Altered Cardiovascular Variability in Obstructive Sleep Apnea

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Background—Altered cardiovascular variability is a prognostic indicator for cardiovascular events. Patients with obstructive sleep apnea (OSA) are at an increased risk for cardiovascular disease. We tested the hypothesis that OSA is accompanied by alterations in cardiovascular variability, even in the absence of overt cardiovascular disease.

Methods and Results—Spectral analysis of variability of muscle sympathetic nerve activity, RR interval, and blood pressure were obtained during undisturbed supine rest in 15 patients with moderate-to-severe OSA, 18 patients with mild OSA, and 16 healthy control subjects in whom sleep disordered breathing was excluded by complete overnight polysomnography. Patients with OSA were newly diagnosed, never treated for OSA, and free of any other known diseases. Patients with moderate-to-severe OSA had shorter RR intervals (793±27 ms) and increased sympathetic burst frequency (49±4 bursts/min) compared with control subjects (947±42 ms; 24±3 bursts/min; P=0.008 and P<0.001, respectively). In these patients, total variance of RR was reduced (P=0.01) and spectral analysis of RR variability showed an increase in low frequency normalized units, a decrease in high frequency normalized units, and an increase in the ratio of low to high frequency (all P<0.05). Even though blood pressure was similar to that of the control subjects, blood pressure variance in patients with moderate-to-severe OSA was more than double the variance in control subjects (P=0.01). Patients with mild OSA also had a reduction in RR variance (P=0.02) in the absence of any significant difference in absolute RR interval. For all patients with OSA, linear regression showed a positive correlation (r=0.40; P=0.02) between sleep apnea severity and blood pressure variance.

Conclusions—Cardiovascular variability is altered in patients with OSA. This alteration is evident even in the absence of hypertension, heart failure, or other disease states and may be linked to the severity of OSA. Abnormalities in cardiovascular variability may be implicated in the subsequent development of overt cardiovascular disease in patients with OSA. (Circulation. 1998;98:1071-1077.)

Key Words: nervous system, autonomic ■ nervous system, sympathetic ■ sleep ■ blood pressure ■ heart rate

Obstructive sleep apnea (OSA) has been linked to hypertension,12 heart failure,3 myocardial ischemia,4 myocardial infarction,5 stroke,6 and vascular complications.7 Patients with OSA may have increased mortality rates.8,9 The mechanisms underlying the association between OSA and cardiovascular disease are not known. Sympathetic drive is increased in OSA10,11; therefore, abnormalities in autonomic cardiovascular regulation may be implicated. In patients with overt cardiovascular disease, altered autonomic regulation, manifesting as abnormalities in cardiovascular variability, may be linked to adverse cardiovascular outcomes. Heart rate variability is markedly reduced in patients with heart failure12–14 and in patients after myocardial infarction.15 Decreased heart rate variability in patients with idiopathic dilated cardiomyopathy independently predicts the risk of cardiac death or heart transplantation.16 After myocardial infarction, depressed heart rate variability is a powerful prognostic indicator of both arrhythmic complications and death.15,17,18 Increased blood pressure variability in hypertension is linked independently to target organ damage.19–21 There are no studies of the heart rate, blood pressure, and sympathetic nerve variability in awake, otherwise normal patients with OSA in comparison with matched control subjects.

Spectral analysis of heart rate variability is a widely used noninvasive technique for the assessment of autonomic indexes of neural cardiac control.22–24 In normal humans, short-term RR interval variability occurs predominantly at a low frequency (LF) (0.04 to 0.14 Hz) and a high frequency (HF) (±0.25 Hz, synchronous with the respiratory frequency).25,26 Similar variability profiles are present in direct recordings of sympathetic nerve traffic25 and blood pressure.25,26

Whether patients with sleep apnea have abnormalities in cardiovascular variability, in the absence of existing cardio-
vascular disease, is not known. We tested the hypothesis that cardiovascular variability is altered in patients with OSA and that the severity of cardiovascular variability derangement is linked to the severity of OSA. We therefore compared variability characteristics of simultaneous recordings of MSNA, RR interval, blood pressure, and respiration in patients with mild OSA, patients with moderate-to-severe OSA, and matched normal control subjects in whom OSA was excluded by complete overnight polysomnographic monitoring.

Methods

Subjects

Measurements were obtained in three groups of subjects: normal control subjects (n=16), patients with mild OSA (n=18), and patients with moderate-to-severe OSA (n=15). The three groups were similar in age, body mass index, blood pressure, and gender distribution (Table 1). The patients with sleep apnea were newly diagnosed, normotensive, free of any other known diseases, and receiving no medications; had never been treated for sleep apnea; and were otherwise healthy. All patients with sleep apnea also were free of any cardiac history, limitation or changes in exercise tolerance, and symptoms or signs suggestive of congestive heart failure. Mean apnea-hypopnea index (AHI) was 15 ± 1 events/h for the 18 patients with mild OSA and 61 ± 8 events/h for the 15 patients with moderate-to-severe OSA.

The decision to divide the patients with OSA into two groups (mild and moderate to severe) was prospective and was based on the AHI (number of apneas or hypopneas per hour of sleep). Patients with an AHI of <20 were classified as the mild group, and those with an AHI of >20 were classified as the moderate-to-severe group. This classification followed earlier studies showing that mortality rates in patients with OSA and an AHI of >20 was markedly increased in comparison with patients with OSA and an AHI of <20.9

The 16 healthy control subjects were closely matched for age and body mass index (Table 1). Because of the high prevalence of occult OSA in apparently normal, asymptomatic obese subjects,27 sleep-disordered breathing was excluded in all control subjects by complete overnight polysomnographic studies.

Informed written consent was obtained from all subjects. The study was approved by the institutional human subjects review committee.

Measurements

MSNA was recorded continuously by obtaining multiunit recordings of postganglionic sympathetic activity to muscle circulation, measured from a nerve fascicle in the peroneal nerve posterior to the fibular head, as described previously.25 Electrical activity in the nerve fascicle was measured using tungsten microelectrodes (shaft diameter of 200 μm, tapering to an uninsulated tip of 1 to 5 μm). A subcutaneous reference electrode first was inserted 2 to 3 cm from the recording electrode, which was inserted into the nerve fascicle. The neural signals were amplified, filtered, rectified, and integrated to obtain a mean voltage display of sympathetic nerve activity.

All subjects were studied during the daytime (in the morning or the early afternoon). Studies were conducted in the same room and ≥3 hours after the last meal. After the placement of electrodes and monitoring equipment, subjects were allowed to rest in the supine position for ≥15 minutes before measurements were obtained. Simultaneous measurements of the ECG, respiration (pneumograph), oxygen saturation (Nellcor pulse oximeter), arterial pressure (Finapres system), and MSNA were recorded on a Gould 2800 S recorder and a Pentium PC. These measurements were obtained while subjects were awake, during 10 minutes of undisturbed supine rest. None of the subjects or patients had apneas, hypopneas, or oxygen desaturation during the study.

Data Analysis

Sympathetic bursts were identified by a single observer (K.N.). The intraobserver and interobserver variabilities in our laboratory have been reported to be 4.3 ± 0.3%29 and 5.4 ± 0.5%,30 respectively. Sympathetic activity was calculated as bursts/min and bursts per 100 heartbeats after careful inspection of the mean voltage neurogram. Analog-to-digital conversion was performed in real time at 600 samples/s/channel. The data then were analyzed off-line with a personal computer (Aptiva, IBM). The principles of the software for data acquisition and spectral analysis have been described elsewhere.25 This method allows spectral analysis of respiration, RR interval, beat-to-beat blood pressure, and sympathetic nerve activity. In brief, a derivative-threshold algorithm provided the continuous series of RR intervals (tachogram) derived from the ECG. Isolated artifacts were detected and removed. From the arterial pressure signal, beat-to-beat systolic (systogram) and diastolic (diastogram) values were calculated. A specially designed interpolation program was used to minimize any effects of occasional calibration signals on spectral analysis of the Finapres recordings. The signals of sympathetic nerve activity and respiratory activity were sampled once every cardiac cycle, thus obtaining a neurogram and a respirogram synchronized with the tachogram. Before sampling, the neurogram was preprocessed to provide, for each cardiac cycle, the time-integrated value of the signal.

All variability series were analyzed by means of autoregressive parametric spectral and cross-spectral algorithms that automatically provide the number, center frequency, and power of each oscillatory component.25 The LF and HF spectral components of RR interval, SBP, and MSNA were expressed in absolute and normalized units (NU). The NU were obtained by calculating the percentage of LF and HF variability with respect to the total power after subtracting the power of the very low frequency component (frequencies of <0.03 Hz).18,23,31 The HF oscillation in each subject was related to the respiratory signal. Occasionally, a small amount of power was detected at frequencies higher than the respiratory frequency. This amount of variance was not taken into account in the calculation of the normalized HF power. Therefore, the sum of the normalized LF and HF powers did not equal 100% in all subjects. A coherence (K²) function then was used to determine the amount of linear coupling among the series of RR interval, sympathetic nerve activity, systolic...
blood pressure (SBP), and respiration.\textsuperscript{25,31} This measure has the same meaning as the squared correlation coefficient (explained variance) in a linear regression equation and allows a determination of the amount of linear coupling between the oscillations present in different time series.

The presence of LF components in respiration prevents interpretation of the LF and HF components of cardiovascular variabilities because of overlap of the respiratory oscillation with the LF oscillation.\textsuperscript{32,33} The respiratory variability had a significant LF component in 4 normal control subjects, 5 patients with mild OSA, and 4 patients with moderate-to-severe OSA. Consequently, we obtained meaningful data on the LF and HF components of cardiovascular variability in 12 control subjects, 13 patients with mild OSA, and 11 patients with moderate-to-severe OSA.

**Statistical Analysis**

Results are expressed as mean±SEM, except for the demographics presented in Table 1, for which values represent mean±SD. Statistical analysis consisted of one-way ANOVA, followed by Scheffe’s test for multiple comparisons, to allow pairwise testing for significant differences between the groups. Because of a skewed distribution, we used the ln transform of the LF-to-HF ratios. Correlations were estimated with use of the Pearson coefficient. A value of \( P<0.05 \) was considered significant.

**Results**

The RR interval was significantly shorter in patients with moderate-to-severe OSA (793±27 ms) than in the normal subjects (947±42 ms; \( P=0.008 \)) (Figures 1 and 2). Variance of RR interval was reduced significantly in both patients with mild OSA (\( P=0.02 \)) and patients with moderate-to-severe OSA (\( P=0.01 \)) (Figure 1).

Although blood pressure was similar in the three groups (Table 1, Figure 1), SBP variance in patients with moderate-to-severe OSA (22±3 mm Hg) was greater than that in the control subjects (9±3 mm Hg; \( P=0.01 \)) and greater than that in patients with mild OSA (12±3 mm Hg; \( P=0.03 \)).

Whether expressed in absolute burst frequency or bursts per 100 heart beats, MSNA was markedly elevated in both patients with mild OSA (46±3 bursts/min; 64±4 bursts per 100 heart beats) and patients with moderate-to-severe OSA (49±4 bursts/min; 63±4 bursts per 100 heart beats) compared with the control subjects (24±3 bursts/min; 38±4 bursts per 100 heart beats) (\( P<0.001 \) for each comparison).

Patients with moderate-to-severe OSA had an increased normalized LF variability of RR interval (\( P=0.045 \)) and a decreased normalized HF variability of RR interval (\( P=0.04 \)) compared with the control subjects (Table 2, Figures 3 and 4). The LF-to-HF ratio of RR variability, but not of SBP variability or MSNA variability, was increased significantly in the patients with moderate-to-severe OSA (Table 2) compared with the control subjects and patients with mild OSA (both \( P=0.04 \)). The normalized LF and HF components of RR, SBP, and MSNA variability in patients with mild OSA were not different from those observed in the control subjects (Table 2).
The center frequencies of the LF and HF components of the patients with OSA did not differ from those of the control subjects. The coherence among the LF variability of RR, SBP, and MSNA in the patients with sleep apnea was similar to that in the control subjects (>0.5 in all three subject groups). The linear coupling among the HF components of RR interval variability, MSNA, and respiration were similar and correlated significantly for the control subjects, the patients with mild OSA, and the patients with moderate-to-severe OSA.

When the two groups of patients with OSA were pooled together (n=33), AHI correlated negatively with RR interval \( r = -0.37, P = 0.04 \) and positively with both MSNA \( r = 0.44, P = 0.01 \) and SBP variability \( r = 0.40, P = 0.02 \). MSNA was correlated negatively with RR interval \( r = -0.56, P = 0.001 \) and RR variability \( r = -0.44, P = 0.01 \) and positively with SBP variability \( r = 0.38; P = 0.03 \). In patients with sleep apnea in whom frequency domain analysis was feasible \( n = 24 \), AHI correlated positively with the normalized LF component of the RR interval \( r = 0.42, P = 0.04 \) and negatively with the normalized HF component of the RR interval \( r = -0.41; P = 0.047 \).

**Discussion**

The novel findings in this study are that (1) cardiovascular variability is altered in patients with OSA, and this alteration occurs even in the absence of hypertension, heart failure, or other disease states; and (2) the degree of derangement in cardiovascular variability may be linked to the severity of OSA.

Altered cardiovascular variability affects predominantly patients with moderate-to-severe sleep apnea. In addition to faster heart rate and increased sympathetic burst frequency, RR variability is decreased and blood pressure variability is markedly increased in these patients. Normalized LF variability of RR and LF-to-HF ratio of RR variability are increased, and normalized HF variability of RR is decreased. In patients with mild sleep apnea, these abnormalities are less pronounced, with significant differences from normal control subjects evident only in a decreased RR variability and an increase in MSNA burst frequency. It is intriguing that mild sleep apnea also manifests increased RR variability even in the absence of both the significant RR shortening and increased blood pressure variability seen in moderate-to-severe sleep apneas. It may be that abnormalities in control mechanisms regulating RR variability precede the development of abnormalities in blood pressure variability and absolute heart rate.

The reason for the absence of a clear increase in LF-to-HF ratio of MSNA variability is not known. It may be that in this particular context, the LF-to-HF ratio is a less sensitive index of sympathetic drive. Alternatively, it may be that the progression of changes in autonomic drive in OSA first affects heart rate and absolute MSNA, before changes in MSNA variability become evident.

Previous studies of cardiovascular variability in sleep apnea have analyzed mainly measurements obtained during sleep.\(^{34,35}\) Repetitive apneas trigger marked fluctuations in both blood pressure and heart rate with consequent effects on the estimates of cardiovascular variability.\(^{11}\) The validity of spectral measures during repetitive apneas and consequent respiratory irregularity also has been questioned.\(^{32}\) Data for the present study therefore were obtained during wakefulness and in the absence of either apneas or hypoxemia.
Prior studies have reported that patients with OSA have increases in direct intraneural measurements of sympathetic nerve traffic.\textsuperscript{10,11} However, there have been no previous comparisons of sympathetic activity in patients with sleep apnea compared with subjects without sleep apnea who have similar body mass index and blood pressure. Thus, the contribution of obesity and blood pressure to high sympathetic traffic in patients with sleep apnea was uncertain. The present study shows that obesity and hypertension do not account for the high sympathetic neural traffic in patients with OSA.

This study had several strengths. First, all participants were free of medications. Second, normal control subjects were matched for age and body mass index, thus ruling out any potential confounding influence of age or obesity on our data. Third, given the high prevalence of OSA in asymptomatic, apparently normal obese subjects\textsuperscript{27} and the lack of reliable screening tests for sleep apnea,\textsuperscript{36} we ruled out sleep-related breathing disorders in our control subjects by complete overnight polysomnographic recordings. Fourth, all patients with sleep apnea were normotensive, free of other known diseases, newly diagnosed, and never treated for sleep apnea. Last, all measures were obtained in the absence of potential confounding influences such as age, body mass index, or, in particular, blood pressure.

Thus, the variability derangements in moderate-to-severe sleep apneics are not explained by factors such as age, body mass index, or, in particular, blood pressure. Tachycardia, decreased heart rate variability,\textsuperscript{37} increased blood pressure variability,\textsuperscript{38} and an increase in the LF-to-HF ratio of RR variability\textsuperscript{37} are characteristic abnormalities of patients with OSA.

**Figure 3.** Power spectral analysis of simultaneous recordings of RR variability, SBP variability, MSNA variability, and respiration (Resp) in the control subject (left) and in the patient with OSA (right) shown in Figure 2. RR variance is decreased and SBP variance is increased in the patient with OSA compared with the control subject. There is a relative predominance of the LF component over the HF component of RR interval in the patient with OSA. LF components are clearly present in the MSNA variability profiles of both subjects. PSD indicates power spectral density; au, arbitrary units. The vertical axes for MSNA and respiration are not numbered because these show arbitrary units.

**Figure 4.** Normalized LF and HF components of RR interval in control subjects (n=12), patients with mild OSA (n=13), and patients with moderate-to-severe OSA (n=11). The mean LF power of RR interval variability was higher and the mean HF power was lower in the patients with OSA compared with the control subjects. *P<0.05 versus control subjects. Data are mean±SEM.
hypertension. Increased blood pressure variability in hypertension patients is associated with an increased likelihood of target organ damage, independent of the absolute blood pressure level. Thus, an excessive blood pressure variability may constitute an independent risk factor for cardiovascular disease. In our study, however, these abnormalities of heart rate and blood pressure variability were manifest in normotensive sleep apneic patients, in whom absolute blood pressure levels were similar to those of the control subjects. Patients with sleep apnea are at increased risk for hypertension. In epidemiological studies of normotensive subjects, reduced heart rate variability is predictive of the subsequent development of new-onset hypertension. We therefore speculate that abnormalities in cardiovascular variability may precede, and possibly predispose to, the development of hypertension in patients with sleep apnea. The fast heart rates, increased LF-to-HF ratio of RR variability, and increased sympathetic burst frequency are consistent with a state of heightened sympathetic cardiovascular drive in sleep apnea. Increased sympathetic drive may be implicated in the pathogenesis of a number of cardiovascular risk factors, including insulin resistance, hypertension, and the evolution of cardiovascular hypertrophy.

Heart rate variability in sleep apnea is reduced, an abnormality that predicts morbidity and mortality rates in patients with diabetes or heart failure or after myocardial infarction. Blood pressure variability in sleep apneics is increased (about twice that of normal subjects), an abnormality that is linked to end-organ damage in patients with hypertension. These abnormalities are evident in sleep apnea even in the absence of diabetes or detectable cardiovascular disease. Why should cardiovascular variability be deranged in otherwise normal patients with moderate-to-severe sleep apnea? MSNA in patients with OSA was positively correlated with blood pressure variability. Although the mechanism underlying increased blood pressure variability in patients with OSA will require further investigation, the increased sympathetic drive may be implicated in increased daytime blood pressure variability in these patients. It may be that repetitive sympathetic activation and blood pressure surges that occur in response to apneic episodes during sleep cause an impairment of baroreflex and other cardiovascular reflex functions that carry over even into daytime wakefulness.

In conclusion, we demonstrated that cardiovascular variability is altered in patients with OSA. This alteration is evident even in the absence of hypertension, heart failure, or other disease states. The degree of alteration in cardiovascular variability may be linked to the severity of OSA. Abnormalities in cardiovascular variability may be implicated in the subsequent development of overt cardiovascular disease in patients with OSA.

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