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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

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respiratory events resulting from CPAP treatment. Randomized studies are necessary before clinical recommendations can be made.

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 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 ≥ 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 minutes were discarded and the following five minutes selected for analysis. We assumed a heart rate in the range of 40–120 beats/min, so any traces with < 200 or > 600 RR intervals were assumed to have excessive artifact and were not analyzed. Finally, pNN10, pNN20 and pNN50 were calculated for data analysis within each positional/breathing condition (supine/normal breathing, supine/paced breathing, or standing/normal breathing). The pNN*x* metrics were computed by dividing NN*x* (for example, NN50 is the number of successive NN pairs that differ by more than 50 ms) by the total number of NN pairs. Previous research has demonstrated high reproducibility of pNN50 over one week in healthy volunteers (R^2 = 0.98); [18] however, reproducibility measured over three weeks was low in a sample of heart failure patients [19]. In a study of type 1 diabetics, the correlation co-efficient of pNN50 measurements compared to baseline declined from 0.98 at 3 months, to 0.81 at 12 months [20].

Statistical analysis

All statistical tests were performed using SPSS (Version 20, IBM, NY USA). Between-group comparisons at a single time-point (Table 1) were made using Mann–Whitney tests or Chi-Square tests. Within-group comparisons over multiple time-points (Table 2) were made using Friedman's ANOVA on ranks, followed by Wilcoxon Matched-Pairs tests with a Bonferroni correction when the global test was statistically significant at $p \leq 0.05$. Analyses of treatment group (between-subjects, CPAP or surgery), time (within-subjects, three time-points), and positional/breathing condition (within-subjects, three conditions) were made using mixed-design ANOVA, followed by simple pairwise contrasts for time and positional/breathing condition. For the time contrast, baseline was selected as the reference category; for the positional/breathing condition contrast, supine/normal breathing was selected as the reference category. Standardized residuals were assessed, in order to ensure that the assumptions for mixed-design ANOVA were met. All *p*-values are 2-sided, and considered significant at $p \leq 0.05$.

Results

Description of subjects

The CPAP group consisted of $n = 15$ subjects receiving a median therapeutic CPAP level of 11 cmH_2O (lower quartile 8.0, upper quartile 12.0), while the bariatric surgery group consisted of $n = 12$ subjects (see Table 1 for descriptive characteristics). The surgical group had a significantly greater BMI and a greater proportion of women, reflective of clinical practice. OSA severity was not significantly different between the two groups at baseline.

Missing data

Objective CPAP adherence data were available for seven of the 15 subjects (median 7.1 h/night, interquartile range [6.5, 7.6]). Comparing subjects for whom CPAP adherence data were available vs. absent, there were no significant differences in baseline BMI, neck circumference, AHI, oxygen saturation (SpO_2) nadir, % of total sleep time with $SpO_2 < 90\%$, or arousal index and no significant difference in residual AHI at either follow-up (all $p > 0.05$).

Excessive artifact in the ECG recording resulted in missing HRV estimates for $n = 1$ at baseline (CPAP group), $n = 1$ at 6 month follow-up (surgery group), and $n = 1$ at 12–18 month follow-up (CPAP group). One subject (surgery group) did not attend the 12–18 month follow-up.

Effects of CPAP and surgery on body habitus & sleep-disordered breathing

Table 2 summarizes the effects of CPAP and surgery on measurements of body habitus and sleep-disordered breathing. Only surgery was associated with a significant reduction in obesity as measured by the BMI and neck circumference, whereas both treatments significantly improved the AHI and arousal index.

Evaluation of pNNx measurements within the CPAP and surgery groups (time effect)

Table 3 summarizes all pNN10, pNN20 and pNN50 measurements. We hypothesized significant increases in pNN10, pNN20 and pNN50 within both groups under all positional/breathing conditions, which using a mixed ANOVA analysis would be reflected in a significant main effect of time while holding both treatment group and positional/breathing condition constant. The main effect of time approached statistical significance for pNN10 ($p = 0.09$), and reached statistical significance for pNN20 and pNN50 (both $p \leq 0.01$). In pairwise comparisons, there was a statistically significant increase in pNN10 between baseline and 6 months ($p = 0.03$); for pNN20 and pNN50, there were statistically significant increases between both baseline and 6 months (both $p \leq 0.01$) and baseline and 12–18 months (both $p \leq 0.01$).

Evaluation of pNNx measurements between the CPAP and surgery groups (treatment effect)

Testing the main effect of treatment revealed no statistically significant differences between the CPAP and surgery groups for pNN10 ($p = 0.42$), pNN20 ($p = 0.23$), or pNN50 ($p = 0.23$) while holding both time and positional/breathing condition constant. There was, however, a

significant time-by-treatment interaction in pNN50 (p =0.04); see Fig. 1. In subsequent pairwise comparisons, the increase in pNN50 between baseline and 6 months was significantly greater in the surgery group compared with the CPAP group (p = 0.02); the difference between groups in terms of the increase in pNN50 between baseline and 12–18 months did not reach statistical significance (p = 0.06).

Although not planned *a priori*, we also ran a multiple linear regression model to investigate whether the difference in pNN50 at six months could be due to the marked change in NN interval seen in the surgery group which was not evident in the CPAP group. Intervention was a significant independent predictor of supine pNN50 (beta coefficient 0.13, standard error 0.06, *standardized beta coefficient 0.35;* p = 0.04) after controlling for supine NN interval, which was also statistically significant (beta coefficient 0.83, standard error 0.26, *standardized beta coefficient 0.50;* $p < 0.01$). We also found moderate/strong correlations between supine/normal breathing NN interval and pNN50 at all time points in the CPAP group (Spearman coefficients 0.64 (p = 0.01), 0.66 (p = 0.01), 0.35 (p = 0.22) at baseline, 6 months, and 12–18 months respectively). Similar correlations were found in the surgery group (Spearman coefficients 0.57 (p = 0.06), 0.61 (p = 0.05), 0.65 (p = 0.03) at baseline, 6 months, and 12–18 months respectively).

The time-by-treatment interaction approached significance for pNN20 (p = 0.07; see Fig. 2) but was not significant for pNN10 (p = 0.96; see Fig. 3). Representative tracings from one subject in each group are presented in Fig. 4, including baseline and 6-month pNN50 data recorded in the supine/normal breathing condition (selected due to the statistically significant difference evident in this metric at this time point).

Evaluation of pNNx measurements between the three positional/breathing conditions

The main effect of positional/breathing condition while holding both time and treatment constant was significant for pNN10, pNN20 and pNN50 ($p \leq 0.01$). In pairwise comparisons, pNN10 was significantly lower when measured during the standing/normal breathing condition compared with the supine/normal breathing condition ($p \leq 0.01$), with no significant difference between the supine/normal breathing and supine/paced breathing conditions (p = 0.70). These same trends were evident for pNN20 ($p \leq 0.01$ and p = 0.63 respectively) and pNN50 ($p \leq 0.01$ and p = 0.46 respectively).

Discussion

In this study, we measured different thresholds of pNN*x* HRV metrics (x = 10, 20 and 50 ms) measured over a 5-min period while awake, 6 months and 12–18 months following either CPAP treatment or weight-loss surgery under three positional/breathing conditions (supine/normal breathing, supine/paced breathing, and standing/normal breathing) in a sample of obese, normotensive subjects free from cardiovascular co-morbidities. Our primary hypothesis was that both CPAP and surgery would be associated with significant increases in pNN10, pNN20 and pNN50 under all positional/breathing conditions, reflecting a reversible effect of OSA on autonomic function. This hypothesis was supported for pNN20 and pNN50, with statistically significant increases in HRV evident at 6 months and 12–18 months; for pNN10, a statistically significant increase in HRV was evident only at 6

months although this could represent a lack of statistical power due to the pilot nature of our study.

Although this non-randomized study was not designed to make direct treatment comparisons, we also found a significant time-by-treatment interaction for pNN50; that is, despite similar HRV at baseline, the subjects who underwent surgery exhibited a greater improvement in pNN50 than those who underwent CPAP treatment ($p = 0.04$). A similar trend was evident for pNN20, which did not reach statistical significance ($p = 0.07$). It would appear that in our sample, improvements in pNN*x* HRV metrics were driven largely by weight loss rather than an improvement in sleep-disordered breathing. These data are in agreement with previous studies reporting a marked decrease in muscle sympathetic nerve activity [21] and a trend towards an increase in pNN50 [22] in OSA subjects following a hypocaloric diet resulting in substantial weight loss, coupled with a report that pNN50 remained unchanged after three months of CPAP without weight loss [23]. Possible mechanisms by which substantial weight loss might restore autonomic balance include, but are not limited to, changes in inflammatory cytokines, improved glycemic control, improved endothelial function, and/or increased exercise levels [24,25]. Obesity, however, does not independently explain the onset of autonomic dysfunction in OSA as several studies have shown impaired HRV in obese OSA subjects compared with BMI-matched controls [7,8].

A secondary rationale behind this study was to evaluate the applicability of the three pNN*x* metrics, which may indicate vagal dysfunction, by investigating which measurements were most responsive to clinically relevant treatments to help guide the design of future randomized comparative effectiveness studies. Of the thresholds we adopted ($x = 10$, 20 or 50), pNN50 has been the most widely used [26]; there is some evidence that using a lower threshold ($x < 50$ ms) may be more useful [27] although this notion has been debated [28]. Our data detected a greater difference between the CPAP and surgery groups when using pNN50, a difference which gradually diminished when analyzing pNN20 and then pNN10. Other groups have reported that thresholds between pNN5 and pNN28, rather than the standard pNN50, are optimal in order to show differences between various states (clozapine-treated subjects vs. controls [29], congestive heart failure vs. controls, wakefulness vs. sleep, old vs. young [27]), although pNN*x* thresholds < 8 ms are not advised unless the sampling rate is above the level typically used in Holter monitors (i.e. >128 Hz). To our knowledge, our study is the first to evaluate different pNN*x* thresholds in an interventional OSA study, and it would appear that with two reasonably effective treatment options, the more subtle differences in HRV reflecting very short-term control of sinus rhythm measurable by pNN10 and pNN20 are not beneficial above and beyond the standard pNN50. Some had speculated that with improvements in technology, the use of a 50 ms threshold is no longer required and that lower thresholds would improve sensitivity; however, our new data suggest no major advantage to altering the threshold.

Our three positional/breathing measurement conditions were selected based on the work of Wiklund et al. [14], who analyzed frequency-domain HRV during supine/normal breathing, supine/paced breathing at 12 breaths/min, and immediately following a passive head-up tilt to 70°. The paced breathing condition stimulates parasympathetic activity while also controlling for respiratory rate which has been shown to affect HRV [15]. The standing/tilt

condition provides a baroreflex challenge, as an intact reflex is required in order to induce immediate vasoconstriction and stabilize blood pressure. Wiklund et al. found reduced high-frequency HRV in OSA subjects compared to controls under all three conditions, indicating parasympathetic dysfunction. Similarly, Hilton et al. found reduced high-frequency HRV in OSA subjects compared with controls while supine and immediately following standing [13].

Several studies have shown that both respiratory rate and tidal volume can have an effect on HRV [15]. If HRV is thought to reflect the autonomic influence on sinus rhythm then eliminating additional influences on HRV would seem prudent; however, there does not appear to be consensus in the literature as to whether standardization of respiratory rate and/or tidal volume is required [15,26]. Indeed, a 2007 study reported that although respiratory rate had a marked effect on blood pressure variability and most commonly-reported indices of HRV including pNN50, standardizing respiratory rate across subjects at 6 breaths/min did not lead to consistent improvements in reproducibility [30]. There were no significant differences in pNN10, pNN20 or pNN50 when measured while supine/normal breathing compared with supine/paced breathing. Further, for all three positional/breathing conditions, the magnitude of improvement over time was similar. In future studies, we would therefore favor the supine/normal breathing condition to enable straightforward comparisons of routinely-collected clinical data; however, we acknowledge that without standardizing to respiratory rate and/or tidal volume, the supine/normal breathing condition does not isolate changes in vagal activity.

Our study has several limitations. A post-hoc regression analysis indicated that intervention was significantly associated with supine pNN50 at 6 months after controlling for NN interval, which increased markedly in the surgery group but not in the CPAP group; however, pNN*x* measurements are largely dependent on heart rate and we acknowledge that our small dataset is not ideal for investigating the meaning of pNN*x* changes independent of changes in heart rate. The pragmatic approach whereby patients were assigned clinically to treatment probably introduced bias, and meant that the two groups differed in several aspects, most notably gender and BMI, which we were unable to control for statistically due to the small sample size. In these respects, the two groups resembled the populations typically seen in CPAP and bariatric surgery clinics, the latter of which tends to contain a higher proportion of females and a greater degree of obesity. Our careful screening to exclude cardiopulmonary/endocrine co-morbidities, including the exclusion of those taking antihypertensives, was designed to find patients with straightforward, uncomplicated OSA; however, this approach resulted in a normotensive sample with is not necessarily generalizable. We did not measure tidal volume, and during both normal breathing conditions (supine and standing) we did not measure respiratory rate as making these measurements can affect breathing itself; therefore, we cannot comment on how these parameters varied between subjects. Obesity can cause a decrease in tidal volume [31], and therefore it is unclear as to what extent the increase in HRV in the surgery group was due to the reduction in AHI rather than an increase in tidal volume. Our choice to study subjects undergoing CPAP through a clinical rather than a research laboratory led to missing CPAP adherence data. As such, we were unable to investigate whether the inferior effect of CPAP

on HRV compared with surgery was due to sub-optimal usage or whether this finding represents a true effect of the magnitude of weight loss on autonomic function. We chose to standardize the time of day that our ECG recordings were made; however, future studies should focus on defining the time-of-day effect which is of particular importance in the setting of a sleep disorder. The day-to-day reproducibility of pNNx measurements in OSA subjects should also be a focus of future research.

Despite these limitations, our study provides insight as to whether changes in pNN10, pNN20 and pNN50 in response to CPAP and weight-loss surgery in obese subjects, which will be important when designing future randomized comparative effectiveness trials. Our data also suggest a possible divergence between the effects of weight loss resulting from bariatric surgery, and the amelioration of obstructive respiratory events resulting from CPAP treatment. More definitive, randomized studies are necessary before clinical management recommendations can be made. Future research is required to determine whether reduced HRV in subjects free from cardiovascular co-morbidities is indicative of future cardiovascular events, and whether this effect may be ameliorated by either weight loss and/or CPAP.

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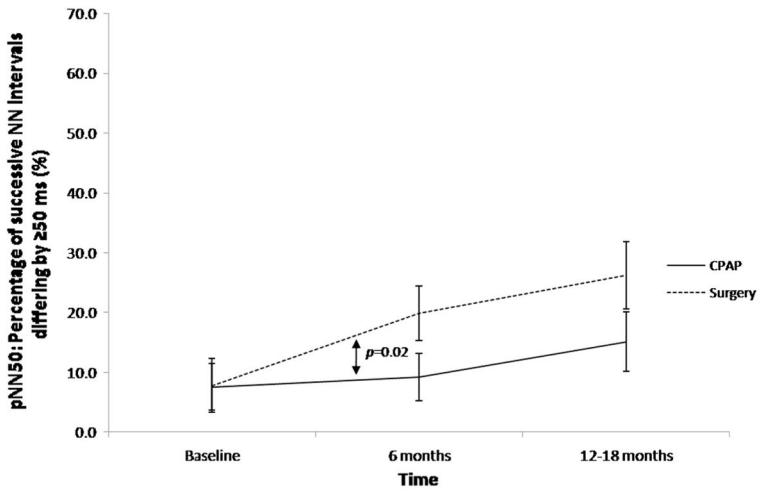

Fig. 1.

Time-by-treatment interaction graph for pNN50. Data are presented as mean and standard error. There was a significant main effect of time ($p \leq 0.01$), but no significant main effect of treatment ($p = 0.23$). There was a significant time-by-treatment interaction, with the increase in pNN50 between baseline and 6 months being greater in the surgery group compared with the CPAP group ($p = 0.02$).

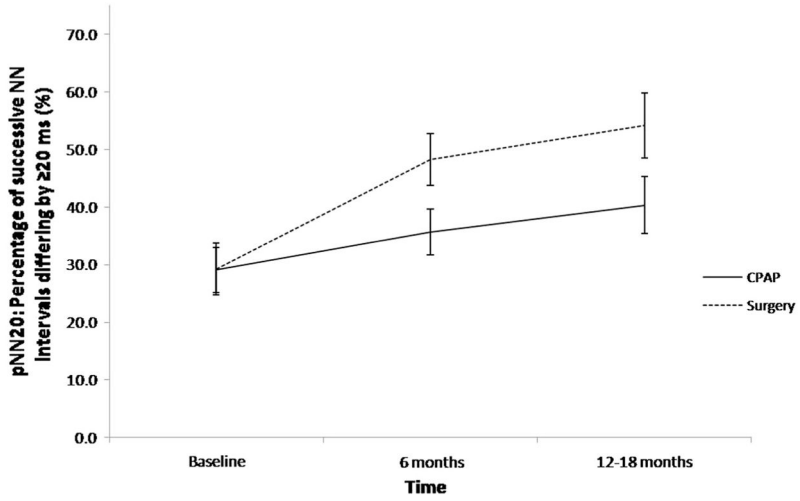

Fig. 2.

Time-by-treatment interaction graphs for pNN20. Data are presented as mean and standard error. There was a significant main effect of time ($p \leq 0.01$), but no significant main effect of treatment ($p = 0.23$). The time-by-treatment interaction approached but did not reach statistical significance ($p = 0.07$).

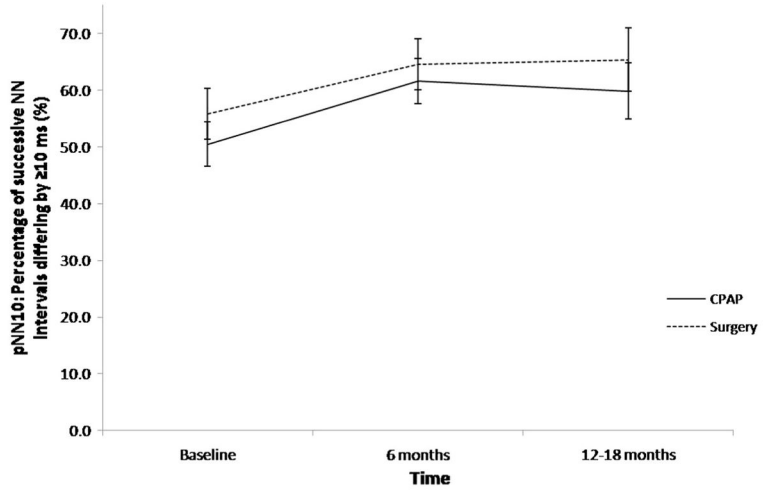

Fig. 3.

Time-by-treatment interaction graphs for pNN10. Data are presented as mean and standard error. The main effect of time approached but did not reach statistical significance (p = 0.09), and there was no significant main effect of treatment (p = 0.42). There was no significant time-by-treatment interaction (p = 0.96).

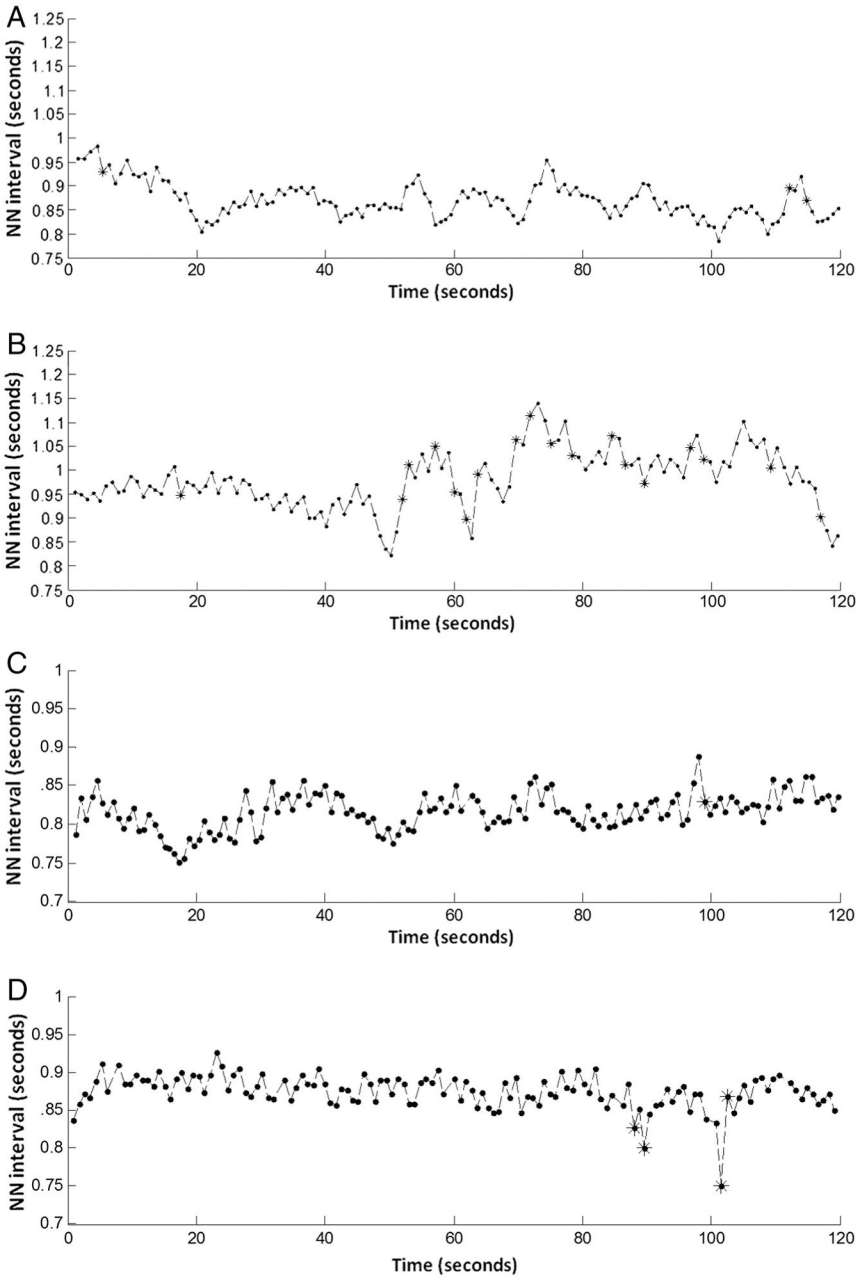

Fig. 4.

Representative tracings of NN intervals highlighting pNN50 at baseline and 6 months in individuals undergoing bariatric surgery and CPAP therapy. NN-intervals recorded in the supine/normal breathing condition are shown (A) pre-surgery, (B) 6 months post-surgery, (C) pre-CPAP, and (D) 6 months post-CPAP. NN intervals differing by more than 50 ms from the previous NN interval (used to calculate pNN50) are highlighted as *. In the surgery patient, pNN50 in this trace was 2.2% at baseline and 14.9% at 6 months; in the CPAP patient, pNN50 in this trace was 0.7% at baseline and 3.1% at 6 months.

Table 1

Subject characteristics at baseline.

	CPAP group (*n* = 15)	Surgery group (*n* = 12)	*p*-value (between groups)
Descriptive data			
Males (number, %)	11 (73%)	2 (17%)	<**0.01**
Age (years)	48 (37, 52)	43 (37, 49)	0.72
BMI (kg/m^2)	33.8 (31.3, 37.9)	43.7 (42.0, 51.4)	<**0.01**
Neck circumference (cm)	44.0 (41.9, 46.0)	41.1 (39.6, 47.9)	0.38
Brachial systolic BP (mmHg)	118 (110, 132)	123 (116, 137)	0.17
Brachial diastolic BP (mmHg)	72 (67, 85)	75 (71, 81)	0.91
Sleep data			
AHI during diagnostic PSG (/h)	36.5 (24.7, 77.3)	18.1 (16.3, 67.5)	0.17
SpO_2 nadir during diagnostic PSG (%)	73.0 (53.0, 81.0)	78.0 (72.8, 82.8)	0.13
% of total sleep time with SpO_2 < 90 (%)	24.4 (6.6, 51.3)	10.6 (6.1, 24.6)	0.24
Arousal index (/h)	37.2 (19.4, 72.6)	36.5 (27.2, 54.5)	0.98
Laboratory values			
Total cholesterol (mg/dL)	164 (149, 202)	181 (167, 230)	0.08
Low-density lipoprotein (mg/dL)	103 (86, 128)	116 (105, 148)	0.15
High-density lipoprotein (mg/dL)	44 (36, 50)	43 (34, 55)	0.94
Fasting glucose (mg/dL)	93.0 (82.0, 103.0)	95.5 (88.3, 99.0)	0.91
Glycated hemoglobin (%)	5.7 (5.4, 6.3)	5.7 (5.4, 6.0)	0.58
First follow-up time-point (days)	161 (141, 217)	204 (174, 245)	**0.05**
Second follow-up time-point (days)	443 (405, 580)	389 (353, 496)	0.09

Data are presented as median (25th percentile, 75th percentile). AHI = apnea–hypopnea index; BMI = body mass index; BP = blood pressure; CPAP = continuous positive airway pressure; PSG = polysomnography; SpO_2 = oxygen saturation. Bold indicates $p \leq 0.05$.

Table 2

Changes in body habitus, sleep-disordered breathing, and blood pressure with CPAP and bariatric surgery.

	CPAP group			Surgery group		
	Baseline	**6 months**	**12–18 months**	**Baseline**	**6 months**	**12–18 months**
BMI (kg/m^2)	33.8 (31.3, 37.9)	34.1 (31.7, 39.1)	34.2 (30.4, 39.0)	43.7 (42.0, 51.4)	32.7 (30.1, 38.7)*	28.3 (25.3, 37.5)*
Neck circumference (cm)	44.0 (41.9, 46.0)	43.1 (41.5, 45.0)	43.1 (41.0, 46.0)	41.1 (39.6, 47.9)	37.8 (35.1, 41.1)*	35.5 (32.1, 37.5)*
AHI during diagnostic PSG (/h)	36.5 (24.7, 77.3)	5.3 (1.6, 10.9)*	3.8 (1.2, 10.6)*	18.1 (16.3, 67.5)	10.5 (5.0, 20.8)*	6.5 (1.9, 12.8)*
SpO_2 nadir during diagnostic PSG (%)	73.0 (53.0, 81.0)	84.0 (81.0, 89.0)*	79.0 (73.0, 88.0)	78.0 (72.8, 82.8)	79.0 (74.0, 88.0)*	84.0 (79.0, 91.0)*
% of total sleep time with $SpO_2 < 90$ (%)	24.4 (6.6, 51.3)	7.9 (3.0, 16.8)	5.2 (0.5, 21.0)	10.6 (6.1, 24.6)	19.3 (3.8, 46.5)	8.7 (1.8, 17.8)
Arousal index (/h)	37.2 (19.4, 72.6)	16.2 (11.1, 28.6)*	13.2 (6.7, 21.5)*	36.5 (27.2, 54.5)	29.5 (18.6, 35.7)*	22.4 (15.5, 35.5)*
Brachial systolic BP (mmHg)	118 (110, 132)	122 (114, 128)	120 (118, 132)	123 (116, 137)	117 (109, 131)	115 (100, 133)
Brachial diastolic BP (mmHg)	72 (67, 85)	75 (65, 80)	80 (76, 84)	75 (71, 81)	71 (67, 78)	66 (64, 78)

Data are presented as median (25th percentile, 75th percentile). AHI = apnea–hypopnea index; BMI = body mass index; CPAP = continuous positive airway pressure; PSG = polysomnography; SpO_2 = oxygen saturation.

*Significant difference compared with baseline ($p \leq 0.05$, corrected for multiple comparisons).

Table 3

pNN*x* measurements at three time points with CPAP and bariatric surgery under three positional/breathing conditions.

			NN interval (ms)		pNN10 (%)		pNN20 (%)		pNN50 (%)	
Group	**Time**	**Positional/Breathing Condition**	**Mean ± SD**	**Median (25th %, 75th %)**	**Mean ± SD**	**Median (25th %, 75th %)**	**Mean ± SD**	**Median (25th %, 75th %)**	**Mean ± SD**	**Median (25th %, 75th %)**
CPAP	Baseline	Supine/Normal Breathing	925.4 ± 157.3	905.0 (816.0, 1015.5)	57.8 ± 20.8	61.2 (52.9, 71.7)	35.9 ± 17.6	29.7 (26.4, 47.1)	9.2 ± 13.0	4.7 (1.6, 12.0)
		Supine/Breathing at 12 breaths/min	927.2 ± 160.2	853.0 (814.0, 1026.5)	59.2 ± 21.2	62.7 (54.6, 68.9)	37.4 ± 18.7	36.1 (24.8, 48.0)	9.0 ± 13.3	3.5 (1.7, 12.3)
		Standing/Normal breathing	742.6 ± 142.6	696.0 (669.5, 775.5)	34.4 ± 21.7	35.2 (25.3, 43.2)	13.9 ± 20.5	9.2 (5.6, 12.1)	4.4 ± 13.7	0.6 (<0.01, 1.5)
	6 months	Supine/Normal Breathing	944.7 ± 129.0	877.0 (856.5, 1061.0)	66.6 ± 15.1	68.8 (61.1, 74.8)	41.6 ± 21.7	43.2 (20.6, 54.9)	11.1 ± 13.7	8.2 (2.7, 12.5)
		Supine/Breathing at 12 breaths/min	942.9 ± 117.1	887.0 (851.5, 1052.0)	66.9 ± 16.4	68.5 (57.2, 78.8)	42.1 ± 20.6	46.5 (26.2, 56.9)	11.0 ± 11.4	7.9 (2.9, 15.6)
		Standing/Normal breathing	791.8 ± 125.3	780.0 (703.0, 859.0)	51.4 ± 19.8	49.8 (36.4, 65.2)	23.3 ± 21.3	15.7 (9.1, 30.9)	5.4 ± 10.7	1.7 (0.7, 3.2)
	12–18 months	Supine/Normal Breathing	977.6 ± 127.2	943.0 (876.0, 1063.0)	65.1 ± 22.1	66.3 (61.1, 80.3)	46.8 ± 20.8	42.0 (32.7, 61.7)	15.9 ± 17.5	10.0 (3.7, 22.0)
		Supine/Breathing at 12 breaths/min	997.2 ± 111.2	987.0 (894.0, 1055.0)	66.1 ± 23.0	70.5 (54.1, 83.7)	47.7 ± 24.5	47.0 (22.2, 71.2)	20.1 ± 20.6	12.9 (3.7, 39.1)
		Standing/Normal breathing	811.8 ± 128.0	767.0 (734.0, 855.0)	48.3 ± 23.7	48.3 (40.4, 59.1)	26.6 ± 23.2	17.8 (11.9, 33.1)	9.3 ± 15.5	2.2 (1.5, 13.2)
Surgery	Baseline	Supine/Normal Breathing	866.5 ± 67.1	841.0 (830.5, 881.3)	66.0 ± 17.6	67.4 (55.1, 79.5)	37.4 ± 23.6	31.5 (22.6, 56.2)	11.0 ± 20.6	2.3 (0.8, 15.5)
		Supine/Breathing at 12 breaths/min	868.6 ± 57.5	867.0 (825.8, 903.0)	62.6 ± 19.0	62.8 (48.5, 76.7)	33.3 ± 26.0	27.2 (14.0, 47.1)	10.2 ± 23.0	1.6 (0.9, 6.0)
		Standing/Normal breathing	743.4 ± 80.5	727.5 (658.3, 809.5)	38.9 ± 27.8	28.0 (18.5, 70.5)	17.1 ± 22.9	5.8 (1.4, 32.7)	2.3 ± 3.5	1.0 (<0.01, 3.5)
	6 months	Supine/Normal Breathing	1012.5 ± 112.1	1015.5 (891.8, 1072.5)	74.1 ± 25.5	82.8 (68.4, 89.2)	60.3 ± 19.8	64.1 (46.1, 74.9)	25.9 ± 22.7	18.4 (6.9, 52.0)
		Supine/Breathing at 12 breaths/min	1015.2 ± 129.4	1025.5 (887.8, 1086.3)	73.1 ± 26.4	80.9 (63.1, 89.5)	59.9 ± 23.1	61.7 (40.3, 81.0)	29.4 ± 25.2	24.3 (2.2, 55.2)
		Standing/Normal breathing	788.0 ± 112.4	764.5 (709.5, 894.0)	46.5 ± 24.5	47.2 (34.1, 67.1)	24.6 ± 22.3	17.4 (7.2, 40.8)	4.3 ± 8.8	1.3 (0.4, 3.6)
	12–18 months	Supine/Normal Breathing	1048.0 ± 146.6	1030.0 (958.2, 1150.0)	73.9 ± 25.7	82.2 (66.9, 89.8)	66.9 ± 17.3	70.0 (55.2, 79.5)	32.5 ± 23.8	26.9 (13.9, 49.1)
		Supine/Breathing at 12 breaths/min	1049.6 ± 166.3	1017.5 (985.8, 1155.0)	72.8 ± 25.6	77.2 (66.1, 91.5)	62.6 ± 21.1	56.7 (43.6, 83.8)	31.6 ± 29.6	16.0 (6.7, 58.9)
		Standing/Normal breathing	829.0 ± 181.2	859.5 (625.0, 988.8)	49.4 ± 28.0	53.0 (23.0, 65.6)	33.1 ± 25.8	30.1 (13.8, 54.6)	14.7 ± 16.5	5.3 (1.8, 30.1)

pNN*x* = % of successive NN intervals differing by ≥ *x* ms (*x* = 10, 20 or 50); SD = standard deviation.