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Effect of Mild Hyperglycemia on Autonomic Function in Obstructive Sleep Apnea

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Abstract

Obstructive sleep apnea (OSA) has been hypothesized to cause a hypersympathetic state, which may be the mechanism for the increased incidence of cardiovascular disease in OSA. However, there is a high prevalence of hyperglycemia in OSA patients which may also contribute to autonomic dysfunction.

Thirty-five patients with OSA and eleven controls with average body-mass index (BMI) of 32.0 ± 4.6 underwent polysomnography, glucose tolerance testing, autonomic function tests, lying and standing catecholamines, overnight urine collection, and baseline ECG and continuous blood pressure measurements for spectral analysis. A linear regression model adjusting for age and BMI was used to analyze spectral data, other outcome measures were analyzed with Kruskal-Wallis test.

Twenty-three OSA patients and two control patients had hyperglycemia (based on 2001 American Diabetes Association criteria). AHI correlated with total power and low frequency (LF) power ($r=0.138$, 0.177 , $p=0.031$; and $r=0.013$) but not with the LF/high frequency (HF) ratio ($p=0.589$). Glucose negatively correlated with LF systolic power ($r=-0.171$, $p=0.038$) but not AHI ($p=0.586$) and was marginally associated with pnn50, total power, LF, and HF power (p ranged from 0.07 to 0.08).

These data suggest that patients with OSA and mild hyperglycemia have a trend towards lower heart rate variability and sympathetic tone. Hyperglycemia is an important confounder and should be evaluated in studies of OSA and autonomic function.

1. Introduction

Obstructive sleep apnea (OSA) is a common disorder affecting 2-4% of the United States population. OSA confers an increased risk in cardiovascular disease and stroke. One mechanism attributed to OSA is hyperactivity of the sympathetic nervous system secondary to chronic intermittent hypoxia occurring during sleep (1-3). Multiple studies have demonstrated evidence of hypersympathetic activity and altered autonomic function in patients with sleep apnea (4-6).

OSA is also highly linked with diabetes mellitus and increased insulin resistance, with a high prevalence of prediabetes and undiagnosed diabetes observed in our previously published cohort (7) as well as other cohorts (8-10). In addition, a high number of patients have hyperglycemia which is not detected by fasting glucose (7). There is significant evidence that even mild hyperglycemia alters autonomic function (11-13) and that hypersympathetic activity can be observed in early diabetes (14).

Previous studies of autonomic function in OSA have either not measured glucose (relying on patient self-report of diabetes), or have only used fasting glucose as a screen to rule out hyperglycemia in their cohort. We hypothesized that hyperglycemia may significantly affect measures of autonomic function such as heart rate variability, catecholamine levels, and other autonomic function tests independent of OSA status. We assessed glycemic status, autonomic function and peripheral nerve function in mildly obese patients with a new diagnosis of OSA and followed them after treatment with continuous positive airway pressure (CPAP) to determine if there were any changes after treatment. We report here the initial cross-sectional results.

2. Methods

2.1 Participants

Volunteers with symptoms of disturbed sleep such as snoring and excessive daytime sleepiness were recruited for this longitudinal study. Subjects recruited with normal polysomnograms (PSGs) in the Vanderbilt Sleep Disorders Center were recruited as normal controls. Study participants were between 21 and 75 years of age, with no known history of diabetes or other disorders known to affect the autonomic system. All patients on antihypertensive, anticholinergic, or other medications known to affect autonomic testing were requested to hold medication for at least 3-5 half lives and to withhold caffeine use. Patients unable to hold medications safely for this time period were excluded from the study. To avoid treatment bias, previous treatment of OSA was also an exclusion criteria. Because the study included repeated measurements after continuous positive airway pressure (CPAP) treatment to follow both glucose and autonomic function measures, patients could not be on hypoglycemic medications during the study. Therefore, patients with glucose levels consistent with diabetes were excluded from the study for safety concerns. To avoid obesity as a confounding effect, participants with a body mass index (BMI) of 25-40 were included in the study.

2.2 Definitions

OSA was defined as an apnea-hypopnea index (AHI) greater than 5 events/hour with either 3% desaturation or EEG arousal present (15). Glucose status was defined using the 2004 American Diabetes Association criteria (fasting glucose < 100 mg/dL normal, 100-125 mg/dL impaired fasting glucose, > 125 mg/dL diabetic; 2-hour glucose <140 mg/dL normal, 140-199 mg/dL impaired glucose tolerance, 200 mg/dL diabetic (16)).

2.3 Procedures

This study was approved by the Vanderbilt University Internal Review Board and subjects were consented according to the Declaration of Helsinki. The study was posted on clinicaltrials.gov (NCT00681161). All subjects received a complete physical examination with a detailed neurological exam. Eligible subjects came to the Vanderbilt Clinical Research Center for PSG and for 3-hour glucose tolerance testing (OGTT) the following morning. Urine was collected overnight for catecholamine measurement. Participants were kept fasting overnight during their PSG. Study participants with OSA and glucose levels below the diabetic range were invited back for baseline autonomic testing and nerve

conduction studies. Study participants were instructed to avoid food and caffeine for 3 hours prior to the autonomic testing. Medications known to interfere with autonomic testing were held for 24-48 hours prior to testing.

2.3.1 Autonomic Evaluation—Recording of ECG, and hemoglobin saturation (SpO₂), were measured with a patient monitor with Nellcor technology (Vital-Guard 450C, Ivy Biomedical Systems, Inc., Branford, CT).

Continuous blood pressure was measured by volume clamp method (17) on the middle finger of the non-dominant hand (Nextfin, BMEYE B.V., Amsterdam, The Netherlands) and verified using oscillometric determined brachial BP (Vital-Guard 450C, Ivy Biomedical Systems, Inc., Branford, CT) on the contralateral arm. After a period of at least 30 minutes in supine position, ten minutes of resting supine heart rate and blood pressure data were recorded for spectral analysis. The degree of sinus arrhythmia was assessed during controlled breathing (5 seconds inhalation and 5 seconds exhalation (6 cycles/min) during 90 seconds). The sinus arrhythmia ratio was calculated as the ratio of the longest to the shortest RR interval. Responses of blood pressure fall and heart rate acceleration was determined during 30 seconds of hyperventilation. A Valsalva maneuver was performed where the patient blows through a mouthpiece connected to a closed pipe with a pressure transducer and a small leakage (22 gauge hole) for 15 seconds. Blood pressure fall during early phase two, blood pressure recovery during late phase 2, and blood pressure overshoot were determined. The Valsalva ratio of heart rate was calculated. The blood pressure increase to isometric exercise during squeezing a handgrip dynamometer (Model 76618, Lafayette Instrument Co., Indiana) with the dominant hand at 30% of maximal voluntary contraction for three minutes was determined. A cold pressor test was performed where the patient put the dominant hand into ice water for one minute and the blood pressure increase at one minute was recorded. Orthostatic vital signs were determined by measuring heart rate and brachial blood pressure (Dinamap 1846SX, Critikon, Tampa, FL) on the non-dominant arm and following at least 30 minutes supine and at 1, 3, 5, and every 5 minutes until 30 minutes after standing.

Blood for catecholamine determination during supine and upright were drawn through intravenous catheter on the contra-lateral arm.

QSART: QSART testing was performed using the QSweat device (WR Electronics, Rochester, MN) using the technique of Low et al (18). Capsules were placed at four standard sites: distal forearm, proximal leg, distal leg, and foot. 10% acetylcholine solution was iontophoresed using a current of 2.0 mA. Results were recorded in microliters of sweat volume. A study was determined to be abnormal if one or more sites were below the 5th percentile for age and gender using previously published normative data, or if there was a proximal distal gradient with a distal site <1/3 the volume of the proximal leg site.

Spectral Analysis: Signals were digitized at a sampling rate of 500 Hz (DI720USB, DATAQ Instruments, Akron, OH), and then processed with user software written in PV-Wave (Visual Numerics Inc., Houston, TX).

Heart Rate Variability in the Time Domain. Standard deviation (SD RRI), root mean squared of successive differences of R-R intervals (RMSSD RRI) and percentage of interval changes greater than 50 milliseconds to normal sinus R-R intervals (PNN50) were calculated (19).

Spectral Analysis. Beat-to-beat values of detected R-R intervals and BP values were linear interpolated, low-pass filtered (cutoff 0.5 Hz) and re-sampled at 4 Hz. Data segments of 300

s were used for spectral analysis. Linear trends were removed and power spectral density was estimated with the FFT-based Welch algorithm using segments of 256 data points with 50% overlapping and Hanning window (20). The power in the frequency range of low frequencies (LF: 0.04 to 0.15 Hz) and high frequencies (HF: 0.15 to 0.40 Hz) was calculated following Task Force recommendations (19).

Baroreflex Gain was defined as the mean magnitude value of the transfer function between BP and RRI in the low-frequency (BRS LF) and high-frequency (BRS HF) band with negative phase and squared coherence value greater than 0.5.

Spontaneous Baroreflex Slope was calculated as the slope of the linear regression line between the systolic BP and the subsequent R-R intervals using sequences defined as an episode of at least three heart beats with more than 0.5 mm Hg systolic BP changes and 5 msec R-R interval changes. The averaged value of all slopes with a correlation coefficient greater than 0.85 was calculated for sequences with rising (BRS SEQU) and falling BP (BRS SEQDOWN) (21).

2.3.2 Polysomnography—Subjects underwent polysomnography (PSG) in the Vanderbilt Clinical Research Center (CRC). Subjects were studied with standard polysomnographic techniques, using four EEG channels (C3, C4, O1, O2 by the International 10-20 system), 3 chin electromyogram (EMG) leads, 2 electrooculogram (EOG) leads, 2 electrocardiogram (ECG) leads, snoring sound, respiratory effort using the chest and abdomen, airflow at the nose and mouth using thermocouples and nasal pressure cannulas, 2 bilateral surface EMG electrodes (placed over the anterior tibialis muscles) were recorded. Oxyhemoglobin saturation (SaO₂) was monitored by pulse oximetry.

Experienced polysomnographic technologists used standard techniques to score manually all recordings for sleep stages, respiratory events and limb movements. PSG measures followed the American Academy of Sleep Medicine recommendations for sleep staging and respiratory scoring (15). Studies were then reviewed by one of the authors (KB), a board-certified sleep specialist.

2.3.3. Glucose and Insulin Regulation—Subjects were kept fasting for a minimum of 8 hours before glucose evaluation. Fasting samples were drawn for glucose and insulin levels for the HOMA-IR calculation (Homeostasis model approximation for determining insulin resistance, $\text{HOMA IR} = \text{G}_0\text{I}_0/22.5$). Adults <35 with normal BMI and insulin resistance have a HOMA of 1.0, with increasing values indicating greater insulin resistance (23;24). A 3-hour oral glucose tolerance test (OGTT) with 75 g glucose was performed. Blood samples for glucose and insulin were drawn every 30 minutes during a 3-hour OGTT for a composite insulin sensitivity index (ISI) measurement derived by DeFronzo's calculation: $10,000/[(\text{G}_0\text{I}_0)(\text{G}_{\text{avg}}\text{I}_{\text{avg}})]^{1/2}$. This has been shown to approximate insulin sensitivity calculated from the insulin clamp ($R=0.76$). Decreasing values indicate loss of insulin sensitivity (25). Fasting insulin levels above 40 U/mL were considered abnormal.

3. Statistical Methods

For patient baseline demographics, catecholamine levels, spectral analysis of heart rate variables and autonomic function tests, data were summarized with mean $\pm$ standard deviation for continuous variables and with percentages for categorical variables. Unadjusted comparisons between control patients, hyperglycemic, and normoglycemic OSA patients, and between hyperglycemic and normoglycemic OSA patients were conducted using Kruskal-Wallis test and Wilcoxon rank sum test for continuous variables and the Pearson chi-square test for categorical variables.

Linear regression model was used to examine the effects of glucose and AHI on heart rate and blood pressure variability. For each outcome variable, logarithm transformation was used to obtain normally distributed values when needed, and two models were constructed: simple linear model for estimating crude effect and multiple linear regression model for estimating adjusted effect by additionally including pre-specified confounding variables age and BMI.

4. Results

4.1 Patient Characteristics

Forty-six patients were recruited, thirty-five patients met diagnostic criteria for OSA and eleven had normal polysomnograms without significant breathing disturbances. Of the 46 patients included in the final analyses, twenty-two patients had hyperglycemia based on baseline oral glucose tolerance test results (nineteen had OSA), with either elevated fasting glucose (n=11 subjects), impaired glucose tolerance (n=10 subjects), or both (n=1 subject). There were more women than men in all groups but there were no differences between percentage of women in either OSA or hyperglycemia groups ($p=0.76$, 0.92 respectively). There was no significant differences between patients with elevated fasting glucose or impaired glucose tolerance for any variable. Therefore, these groups were combined for all subsequent analyses, we define this combined group the hyperglycemic group.

Patients with OSA (n=35) were significantly older than the control patients (n=11, mean $\pm$ SD; 46.9 ± 9.2 vs. 36.5 ± 11.7 years, $p=0.009$) and were more obese (32.9 ± 4.2 vs. 28.9 ± 3.5 kg/m², $p=0.008$), but comparing patients with (n=22) and without hyperglycemia (n=24) did not demonstrate any differences in age or BMI (hyperglycemic patient mean age 46.0 ± 8.6 vs. normoglycemic patients age 43.0 ± 12.2 years, $p=0.79$, and hyperglycemia patient BMI 32.3 ± 3.8 vs. normoglycemic patient BMI 31.7 ± 4.9 kg/m², $p=0.35$) (see Table 1).

The insulin sensitivity index was not different between hyperglycemic and normoglycemic patients (4.3 ± 2.4 vs. 5.7 ± 2.9 , $p=0.10$), but HOMA-IR was (2.8 ± 1.4 vs. 2.0 ± 1.5 , $p=0.05$), although both were significantly different between control patients and OSA patients (ISI 4.6 ± 2.5 vs. 7.7 ± 2.5 , $p=0.01$ and HOMA-IR 1.7 ± 1.4 vs. 2.7 ± 1.4 , $p=0.029$). Triglycerides were not significantly higher in the hyperglycemic group (129 ± 78 vs. 124 ± 62.5 , $p=0.629$).

4.2 Autonomic Function Test Results

Autonomic Function Tests—There were no significant differences between hyperglycemic and normoglycemic patients after analysis of standard autonomic function tests. There was a trend to a lower heart rate among control patients compared to OSA patients (61 ± 12 vs. 68 ± 8 and 70 ± 13) but this was not significant ($p = 0.14$). There were no differences between healthy controls and OSA patients in baseline heart rate, blood pressure, sinus arrhythmia, heart rate or blood pressure response to Valsalva maneuver, isometric hand grip, or cold pressor test. There was no difference between the groups in sweat volumes at any site.

Heart rate and blood pressure variability—Heart rate variability was calculated from 34 patients who had artifact-free ECG segments while supine before testing began. Age, BMI, glucose, and AHI were analyzed independently and then stepwise. The glucose value used was the 2 hour glucose level from their initial OGTT. BMI did not have a significant effect alone on any of the main variables but was kept in the model as a variable of interest. Gender did not have a significant effect on heart rate variability in our data. Therefore it was not included in the final model. Due to the small number of patient ECG data that could be

analyzed, the model was limited to four variables to avoid over fitting of the model. The variables analysed included age, BMI, AHI and 2 hour glucose in mg/dL.

Age significantly affected Pnn50, and HF RRI, with a trend in TP RRI and LF RRI. All of the correlations measured were modest with no r^2 value greater than 0.2 but significantly different from zero. Unadjusted, glucose had no effect on any heart rate or blood pressure variables. However, after adjusting for age, BMI, and AHI, there was a correlation with lower LF RRI and TP RRI associated with abnormal glucose ($r^2 = -0.19$, $p = 0.03$; $r^2 = -0.15$, $p = 0.04$) and trend towards a lower low frequency of systolic blood pressure ($r^2 = -0.11$, $p = 0.06$) (Table 3). AHI was initially and after adjustment was not associated with any variable except LF RRI ($r^2 = 0.13$, $p = 0.05$).

5. Discussion

The results of this study suggest that mild hyperglycemia may affect heart rate variability, but does not independently contribute to autonomic dysfunction in patients with obstructive sleep apnea. This finding suggests that more severe alterations in glucose may be needed before significant abnormalities are detectable in standard tests of autonomic function.

We obtained healthy overweight and obese controls (BMI over 25) to rule out potential effects of obesity on autonomic function (26). However, either due to the small sample size or the mild OSA present, we did not detect a difference in autonomic function between our OSA patients and control patients which is different from previously published manuscripts. This could be due to the small sample size, but is more likely due to the mild severity of OSA in our patient sample.

There is increasing evidence that impaired glucose tolerance and prediabetes may contribute to peripheral nerve dysfunction (27;28), and there is some evidence to support development of autonomic changes prior to development of diabetes (12). A previous study demonstrated lower sweat volumes in asymptomatic patients with impaired glucose tolerance (13). We did not observe similar findings, which may have been due to several factors, including a younger population and normal neurologic exams with no evidence of peripheral neuropathy, which may indicate that longer periods of sustained hyperglycemia are needed before sweating derangements are evident. It is not clear what degree of hyperglycemia is required or if there are other specific risk factors such as elevated triglycerides which may increase the prevalence of neuropathy in patients with mild hyperglycemia.

Spectral analysis of heart rate variability has become an attractive measure of autonomic function due to the lack of special equipment needed, and ease of obtaining data. Lower heart rate variability detected through analysis of 12-lead ECG data was significantly associated with higher cardiovascular mortality in subjects enrolled in the ACCORD study (29). The neural control of heart rate is regulated at the sinoatrial node by interaction of sympathetic and vagal efferent discharge. High frequency fluctuations in heart rate have a significant vagal component and are tied to respiratory rate. The low frequency rhythmic fluctuations in heart rate are thought to be secondary to sympathetic modulation, but considerable evidence also suggests a significant vagal component as they are decreased after atropine as well as stellectomy. This ambiguity may limit the interpretation of frequency analyses as they do not always correlate with other measures of autonomic function (30). However, in many instances, spectral analysis enables evaluation of autonomic input not easily obtained through other methods. Our study suggests that frequency analysis may be a more sensitive tool than standard autonomic function tests in detecting early involvement of the autonomic system compared to other standard autonomic

tests. However, our results should be interpreted with caution given the small effect size, and multiple observations reported.

We did not observe evidence of hyper-sympathetic input of heart rate or in any other autonomic test performed, either in hyperglycemic patients or in patients with sleep apnea compared to controls, which may have been due to the mild sleep apnea present in our cohort. Previous studies have demonstrated a dose-dependent effect of OSA (22). We also analyzed ECG data from our patients while awake for spectral analysis, whereas many of the studies previously performed analyzed ECG data from PSGs. The advantage of this method was to obtain data in a controlled environment, with patients not on any medications known to affect heart rate or autonomic function; this is not possible in ECG data abstracted from PSGs performed in large sleep laboratories.

We again have shown that approximately 50% of the OSA patients had hyperglycemia, and a significant correlation between hyperglycemia and sleep apnea. Hyperglycemia is highly prevalent in patients with sleep apnea, and conversely, sleep apnea is highly prevalent in diabetic populations independent of obesity and age. It is not known whether the presence of OSA is a risk factor for other diabetic complications.

In conclusion, mild hyperglycemia present in OSA may have an early effect on heart rate variability, and may contribute to autonomic dysfunction observed in these patients. However, major autonomic dysfunction consistent with diabetes was not observed in our hyperglycemic OSA patients. Future studies are needed to determine if measures of heart rate variability alone are superior to other measures of autonomic function in this cohort.

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Table 1

Characteristics of 46 patients with and without hyperglycemia (impaired fasting glucose or impaired glucose tolerance).

	Impaired fasting glucose patients (n = 10)	Impaired glucose tolerance patients (n = 12)	Normoglycemic patients (n=24)	P value
Age	47±7	45±10	44±12	0.93
Female	68 (15)	75(9)	70 (16)	0.38 [†]
African-American	10 (1)	8 (1)	0 (0)	0.34 [†]
Body-mass index	31.4±3.2	33.2±4.3	31.2±4.7	0.41
AHI	16±18	23±21	11±11	0.23
REM AHI	26±24	23±33	14±15	0.29
Minimum O2 saturation	85±6	83±5	85±7	0.22
Epworth Sleepiness Scale	7±6	9±4	10±6	0.73
Fasting glucose mg/dL	109±5	91 ±7	89±5	0.001*
2 hour glucose mg/dL	119±16	157±11	111±19	<0.001*
HOMA-IR	2.4±0.9	3.2±1.7	2.2±28	0.12
ISI	4.2±1.3	4.4±3.2	5.7±2.9	0.23

% (N); or mean ± standard deviation (SD)

AHI = apnea-hypopnea index; REM = rapid eye movement sleep; HOMA-IR = Homeostasis model approximation for determining insulin resistance; ISI = Insulin sensitivity index

Table 1. P values were reported for comparisons between normoglycemic, impaired fasting glucose and impaired glucose tolerance patients. Fasting glucose above 100 mg/dL and 2 hour glucose above 140 mg/dL were used in accordance with the 2009 American Diabetes Association criteria.

[†] Chi squared test used, p values for other variables were based Kruskal-Wallis test.

Table 2

Characteristics of 46 patients with and without obstructive sleep apnea (OSA) N (%); or Mean $\pm$ standard deviation (SD).

	OSA patients (n=35)	Control patients (n=11)	P value
Age	47.1 $\pm$ 9.3	36.5 $\pm$ 11.7	0.009*
Female	69 (24)	64 (7)	0.76 [†]
African-American	3 (1)	9 (1)	0.14 [†]
Body-mass index	32.8 $\pm$ 4.2	28.9 $\pm$ 3.5	0.008*
AHI	21 $\pm$ 17	1 $\pm$ 1	<0.001*
REM AHI	26 $\pm$ 25	2 $\pm$ 2	<0.001*
Minimum O2 saturation	83 $\pm$ 6	85 $\pm$ 7	0.16
Epworth Sleepiness Scale	9 $\pm$ 5	Insufficient sample	
Fasting glucose mg/dL	109 $\pm$ 5	89 $\pm$ 5	0.001
2 hour glucose mg/dL	117 $\pm$ 15	112 $\pm$ 19	<0.001
HOMA-IR	2.4 $\pm$ 0.9	2.2 $\pm$ 1.6	0.058
ISI			

AHI = apnea-hypopnea index; REM = rapid eye movement sleep; HOMA-IR = Homeostasis model approximation for determining insulin resistance; ISI = Insulin sensitivity index

[†] Chi squared test used, other variables used Wilcoxon rank-sum test. Epworth Sleepiness scale not reported for controls because not all patients had scale at time of polysomnogram (PSG).

* p value less than 0.05.

Table 3

Results of autonomic function tests comparing hyperglycemic vs. normal glyceemic patients. Shown are Mean $\pm$ standard deviation (SD). Impaired glucose tolerance and impaired fasting glucose patients were combined for the hyperglycemic patient group. Wilcoxon rank-sum test was used for comparisons.

	Hyperglycemic patients (n=22)	Normoglycemic patients (n=24)	P value
Baseline heart rate bpm	69 $\pm$ 13	66 $\pm$ 11	0.68
Baseline SBP¹ mm Hg	113 $\pm$ 10	112 $\pm$ 13	0.36
Baseline DBP² mm Hg	72 $\pm$ 7	69 $\pm$ 8	0.16
Sinus arrhythmia ratio	1.28 $\pm$ 0.14	1.28 $\pm$ 0.16	0.68
Valsalva ratio	1.56 $\pm$ 0.29	1.72 $\pm$ 0.43	0.28
Change in SBP after isometric handgrip mm Hg	16 $\pm$ 9	10 $\pm$ 19	0.17
Change in SBP after cold pressor test mm Hg	22 $\pm$ 14	24 $\pm$ 13	0.46
Forearm sweat volume μL	1.42 $\pm$ 0.81	1.30 $\pm$ 0.89	0.46
Proximal leg sweat volume μL	0.89 $\pm$ 0.53	0.85 $\pm$ 0.46	0.92
Distal leg sweat volume μL	0.90 $\pm$ 0.65	0.98 $\pm$ 0.64	0.77
Foot sweat volume μL	0.54 $\pm$ 0.37	0.45 $\pm$ 0.46	0.37

Table 4

Linear regression analysis of heart rate and blood pressure with glucose before and after adjusting for age, body mass index, and apnea-hypopnea index

Dependent variable	Glucose						
	Unadjusted				Adjusted		
	Estimate	95% CI		p value	Estimate	95% CI	p value
log(Pnn50)	-0.2251	-0.6220	0.1719	0.2577	-0.2016	-0.6081	0.2049
log(LF RRI)	-0.1578	-0.3236	0.0081	0.0616	-0.1550	-0.3259	0.0160
log(HF RRI)	-0.1525	-0.3459	0.0410	0.1187	-0.1524	-0.3479	0.0430
log(TP RRI)	-0.1518	-0.2995	-0.0041	0.0443	-0.1399	-0.2909	0.0111
log(LF_HF ratio)	-0.0053	-0.1109	0.1003	0.9195	-0.0026	-0.1161	0.1109
log(rmssd)	-0.0907	-0.1945	0.0130	0.0845	-0.0839	-0.1871	0.0194
log(LF SYS)	-0.0652	-0.1683	0.0378	0.2074	-0.0899	-0.1994	0.0196
log(BRS lfmm SYS)	-0.0470	-0.1455	0.0515	0.3398	-0.0334	-0.1336	0.0669
log(sig sequp)	-0.0418	-0.1452	0.0617	0.4182	-0.0242	-0.1251	0.0766
log(sig seqdown)	-0.0445	-0.1444	0.0554	0.3723	-0.0236	-0.1207	0.0734

Pnn50= number of normal sinus (NN) intervals with duration greater than 50 ms/number of NN intervals; LF = low frequency; RRI = R-R interval; HF = high frequency; TP = total power; rmssd = root mean square successive difference in heart period; SYS =systolic; BRS lfmm SYS= baroreflex gain--mean magnitude value of the transfer function between bp and rri in low frequency band, sig sequp and sig seqdown refer to the baroreflex slope of the linear regression line between the systolic bp and subsequent r-r intervals using sequences with more than 0.5 mm Hg systolic bp changes and 5 msec r-r interval changes

Table 5

Linear regression analysis of heart rate and blood pressure with AHI before and after adjusting for age, body-mass index, and glucose

Dependent variable	AHI							
	Unadjusted				Adjusted			
	Estimate	95% CI		p value	Estimate	95% CI		p value
log(Pnn50)	−0.0551	−0.3604	0.2502	0.7162	0.0603	−0.2660	0.3866	0.7092
log(LF RRI)	0.0325	−0.0973	0.1622	0.6147	0.0931	−0.0433	0.2294	0.1742
log(HF RRI)	−0.0147	−0.1639	0.1346	0.8431	0.0437	−0.1145	0.2018	0.5783
log(TP RRI)	0.0019	−0.1147	0.1185	0.9738	0.0611	−0.0604	0.1826	0.3134
log(LF_HF ratio)	0.0472	−0.0322	0.1267	0.2357	0.0495	−0.0396	0.1387	0.2666
log(rmssd)	−0.0207	−0.1011	0.0597	0.6043	0.0348	−0.0500	0.1195	0.4097
log(LF SYS)	0.0297	−0.0506	0.1101	0.4572	0.0435	−0.0464	0.1335	0.3315
log(Txy lfmn SYS)	−0.0075	−0.0811	0.0662	0.8380	0.0366	−0.0440	0.1171	0.3622
log(sig sequp)	−0.0356	−0.1088	0.0375	0.3295	0.0069	−0.0718	0.0856	0.8599
log(sig seqdown)	−0.0415	−0.1153	0.0323	0.2615	0.0014	−0.0781	0.0808	0.9722

Pnn50= number of normal sinus (NN) intervals with duration greater than 50 ms/number of NN intervals; LF = low frequency; RRI = R-R interval; HF = high frequency; TP = total power; rmssd = root mean square successive difference in heart period; SYS =systolic; BRS lfmn SYS= baroreflex gain--mean magnitude value of the transfer function between bp and rri in low frequency band, sig sequp and sig seqdown refer to the baroreflex slope of the linear regression line between the systolic bp and subsequent r-r intervals using sequences with more than 0.5 mm Hg systolic bp changes and 5 msec r-r interval changes.