Patients with obstructive sleep apnea have an abnormal peripheral vascular response to hypoxia

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Remsburg, Stacia, Sandrine H. Launois, and J. Woodrow Weiss. Patients with obstructive sleep apnea (OSA) experience repetitive nocturnal oscillations in respiration, which occur in association with sleep disruption, oxygen desaturation, and increases in heart rate (HR) and arterial pressure. In addition to these well-documented acute consequences of sleep-related upper airway obstruction, several lines of evidence now indicate that these nocturnal events may have sustained effects on cardiovascular control. For example, epidemiological (9) and physiological (3) studies indicate that sleep-disordered breathing is an independent risk factor for diurnal systemic hypertension. Furthermore, OSA patients have increased sympathetic activity while awake (4), a finding that resolves with effective therapy (18).

Recently, Hedner et al. (10) found that patients with OSA have a greater pressor response to hypoxia than do age-matched, nonapneic control subjects. In that study, ventilatory responses to progressive isocapnic hypoxia were also greater in untreated patients than in the controls. Both groups had similar tachycardic responses to hypoxia, suggesting a difference between patients and controls in the peripheral vascular response to hypoxic chemostimulation.

The hemodynamic response to hypoxia is complex, involving both direct and reflex effects on the peripheral vasculature (6, 11). Whereas hypoxia directly causes arteriolar vasodilation, hypoxic peripheral chemoreceptor stimulation leads to changes in HR and peripheral sympathetic outflow (7, 8, 13). Animal and human studies indicate that the magnitude and direction of the hemodynamic response are modulated by inputs from lung mechanoreceptors, i.e., bradycardia and regional vasoconstriction in the setting of apnea and tachycardia and less vasoconstriction with unstrained breathing (1, 11). Thus an augmented pressor response to hypoxia might result from abnormalities of either direct or reflex control of vascular tone in OSA patients. To better assess the response of the peripheral circulation to hypoxia in OSA patients, we measured forearm vascular resistance (FVR) during progressive isocapnic hypoxia and during forearm ischemia.

METHODS

Subjects. We recruited 16 otherwise healthy patients with previously diagnosed sleep apnea from the Sleep Disorders Center at the Beth Israel Deaconess Medical Center. Eight healthy age- and gender-matched volunteers served as controls. We excluded subjects taking vasoactive medications or with evidence of preexisting chronic disease including hypertension, cardiovascular or intrinsic lung disease, or diabetes. Each subject had a complete medical history, physical examination, and a diagnostic polysomnogram before participation.

Three patients and two controls were excluded from the final data analysis because of an inability to stay awake throughout the protocol (2 patients), severe anxiety while the patient was breathing through the mouthpiece (1 patient), presence of hypopneas during sleep (1 control), and difficulty in obtaining consistent measurements because of marked respiratory variability in forearm blood flow (FBF) (1 control). As a result, 13 patients and 6 controls completed the entire protocol and were included in the final data analysis. Their characteristics are described in Tables 1 and 2. The mean age of the patients and controls was similar, but the patients had higher weights and significantly greater body mass indexes (BMIs; calculated as (body weight in kg)/(height in cm)2). We made no attempt to match patients and controls for degree of physical fitness. Although fitness was not quantified, five of six controls exercised regularly, but no patients did.

Measurements. FBF was measured by venous occlusion plethysmography and was expressed in milliliters per 100 ml of limb tissue within the strain gauge per minute (5). A mercury-in-Silastic strain gauge was placed at the midpoint of the palm of each subject's hand to measure changes in blood volume resulting from venous occlusion. We calculated the time constant of the strain gauge as the time required for the strain gauge output to decrease to 63% of its initial value following venous occlusion. This value was used to determine the exponential constant of the strain gauge and the duration of the occlusion. The strain gauge output was calibrated to reflect changes in forearm volume, and the FBF was calculated by dividing the change in volume per minute by changes in the cross-sectional area of the volar forearm. Subjects were seated with the arm positioned at 90° of elbow flexion. Measurements were made during spontaneous inspiration and expiration at baseline and at 80% and 60% of baseline SaO2 values. The average FBF during inspiration was measured by placing the strain gauge over the volar forearm and occluding the venous return with a pneumatic cuff. Measurements were also obtained during recovery from 5 min of forearm ischemia. MAP increased similarly in both groups during hypoxia (mean increase at 80% SaO2: OSA patients, 9 ± 11 mmHg; controls, 12 ± 7 mmHg). Forearm vascular resistance, calculated from forearm blood flow and MAP, decreased in controls (mean change = −37 ± 19% at SaO2 80%) but not in patients (mean change = −4 ± 16% at 80% SaO2). Both groups decreased forearm vascular resistance similarly after forearm ischemia (maximum change from baseline −85%). We conclude that OSA patients have an abnormal peripheral vascular response to isocapnic hypoxia.

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Table 1. Characteristics of sleep apnea patients

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Mean ± SD 42.7 ± 11.1 111.5 ± 30.1 35.7 ± 7.3 69.5 ± 27.5

M, male; F, female; BMI, body mass index (body weight in kg)/(height in m)²; AHI, apnea-hypopnea index in events/h of sleep.

Results of the forearm with a distally placed wrist exclusion cuff and a proximal venous occlusion cuff. Before data collection, a series of occlusions was performed at different occlusion pressures from 20 to 50 mmHg. The occlusion pressure that resulted in the steepest slope of the arterial inflow curve was then used for all subsequent trials. This sequence resulted in venous occlusion pressures between 20 and 40 mmHg being used in all subjects. Measurements of FBF were made with the wrist exclusion cuff inflated to 200 or 50 mmHg above the highest resting arterial pressure; intermittent venous occlusions were performed in series of three, each with a duration of 6–10 s.

Arterial pressure was measured continuously by digital photoplethysmography (Finapres, Ohmeda), and mean arterial pressure (MAP) was calculated as one-third the pulse pressure plus diastolic pressure. We calculated FVR by dividing the MAP by FBF. We also continuously recorded electrocardiogram, arterial oxygen saturation by pulse oximetry (SaO₂), respiration by calibrated inductance plethysmograph, and end-tidal CO₂ by mass spectrometer. Blood pressure and ventilation were obtained from all heartbeats and breaths at the specified saturation ±1%. All measurements were made with the subjects in the supine position. All studies took place between 5:00 and 7:00 PM.

Protocol and data analysis. The study was approved by the hospital Committee on Clinical Investigations, and all subjects gave written informed consent. We measured FBF at baseline, during progressive isocapnic hypoxia between oxygen saturations of 95 and 80%, and after 5 min of forearm ischemia. Progressive isocapnic hypoxia was induced by a standard rebreathing circuit (16). We made measurements at SaO₂ of 90, 85, and 80% during the 3- to 4-min hypoxic ramp. A recovery period of 10 min was followed by repeat measurements of FBF and MAP to confirm a return to baseline.

Table 2. Characteristics of nonapneic control subjects

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Mean ± SD 34.8 ± 5.9 83.0 ± 9.8 25.5 ± 3.6

M, male; F, female; BMI, body mass index (body weight in kg)/(height in m)²; AHI, apnea-hypopnea index in events/h of sleep.

Forearm ischemia was then produced by inflating a cuff on the upper arm to 220 or 50 mmHg greater than the highest resting systolic pressure (if >170 mmHg) for 5 min. Venous occlusions were performed immediately on release of ischemia and at 15- to 30-s intervals, until FVR returned to the preschismic baseline. Note was made of the minimal FVR and the time from cuff deflation to return to baseline FVR. The minimal FVR after ischemia was then used for comparison among subjects.

Data were tested for normality, and a Friedman test, a nonparametric analysis of variance, was used to evaluate changes in FVR, MAP, and HR. In addition, an unpaired t-test was used to compare the percent change of FVR, MAP, and HR from baseline between patients and normal subjects. The data are presented as means ± SD.

Results

Baseline awake MAP and FVR were similar for patients with OSA (MAP = 93 ± 9 mmHg; FVR = 45 ± 25 units) and for controls (MAP = 92 ± 12 mmHg; FVR = 56 ± 31 units). Resting HR was significantly higher for patients (at baseline, HR = 75 ± 12 beats/min) compared with controls (HR = 59 ± 8 beats/min, P < 0.01). Baseline FVR did not correlate with MAP (r = 0.3743), age (r = −0.05848), or severity of OSA as indicated by the nadir of oxygen saturation (r = 0.4589) or apnea-hypopnea index (r = −0.246). For patients, baseline FVR correlated negatively with BMI (r = −0.73) and weight (r = −0.78). This relationship was not present for the control subjects, across a narrower weight range (BMI, r = −0.23; weight, r = 0.1496).

With progressive isocapnic hypoxia, both patients (Table 3) and controls (Table 4) exhibited a mild pressor response between baseline and 80% SaO₂ (Fig. 1). The magnitude of the pressor response was similar for the two groups (change in MAP from baseline to SaO₂ 80%, 15 ± 6 mmHg; 80%, 12 ± 7 mmHg; 80%, 10 ± 11%).

Whereas there was much variability in baseline FVR among both patients and controls, within a single subject there was minimal variability across repeated baseline measurements. When exposed to progressive hypoxia, in addition to the increase in arterial pressure, control subjects all demonstrated forearm vasodilation with a decrease in FVR of 37 ± 19% (P = 0.023) at an SaO₂ of 80% (Table 4). In contrast, there was no significant change in FVR in the patients during the hypoxic challenge (change in FVR at SaO₂ 80%, 4 ± 16%, P = not significant). In addition, unlike the controls, the patients’ responses were characterized by variability, as approximately one-half the subjects had reduced FVR, similarly to the controls, but the remaining patients displayed vasoconstriction in response to hypoxic exposure (Table 3, Fig. 2).

During progressive hypoxia (Fig. 3), HR increased in both patients (HR change at SaO₂ 80%, 15 ± 11%) and controls (HR change at SaO₂ 80%, 15 ± 11%), but the magnitude of the tachycardic response was greater in the controls (P = 0.028).

Ventilatory responses to progressive hypoxia were variable for subjects in both groups. Mean ventilatory responses were similar, however, for patients and con-
controls, and in both groups the responses fell within the normal range for this laboratory (slope of ventilatory response: OSA patients $= 2.8 \pm 1.8$ l/min per 1% fall in $\text{SaO}_2$; controls $= 2.05 \pm 0.88$ l/min per 1% fall in $\text{SaO}_2$).

Forearm ischemia was followed by reactive hyperemia in all subjects. Immediately after 5 min of resting forearm ischemia, both patients and controls vasodilated, decreasing FVR at maximum to 15% of their baseline values (OSA patients, %change from baseline $= 28 \pm 12$%; controls, %change from baseline $= 30 \pm 2$%). There was no significant change in arterial pressure in either group after forearm ischemia.

### DISCUSSION

This study of OSA patients and nonapneic control subjects of similar age, waking arterial pressure, and FVR yielded three major findings. First, we found that patients and controls had a similar, mild pressor response to progressive isocapnic hypoxia. Second, nonapneic controls had a greater tachycardic response to hypoxia than did patients, and, in addition, controls had forearm vasodilation that was not seen in patients with OSA. Third, the difference in the circulatory response to hypoxia did not seem to be related to an inability to vasodilate, as demonstrated by the vascular response to forearm ischemia.

A number of studies, both epidemiological and physiological, have suggested an association between OSA and diurnal hypertension (3, 8, 9, 14). Hla et al. (9) found that even mild sleep-disordered breathing was significantly associated with hypertension after correcting for age, obesity, and gender. Working in an animal model, Brooks and co-workers (3) showed that repetitive upper airway occlusions during sleep resulted in sustained waking hypertension. Whereas the association of sleep-disordered breathing and hypertension is increasingly well documented, the mechanism by which OSA contributes to or causes hypertension has not yet been elucidated.

One popular theory is that intermittent hypoxia causes sustained activation of the sympathetic nervous system and resultant hypertension. Fletcher et al. (7) found that rats exposed to repetitive intermittent hypoxia developed sustained increases in arterial pressure. Development of hypertension in this model required intact chemoreceptors. In healthy human volunteers, Morgan and co-workers (15) found that sustained hypoxia, when combined with hypercapnia, resulted in sympathetic activation that persisted for 20 min after the exposure. These findings are suggestive of a role for chemoreceptor-induced sympathetic activation contributing to hypertension in OSA patients, and this hypothesis is further supported by the finding that OSA patients display augmented sympathetic activity even while awake, without hypoxia and hypercarbia. Carlson and colleagues (4) measured sympathetic activity...
by direct peroneal nerve recordings and showed that OSA patients had higher sympathetic nerve traffic than did nonapneic controls. Recently, Waravdekar et al. (18) demonstrated that continuous positive airway pressure treatment of OSA patients results in decreases in waking sympathetic nerve traffic, suggesting that OSA, rather than some other factor such as obesity, is responsible for the sympathetic hyperactivity.

Others have examined the effects of acute isocapnic hypoxia on arterial pressure and ventilation in patients with OSA compared with younger, healthy volunteers. Hedner et al. (10) found that OSA patients had a pressor response to hypoxia not seen in unmatched controls without sleep apnea. This suggested to us that patients with OSA might have increased peripheral vasoconstriction, in part due to an augmented circulatory response to hypoxia. If true, this might provide another link between nocturnal hypoxia and sustained daytime hypertension. Our finding that OSA patients do not show vasodilation when exposed to isocapnic hypoxia is supportive of this hypothesis.

Our findings differ from those of Hedner et al. (10) in two crucial ways, however. First, we did not find augmented ventilatory responsiveness to hypoxia in our patients compared with the nonapneic controls. Second, we found no differences between patients and controls in the pressor response to hypoxia. We did, however, find differences between the two groups in the way they augmented arterial pressure during hypoxia. These differences between our findings and those of Hedner et al. deserve further comment. Similar ventilatory responses between patients and controls should not be interpreted as demonstrating identical respiratory sensitivity to hypoxia in our study. Unlike Hedner and co-workers, we performed all studies with our subjects supine. We did this to maximize subject comfort during the prolonged immobilization required for repeated FBF measurements and also to simulate the sleeping position. Because the patients were substantially more obese than the controls, however, the supine position likely imposed a greater ventilatory load on patients than on controls. If we measured mouth occlusion pressure during rebreathing, we might have observed differences between the two groups.

Unlike the subjects studied by Hedner et al. (10), our patients had less of an HR response to hypoxia than did our controls. Again, the supine posture may have influenced our results, through greater activation of low-pressure baroreceptors in our patients. If we had observed similar HR responses, it is likely that the patients would have increased arterial pressure to a greater degree than the controls in our study.

One weakness of our study is the nature of our control group. We were not able to match controls and patients for weight or BMI. This obviously raises the concern that the differences between patients and controls are due to obesity rather than sleep apnea.
This concern is difficult to refute fully and may require additional studies to resolve completely. One argument against obesity being the sole explanation for our findings, however, are the differences among the sleep apnea patients. When only the patients are considered, obesity does not explain why some patients display vasodilatation and some patients display vasoconstriction when exposed to hypoxia.

Another concern raised by this inability to match patients and controls for BMI is the possibility that differences in the portion of FBF going to adipose tissue might account for the differences we observed in response to hypoxia. Although other investigators have found forearm plethysmography reliable in obese patients, the response of adipose tissue to interventions such as drug infusions may influence FBF measurements (2). Thus adipose tissue might contribute disproportionately to the hypoxic vasoconstriction response observed in the patients. Arguing against this interpretation, however, is the variability in the response of the patients. As noted below, the dichotomous response of the patients was not explained by weight or BMI. Another possibility is that skin blood flow accounted for a greater percentage of the FBF in the patients than in the controls. Hypoxia produces skin vasoconstriction in normal human volunteers (12). If skin blood flow accounted for a greater percentage of FBF in patients relative to controls, this might explain the vasconstrictor response in the patients. We have no reason to believe that skin blood flow was different in one group of patients relative to the other, however.

In addition to differences between patients and controls in weight, we also were not able to match them for degree of cardiovascular conditioning. Anecdotally, the control subjects were more conditioned than the patients, possibly explaining the difference in baseline HRs between the two groups. These differences between patients and controls may have contributed to our findings, but we were unable to recruit a cohort of patients with severe OSA, who were not obese, and we did not find obese control subjects without any degree of sleep-disordered breathing.

One final aspect of our data that warrants comment is the variability in responses among the patients. The control subjects displayed a single pattern of response to isocapnic hypoxia, with a decrease in FVR and an increase in MAP likely mediated primarily through an increase in HR. This is the pattern of response previously described in normal volunteers (12). The patient group, however, displayed two distinct patterns of response. Approximately one-half of the patients behaved similarly to the controls. The remaining patients, however, responded differently, with increased FVR and a blunted HR response. We do not know what distinguished the patients who vasodilated from those who vasoconstricted. Post hoc comparisons of the patients who demonstrated vasoconstriction with those who demonstrated vasodilatation failed to disclose differences in weight, BMI, or severity of OSA. In addition, there were no differences regarding age, sleep apnea severity, presence of hypertension, or absence of a normal nocturnal decline in arterial pressure.

We do not currently have an explanation for why patients respond differently from one another when exposed to progressive isocapnic hypoxia. Nor do we have an explanation for the lesser degree of hypoxic forearm vasodilatation in our patients compared with our controls. Although obesity might be important in limiting the amount of vasodilatation observed, that explanation is made less likely by the patients’ ability to match the controls’ response to forearm ischemia. Although our findings may suggest augmented chemoreceptor sensitivity in patients compared with controls, such a conclusion is premature. We did not measure peripheral sympathetic nerve activity in these subjects. Such a measurement would be of great interest.

In conclusion, we found that, as a group, patients with sleep apnea do not vasodilate during isocapnic hypoxia as do nonapneic controls. This abnormal vascular response may be related to the development of diurnal hypertension in OSA patients.

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