Exposure to hypoxia produces long-lasting sympathetic activation in humans

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Xie, Ailiang, James B. Skatrud, Dominic S. Puleo, and Barbara J. Morgan. Exposure to hypoxia produces long-lasting sympathetic activation in humans. J Appl Physiol 91: 1555–1562, 2001.—The relative contributions of hypoxia and hypercapnia in causing persistent sympathoexcitation after exposure to the combined stimuli were assessed in nine healthy human subjects during wakefulness. Subjects were exposed to 20 min of isocapnic hypoxia (arterial O2 saturation, 77–87%) and 20 min of normoxic hypercapnia (end-tidal PCO2, +5.3–8.6 Torr above eupnea) in random order on 2 separate days. The intensities of the chemical stimuli were manipulated in such a way that the two exposures increased sympathetic burst frequency by the same amount (hypoxia: 167 ± 29% of baseline; hypercapnia: 171 ± 23% of baseline). Minute ventilation increased to the same extent during the first 5 min of the exposures (hypoxia: +4.4 ± 1.5 l/min; hypercapnia: +5.8 ± 1.7 l/min) but declined with continued exposure to hypoxia and increased progressively during exposure to hypercapnia. Sympathetic activity returned to baseline soon after cessation of the hypercapnic stimulus. In contrast, sympathetic activity remained above baseline after withdrawal of the hypoxic stimulus, even though blood gases had normalized and ventilation returned to baseline levels. Consequently, during the recovery period, sympathetic burst frequency was higher in the hypoxia vs. the hypercapnia trial (166 ± 21 vs. 104 ± 15% of baseline in the last 5 min of a 20-min recovery period). We conclude that both hypoxia and hypercapnia cause substantial increases in sympathetic outflow to skeletal muscle. Hypercapnia-evoked sympathetic activation is short-lived, whereas hypoxia-induced sympathetic activation outlasts the chemical stimulus.

sympathetic nervous system; chemical stimuli

TO INVESTIGATE THE PATHOGENETIC link between sleep-disordered breathing and hypertension, our laboratory has conducted two previous studies of the neurocirculatory consequences of acute exposure to blood-gas perturbations in healthy subjects during wakefulness. The major finding of these studies is that 20-min exposure to asphyxia (combined hypoxia and hypercapnia), applied in either sustained or intermittent fashion, caused sympathoexcitation that persisted after withdrawal of the chemical stimuli (31, 49). In contrast, exposure to hypercapnia, which was delivered with a hyperoxic background that greatly attenuated input from carotid chemoreceptors (21), did not cause sustained increases in muscle sympathetic nerve activity. These findings suggest that either hypoxia or peripheral chemoreceptor stimulation (by hypoxia or hypercapnia) is required to produce persistent sympathetic activation. To clarify the contribution of hypoxia vs. hypercapnia to the sympathetic carryover effect produced by asphyxia, we exposed healthy subjects to isocapnic hypoxia and normoxic hypercapnia on 2 separate days and examined the neurocirculatory and ventilatory responses to these two chemical stimuli individually. Our rationale was that, if the carryover effect on sympathetic outflow requires nonspecific peripheral chemoreceptor stimulation, we should see persistent sympathoexcitation after exposure to both hypoxia and hypercapnia. On the other hand, if this carryover effect is dependent on hypoxia acting either peripherally or centrally, a persistent increase in sympathetic outflow should be observed only after the hypoxic exposure.

METHODS

Subjects. Fourteen healthy volunteers (9 men and 5 women, aged 28 ± 9 (SD) yr) served as subjects. All were free from cardiovascular, pulmonary, and neurological diseases as evaluated by history and physical examination. All subjects were nonsmokers, and they were taking no medications. This study was approved by the University of Wisconsin Health Sciences Human Subjects Committee. All subjects provided informed consent.

General procedures. All experiments commenced at the same time of day (1300), and the room temperature was maintained at 24 ± 1°C. Subjects were studied in the supine position. Respiratory and cardiovascular variables and sympathetic nerve activity were recorded continuously on paper (model TA 4000; Gould, Cleveland, OH) and on magnetic tape (model 4000A, PCM; Vetter, Rebersburg, PA). The signals were also routed to a computer for off-line analysis of the data.

Respiratory variables. Subjects breathed through a leak-free nasal mask to which a pneumotachograph (model 5719; Hans Rudolph, Kansas City, MO) was attached for measurement of tidal volume and breathing frequency. Minute ventilation (V̇E) was calculated by multiplying tidal volume by respiratory rate (V̇E = TV × FR).

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breathing frequency. End-tidal O₂ (PetCO₂) and CO₂ tensions (PetCO₂) were sampled from the mask and measured by gas analyzers (models S-3A/I and OD-3; Ametek, Pittsburgh, PA). Arterial O₂ saturation (Sao₂) was measured by using a pulse oximeter (Biox model 3740; Ohmeda, Madison, WI).

Cardiovascular variables. Heart rate was taken from the electrocardiogram, and arterial pressure was measured at 1-min intervals by using an automated arm-cuff sphygmmomanometer (Dinamap model 1846SX/P; Critikon, Tampa, FL). Blood flow was measured in the left leg by venous occlusion plethysmography (14). During this measurement, the limb was elevated above the level of the right atrium to collapse the veins. A collecting cuff positioned above the knee was rapidly inflated to 40 mmHg for four to five cardiac cycles every 30 s. Sixty-second averages of the blood flow measurements were used in the computation of results. Vascular resistance was calculated as mean arterial pressure (one-third pulse pressure + diastolic pressure) divided by blood flow (in ml·100 ml-tissue⁻¹·min⁻¹).

Sympathetic nerve activity. Postganglionic muscle sympathetic nerve activity in the right tibial (peroneal) nerve was recorded by using intraneural microelectrodes (42). Placement of the recording electrode in a muscle nerve fascicle was confirmed by the 1) presence of muscle twitches, not paresthesias, in response to electrical stimulation; 2) characteristic pattern of discharge in pulse-synchronous bursts; 3) different activity in response to tapping or stretching of muscle, but not gentle stroking of skin, in the appropriate receptive fields; and 4) absence of neural activation in response to arousal stimuli. The neural signals were amplified (total gain = 100,000), filtered (band pass = 700–2,000 Hz), and integrated (time constant = 100 ms); and signal-to-noise ratio > 3:1 was required for an acceptable neural recording. Sympathetic bursts were identified by inspection of the mean voltage neurogram (48). For purposes of quantification, muscle sympathetic nerve activity was expressed as burst frequency (bursts/min) and burst amplitude (arbitrary units).

Experimental protocols. The 20-min hypoxic and hypercapnic exposures occurred on 2 separate days at least 1 mo apart. The order of the exposures was randomized, with 7 out of 14 subjects receiving the hypoxic exposure first. In the isocapnic hypoxia trial, 95% nitrogen was added to the breathing circuit for two to three breaths, followed by 10–12% O₂, so that Sao₂ fell to 80%. PetCO₂ was maintained at the eupneic level by increasing the inspired CO₂ fraction as necessary. In the normoxic hypercapnia trial, a gas mixture of 5–8% CO₂ was added to the breathing circuit so that PetCO₂ rose by +7 Torr. To prevent the rise in arterial PO₂ that normally accompanies exposure to hypoxia, we added N₂, as necessary, to the breathing circuit. Thus Sao₂ was maintained at the room-air baseline level during the CO₂ breathing. In the second trial, we titrated the chemical stimuli to match the amount of sympathetic activation observed in the first visit. During isocapnic hypoxia, the average Sao₂ was 80.2 ± 1% (range, 77–87%) with PetCO₂ maintained at the eupneic level (43.2 ± 1.0 vs. 41.8 ± 2.1 Torr, P > 0.05). During normoxic hypercapnia, the average increase in PetCO₂ was +6.5 Torr (range, 5.3–8.6 Torr) above the eupneic level, and neither Sao₂ (97.6 ± 0.3 vs. 97.3 ± 0.3%) nor PetCO₂ (110 ± 4 vs. 102 ± 4 Torr) was changed relative to the eupneic levels (both P > 0.05).

Both hypoxia and hypercapnia caused significant increases in Ve; however, the time course of responses to the two stimuli was dissimilar (Figs. 1 and 2). Ventilation rose progressively during the hypercapnic exposure, whereas Ve peaked early in the hypoxic exposure and then declined. Ve returned to baseline levels within the first 5 min after removal of the chemical stimuli in both the hypoxia (7.9 ± 0.7 vs. 8.0 ± 0.7 l/min, P > 0.05) and hypercapnia (9.4 ± 0.6 vs. 7.7 ± 0.4 l/min, P > 0.05) trials. All other respiratory variables, such as PetCO₂, PetO₂, and Sao₂, also returned to baseline levels after the return to room-air breathing (Table 1).

Effect of hypoxia and hypercapnia on muscle sympathetic nerve activity. By design, sympathetic burst frequency increased to the same extent during the hypoxic and hypercapnia trials (Figs. 1 and 2). During the final 5 min of the exposures, sympathetic burst frequency had increased to 167 ± 28% of baseline in hypoxia and 171 ± 23% of baseline in hypercapnia (P > 0.05). After the hypoxic exposure, burst frequency remained elevated for the duration of the recovery period. In contrast, after hypercapnic exposure, burst...
frequency returned to the baseline level within 5 min after resumption of room-air breathing (114 ± 6% of baseline, *P* < 0.05). The difference in burst frequency between hypoxia and hypercapnia trials was statistically significant during the final 10 min of the recovery period. Neither hypoxia nor hypercapnia affected sympathetic burst amplitude. There was a very strong association between sympathetic burst frequency and **V˙E** in the hypercapnia trial (*r* = 0.98, *P* < 0.05), but only weak association between the two variables in the hypoxia trial (*r* = 0.53, *P* < 0.05). Figure 1 shows a representative subject, in whom we were able to observe sympathetic nerve activity for 60 min after removing the chemical stimuli in both the hypoxia and hypercapnia trials. In this subject, the hypoxia-induced sympathetic activation persisted for the entire 60-min recovery period, whereas sympathetic activation was not maintained in the recovery period after hypercapnic exposure.

**Cardiovascular response to hypoxia and hypercapnia.** Both hypoxia and hypercapnia caused significant increases in heart rate and systolic blood pressure that returned to baseline levels after the withdrawal of chemical stimuli (Fig. 3). Neither exposure affected diastolic pressure. Hypoxic exposure caused small, statistically insignificant increases in leg blood flow and decreases in leg vascular resistance, whereas, during the hypercapnic exposure, these variables remained stable (Fig. 4).

**DISCUSSION**

Previously, we found that brief exposure to asphyxia (combined hypoxia and hypercapnia) produced a memory-like effect whereby sympathetic outflow to skeletal muscle remained elevated after withdrawal of the chemical stimuli. In the present study, we sought to determine the relative importance of hypoxia and hyp-
percapnia in causing this persistent sympathetic activation. The major findings are that exposure to hypoxia evoked an increase in sympathetic nerve activity that outlasted the chemical stimulus. In contrast, exposure to hypercapnia, which caused a comparable acute increase in sympathetic nerve activity, failed to produce long-lasting sympathetic activation.

**Critique of methods.** Because the hypoxia and hypercapnia exposures were conducted on 2 separate days, day-to-day variability in baseline levels of sympathetic outflow or in sympathetic responsiveness may have contributed to our findings. To minimize this possibility, we conducted the hypoxia trials and hypercapnia trials in random order. Also, our primary analysis of the carryover effect on muscle sympathetic nerve activity was based on burst frequency measurements. In our experience and that of other investigators, indexes of burst frequency are stable in repeated measures made on separate days (<15%) (42). Finally, we normalized the sympathetic nerve activity data by expressing responses to hypoxia and hypercapnia as the percentage of each individual’s baseline level. Therefore, we consider it unlikely that our finding of persistent sympathetic activation after exposure to hypoxia, but not hypercapnia, can be explained on the basis of day-to-day variability in sympathetic outflow.

The possibility of shifts in electrode position also threatens the validity of our conclusion regarding long-

### Table 1. Group mean values for chemical stimuli produced by isocapnic hypoxia and normoxic hypercapnia

<table>
<thead>
<tr>
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<th>Isocapnic Hypoxia</th>
<th>Normoxic Hypercapnia</th>
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<tr>
<td></td>
<td>Baseline</td>
<td>Exposure</td>
</tr>
<tr>
<td><strong>PetCO₂, Torr</strong></td>
<td>41.8 ± 2.1</td>
<td>43.2 ± 1.0</td>
</tr>
<tr>
<td><strong>PetO₂, Torr</strong></td>
<td>101 ± 2</td>
<td>48 ± 2</td>
</tr>
<tr>
<td><strong>SaO₂, %</strong></td>
<td>96.1 ± 0.3</td>
<td>80.2 ± 1.0</td>
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Values are means ± SE; n = 11 subjects. PetCO₂, end-tidal PCO₂; PetO₂, end-tidal PO₂; SaO₂, arterial O₂ saturation.

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**Fig. 3.** Group mean ± SE values (n = 11) for heart rate (A) and arterial blood pressure (B) before, during, and after 20-min exposure to isocapnic hypoxia (● or ⋄) and normoxic hypercapnia (○ or ◆). The dashed vertical lines indicate the duration of exposure. SBP, systolic blood pressure; DBP, diastolic blood pressure. *Significant difference vs. baseline, *P* < 0.05. There was no difference between hypoxia vs. hypercapnia at any time point.

**Fig. 4.** Group mean ± SE values (n = 11) showing the changes in leg blood flow (A) and leg vascular resistance (B) before, during, and after 20-min exposure to isocapnic hypoxia (●) and normoxic hypercapnia (○). Neither exposure produced statistically significant changes in leg blood flow or vascular resistance.
lasting sympathetic activation after hypoxic exposure. We minimized this possibility by closely monitoring the baseline of the mean voltage neurograms and excluding from analysis experiments in which baseline shifts occurred. It is also possible that the sustained sympathetic activation seen after hypoxic exposure was caused by nonspecific subject discomfort that led to a time-dependent increase in sympathetic outflow during these rather long experiments. This possibility is unlikely because sympathetic outflow returned to baseline after the hypercapnic exposure, which was the same duration as the hypoxia trial. Furthermore, our laboratory previously observed that sympathetic activity remained stable during 40 min of room-air breathing during time control experiments (31).

In this study, we recorded sympathetic discharge that is targeted to vascular structures in leg muscle. This discharge is representative of sympathetic outflow to skeletal muscle vascular beds throughout the body (34). Although resting levels of muscle sympathetic nerve activity are well correlated with norepinephrine spillover in the heart and kidney (45, 46), we cannot extrapolate our findings concerning effects of chemical stimuli on muscle sympathetic nerve activity to other organs or vascular beds.

Neurocirculatory and ventilatory responses to hypoxia and hypercapnia. In the present study, exposures to both hypoxia and hypercapnia caused substantial increases in sympathetic outflow and $V_{\dot{E}}$. We titrated the level of the chemical stimulus in the second exposure to match the amount of sympathetic activation produced by the initial exposure; therefore, by design, the sympathetic responses to hypoxia and hypercapnia were similar. In contrast, the ventilatory responses to the two stimuli were quite different. After comparable initial increases, $V_{\dot{E}}$ increased progressively during continued exposure to hypercapnia, whereas it declined during continued exposure to hypoxia. This “roll-off” phenomenon for $V_{\dot{E}}$, which has been described by previous investigators (3, 22, 44), was not accompanied by a parallel decrease in sympathetic activity. Consequently, the levels of $V_{\dot{E}}$ and sympathetic activation were not correlated during exposure to hypoxia, whereas they were well-correlated during hypercapnia. This disparity in the neurocirculatory and ventilatory responses to the two chemical stimuli was especially evident during the recovery periods after the exposures. Ventilation and sympathetic nerve activity decreased in parallel to baseline levels after the hypercapnic exposure. In contrast, even though $V_{\dot{E}}$ normalized promptly after removal of the hypoxic stimulus, hypoxia-induced sympathetic activation persisted into the recovery period.

Neural pathways involved in hypoxia-induced sympathetic activation. Exposure to hypoxia evokes increases in sympathetic outflow via two partially distinct mechanisms: 1) stimulation of peripheral chemoreceptors and 2) activation of oxygen-sensitive cells within the brain stem. Hypoxia stimulation of the carotid chemoreceptors produces reflex increases in sympathetic outflow to the heart and to the renal, splanchnic, and skeletal muscle vascular beds (30). Afferent nerve signals traveling in the carotid sinus and hypoglossal nerves are relayed via the nucleus of the solitary tract to those neurons in the rostral ventrolateral medulla (RVLM) that are thought to be responsible for generating sympathetic “tone” (see Ref. 15 for detailed description). The respiratory periodicity that is evident in the discharge of these presympathetic neurons (and also in some pre- and postganglionic sympathetic neurons) suggests that they are linked to the central respiratory rhythm generator. Nevertheless, in anesthetized animals, elimination of all central respiratory activity by muscimol injection abolished respiratory oscillations in postganglionic nerve traffic but did not attenuate the sympathetic response to stimulation of peripheral chemoreceptors (25). In addition, increases in cervical preganglionic sympathetic nerve activity could be elicited by peripheral chemoreceptor stimulation even when phrenic discharge was abolished by hyperventilation hypocapnia (23). During hyperventilation-induced apnea in humans, muscle sympathetic nerve activity increased before resumption of respiratory activity in response to gradually accumulating chemoreflex stimuli (38). Taken together, these findings suggest that some chemoreceptor information can reach the presympathetic RVLM neurons without an intervening relay within the respiratory network.

The presympathetic neurons of the RVLM also act as important mediators of hypoxia’s central effects. Severe hypoxia can activate RVLM neurons directly (39). In anesthetized rats, systemic hypoxia caused activation of RVLM presympathetic neurons and neurons of the lumbar sympathetic chain, an effect that persisted after the section of the carotid sinus nerves (39). This sympathetic activation, which could not be evoked by systemic hypercapnia, was accompanied by decreased activity in respiratory neurons in the RVLM and in the phrenic nerve. Similarly, other investigators have found that severe systemic hypoxia can elicit increases in sympathetic outflow after denervation of peripheral chemoreceptors (20) and after splitting of the lower medulla (26). In anesthetized animals, only severe levels of hypoxia (i.e., inspired $O_2$ fraction $\leq 10\%$) have thus far been shown to stimulate RVLM presympathetic neurons (39). Therefore, direct stimulation of brain stem neurons by the moderate levels of hypoxia (inspired $O_2$ fraction $= 12–13\%$) used in our study may or may not have contributed to the increase in muscle sympathetic nerve activity that we observed.

Mechanisms of hypercapnia-induced sympathetic activation. Increases in $P_{CO_2}$ stimulate sympathetic outflow by both peripheral (carotid chemoreceptor) and central neural mechanisms (12, 16, 27). The cells responsible for mediating the central component of the neurocirculatory response to hypercapnia are thought to be located in RVLM regions that have some overlap with central $CO_2$ chemoreceptors (27). Are these the same medullary cells that respond to hypoxia? The observation that hypercapnia did not excite presympathetic neurons in the RVLM that were activated by
hypoxia (39), taken together with the finding that hypercapnia and hypoxia caused different patterns of Fos expression in medullary neurons (40), suggests that central processing of hypoxic and hypercapnic stimuli occurs at distinct locations. As is the case with hypoxia, existing evidence suggests that CO₂-induced increases in sympathetic outflow can occur independently of increases in activity of central respiratory network (24, 38, 41).

Mechanism for the persistent sympathetic activation after hypoxic exposure. The present findings demonstrate that generic chemoreceptor stimulation is not sufficient to produce an aftereffect on sympathetic discharge; instead, hypoxia is required. We consider it unlikely that the marked increase in sympathetic outflow evoked during hypoxic exposure could, per se, have had a stimulatory effect on postganglionic activity, because hypercapnia-induced sympathoexcitation of comparable magnitude failed to do so. Moreover, muscle sympathetic activity is increased substantially by other experimental interventions (e.g., lower body suction, static exercise), yet it returns promptly to baseline levels after removal of the stimuli (29, 43). We also consider it unlikely that the sustained sympathetic activation that we observed after hypoxic exposure was caused by continued chemoreceptor stimulation because end-tidal gases (and presumably arterial blood gases) normalized soon after withdrawal of the stimuli. The finding that ventilation also returned to baseline promptly after the exposure in our study is consistent with this notion. Instead, our findings point to the possibility of long-lasting facilitation of sympathetic outflow that is dependent on prior hypoxic stimulation. We speculate that this memory-like effect occurs in RVLM neurons responsible for generating sympathetic “tone” and that it is caused by a modulatory effect of brain hypoxia on central processing of afferent input from peripheral chemoreceptors.

Long-term potentiation of synaptic transmission, the proposed mechanism underlying learning and memory (28), is generally thought to require gene transcription and new protein synthesis (32). Previous investigators have observed increased levels of Fos, a protein marker of synaptic activation and gene transcription, in RVLM regions with excitatory inputs to sympathetic preganglionic neurons after relatively brief (60 min) and longer term (8 h/day for 30 days) exposures to hypoxia (13, 18). Increased Fos expression in the RVLM was also observed after 10 min of electrical stimulation of the carotid sinus nerves (5). Similar increases have been observed after exposure to hypercapnia; however, high levels of inspired CO₂ fraction (13%) seem to be required for Fos expression (35).

Absence of a hypoxia-induced aftereffect on ventilation. The slowly disappearing posthypoxic effect on sympathetic outflow that we observed may be analogous to the ventilatory acclimatization that maintains breathing above baseline levels for hours and even days after exposure to the hypoxia of high altitude (2). If so, why didn’t our subjects demonstrate a persistent increase in ventilation after hypoxic exposure? One possibility is that we maintained eucapnia during the hypoxic exposures. Previous studies that employed isolated carotid body perfusion to increase ventilation suggest that brain hypoxia and hypocapnia are both required to produce long-term facilitation of breathing (4).

Hemodynamic responses to hypoxia vs. hypercapnia. Both hypoxia and hypercapnia caused increases in heart rate and systolic blood pressure that returned to baseline during the recovery period. The lack of change in diastolic blood pressure is consistent with the unchanged or even decreased peripheral vascular resistance that we observed in our study. We speculate that increases in sympathetic vasoconstrictor outflow did not raise leg vascular resistance because of the overriding vasodilatory influence of hypoxia and hypercapnia on vascular smooth muscle (12, 17). This idea is consistent with recent information from a canine model of obstructive sleep apnea (36). In that study, systemic blood pressure fell during apneas that occurred under conditions of autonomic blockade, an effect that was prevented by administration of supplemental oxygen. The authors interpreted this finding to mean that the neurally mediated increase in blood pressure caused by hypoxia occurs against a background of concomitant vasodilation. Although the sympathoexcitation observed in our experiments did not cause vasoconstriction in the leg, this chemoreflex-induced increase in muscle sympathetic nerve activity may have supported blood pressure by preventing marked vasodilation.

Why was blood pressure not elevated in the recovery period after hypoxic exposure when sympathetic outflow remained elevated and the local vascular effects of hypoxia had presumably dissipated? We cannot answer this question on the basis of the present data. We can only speculate that either the amount of sympathetic activation was insufficient to raise total peripheral resistance or the exposure was not long enough to engage pro-hypertensive mechanisms such as the renin-angiotensin system (6). The present finding of persistent sympathoexcitation without concomitant blood pressure elevation after hypoxic exposure is consistent with our laboratory’s previous observations after 20-min exposures to sustained asphyxia (31) and intermittent asphyxia (49).

Sympathetic nervous system activity is heightened and blood pressure is elevated in patients with obstructive sleep apnea syndrome (1, 11, 37, 47). In a rat model of sleep apnea, Fletcher and colleagues (10) demonstrated that intermittent exposure to hypoxia for 8 h/day during sleep raises daytime blood pressure in as few as 35 days. This hypertensive effect is critically dependent on the sympathetic nervous system because it is not seen after carotid body denervation (8) or chemical sympathectomy with 6-OH dopamine (9). Furthermore, these investigators have determined that addition of hypercapnia to the hypoxic stimulus produces no added effect on blood pressure (7); thus the key stimulus in causing this hypertensive response in rats is hypoxia. In this regard, the findings of Fletcher et al. (7–10) are consistent with those of the present...
study, in which milder and shorter duration exposure to hypoxia, but not hypercapnia, caused a persistent increase in sympathetic outflow in humans.

In summary, the present study demonstrates that the long-lasting sympathoexcitation evoked by brief exposure to asphyxia previously reported by our laboratory (31, 49) is critically dependent on hypoxia. Persistent sympathetic activation caused by hypoxic exposure may explain the chronically elevated sympathetic nervous system activity that accompanies sleep-disordered breathing and may contribute to the sustained hypertension observed in such individuals (1, 19, 33).

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