Peripheral vascular resistance increases after termination of obstructive apneas

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Anand, Amit, Stacia Remsburg-Sailor, Sandrine H. Launois, and J. Woodrow Weiss. Peripheral vascular resistance increases after termination of obstructive apneas. J Appl Physiol 91: 2359–2365, 2001.—The mechanisms by which obstructive apneas produce intermittent surges in arterial pressure remain poorly defined. To determine whether termination of obstructive apneas produce peripheral vasoconstriction, we assessed forearm blood flow during and after obstructive events in sleeping patients experiencing spontaneous upper airway obstructions. In all subjects, heart rate was monitored with an electrocardiogram and blood pressure was monitored continuously with digital plethysmography. In 10 patients (protocol 1), we used forearm plethysmography to assess forearm blood flow, from which we calculated forearm vascular resistance by performing venous occlusions during and after obstructive episodes. In an additional four subjects, we used simultaneous Doppler and B-mode images of the brachial artery to measure blood velocity and arterial diameter, from which we calculated brachial flow continuously during spontaneous apneas (protocol 2). In protocol 1, forearm vascular resistance increased 71% after apnea termination (29.3 ± 15.4 to 49.8 ± 26.5 resistance units, P < 0.05) with all patients showing an increase in resistance. In protocol 2, brachial resistance increased at apnea termination in all subjects (219.8 ± 22.2 to 358.3 ± 46.1 mmHg·l⁻¹·min⁻¹; P = 0.01). We conclude that termination of obstructive apneas is associated with peripheral vasoconstriction.

forearm blood flow; vasoconstriction; upper airway obstructions

NOCTURNAL OSCILLATIONS in arterial pressure are the hemodynamic hallmark of obstructive sleep apnea (OSA). The peak arterial pressure of the apnea-recovery cycle occurs 5–7 s after apnea termination, in association with both the nadir of oxygen saturation and arousal from sleep (20). The changes in cardiac function that occur with obstructive apneas are less well defined. Garpestad et al. (9), using a nuclear cardiographic device to estimate beat-by-beat changes in left ventricular stroke volume, demonstrated a decrease in stroke volume during the apneic period with a further abrupt decrease in stroke volume and cardiac output after apnea termination. Bonsignore et al. (3) confirmed the validity of this finding by determining right ventricular output using a flow probe placed in the proximal pulmonary artery in sleeping patients. This suggests that vascular resistance must increase at apnea termination to account for the arterial pressure peak. At present there are no studies that have looked at vascular resistance during apnea and recovery asleep in patients with OSA.

Recent research has focused on hypoxic chemostimulation (1, 17, 23) and arousal (6, 11), the sudden disruption of sleep, as two factors that might account for the sudden change in pressure in the postapnea period. Evidence suggests that both transient hypoxia (1, 17) and arousal (2, 20) may each lead to increases in arterial pressure, making it difficult to assign a primary causal role to either factor. Several recent studies suggest, however, that the pattern of the cardiovascular response to upper airway obstruction during sleep may help determine whether arousal or chemostimulation primarily accounts for the hemodynamic response to obstructive apneas. Evidence from these studies suggests that arousal may elicit a specific patterned cardiovascular response. McNamara and colleagues (15), studying normal infants, first suggested that tactile arousal elicits a behavioral response with components of the startle reaction. Horner et al. (11) next studied the heart rate response of dogs to acoustic arousal using different pharmacological agents and determined that the heart rate response to arousal was different from a simple return to the waking state. In part on the basis of these findings, Launois et al. (12) suggested that arousal might elicit a specific patterned hemodynamic response resembling the cardiovascular defense reaction. Using a porcine model, she and her co-workers confirmed that acoustic and other nonrespiratory arousals most frequently elicit visceral vasoconstriction and limb vasodilation: the pattern of the...
cardiovascular defense reaction (24). In a follow-up study, however, these investigators found that airway occlusions in sleeping pigs elicited a response different from that observed to nonrespiratory arousals (13). Airway occlusions produced visceral vasoconstriction but with limb vasoconstriction, distinct from nonrespiratory arousals.

On the basis of these findings, we hypothesized that spontaneous apneas in humans would elicit a patterned hemodynamic response distinct from the cardiovascular defense reaction. To test this hypothesis, we measured limb blood flow during and after spontaneous apneas in patients with documented OSA.

METHODS

Subjects

We recruited otherwise healthy patients with previously diagnosed sleep apnea from the Sleep Disorders Center at the Beth Israel Deaconess Medical Center. We excluded subjects taking vasoactive medications or with evidence of preexisting chronic disease, including hypertension, cardiovascular disease, intrinsic lung disease, or diabetes. Each subject had a complete medical history, physical examination, and diagnostic polysomnogram before participation. The studies were approved by the hospital Committee on Clinical Investigations, and all subjects gave written, informed consent.

We recruited 15 patients to participate in protocol 1 and an additional 6 patients to participate in protocol 2. No patient participated in both protocols. We excluded 7 patients from the final data analysis for the following reasons: difficulty obtaining consistent forearm blood flow (FBF) measurements because of marked respiratory variability (3 patients, protocol 1); marked cuff jump with inflation of the venous occlusion cuff (2 patients, protocol 1); absence of obstructive apneas during the research study (1 patient, protocol 2); or equipment malfunction (1 patient, protocol 2). As a result, 10 patients completed protocol 1 and 4 patients completed protocol 2, and all were included in the final data analysis. The clinical and anthropometric characteristics of all subjects who completed each protocol are described in Table 1.

Measurements

FBF. We measured FBF by venous occlusion plethysmography. Flow was expressed in milliliters per 100 ml of limb tissue within the strain gauge per minute. We calculated forearm vascular resistance (FVR) by dividing the mean arterial pressure by FBF.

At the beginning of the study, we placed a mercury-in-Silastic strain gauge at the midpoint of the forearm with a distally placed wrist exclusion cuff and a proximal venous occlusion cuff. We placed the subject’s arm in a passive position above the level of the left atrium. Before data collection, while the patient was awake, we performed a series of occlusions at different pressures ranging from 20 to 50 mmHg. We used the occlusion pressure that resulted in the steepest slope of the arterial inflow curve for all subsequent trials. This sequence resulted in venous occlusion pressures between 25 and 45 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 systolic arterial pressure; intermittent venous occlusions were each maintained for a duration of 6–10 s.

Brachial blood flow. We measured brachial blood flow using a 7.5-Hz transducer applied to the brachial artery in the biceps ridge proximal to the antecubital fossa. We expressed brachial blood flow in milliliters per minute. We calculated brachial vascular resistance by dividing mean arterial pressure (mmHg) by brachial blood flow. We acquired simultaneous Doppler and B-mode images of the brachial artery using a Phillips P700 machine. The Doppler probe was positioned over the brachial artery at an angle of insonation between 40° and 60° to obtain a stable velocity profile. This was kept constant during measurements made during sleep. Arterial diameter was measured from longitudinal B-mode images acquired with the transducer applied to the vessel so that both near and far walls were clearly identifiable. We derived blood velocity from pulsed Doppler signals processed by a real-time fast Fourier transform spectrum analyzer to produce a Doppler spectrum. Frequency was converted to flow velocity (in cm/s) by using the Doppler equation. Real-time images and velocities were captured and recorded directly to computer memory (DT3152 Frame Grabber, Data Translation, Marlboro, MA) for later analysis by using custom software (see below). Image acquisition was gated to the R wave of the electrocardiogram and adjusted to store five images of an ~30-Hz signal, allowing estimation of brachial artery diameter and flow velocity at an offset of one beat. That is, the first diameter was discarded, and flow velocity was shifted. This system thus permits sampling of every beat, and each set of R-wave-gated diameters and velocities can be related to the cardiac cycle within which it occurs.

By acquiring images as described, we were able to correlate diameter and velocity. We determined brachial diameters from the digitized B-mode images using customized software (CVI Analysis, Information Integrity, Stow, MA). Mean blood flow velocity is derived from the equation

\[ Q_{ba} = \pi D^2/8 \times V_m \]

where \( Q_{ba} \) is brachial artery blood flow, \( D \) is the diameter of the brachial artery, and \( V_m \) is the mean flow velocity across the vessel.

### Table 1. Subject characteristics

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Means ± SD

<table>
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<th>Mean ± SD</th>
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<tr>
<td>1</td>
<td>44.6 ± 7.3</td>
<td>35.1 ± 5.3</td>
<td>75.8 ± 20.4</td>
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<td>2</td>
<td>38.0 ± 10.6</td>
<td>34.3 ± 5.9</td>
<td>101.2 ± 10.3</td>
</tr>
</tbody>
</table>

M, male; F, female; BMI, body mass index (weight in kg)/height in cm); AHI, apnea-hypopnea index in events per hour of sleep. Age is in yr.

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Arterial pressure. During protocol 1, arterial pressure was measured continuously by digital photoplethysmography (Finapres, Ohmeda), and mean arterial pressure was calculated as one-third the pulse pressure plus diastolic pressure. During protocol 2, we also measured arterial pressure using digital photoplethysmography but we used the Portapress (TNO, Amsterdam).

Muscle sympathetic nerve activity. We obtained nerve recordings using standard tungsten microelectrodes inserted into the peroneal nerve posterior to the fibular head, after localization by surface stimulation. Signals were filtered, amplified, and full-wave rectified. The rectified signal was integrated for display on an oscilloscope and for recording (Nerve Traffic Analyzer, model 662c-3, University of Iowa Bioengineering, Iowa City, IA). Electrode position in muscle fibers was confirmed by pulse-synchronous bursts of activity occurring 1.2–1.4 s after the QRS complex, reproducible activation during the second phase of the Valsalva maneuver, elicitation of afferent nerve activity elicited by mild muscle stretching, and the absence of response to startle (loud unexpected noise). We expressed integrated activity per minute in arbitrary international units.

Polysomnography. We performed sleep monitoring using standard techniques (19). We monitored central and occipital electroencephalogram (EEG; C4/A1, O2/A1). In addition, we monitored electrooculogram; submental electromyogram; and nasal and oral airflow by thermistors, nasal pressure catheter, or monitoring end-tidal CO2 (mass spectrometer, Perkin Elmer), and we monitored respiratory effort by inductance plethysmography (Respitrace). All studies took place between the hours of 9:00 PM and 3:00 AM.

Protocol and Data Analysis

Protocol 1. We measured FBF at baseline before sleep onset and then during and immediately after spontaneous apneas developing during stable stage 2 non-rapid eye movement (NREM) sleep. We made baseline measurements with
the patient resting supine, after at least 10 min of quiet waking, which was confirmed by EEG monitoring. Most subjects required frequent verbal stimulation to remain awake while supine. At baseline, we made five measurements of FBF with each occlusion lasting 6–8 s. Arterial pressure was measured from all beats coincident with the period of occlusion.

We began data collection after at least 10 min of stage 2 NREM sleep when the patient displayed repetitive, stereotypical apneas each lasting longer than 10 s. We alternated venous occlusions during apnea with occlusions initiated at the onset of apnea termination. We attempted to perform occlusions so that cuff inflation occurred coincident with the peak of arterial pressure in the postapnea period. This permitted measurement of FBF during a period of arterial pressure stability but did not allow us to measure FBF during the rapid rise in pressure that immediately follows apnea termination. We determined apnea termination in real time as the first evidence of airflow evident in the oronasal thermocoupler. We included in data analysis measurements made during and immediately after apnea termination. We attempted to perform occlusions during apneas lasting longer than 10 s. We alternated venous occlusions after apnea. Apnea and recovery Doppler flow data from protocol 1 were compared by using a paired t-test. We considered a P value <0.05 to be statistically significant.

**RESULTS**

The results of protocol 1 are summarized in Table 2. Heart rate, arterial pressure, and FBF varied significantly across the treatment conditions. For all three variables, recovery was different from both baseline and apnea (P < 0.05), but baseline and apnea were not different from one another (P = NS). FVR increased 71% from apnea to recovery (29.3 ± 15.4 to 49.8 ± 26.5 resistance units) with all patients showing an increase in resistance. Figure 2 displays individual values of FVR at baseline, during apnea, and during recovery.

The results obtained when using venous occlusion plethysmography in protocol 1 were confirmed when...
using ultrasonography in protocol 2. As in protocol 1, blood pressure increased significantly at recovery (77.8 ± 10.0 to 99.3 ± 12.7 mmHg; P = 0.015), whereas blood flow decreased at recovery (360.8 ± 84.4 to 279.5 ± 53.9 ml/min; P = 0.023). Brachial resistance increased at recovery in all subjects (219.8 ± 22.2 to 358.3 ± 46.1 mmHg·1−1·min; P = 0.01). Individual values for mean arterial pressure, brachial artery diameter and blood flow, and brachial vascular resistance are presented in Table 3.

### DISCUSSION

The major finding of this study is that limb vasoconstriction occurs after apnea termination in association with increases in arterial pressure and heart rate, and simultaneous with the nadir of oxygen saturation in the apnea-recovery cycle. We confirmed this vasoconstriction using two independent methods.

Many early clinical reports noted the association between obstructive apneas during sleep and oscillations in arterial pressure and heart rate (5, 10, 18, 26). These reports demonstrated that the highest heart rate and pressure of the apnea-recovery cycle occur immediately after apnea termination (26). The physiological events leading to these hemodynamic fluctuations remain controversial, however. The increase in pressure occurs coincident with an abrupt increase in lung volume, a sudden change in sleep state, and the nadir of oxygen saturation. Although each of these factors may play a role, most investigation has concentrated on arousal, the sudden change in sleep state, and oxygen desaturation as most likely to account for the arterial pressure surge that follows resolution of an obstructive event. Working in this laboratory, Ringler and colleagues (20) studied patients with OSA and compared spontaneous apneas to apneas in which supplemental oxygen was provided at flows sufficient to ameliorate, but not eliminate, desaturations. They then further compared those events with the events after acoustic arousals induced in the same patients sleeping without obstructions on nasal continuous positive airway pressure at levels determined to eliminate obstructions. In this study, supplementary oxygen did not alter the peak arterial pressure after apnea termination, leading the authors to conclude that oxygen desaturation was not necessary to produce the abrupt increase in arterial pressure after apnea termination. These authors also found that acoustic tones sufficient in intensity to disrupt sleep resulted in the same arterial pressure change that occurred after naturally occurring apneas. From this, they concluded that arousal from sleep was sufficient to recreate the hemodynamic response to upper airway obstruction during sleep.

Other investigations have also suggested that arousal might account for the nocturnal oscillations that characterize sleep apnea. Davies et al. (7) used tactile stimuli to produce arousals in sleeping normal volunteers. These authors reported that these nonrespiratory arousals were associated with increases in arterial pressure, and, furthermore, the increase in pressure was proportional to the degree of arousal. Brooks and colleagues (4), using a unique animal model of upper airway obstruction during sleep, found that sleep disruption caused by acoustic stimulation raised nocturnal pressure to the same degree as repetitive induced obstructions.

Other investigations suggest, however, that hypoxia is necessary for the postapnea surge in arterial pressure. Aardweg and Karemaker (1), for example, produced hypoxic breath holds in normal individuals by rebreathing and observed marked elevations of pressure after release of the apnea. Studying sleep apnea patients, Leuenberger and colleagues (14) recorded sympathetic nervous system activity during spontaneous apneas and during apneas in which oxygen supplementation completely abolished desaturations. MSNA decreased with oxygen supplementation as did the change in arterial pressure during the apnea-recovery cycle. Peak pressure was unaltered, however, as oxygen supplementation reduced the nadir of pressure achieved during the apnea. Morgan et al. (16) measured MSNA during voluntary breath holds in normal volunteers. Oxygen desaturation was mild during the breath holds; however, administration of oxygen before breath hold reduced the sympathetic response in similar manner to that observed by Leuenberger et al. (14) in sleep apnea patients having spontaneous obstructions. Morgan and colleagues (16) speculated that the degree of chemostimulation was likely augmented by the mild hypercapnia that resulted from the breath hold, accounting for the effect of supplementary oxygen.

Whatever the stimulus, arousal or hypoxia, our data suggest that the postapneic increase in arterial pressure is mediated through peripheral vasoconstriction. This finding is consistent with several studies that

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**Table 3. Arterial pressure, brachial diameter, brachial flow and brachial resistance during and after spontaneous obstructive apneas**

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>MAP, mmHg</th>
<th>Dia, mm</th>
<th>BBF, ml/min</th>
<th>BVR, mmHg·1−1·min</th>
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<td>118</td>
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<tr>
<td><strong>Means ± SD</strong></td>
<td><strong>77.8 ± 10.0</strong></td>
<td><strong>99.3 ± 12.7</strong></td>
<td><strong>5.55 ± 0.12</strong></td>
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**Dia,** brachial diameter; **BBF,** brachial blood flow; **BVR,** brachial vascular resistance. *P < 0.05, recovery compared with apnea.
examined cardiac output changes after obstructive apneas. Garpestad et al. (9), using a nuclear probe, demonstrated a decrease in left ventricular stroke volume and cardiac output in the immediate postapnea period. Escourrou and co-workers (8), using pulse contour analysis, also found a decrease in stroke volume, although this was buffered by tachycardia to maintain cardiac output. Bonsignore and colleagues (3) used a right ventricular flow probe in OSA patients to provide additional documentation of a decrease in cardiac function after release of obstruction. All these studies thus are consistent with our finding that peripheral vasoconstriction underlies the postapnea increase in arterial pressure.

Our findings in patients with OSA are similar to those of Launois and colleagues (13) in their animal model that created airway obstructions in sleeping pigs. That is, airway obstruction produces limb vasoconstriction. One interesting difference between these patients and the porcine model of airway occlusion described by Launois et al. is the minimal variability in the response we observed in our patients. Although Launois and colleagues described the predominant pattern as being limb and visceral vasoconstriction, there was variability in the behavior of the animals, with a minority of airway occlusions (one-third) followed by limb vasodilation. In our OSA patients, however, the responses were consistent, with all apneas followed by forearm vasoconstriction. These findings are consistent with a recent report by Schnall et al. (21), who reported a consistent pattern of digital vasoconstriction at apnea termination in OSA patients using a finger plethysmograph.

The mechanisms by which vasoconstriction occurs at apnea termination is uncertain. In humans, short-term regulation of vascular tone is predominantly accomplished through alterations of sympathetic tone. Leuenberger and colleagues (14) have shown, however, that sympathetic activity measured by microneurography decreases abruptly at end apnea. Possibly the vasoconstriction we demonstrate is a delayed consequence of increased sympathetic activity during the apnea.

Several technical limitations of our study should be noted. First, using venous occlusion plethysmography, we were unable to precisely time cuff inflation so that measures made during the apnea spanned much, but not all, of the period of obstructed respiration. Furthermore, we were unable to measure FBF during the entire apnea-recovery cycle using plethysmography. We were forced to make our measurements during adjacent spontaneous events. Thus our plethysmographic data do not truly show changes in forearm flow during a continuous event. This weakness is balanced, however, by the use of Doppler flow measurements in protocol 2. The consistency of our findings using this independent measurement supports, we believe, the findings using plethysmography. Our Doppler measurements, however, could only be reliably made during apnea. The limitations of this technique in a sleeping patient are underscored by the variability of the measure on account of placement of the probe at the same angle of insonation on the vessel wall awake and asleep, a small amount of motion artifact with change in state, and the inability of our software program to record large quantities of digitized data in real time.

In summary, this study demonstrates limb vasoconstriction after apnea termination in a group of patients with OSA. These findings are consistent with the results in an animal model of airway occlusion during sleep and with human studies that have measured cardiac function in OSA patients. The mechanism of this vasoconstriction remain speculative.

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REFERENCES


