Potentiation of Sympathetic Nerve Responses to Hypoxia in Borderline Hypertensive Subjects

VIREND K. SOMERS, ALLYN L. MARK, AND FRANÇOIS M. ABBOUD

SUMMARY We tested the hypothesis that sympathetic nerve responses to stimulation of chemoreceptors by hypoxia are exaggerated in borderline hypertensive humans. We compared responses to isocapnic hypoxia in eight borderline hypertensive subjects and eight normotensive control subjects matched for age, sex, weight, and height without a family history of hypertension. Measurements of heart rate, mean blood pressure, minute ventilation, and sympathetic nerve activity to muscle were made before and during hypoxia. We also measured responses to a period of voluntary apnea during hypoxia. There were no significant differences between the increases in heart rate, blood pressure, and ventilation in response to hypoxia in the two groups. However, during hypoxia sympathetic activity in the hypertensive subjects increased by 40.6 ± 13.6% (mean ± SE), greater than the increase of 20.4 ± 5.0% in the control subjects (p<0.05). In six hypertensive and six control subjects, when apnea was performed during hypoxia, sympathetic activity increased by 605.0 ± 294.3% in the hypertensive subjects and by only 52.8 ± 17.3% in the control subjects (p<0.001). We conclude that the chemoreceptor reflex is enhanced in borderline hypertensive subjects and results in exaggerated increases in sympathetic nerve activity during hypoxia. This enhanced chemoreceptor reflex is especially obvious when the inhibitory influence of breathing and thoracic afferent activity is eliminated by apnea. This exaggerated response may contribute to excess sympathetic activity in borderline hypertensive subjects and to adverse consequences of sleep apnea in hypertensive subjects.

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KEY WORDS • sympathetic activity • chemoreceptor stimulation • microneurography • borderline hypertension

There is evidence for increased sympathetic activity in humans with borderline or mild hypertension. This increase may result from central nervous system abnormalities or from impairment of the influence of inhibitory arterial baroreceptors. In addition, increases in sympathetic activity could result in part from increased sensitivity of excitatory peripheral chemoreceptors. We have found that stimulation of chemoreceptors in dogs causes selective increases in peripheral sympathetic activity, with significant reflex vasoconstriction in skeletal muscle and reflex dilatation in the paw. In humans, hypoxia may increase minute ventilation, blood pressure, and heart rate and cause hand vasoconstriction. In recent abstracts, Blumberg and Oberle reported increases in sympathetic nerve activity to muscle during systemic hypoxia.

It has been suggested that the chemoreceptor reflex is exaggerated in spontaneously hypertensive rats and in hypertensive humans and that this reflex may be involved in the pathophysiology of essential hypertension. Spontaneously hypertensive rats have a respiratory alkalosis that may result from an increased ventilatory drive even during normoxic conditions. In addition, carotid sinus nerve chemoreceptor discharge is increased in spontaneously hypertensive rats in response to hypoxia, but not hypercapnia. Trzebski et al. have reported an increased inspiratory drive in response to hypoxia in hypertensive young men.

We used direct intraneural recordings of sympathetic nerve activity to test the hypothesis that borderline hypertensive subjects had an exaggerated increase in sympathetic nerve activity during hypoxic stimulation of the chemoreceptor reflex. An increase in sympathetic nerve responsiveness to hypoxic chemoreceptor stimulation could contribute to increased sympathetic nerve activity in borderline hypertensive subjects and to adverse consequences of sleep apnea in hypertensive subjects.

From the Departments of Medicine and Physiology, the Cardiovascular Center and the Veterans Administration Medical Center, University of Iowa College of Medicine, Iowa City, Iowa.

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Address for reprints: François M. Abboud, M.D., Department of Internal Medicine, University of Iowa College of Medicine, Iowa City, IA 52242.
Subjects and Methods

Eight borderline hypertensive men and eight normotensive men (matched for age, weight and height) without a family history of hypertension were studied (Table 1). Subjects having blood pressure levels intermittently above 150/90 mm Hg were defined as borderline hypertensive. Normotensive subjects were those in whom blood pressure readings were consistently less than 135/85 mm Hg. All subjects were otherwise healthy, not regular smokers, only social drinkers, and receiving no medications. The study was approved by the institutional committee on human investigation, and all subjects gave informed written consent.

We measured blood pressure (Physio-Control LifeStat 200 semiautomated sphygmomanometer, Redmond, WA, USA), heart rate, end-tidal CO₂ (Hewlett-Packard 47210A capnometer, Andover, MA, USA), oxygen saturation (Nellcor N-100 C pulse oximeter, Hayward, CA, USA), ventilatory rate, and minute ventilation (Bourns LS-75 Ventilomonitor, Riverside, CA, USA). Sympathetic activity was obtained from direct multiunit recordings from a nerve fascicle to the skin or the tongue, and from the reference electrode was inserted subcutaneously about 3 cm away. All 16 subjects breathed the following gas mixtures in a Latin square design: 1) 14% O₂, 86% N₂; 2) 10% O₂, 90% N₂; 3) 10% O₂, 90% N₂ with titrated CO₂ to maintain isocapnia; 4) 7% CO₂, 93% O₂.

At least 20 minutes was allowed between exposures to the different gas mixtures. Only data dealing with the responses to isocapnic hypoxia are presented in this report. Subjects underwent 3 minutes of baseline recordings, when they breathed room air through a mouthpiece and a three-way valve. Breathing exclusively through the mouth was ensured by using a nose clip. Baseline recordings (breathing room air for 3 minutes) were followed by exposure to isocapnic hypoxia (i.e., 10% O₂, 90% N₂, with CO₂ titrated to maintain isocapnia) for 5 minutes. The gas mixture was breathed from a 130-L reservoir bag. In addition, toward the end of the 5-minute hypoxic stress, six hypertensive and six control subjects underwent a brief period (<15 seconds) of voluntary end-expiratory apnea.

The mean voltage neurogram, electrocardiogram, end-tidal CO₂, oxygen saturation, and respiratory movements were displayed on a Gould 2800 S recorder (Cleveland, OH, USA). Sympathetic bursts were identified by inspection of the mean voltage neurogram, and sympathetic activity was calculated as bursts/minute × mean burst amplitude and expressed in arbitrary units.¹²

Statistical analysis of paired observations was performed using either Student's t test (two-tailed) or Wilcoxon's signed rank test, where indicated. Significance was assumed at the 5% level. Responses to isocapnic hypoxia were contrasted to baseline recordings on room air. Responses to a period of apnea during exposure to isocapnic hypoxia were compared with responses during a period of apnea of identical duration while the subject was breathing room air. Values obtained in the hypertensive subjects were compared with those obtained in the normotensive subjects. Results are presented as means ± 1 SE.

Results

Resting Values

Frequency of sympathetic nerve activity (bursts/ min) and minute ventilation at rest while subjects were breathing room air did not differ significantly in the two groups. End-tidal CO₂ was also similar in the normotensive (40.4 ± 1.1 mm Hg) and the hypertensive subjects (39.6 ± 1.4 mm Hg). Oxygen saturation averaged 97.0 ± 0.4% in the normotensive and 97.8 ± 0.5% in the hypertensive subjects (p = NS). Heart rate was also similar in both groups, but blood pressure was higher in the hypertensive subjects (see Table 1).

Effects of Hypoxia

Oxygen saturation during hypoxia did not differ in the normotensive (81.5 ± 1.1%) and hypertensive subjects (81.9 ± 0.8%). Both hypertensive and normotensive subjects showed small increases in blood pressure and heart rate and significant increases in minute ventilation during hypoxia. The magnitude of these increases was not significantly different between the two groups (Table 2 and Figure 1). In contrast, sympathetic nerve activity increased by 20.4 ± 5.0% in the normotensive subjects but by 40.6 ± 13.6% in the hypertensive subjects (p < 0.05; see Figures 1 and 2).

Effects of Apnea During Hypoxia

The duration of apnea during hypoxia was brief and did not differ in the two groups (13.5 ± 2.1 seconds in the normotensive subjects and 14.8 ± 1.4 seconds in the hypertensive subjects). During apnea, oxygen saturation fell to 67.3 ± 4.7% in the normotensive subjects and to 66.8 ± 4.6% in the hypertensive subjects.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normotensive (n = 8)</th>
<th>Hypertensive (n = 8)</th>
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<tbody>
<tr>
<td>Age (yr)</td>
<td>26.8 ± 1.6</td>
<td>26.0 ± 2.0</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>88.1 ± 7.2</td>
<td>87.5 ± 4.6</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>179.0 ± 2.0</td>
<td>181.3 ± 2.5</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>63.4 ± 3.7</td>
<td>64.0 ± 3.0</td>
</tr>
<tr>
<td>Mean blood pressure (mm Hg)</td>
<td>84.5 ± 2.2</td>
<td>94.9 ± 2.1*</td>
</tr>
<tr>
<td>Minute ventilation (L/min)</td>
<td>7.4 ± 0.5</td>
<td>8.1 ± 0.5</td>
</tr>
</tbody>
</table>

Values are means ± SE. *p < 0.01, compared with normotensive values.
Table 2. Responses to Hypoxia

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normotensive (n=8)</th>
<th>Hypertensive (n=8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td>Baseline</td>
<td>Hypoxia</td>
</tr>
<tr>
<td>63.4±3.7</td>
<td>82.3±3.7*</td>
<td></td>
</tr>
<tr>
<td>Mean blood pressure (mm Hg)</td>
<td>Baseline</td>
<td>Hypoxia</td>
</tr>
<tr>
<td>84.5±2.2</td>
<td>87.5±2.8</td>
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<td>Baseline</td>
<td>Hypoxia</td>
</tr>
<tr>
<td>7.4±0.5</td>
<td>13.6±1.3*</td>
<td></td>
</tr>
</tbody>
</table>

Values are means ± SE. *p<0.01, compared with respective baseline values.

(p = NS). Increases in heart rate tended to be greater in the normotensive subjects (38.3 ± 9.3%) than in the hypertensive subjects (17.2 ± 5.9%), when compared with heart rates during apnea on room air, but these differences were not significant.

Sympathetic nerve activity, however, increase by 52.8 ± 17.3% in the normal subjects and by 605.0 ± 294.3% in the hypertensive subjects (p < 0.001) with apnea during hypoxia (Figures 3 and 4). For these subjects (i.e., six in each group) during breathing, hypoxia resulted in increases in nerve activity of 20.8 ± 6.9% in the normotensive and 44.7 ± 18.3% in the hypertensive subjects (see Figures 4 and 5).

Discussion

These data show that the increase in sympathetic activity to muscle in response to hypoxia is more marked in borderline hypertensive subjects. This hyperresponsiveness is especially obvious during apnea. Apnea enhanced the sympathetic nerve response to hypoxia on the average by more than 12-fold in the hypertensive subjects and by less than threefold in the normotensive subjects. Thus, during apnea, when the pulmonary afferent–mediated inhibition of sympathetic activity is excluded, there is a striking augmentation of the sympathetic response to hypoxia in the hypertensive subjects. It seems, therefore, that borderline hypertensive persons have an exaggerated chemoreceptor sensitivity to hypoxia. Furthermore, it appears that, during breathing, the pulmonary afferent inhibition of sympathetic activity is more profound in borderline hypertensive subjects.

Explanations for these data include the possibility that structural changes in vessels of the carotid body (e.g., narrowed arteriolar lumens) are present in early hypertension and that these changes predispose to a greater chemoreceptor stimulation by hypoxia. Also, in a hypoxic situation, there may be a higher level of efferent sympathetic vasoconstrictor activity to arterioles within the carotid body in hypertensive subjects, hence possibly amplifying the hypoxic stimulus.

There may also be a nonspecific sympathetic hyperresponsiveness of borderline subjects to all excitatory stimuli. This possibility is unlikely since Fukuda et al. have shown that the chemoreceptor hyperresponsiveness in spontaneously hypertensive rats exists only to a hypoxic and not to a hypercapnic stimulus. Furthermore, the hypertensive subjects in the study by Trzebski et al. showed an increased response to hypoxia but not to hypercapnia.

The chemoreceptor reflex may also be augmented because of an associated decrease in baroreceptor activity. An interaction between arterial baroreceptors and the chemoreceptor reflex has been demonstrated by our group, such that a decrease in baroreceptor input causes an augmentation of the chemoreceptor reflex and vice versa. Since the arterial baroreflex is decreased in hypertensive subjects, an exaggerated chemoreceptor reflex might be anticipated on that basis.

Although there was an increased sympathetic re-

**Figure 1.** Percent increases in mean blood pressure, heart rate, minute ventilation, and sympathetic nerve activity in eight borderline hypertensive subjects and eight normotensive controls. During hypoxia, the increase in sympathetic nerve activity was significantly greater in the hypertensive subjects.

**Figure 2.** Sympathetic nerve activity during exposure to room air and 10% O2 in a normotensive subject and a borderline hypertensive subject. Hypoxia produced a greater increase in sympathetic nerve activity in the hypertensive subject.
CHEMOREFLEX RESPONSES IN BORDERLINE HYPERTENSION/Somers et al.

Figure 3. Sympathetic nerve activity during 10 to 15 seconds of apnea in a normotensive subject and a borderline hypertensive subject while on room air and while on 10% O2. During hypoxia, the increase in sympathetic nerve activity with apnea was particularly pronounced in the hypertensive subject.

Response in the hypertensive subjects, there was no evidence of an increased ventilatory response. The discrepancy between our findings regarding these variables and the findings of Trzebski et al.4 may be explained by methodological differences (i.e., the use of a rebreathing technique to induce hypoxia and a greater degree of chemoreceptor stimulation with a lower level of oxygen saturation5). Alternatively, there may be a dissociation between the sympathetic and the ventilatory responses to hypoxia in the hypertensive subjects (i.e., the abnormality in the hypertensive subjects' response to a hypoxic stimulus may be more selective toward muscle sympathetic efferent activity than to ventilation). This possibility suggests that the abnormality includes a central selective augmentation of the chemoreflex rather than or in addition to the increased sensitivity to the peripheral chemoreceptor sensory input.

The absence of a greater pressor response to hypoxia in the hypertensive subjects may result from an effective buffering of blood pressure by baroreceptors and the selective local vasodilator effect of hypoxia on blood vessels.19-20 Hypoxia also may directly inhibit certain vasoconstrictor responses.5

The tendency toward a lower heart rate response to hypoxia in the hypertensive group during breathing and apnea may reflect an augmented parasympathetic response to hypoxia in the hypertensive group. In animals, the chemoreceptor reflex causes marked cardiac parasympathetic stimulation but the bradycardia is apparent only in the absence of hyperventilation.21

The increased chemoreceptor-mediated sympathetic response to hypoxia in hypertensive subjects found in the present study raises the possibility that there may be a higher level of sympathetic activity in normoxic conditions in hypertensive subjects, due to tonic chemoreceptor afferent discharge. There was no evidence for an increased burst frequency of baseline sympathetic activity between groups and between subjects. The absolute value of resting activity depends on the placement of the electrode in the nerve and the number of sympathetic fibers that are "sampled" by it. Large differences may need to be present to allow detection of differences by measurements of absolute values. On the other hand, a difference in the percent increase in activity with a stimulus is easily detectable as a result of normalization.

Our findings of chemoreceptor hyperexcitability are in the context of young borderline hypertensive subjects. It is not known if this phenomenon is present in
people with established hypertension. If the chemoreceptor hyperexcitability persists into the established hypertension phase, this may have important consequences during sleep apnea. Hypertensive patients are known to be at high risk for sleep apnea. Those with left ventricular hypertrophy are also more prone to complex ventricular arrhythmias and sudden death. High levels of sympathetic activity resulting from the combined effects of hypoxia and apnea may precipitate cardiac arrhythmias and sudden death in these people, especially in the presence of coexisting ischemic heart disease.

In conclusion, our data suggest that borderline hypertensive subjects have an exaggerated sympathetic nerve response to hypoxic stimulation of the chemoreceptor reflex. This increased responsiveness is especially obvious when the modulating influence of breathing (mediated by thoracic afferents) on sympathetic nerve activity is eliminated by apnea.

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References

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V K Somers, A L Mark and F M Abboud

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