Contribution of Tonic Chemoreflex Activation to Sympathetic Activity and Blood Pressure in Patients With Obstructive Sleep Apnea

Krzysztof Narkiewicz, MD, PhD; Philippe J.H. van de Borne, MD, PhD; Nicola Montano, MD, PhD; Mark E. Dyken, MD; Bradley G. Phillips, BSc, PharmD; Virend K. Somers, MD, PhD

Background—Muscle sympathetic nerve activity (MSNA) is increased in patients with obstructive sleep apnea (OSA). We tested the hypothesis that tonic activation of excitatory chemoreceptor afferents contributes to the elevated sympathetic activity in OSA.

Methods and Results—Using a double-blind, randomized, vehicle-controlled design, we examined the effects of chemoreflex deactivation (by comparing effects of breathing 100% oxygen for 15 minutes with effects of breathing room air for 15 minutes) on MSNA, heart rate, blood pressure, and minute ventilation in 14 untreated patients with OSA and in 12 normal subjects matched for age and body mass index. All control subjects underwent overnight polysomnography to exclude the existence of occult OSA. Baseline MSNA was markedly elevated in the patients with OSA compared with the control subjects (44 ± 6 versus 30 ± 3 bursts per minute; P = .01). In both control subjects and patients with OSA, heart rate decreased during administration of 100% oxygen but did not change during administration of room air. By contrast, both MSNA (P = .008) and mean arterial pressure (P = .02) were significantly reduced during chemoreflex deactivation by 100% oxygen only in patients with OSA but not in control subjects.

Conclusions—Tonic activation of excitatory chemoreflex afferents may contribute to increased efferent sympathetic activity to muscle circulation in patients with OSA. (Circulation. 1998;97:943-945.)

Key Words: nervous system, autonomic nervous system, sympathetic nervous system, apnea, sleep blood pressure heart rate
Sympathetic nerve activity to muscle was recorded as described previously.7 Breathing was via a mouthpiece with a nose clip to ensure exclusive mouth breathing. Minute ventilation was determined with an S430 ventilation measuring system (KL Engineering) that uses a precision, ultralight, unidirectional, inertia-compensated, turbine flow transducer. Breathing was via a mouthpiece with a nose clip to ensure exclusive mouth breathing. Sympathetic activity was also expressed as bursts per minute, which allows a comparison of sympathetic discharge between individuals,2,8 thus permitting a comparison of resting MSNA between sleep apnea patients and control subjects. Measurements were made by a single observer (K.N.) blinded to subject and intervention.

Demographic data and baseline characteristics during breathing of room air were compared by use of an unpaired t test. The responses to administration of 100% oxygen and room air were assessed as comparisons between measurements taken during the last 5 minutes of baseline with measurements averaged over 15 minutes of hyperoxia or room air administration. Data were analyzed by repeated-measures ANOVA with time (before versus during gas administration) as within factor and gas (100% oxygen versus room air) as between factor. The P values for differences within a session were obtained by post hoc tests (planned contrasts). The key variable was the gas-by-time interaction. Data are presented as mean±SEM. A value of $P<.05$ was considered significant.

### Results

Baseline characteristics of the patients with OSA and control subjects during breathing of room air are shown in Table 1. Oxygen saturation, end-tidal CO$_2$ partial pressure, MAP, and heart rate in patients with sleep apnea were not significantly different from those observed in obese subjects without sleep apnea. Baseline MSNA was markedly elevated in the patients with OSA compared with the control subjects (44±4 versus 30±3 bursts per minute; $P=.01$).

Ventilatory responses to 100% oxygen were not significantly different from those observed during room air in both control

### Table 1. Baseline Measurements of Patients With OSA and Normal Control Subjects

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Patients With OSA (n=14)</th>
<th>Normal Control Subjects (n=12)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxygen saturation, %</td>
<td>98.8±0.3</td>
<td>99.4±0.3</td>
<td>.17</td>
</tr>
<tr>
<td>End-tidal CO$_2$, mm Hg</td>
<td>36±2</td>
<td>37±1</td>
<td>.80</td>
</tr>
<tr>
<td>Minute ventilation, L/min</td>
<td>8.6±0.6</td>
<td>7.3±0.6</td>
<td>.11</td>
</tr>
<tr>
<td>MAP, mm Hg</td>
<td>96±3</td>
<td>89±4</td>
<td>.08</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>67±4</td>
<td>65±4</td>
<td>.43</td>
</tr>
<tr>
<td>MSNA, bursts per minute</td>
<td>44±4</td>
<td>30±3</td>
<td>.01</td>
</tr>
</tbody>
</table>

Values are mean±SEM.

### Table 2. Effects of 100% Oxygen and Room Air in Normal Subjects and in Patients With Sleep Apnea

<table>
<thead>
<tr>
<th>Measurement</th>
<th>100% Oxygen</th>
<th>Room Air</th>
<th>Interaction, 100% Oxygen vs Room Air, $P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal subjects (n=12)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minute ventilation, L/min</td>
<td>7.2±0.6</td>
<td>7.5±0.7</td>
<td>7.9±0.8</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>65±4</td>
<td>62±3†</td>
<td>65±4</td>
</tr>
<tr>
<td>MAP, mm Hg</td>
<td>89±3</td>
<td>86±3†</td>
<td>87±3</td>
</tr>
<tr>
<td>MSNA, bursts per minute</td>
<td>30±3</td>
<td>26±3*</td>
<td>30±3</td>
</tr>
<tr>
<td>Integrated MSNA, %</td>
<td>100</td>
<td>90±3</td>
<td>100</td>
</tr>
<tr>
<td>Patients with sleep apnea (n=14)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minute ventilation, L/min</td>
<td>8.4±0.6</td>
<td>8.2±0.4</td>
<td>8.1±0.6</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>66±2</td>
<td>62±2†</td>
<td>65±2</td>
</tr>
<tr>
<td>MAP, mm Hg</td>
<td>98±4</td>
<td>94±3†</td>
<td>95±3</td>
</tr>
<tr>
<td>MSNA, bursts per minute</td>
<td>43±4</td>
<td>37±4†</td>
<td>43±4</td>
</tr>
<tr>
<td>Integrated MSNA, %</td>
<td>100</td>
<td>83±3‡</td>
<td>100</td>
</tr>
</tbody>
</table>

Values are mean±SEM.

$P$ values for the gas×time interaction term (ANOVA): *$P<.05$, †$P<.01$, ‡$P<.001$ vs before gas administration (planned contrasts).
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normal-weight young subjects. Another possible explanation gen elicits reductions in MSNA and not blood pressure, but in
activation. Previous studies in humans show that 100% oxy-
pressure and heart rate, probably mediated by sympathetic
even during normoxia has significant effects on both blood
excitatory chemoreflex afferents.

OSA might be explained in part by tonic activation of
elevated sympathetic nerve activity to muscle in patients with
with OSA but not in normal, obese control subjects. Thus,
MSNA and blood pressure in normoxic, normotensive patients
icates that chemoreflex deactivation with hyperoxia decreases
This double-blind, randomized, vehicle-controlled study indi-
torward a fall in MAP and MSNA in the obese control subjects
in our study. This underscores the importance of the double-
blind, vehicle-controlled study design.
The fall in MSNA and heart rate elicited by 100% oxygen was
evident even though baseline oxygen saturation was normal
in patients with sleep apnea and was accompanied by a
fall in blood pressure. This suggests a causal interaction
between the reductions in MSNA, heart rate, and blood
pressure, because reductions in blood pressure would other-
wise elicit increases in MSNA and heart rate. We also confirm
previous findings of higher MSNA in patients with sleep
apnea. Norepinephrine may be an important contributor to
increased chemoreceptor drive. We speculate that the
chronic levels of efferent sympathetic activity in patients
with OSA may be implicated in the high tonic arterial
chemoreceptor drive.

In conclusion, chemoreflex deactivation decreases MSNA
and blood pressure in patients with OSA but not in normal
obese subjects without sleep–related disordered breathing.
Thus, tonic chemoreflex activation may contribute to
increased sympathetic activity and blood pressure in patients
with OSA.

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and an NIH Sleep Academic Award (Dr Somers). We thank Diane
Davison, RN, MA, for technical assistance.

Discussion
This double-blind, randomized, vehicle-controlled study indi-
cates that chemoreflex deactivation with hyperoxia decreases
MSNA and blood pressure in normoxic, normotensive patients
with OSA but not in normal, obese control subjects. Thus,
elevated sympathetic nerve activity to muscle in patients with
OSA might be explained in part by tonic activation of
excitatory chemoreflex afferents.

Studies in animals indicate that tonic chemoreflex activation
even during normoxia has significant effects on both
blood pressure and heart rate, probably mediated by sympathetic
activation. Previous studies in humans show that 100% oxygen
elicits reductions in MSNA and not blood pressure, but in
normal-weight young subjects. Another possible explanation
for the previously observed decrease in MSNA during 100% oxygen
in normal subjects might be acclimation to the
laboratory setting and to mouthpiece breathing. In the present
study, 100% oxygen decreased MSNA and MAP in both
normal obese control subjects and patients with OSA. How-
ever, the changes in MSNA and MAP during administration
of 100% oxygen were significantly different from those during
room air administration only in patients with OSA, because
room air breathing was also accompanied by a tendency

Recordings of MSNA in a single patient with OSA during adminis-
tration of 100% oxygen (top) and room air (bottom). MSNA, MAP,
and heart rate (HR) decreased during administration of 100% oxy-
gen but did not change during administration of room air.

subjects and patients with OSA (Table 2). In both control
subjects and patients with OSA, heart rate decreased during
100% oxygen but did not change during room air (Table 2).
In patients with OSA, chemoreflex deactivation decreased
MSNA (P = .008) and MAP (P = .02) (Figure, Table 2). By
contrast, the effects of 100% oxygen and room air on MSNA
and MAP in control subjects were not different (Table 2). The
changes in MSNA during 100% oxygen administration in
patients with OSA did not correlate with the baseline oxygen
saturation levels (r = .31; P = .27).

This double-blind, randomized, vehicle-controlled study indicates
that chemoreflex deactivation with hyperoxia decreases
MSNA and blood pressure in patients with obstructive
2. Somers VK, Dyken ME, Clary MP, Abboud FM. Sympathetic neural
3. Binet L, Jeayrous P. Le role des chemorecepteurs arteriels dans la controle
de la respiration pulmonaire chez l'homme. Arch Int Pharmacodyn. 1962;
139:328–335.
4. Loeschke GC. Spielen fü für die Ruheatmung des Menschen vom O2-Druck
abhängige Erregungen der Chemoreceptoren eine Rolle? Pflegers Arch. 1953;
5. Honig A. Peripheral arterial chemoreceptors and reflex control of sodium
6. Seals DR, Johnson DG, Fregosi RF. Hyperoxia lowers sympathetic activity
at rest but not during exercise in humans. Am J Physiol. 1991;260:
R873–R878.
1983:36–51.
8. Schober HP, Fischer T, Heuzer K, Geiger H, Schneider RE. Pre-
1480–1485.
9. Przybylski J, Trzebski A, Czyzewski T, Jodkowski J. Responses to
hyperoxia, hypoxia, hypercapnia and almitrine in spontaneously hyper-
10. Milom WK, Sadig T. Interaction between norepinephrine and hypoxia on
carotid body chemoreception in rabbits. J Appl Physiol. 1983;55:
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References
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2. Somers VK, Dyken ME, Clary MP, Abboud FM. Sympathetic neural
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