Increased vasoconstrictor sensitivity in obstructive sleep apnea

HOLGER KRAICZI,1 JAN HEDNER,2 YÜKSEL PEKER,2 AND JAN CARLSON2

Departments of 1Clinical Pharmacology and 2Pulmonary Medicine, Sahlgrenska University Hospital, S-413 45 Gothenburg, Sweden

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WHILE SLEEPING, PATIENTS WITH obstructive sleep apnea (OSA) are exposed to repetitive respiratory pauses that frequently cause systemic hypoxia, activation of the sympathetic nervous system (19), vasoconstriction (17), and increased blood pressure (38). Although it is unknown whether these autonomic and hemodynamic fluctuations translate into permanent vascular dysfunction, it has been suggested that vascular sensitivity to vasoconstrictors is increased in OSA, even in the absence of hypertension (20). This hypothesis is based mainly on an increased pressor response to short-term hypoxia in both patients with OSA (20) and animals exposed to long-term intermittent hypoxia (25). However, the blood pressure response to chemoreceptor activation is a result of a complex interaction of a variety of regulatory components and, thus, may not adequately measure responsiveness toward vasoconstrictive challenges at the vascular level. To specifically investigate whether arteriolar vasoconstrictor sensitivity is increased in OSA, we performed the present study and compared forearm vascular conductance during intra-arterial infusion of incremental doses of the vasoconstrictor angiotensin II between OSA patients and healthy control subjects.

Previous results from our group suggest that OSA is associated with a reduced cholinergic responsiveness of forearm resistance arteries (4) and, therefore, impaired endothelial function (15). In the second part of the present study, we attempted to reproduce these results and compared the forearm arteriolar dilation during intra-arterial infusion of acetylcholine between OSA patients and control subjects. In contrast to the previous study sample, only subjects without known hypertension or regular medication were included. Moreover, variables identified as potential confounders, particularly age, body mass index (BMI), and blood pressure, were controlled more restrictively.

METHODS

Study population. Ten male patients with OSA and 10 male control subjects (announcement in the local newspaper) roughly matched for age (±5 yr) and BMI (±5 kg/m2) were included in the study (Table 1). Their number of apneas plus hypopneas per self-reported hour of sleep (apnea-hypopnea index) was measured in a previous overnight recording using an ambulatory device for ventilatory monitoring (Edentec, Infiniti Medical, Taby, Sweden) or in a laboratory setting with at least thermistor (in-house), static charge-sensitive bed (Bio-matt, Biorec, Raisio, Finland), and pulse oximeter (BIOX 3700, Ohmeda, Louisville, CO). An apnea or hypopnea event was scored when saturation of hemoglobin with O2 in arterial blood declined by at least 4% during or immediately after a cessation of oronasal airflow or a reduction of the thermistor amplitude by at least 50% during 10 s or longer. The minimal apnea-hypopnea index for OSA patients and the maximal apnea-hypopnea index for control subjects were set at 10/h and 5/h, respectively (Table 1). One patient with OSA, who was screened outside our hospital, was included on the basis of an oxygen desaturation index of 29/h. Control subjects had to be free of excessive daytime sleepiness.

Exclusion criteria for both groups were regular intake of any medication, known arterial hypertension, diabetes mellitus, or dyslipidemia as well as screening blood pressures ≥160 mmHg (systolic) or ≥95 mmHg (diastolic). In addition, the costs of publication of this article were defrayed in part by the payment of page charges. The article must therefore be hereby marked “advertisement” in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.
Table 1. Clinical characteristics of control subjects and OSA patients

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>OSA Patients</th>
<th>P Value</th>
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</thead>
<tbody>
<tr>
<td>Number of subjects</td>
<td>10</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Age, yr</td>
<td>52.8 ± 12.3</td>
<td>52.5 ± 10.6</td>
<td></td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>27.6 ± 2.4</td>
<td>28.4 ± 3.05</td>
<td></td>
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<tr>
<td>Apnea-hypopnea index, h⁻¹</td>
<td>1.6 ± 1.0</td>
<td>39.8 ± 22.6*</td>
<td>0.13</td>
</tr>
<tr>
<td>Serum cholesterol, mmol/l</td>
<td>4.9 ± 0.9</td>
<td>5.8 ± 1.5*</td>
<td></td>
</tr>
<tr>
<td>Serum triglycerides, mmol/l</td>
<td>1.6 ± 1.0</td>
<td>2.1 ± 0.9</td>
<td>0.31</td>
</tr>
<tr>
<td>Serum LDL cholesterol, mmol/l</td>
<td>3.1 ± 0.7</td>
<td>3.9 ± 1.4*</td>
<td>0.11</td>
</tr>
<tr>
<td>Serum HDL cholesterol, mmol/l</td>
<td>1.0 ± 0.3</td>
<td>1.2 ± 0.2*</td>
<td>0.77</td>
</tr>
<tr>
<td>Blood glucose, mmol/l</td>
<td>4.9 ± 0.6</td>
<td>4.6 ± 1.0</td>
<td>0.46</td>
</tr>
<tr>
<td>Blood glycosylated hemoglobin A, %</td>
<td>5.0 ± 0.5</td>
<td>4.9 ± 0.5</td>
<td>0.58</td>
</tr>
<tr>
<td>BP, mmHg, intraarterial</td>
<td>128.7 ± 16.3</td>
<td>128.3 ± 16.0</td>
<td>0.96</td>
</tr>
<tr>
<td>DBP, mmHg, intraarterial</td>
<td>65.5 ± 7.0</td>
<td>73.6 ± 11.8</td>
<td>0.08</td>
</tr>
<tr>
<td>Basal forearm vascular conductance, ml·min⁻¹·dl⁻¹·mmHg⁻¹</td>
<td>0.0264 ± 0.0085</td>
<td>0.0348 ± 0.0165</td>
<td>0.17</td>
</tr>
</tbody>
</table>

Values are means ± SD. OSA, obstructive sleep apnea; BMI, body mass index; LDL, low-density lipoprotein; HDL, high-density lipoprotein; SBP, systolic blood pressure; DBP, diastolic blood pressure. P values determined by Student’s t-test; *n = 9.

subjects with BMI ≥35 kg/m², serum cholesterol ≥7.5 mmol/l or blood glucose ≥6.8 mmol/l at the day before the experiment were replaced. The study had been approved by the Ethics Committee of the Medical Faculty of Göteborg University, and all subjects gave informed consent before participating.

**Measurement of forearm blood pressure and flow velocity.** Blood pressure in the brachial artery of the nondominant arm was recorded with an 18-gauge polyethylene catheter (Viggo-Spectramed, Swindon, UK). The catheter was inserted under local anesthesia (lidocaine 1%) and connected to a Sirecust 403–2p monitor (Siemens, Karlsruhe, Germany) via a DPT-6000 pressure transducer (Peter von Berg GmbH). Five-second averages of systolic and diastolic blood pressures (SBP and DBP, respectively) were obtained from the paper printout of the monitor and used to calculate mean blood pressure (MBP) according to the conventional approximation $MBP = DBP + [1/3(SBP – DBP)]$. Before each reading, the local blood pressure curve was checked visually for artifacts.

Forearm blood flow was measured in the same arm, using the venous occlusion plethysmographic technique originally described by Whitney (44). A mercury-in-elastic strain gauge was placed on the widest part of the forearm, which was resting comfortably on a support slightly above the level of the heart. The strain gauge was connected to an electronically calibrated plethysmograph (Elektromedizin, Kungsbacka, Sweden) linked to a filter pen recorder (BD 101–6, Kipp & Zonen, Delft, The Netherlands). For flow measurements, arm veins were occluded by automated rapid inflation (50 mmHg within ±1 s) of a cuff applied proximal to the elbow. Circulation in the hand was restrained from 1 min before until the end of the flow measurements by inflating a pediatric blood pressure cuff placed around the wrist to 50 mmHg above systolic pressure. By this procedure, the unpredictable influence of arteriovenous shunts in the hand was eliminated. Forearm blood flow at baseline and during all dosage steps of the experimental protocol (see below) was determined by geometric analysis and averaging of three consecutive plethysmographic recordings (41, 42).

**Study procedure.** One day before the experiment, fasting venous blood samples were obtained for determination of blood glucose, glycosylated hemoglobin A, and total, low-density, and high-density lipoprotein-borne cholesterol as well as triglycerides in serum. The samples were immediately sent to the hospital laboratory for routine analysis. One day later, on the day of experiments, subjects had a light, low-fat breakfast at home before arriving at the hospital at ~07:30 AM. Intake of drugs or beverages containing caffeine or alcohol was not allowed within 12 h before the start of the investigation. Experiments took place in a quiet room with a temperature of ~22°C (72°F) with the subjects in a supine position. After instrumentation and subsequent 30- to 60-min rest, forearm flow and intra-arterial blood pressure at baseline were determined (3–6 measurements). Study drugs were then infused intra-arterially with stepwise increments of dosage at contiguous 4-min intervals. First, human angiotensin II (Clinalifa, Läufelings, Switzerland) was infused at dose steps of 10, 30, and 100 pmol/min. After 1 h of rest, acetylcholine was given (Miochol, Ciba Vision, Asken, Sweden) at dosages of 82.5, 165, and 330 nmol/min (15, 30, and 60 μg/min).

**Data handling.** Forearm blood flow was determined during the last 30 s of each 4-min dosage interval of the experimental protocol. The corresponding interval MBP was calculated by averaging MBP values obtained before and after the respective dose interval. Dividing flow velocity by the corresponding interval MBP yielded vascular conductance for a given dose interval.

Analysis of covariance (ANCOVA) was performed to test the significance of factors OSA (patients vs. controls) and dosage (repeated measurements representing three incremental dosages) in determining forearm vascular conductance for each substance studied (STATISTICA 5.0, StatSoft, Tulsa, OK). Baseline conductance was used as covariate (27). To rule out an important influence of baseline MBP distribution on statistical inferences, analyses of covariance were repeated with baseline MBP as an additional covariate. Baseline differences in blood pressure, forearm flow conductance, and clinical-chemical results between controls and OSA patients as well as MBP changes over consecutive infusions were compared with independent samples and paired t-tests, respectively. Differences with P values lower than 0.05 were considered statistically significant.

**RESULTS**

Age, BMI, metabolic variables, and baseline forearm vascular conductance did not differ significantly between control subjects and OSA patients (Table 1). An insignificant between-group difference in MBP at baseline ($P = 0.311$) remained unchanged throughout the experimental i.e., MBP did not differ significantly between OSA patients and control subjects at any measurement point (Table 2). In both groups, we observed a significant increase in MBP from baseline to the highest dosage of angiotensin II (controls: 4.7 mmHg, $P = 0.012$; OSA patients: 6.6 mmHg, $P = 0.018$), whereas all other changes from angiotensin II or acetylcholine baselines remained within random limits.
Table 2. Brachial artery MBP

<table>
<thead>
<tr>
<th>Dosage</th>
<th>Controls</th>
<th>OSA Patients</th>
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<tbody>
<tr>
<td>Angiotensin II</td>
<td></td>
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</tr>
<tr>
<td>Baseline</td>
<td>86.6±9.4</td>
<td>91.8±13.0</td>
</tr>
<tr>
<td>10 pmol/min</td>
<td>87.7±10.6</td>
<td>94.4±12.5</td>
</tr>
<tr>
<td>30 pmol/min</td>
<td>88.0±10.6</td>
<td>95.4±12.3</td>
</tr>
<tr>
<td>100 pmol/min</td>
<td>91.3±9.6*</td>
<td>98.4±12.2*</td>
</tr>
<tr>
<td>Acetylcholine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>89.8±13.2</td>
<td>95.6±10.5</td>
</tr>
<tr>
<td>82.5 mmol/min</td>
<td>90.9±12.6</td>
<td>95.2±10.5</td>
</tr>
<tr>
<td>165 mmol/min</td>
<td>92.3±13.3</td>
<td>95.5±10.4</td>
</tr>
<tr>
<td>330 mmol/min</td>
<td>91.6±13.2</td>
<td>97.5±9.9</td>
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</tbody>
</table>

Values are means ± SD. MBP, mean blood pressure (mmHg).

Intra-arterial infusion of angiotensin II (Fig. 1) resulted in a dose-dependent decrease in forearm vascular conductance in both groups ($P < 0.001$). The extent of vasoconstriction, however, was significantly enhanced in the OSA group, the average conductance of which over all three dosage steps was 39.6% lower than that of the control group ($P = 0.002$; $P = 0.667$ for interaction between factors OSA and dosage), despite slightly increased baseline values. Further correction of ANCOVA results for baseline MBP did not importantly influence the comparison between control subjects and OSA patients ($P = 0.004$ after correction). Because MBP increased during infusion of the last angiotensin II dose (by 6.4 mmHg in the control subjects and 5.0 mmHg in the OSA patients), ANCOVA was repeated with conductance for the highest dosage period calculated from MBP obtained immediately after flow measurements instead of the corresponding interval MBP. However, essentially the same results were obtained (data not shown).

During infusion of acetylcholine (Fig. 2), forearm vascular conductance increased in both groups ($P < 0.001$). Averaged over all three dosage steps, conductance in the OSA subjects was 20.3% lower than in the control subjects, but this difference was not significant ($P = 0.631$ for the group comparison; $P = 0.669$ for the interaction term).

**DISCUSSION**

The results of the present study suggest that the forearm vasoconstrictor response to angiotensin II is increased in normotensive patients with OSA. Because sensitivity to vasoconstrictors is determined by a variety of mechanical and biochemical factors, several mechanisms may have contributed to this finding.

First, increased vasoconstrictor responsiveness in the OSA patients may be a result of early structural alterations of the arteriolar wall. Increased wall-tolumen ratio, in particular, generates greater force and thus enhanced resistance increase at a given concentration of vasoconstrictor (14). A conceivable physiological basis for such vascular remodeling in OSA may be provided by nocturnal blood pressure surges (28), which are an inherent characteristic of disordered breathing during sleep (40). Moreover, increased permanent or nocturnal release of norepinephrine (13), thromboxane A2 (26), and/or endothelin (36) in OSA may have promoted long-term vascular growth resulting in greater vasoconstrictor sensitivity in our sample of OSA patients (18, 30, 37, 45). Recent findings from animal studies that show increased activity of the renin-angiotensin system as a consequence of increased sympathetic tone during intermittent hypoxia (12) lend additional support for an increased growth-promoting influence on the vessel wall in OSA (8). However, histological evidence may be required to reveal whether OSA is associated with structural vascular remodeling, as suggested by the present physiological findings.

Second, greater reduction of vascular conductance during angiotensin II infusion may reflect increased sensitivity of the vessel wall to vasoconstrictors at the
cellular level. In this context, altered endogenous activity of the renin-angiotensin system does not provide a likely explanation for our findings, because experimental angiotensin converting-enzyme inhibition (24, 31) and sodium depletion (2) do not influence the vascular sensitivity to angiotensin II in humans. Alternatively, parts of the constrictive action of angiotensin II may be explained by augmented presynaptic release of norepinephrine (5), reduced reuptake of catecholamines (6), and facilitation of the vasoconstrictive effect of sympathetic activation (43). Therefore, enhanced vasoconstriction in the OSA patients in the present study may be a consequence of increased sympathetic tone, a further well-known characteristic of OSA (3, 19). However, because other vasoconstrictors, e.g., oxygen radicals (9), contribute to the constrictor effect of angiotensin II, norepinephrine is merely one among several conceivable vasoconstrictors that may have augmented the decrease in conductance during angiotensin II infusion in the OSA patients.

Third, angiotensin II-induced vasoconstriction is normally attenuated by concomitant release of nitric oxide (NO) via shear stress-dependent and -independent pathways (9). Consequently, enhanced vasoconstriction during angiotension II infusion in OSA may be the result of reduced coactivation of endothelial NO synthesis or increased NO degradation accompanying activation of NO synthesis. Such diminished net effect of endothelium-dependent NO production is in accordance with previous data showing reduced acetylcholine-induced vasodilation in OSA (4). In addition to this presumed dysfunction at the level of NO synthesis, however, reduced recruitment of counterregulatory vasodilators may also be the consequence of a diminished effect of angiotensin II at the angiotensin II type 2 (AT$_2$) receptor (21), which has been suggested to mediate NO release (39), cGMP production (16), and vasodilation (1). Downregulation of AT$_2$ receptors or disturbed AT$_2$ postreceptor signal transduction is therefore a further possible mechanism behind our observation. Interestingly, norepinephrine, the release of which is permanently increased in OSA (3, 7, 13), downregulates AT$_2$ expression in cardiac myocytes (23), providing some support for this concept.

Finally, the net effect of endogenous vasodilators, e.g., NO, on the extent of pharmacologically induced vasodilation may be nullified by a prevailing neurohumoral and/or paracrine vasoconstrictor overweight. Therefore, increased sensitivity to angiotensin II in OSA as found in the present study may be the result of a shifted balance between endogenous vasoconstrictors (3, 7, 36) and vasodilators to a higher level of activity, exhausting the capability of vasodilator mechanisms to counteract additional vasoconstrictive challenges (10).

The question remains whether the systemic MBP increase observed during infusion of the third angiotensin II dose in the present experiment may have confounded the comparison of vasoconstrictive responses between control subjects and OSA patients. Several reasons, however, may argue against such possibility. First, the blood pressure increase was of the same magnitude in both groups, thus inducing merely a small risk of interference with the between-group comparison. Second, statistical control of the differences in conductance between controls and OSA patients for MBP changes from baseline did not importantly change the results. Third, between-group differences in vasoconstrictor sensitivity were obvious at the first two doses of angiotensin II, when MBP was not different from baseline values. Thus blood pressure changes due to infusion of the highest dose of angiotensin II may not have affected our results.

Increased sensitivity of the vascular wall to vasoconstrictive challenges, as suggested by the present results, provides an explanation for the exaggerated blood pressure response to short-term hypoxia in OSA, a phenomenon that is independent of baseline blood pressure (20). Simultaneously, enhanced hypoxic pressor response and increased vasoconstrictor sensitivity in OSA suggest that the hemodynamic consequences of apneas during sleep, such as repetitive activation of the sympathetic nervous system (19) and blood pressure surges (40), may be aggravated during the natural course of OSA. Moreover, because the blood pressure (but not heart rate) response to physical workload predicts long-term cardiovascular mortality (11), our findings might reflect one mechanism behind the predisposition to cardiovascular disease suggested by epidemiological studies in OSA patients (22, 35).

In contrast to previous results from our group (4), responsiveness of the forearm vasculature to acetylcholine was not significantly reduced in the OSA patients. One explanation for this discrepancy may be the stricter control for potential confounding factors in the present study. In particular, because endothelial function is reduced in hypertension (34), subjects with known hypertension or with previous or concomitant antihypertensive medication were not included in the present study. Moreover, potential confounding effects of age and BMI (4, 32) were minimized by stricter matching for these factors in the present study. Another difference between the present and the previous study was the use of flow conductance rather than resistance as a measure of vascular tone. Because of their reciprocal, i.e., nonlinear, relation, substitution of one index for the other may importantly influence conclusions about vasoconstrictor responsiveness (33). In experiments of the present type, with primary changes in flow rather than in pressure, use of conductance in contrast to resistance reduces the risk of spurious statistical conclusions (29) and was therefore considered more appropriate for the present study. Another reason for the selection of conductance was that the hemodynamic effects of changes in conductance but not resistance are independent of baseline values and, thus, are more likely to adequately reflect the relevance of vascular responses for blood pressure regulation (33). Nevertheless, the discrepancy between the previous and the present results may illustrate that
the detection of endothelial dysfunction in OSA is sen-
tive to the experimental setting. More powerful studies
specifically focusing on endothelium-dependent vascular responsiveness will be required to solve this
problem.

In conclusion, our findings support the hypothesis that sensitivity to vasoconstrictors is increased in pa-
ients with OSA. The functional state of the endo-
the
dependent vasodilator reserve in OSA, however,
remains controversial.

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