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# A pilot study investigating the effects of continuous positive airway pressure treatment and weight-loss surgery on autonomic activity in obese obstructive sleep apnea patients☆,☆☆

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**Abstract**

**Background:** We have previously demonstrated that severity of obstructive sleep apnea (OSA) as measured by the apnea–hypopnea index (AHI) is a significant independent predictor of readily-computed time-domain metrics of short-term heart rate variability (HRV).

**Methods:** We aimed to assess time-domain HRV measured over 5-min while awake in a trial of obese subjects undergoing one of two OSA therapies: weight-loss surgery ($n$ = 12, 2 males, median and interquartile range (IQR) for BMI 43.7 [42.0, 51.4] kg/m$^2$, and AHI 18.1 [16.3, 67.5] events/h) or continuous positive airway pressure (CPAP) ($n$ = 15, 11 males, median BMI 33.8 [31.3, 37.9] kg/m$^2$, and AHI 36.5 [24.7, 77.3] events/h). Polysomnography was followed by electrocardiography during wakefulness; measurements were repeated at 6 and 12–18 months post-intervention.

**Results:** Despite similar measurements at baseline, subjects who underwent surgery exhibited greater improvement in short-term HRV than those who underwent CPAP ($p$ = 0.04).

**Conclusions:** Our data suggest a possible divergence in autonomic function between the effects of weight loss resulting from bariatric surgery, and the amelioration of obstructive respiratory events resulting from CPAP treatment. Randomized studies are necessary before clinical recommendations can be made.

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*Keywords:* Obstructive sleep apnea; Heart rate variability; Weight-loss surgery; Continuous positive airway pressure

## Introduction

Obstructive sleep apnea (OSA) remains both an under-recognized and under-treated disease despite extensive research supporting its deleterious effects and the benefits of therapeutic intervention. OSA has been linked to hypertension, glucose intolerance, and cardiovascular disease [1–3]. Several mechanisms have been proposed to explain the increased risk of cardiovascular disease with OSA, including increased sympathetic drive and therefore impaired autonomic regulation. Altered autonomic function, as measured by changes in heart rate variability (HRV), has been demonstrated in subjects with heart failure and myocardial injury [4]. Decreased variability has been associated with mortality following myocardial infarction [5] and with the development of coronary heart disease in patients with diabetes [6].

Studies in the OSA population utilizing 24-h monitoring [7] and brief clinical measurements [8] have also demonstrated reduced HRV in subjects with moderate/severe disease compared to matched controls, pointing to the potential utility of HRV as a simple, non-invasive method of detecting autonomic dysfunction in OSA subjects without overt cardiovascular disease. Although the mechanisms by

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which OSA leads to altered HRV are not entirely understood, there is evidence that repeated hypoxemia and hypercapnia during obstructive events influence chemoreflexes leading to increased sympathetic drive, particularly at the termination of respiratory events, with a carryover effect during the day [8–10]. Similarly, repeated nocturnal surges in blood pressure may impair baroreflex sensitivity thereby impacting HRV [8].

We have previously demonstrated that time-domain markers of HRV calculated from a five-minute recording during wakefulness are significantly decreased in obese subjects with mild, predominantly asymptomatic OSA, compared with obese but otherwise healthy controls [11]. Specifically, we highlighted the applicability of readily-computed pNN*x* HRV metrics based on interbeat interval variability: pNN10, pNN20 and pNN50 (the % of successive normal beats differing by at least $x$ = 10, 20 and 50 ms, respectively). In separate linear models, we found that the apnea–hypopnea index (AHI), a measure of OSA severity, is a significant predictor of each of these HRV metrics after controlling for age, gender, blood pressure, fasting cholesterol, and glycated hemoglobin [11]. Because this cohort of subjects was rigorously screened for any cardiovascular co-morbidities, we believe this association reflects a deleterious effect of OSA on autonomic regulation even during wakefulness.

To our knowledge, these short-term measurements of time-domain HRV metrics have not been incorporated into an interventional study of OSA. We therefore aimed in the present prospective longitudinal study, to assess the effect of two OSA therapies: bariatric surgery and continuous positive airway pressure (CPAP) on various pNN*x* metrics assessed at three time-points: baseline prior to treatment, 6 months, and 12–18 months after initiation of treatment. At each time-point, measurements were performed under three positional/breathing conditions: supine/normal breathing, supine/paced breathing at 12 breaths/min to assess parasympathetic activity, or standing/normal breathing to provide a baroreflex challenge. We hypothesized significant increases in pNN10, pNN20 and pNN50 within both groups under all positional/breathing conditions, reflecting a reversible effect of OSA on autonomic function. Such data addressing the responsiveness of these HRV metrics as surrogate measures of autonomic control to OSA therapy would be critical to the design of subsequent randomized comparative effectiveness trials.

## Materials and methods

### *Subjects*

Non-smoking, obese subjects (body mass index $\geq$ 30 kg/m$^2$) aged 18–70 years with OSA (AHI > 5 events/h) who were scheduled for either CPAP treatment or bariatric surgery were recruited. Exclusion criteria included the presence of any cardiopulmonary, endocrine, or sleep disorders other than OSA, or consumption of any medications that could affect either cardiopulmonary function or sleep, including antihypertensives. Some of our subjects had participated in prior studies [11], although none of the results in the present manuscript has been previously published. The study was approved by the Partners' Institutional Review Board and all subjects gave written informed consent. Data collection began in 2005, pre-dating the requirement for listing on clinicaltrials.gov.

### *Protocol*

Subjects underwent attended overnight polysomnography (PSG), followed by a single-lead electrocardiogram (ECG) recorded between 8:00 and 9:00 AM in the fasting state (described below). We used a pragmatic design whereby participants who chose to have CPAP treatment were referred to a local clinical sleep laboratory; alternatively, bariatric surgery (either gastric banding or gastric bypass) took place at Brigham & Women's Hospital. By design, both treatment options were undertaken and managed in a clinical rather than a research setting. As such, the type of CPAP device and mask varied across subjects, but a fixed therapeutic pressure was always applied (that is, no auto-adjusting or flexible pressure delivery was used). Subjects returned for follow-up at 6 months and 12–18 months post-intervention, consisting of a repeat PSG and ECG. Subjects in the CPAP group used CPAP during both follow-up PSGs; subjects in the surgery group did not use CPAP at any time during the study.

### *Baseline & follow-up polysomnographic studies*

PSG consisted of electroencephalogram (C4-A1, C3-A2, O2-A1, O1-A2), bilateral electro-oculogram, bilateral chin and tibialis electromyogram, surface electrocardiogram, airflow using thermistor and nasal pressure sensors, abdominal and thoracic respiratory excursion measured by piezo bands, pulse oximetry, and body position. PSGs were scored by experienced sleep technicians according to the Chicago scoring criteria [12]. An apnea was scored as an absence of airflow for at least 10 s, while a hypopnea was scored as a reduction in airflow of at least 50% for at least 10 s, or a discernible reduction in airflow for at least 10 s associated with an arousal or a 3% oxygen desaturation event. Follow-up PSGs were conducted and scored in an identical manner, except that nasal pressure was measured at the CPAP mask using a pneumotachometer where applicable.

### *Electrocardiography & HRV analysis*

ECG was recorded at 1000 Hz in three states for 7- to 17-min each: (1) supine while breathing normally, (2) supine with breathing paced by an audio signal at 12 breaths per minute, and (3) standing while breathing normally [13–15]. ECG data were recorded using Spike2 software (1401plus, Cambridge Electronic Design, Cambridge UK). The ECG signal was first filtered using a bandpass finite impulse response filter with cutoffs at 2 and 30 Hz. A peak detection algorithm was used to identify QRS complexes and the resulting RR intervals were calculated [16,17]. Irregular and ectopic beats were identified (any beat which differed by more than 20% from the previous interval) and were removed, following visual inspection. From the resulting time series of normal-to-normal intervals (NN), the first two

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