Significance will be set at $p<0.05$.

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