Baroreflex control of muscle sympathetic nerve activity as a mechanism for persistent sympathoexcitation following acute hypoxia in humans

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Submitted 5 April 2011; accepted in final form 23 September 2011

THE AUTONOMIC RESPONSE TO acute hypoxia results in predictable changes in various cardiorespiratory measures. For example, chemoreflex activation with acute hypoxia in healthy humans leads to increased ventilation and muscle sympathetic nerve activity (MSNA) (33, 36, 37, 39). However, upon cessation of breathing, a hypoxic inspiratory MSNA remains elevated in the normoxic posthypoxia period for more than 20 min, whereas ventilation and arterial blood pressure quickly return to baseline levels (21, 31, 43). Persistent sympatoexcitation in normoxia has also been reported in pathological conditions where hypoxemia is a common feature, such as obstructive sleep apnea (OSA), and may contribute to hypertension common to the syndrome (7, 18, 24). However, the mechanistic basis for the increased sympathetic vasomotor outflow following exposure to hypoxia is unclear.

Given that the chemoreflex is a strong modulator of sympathetic activity, studies have considered the persistent elevation in MSNA following acute hypoxia to be chemoreceptor mediated. Specifically, acute hypoxia might cause sensitization of the peripheral chemoreceptors, which outlasts the hypoxic stimulus (23). In a previous study, our laboratory demonstrated that peripheral chemoreceptor inhibition with hyperoxia resulted in a transient reduction in MSNA following exposure to acute hypoxia (31). Taken together, the results suggest that hypoxia induces a persistent increase in chemosensitive activity to the rostroventrolateral medulla via the nucleus tractus solitarius, which results in long-lasting sympatoexcitation (9, 30).

However, it is important to recognize that MSNA is also under strong baroreflex control, with sympathetic bursts occurring during periods of low arterial pressure (diastole) and less bursts during high pressures (systole). Furthermore, many of the neural pathways of the baroreflex coincide with those of the chemoreflex, resulting in an interdependent relationship (9, 10, 35, 41). Peripheral chemoreceptor activation with hypoxia impairs and resets the baroreflex to higher pressures, where sympathetic outflow is increased for a given diastolic blood pressure (DBP), although this appears to occur without any change in baroreflex sensitivity (5, 11, 12). The baroreflex is reset to higher pressures in hypoxia and likely contributes to the elevated sympathetic vasoconstrictor drive in hypoxia. However, it is not known if resetting of the baroreflex persists following acute isocapnic hypoxia.

One previous study has demonstrated a persistent resetting of the baroreflex following 30 min of hypoxic apneas (22). However, interpretation of these results is complicated by the apnea-induced hypercapnia, which has been shown to have a long-lasting effect on sympathetic outflow and baroreflex function (6, 39). Accordingly, the purpose of this study was to test the hypothesis that acute exposure to isocapnic hypoxia results in a resetting of the baroreflex, which outlasts the hypoxic stimulus. To test this hypothesis, we continuously recorded MSNA in healthy humans at baseline, during, and following exposure to acute isocapnic hypoxia. Our primary assessment of baroreflex function used the spontaneous baroreflex threshold analysis, which relates the probability of a MSNA burst occurring to spontaneous changes in blood pressure (13, 15, 38, 42). We also tested our hypothesis in a subset of subjects by infusing vasoactive drugs as per the modified Oxford technique to obtain a measure of baroreflex function. A long-lasting resetting of the baroreflex to higher pressures following acute isocapnic hypoxia could provide further explanation for the hypoxia-induced persistent sympatoexcitation.
Hypoxia, where SpO2 was maintained at 80% by the titration of N2 to testing. Following instrumentation of the subject for all physiological measurements and SpO2 were determined at the finger with photoplethysmography (which was calibrated against automated blood pressure measurements) and pulse oximetry (model 3740, Ohmeda, Louisville, CO), and sampled at 1 kHz. A baroreflex threshold analog-to-digital converter (PowerLab/16SP ML 795, ADInstruments, Pittsburgh, PA). Heart rate was determined from the mouth with calibrated gas analyzers (models S-3A/I and CD-A, Colorado Springs, CO) and sampled at 300–5,000 Hz, and band-pass filtered (300–5,000 Hz), and MSNA recordings (Vallbo et al. (40). Following localization of the nerve with surface and subcutaneous stimulation, a recording tungsten microelectrode was inserted into the peroneal nerve at the ankle. Direct multiunit MSNA was recorded from the peroneal nerve at the fibular head with the microneurography technique as our laboratory has previously described (21, 31) and originally developed by Vallbo et al. (40). Following localization of the nerve with surface and subcutaneous stimulation, a recording tungsten microelectrode was advanced and manipulated until a satisfactory electrical signal was obtained. Nerve electrical signals were rectified and amplified (total gain 50,000, custom-built microneurography preamplifier; Yale University, New Haven, CT), band-pass filtered (300–5,000 Hz), and integrated (100-ms time constant; integrator model B973C, Bioengineering, University of Iowa, Iowa City, IA). MSNA recordings (>3:1 signal-to-noise ratio) were confirmed by pulse-synchronous activity, sympathoexcitacion during a breath hold and, in response, light tapping or stretching of the muscle, and no activation in response to gentle touching of the skin or startle stimuli. Data and statistical analyses. All data were acquired using an analog-to-digital converter (PowerLab/16SP ML 795, ADInstruments, Colorado Springs, CO) and sampled at 1 kHz. A baroreflex threshold curve was calculated for each individual using the spontaneous baroreflex threshold technique, similar to that described by Sundlöf and Wallin (38). This noninvasive method determines the occurrence of sympathetic bursts at the corresponding DBP throughout a 4-min steady-state period of data. Briefly, the method produces a linear regression line between burst occurrence and DBP and provides a valid measure of resting baroreflex sympathetic function (13). After a time-shift in the MSNA integrated neurogram is applied to align each MSNA burst to a corresponding R wave, DBP values were grouped into 1-mmHg bins, and the percentage of cardiac cycles with a MSNA burst was calculated for each DBP bin. This analysis provides the likelihood of a burst occurring at each DBP within the section of data. We then calculated a T50 DBP value, or midpoint value, which represents the DBP at which there is a 50% likelihood of a MSNA burst occurring. Due to the strong baroreflex influence on sympathetic outflow, lower DBP is associated with more MSNA bursts, whereas high DBP is less likely to be associated with a burst (Figure 1). To quantify and compare the likelihood of a sympathetic burst occurring between conditions (normoxia vs. hypoxia), the DBP error signal was calculated. The calculation of the DBP error signal involves subtracting the average steady-state DBP from the calculated T50 value. At rest, the error signal tends to be negative; that is, the average DBP is higher than the T50 value, and a sympathetic burst is less likely to occur (42). The term “error” suggests deviation from homeostasis and a subsequent autonomic response to correct the error. The regulation of vasomotor outflow and blood pressure is multifactorial, and we do not wish to imply that differences in the prevailing DBP and T50 evoke an autonomic corrective response. Rather, we use the DBP error signal to relate the difference between pressure and the T50. There was no difference in the results, whether or not statistical weighting was applied to the linear regressions; therefore, to compare our results to previously published data, our results are presented...
without any weighting procedures. Spontaneous baroreflex threshold curves were determined immediately before, during, and 5 min following the isocapnic hypoxia exposure.

Baroreflex sensitivity curves from the modified Oxford technique were determined by the linear regressions between average MSNA (total activity of neurogram) and the means of the 1-mmHg DBP bins. Analysis of the slope occurred from the start of the decrease in DBP from sodium nitroprusside to the peak DBP from phenylephrine HCl (8, 22, 32). DBP was used because MSNA correlates with DBP and not systolic blood pressure (38). To quantify the magnitude of resetting of the baroreflex curves, we compared MSNA during baseline, hypoxia, and posthypoxia during identical levels of DBP (12, 22). The DBP chosen for comparison was the average resting pressure obtained from the transient fluctuations at baseline for each individual.

The effect of hypoxia on cardiorespiratory measures, T50, and error signal was compared with repeated-measures analysis of variance procedures. In the case of a significant F-ratio, differences were further investigated with Dunnett’s post hoc test. The relationships of DBP and error signals, as well as MSNA, were examined with linear regression analysis and the Pearson correlation coefficient. The level of significance was set at P < 0.05 for all statistical comparisons. Group data are presented as means ± SE.

RESULTS

Cardiorespiratory and neural variables. Spontaneous increases and decreases in DBP from baseline were +9.2 ± 1.0 and −8.2 ± 0.7 mmHg, respectively (Table 1). Group mean cardiorespiratory measures are shown in Table 2. There was a significant decrease in SpO2, within the first 4 min of hypoxia, and it was clamped at ~80% for the remainder of the hypoxic exposure (Table 2). Isocapnia was maintained throughout the experiment. Baseline MSNA burst frequency was 20 ± 1 bursts/min, which increased in hypoxia (20 min: +44 ± 9%; P < 0.05) and remained elevated in the posthypoxia period (+33 ± 4%; P < 0.05 vs. baseline). In contrast, there were increases in minute ventilation and heart rate in hypoxia (P < 0.05), but both returned to baseline on termination of hypoxia. Among individuals, MSNA (burst incidence; bursts/100 beats) was related to DBP at baseline (r = 0.55; P < 0.05) and posthypoxia (r = 0.62; P < 0.05), but not in hypoxia (r = 0.47; P > 0.05).

Spontaneous baroreflex threshold slope analysis. Individual baroreflex threshold curves were determined for each subject (Fig. 1), and the data from the group mean threshold curves were used to construct Fig. 2A. The group mean T50 value at baseline was 70 ± 4 mmHg with a slope of −4.2 ± 0.5 bursts-100 heartbeats-1-mmHg-1 (Table 2). In hypoxia, the T50 value increased (75 ± 4 mmHg) and remained elevated relative to baseline into the posthypoxia period (posthypoxia 5 min: 77 ± 4 mmHg, P < 0.05). There was an upward and rightward shift in the threshold curve in hypoxia and posthypoxia (P < 0.05); however, there was no change in the slope of the threshold analyses among conditions (Table 2; Fig. 2A).

DBP error signal. Figure 1 demonstrates the calculation of the DBP error signal in a representative subject. Sympathetic bursts occurred more frequently at lower pressures, and the T50 (DBP at which 50% of the cardiac cycles had a sympathetic burst) was determined from the linear regression of burst occurrence and DBP (1-mmHg bins). The DBP error signal was then calculated by subtracting resting DBP from the T50

Table 2. Effect of 20 min of isocapnic hypoxia on cardiorespiratory measures

<table>
<thead>
<tr>
<th>Method</th>
<th>DBP</th>
<th>Baseline</th>
<th>4 min</th>
<th>8 min</th>
<th>12 min</th>
<th>16 min</th>
<th>20 min</th>
<th>Posthypoxia</th>
</tr>
</thead>
<tbody>
<tr>
<td>SpO2, %</td>
<td>97.4 ± 0.3</td>
<td>87.2 ± 1.7*</td>
<td>81.6 ± 0.9*</td>
<td>80.8 ± 0.8*</td>
<td>80.2 ± 0.8*</td>
<td>80.5 ± 0.8*</td>
<td>96.2 ± 0.4</td>
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</tr>
<tr>
<td>Fs, breaths/min</td>
<td>11.1 ± 1</td>
<td>12.1 ± 1</td>
<td>12.9 ± 1.0*</td>
<td>13.7 ± 1.0*</td>
<td>13.5 ± 0.9</td>
<td>13.1 ± 1.0</td>
<td>11.8 ± 1</td>
<td></td>
</tr>
<tr>
<td>Vt, liter</td>
<td>0.5 ± 0.1</td>
<td>0.7 ± 0.2</td>
<td>0.7 ± 0.2</td>
<td>0.6 ± 0.2</td>
<td>0.6 ± 0.2</td>
<td>0.6 ± 0.1</td>
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</tr>
<tr>
<td>Vt, l/min</td>
<td>4.9 ± 0.6</td>
<td>6.6 ± 0.8*</td>
<td>7.2 ± 0.8*</td>
<td>6.5 ± 0.8*</td>
<td>6.7 ± 0.7*</td>
<td>6.8 ± 0.8*</td>
<td>5.1 ± 0.7</td>
<td></td>
</tr>
<tr>
<td>PETCO2, mmHg</td>
<td>41 ± 1</td>
<td>41 ± 1</td>
<td>42 ± 2</td>
<td>41 ± 1</td>
<td>41 ± 1</td>
<td>41 ± 1</td>
<td>41 ± 1</td>
<td></td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>58 ± 2</td>
<td>65 ± 2*</td>
<td>70 ± 3*</td>
<td>68 ± 3*</td>
<td>68 ± 3*</td>
<td>68 ± 3*</td>
<td>58 ± 3</td>
<td></td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td>91 ± 3</td>
<td>94 ± 3*</td>
<td>95 ± 3*</td>
<td>94 ± 4*</td>
<td>94 ± 4*</td>
<td>94 ± 4*</td>
<td>95 ± 4*</td>
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<tr>
<td>DBP, mmHg</td>
<td>74 ± 3</td>
<td>76 ± 3*</td>
<td>76 ± 3*</td>
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</tr>
<tr>
<td>SBP, mmHg</td>
<td>124 ± 4</td>
<td>129 ± 4*</td>
<td>129 ± 4*</td>
<td>128 ± 4</td>
<td>128 ± 4*</td>
<td>129 ± 4*</td>
<td>128 ± 5*</td>
<td></td>
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<tr>
<td>MSNA</td>
<td>20 ± 1</td>
<td>26 ± 1*</td>
<td>27 ± 2*</td>
<td>28 ± 2*</td>
<td>28 ± 2*</td>
<td>28 ± 2*</td>
<td>26 ± 1*</td>
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</tr>
</tbody>
</table>

| Burst incidence, bursts/100 beats | 35 ± 3 | 40 ± 2* | 40 ± 3 | 42 ± 3* | 42 ± 3* | 41 ± 3* | 46 ± 3* |
| T50, mmHg        | 70 ± 4  | 74 ± 4*  | 74 ± 4*| 75 ± 4* | 74 ± 4* | 74 ± 4* | 77 ± 4* |
| Error, mmHg      | −3.9 ± 0.8 | −2.2 ± 0.7* | −2.0 ± 0.8* | −1.1 ± 1.1* | −1.6 ± 0.9* | −1.4 ± 0.6* | 0.2 ± 0.6* |
| Threshold slope  | −4.2 ± 0.5 | −3.4 ± 0.2 | −3.5 ± 0.3 | −3.4 ± 0.3 | −3.7 ± 0.3 | −3.7 ± 0.3 | −3.9 ± 0.4 |

Values are means ± SE; n = 14. SpO2, oxyhemoglobin saturation; Fs, frequency of breathing; Vt, tidal volume; Vt, inspired minute ventilation; PETCO2, end-tidal partial pressure of CO2; HR, heart rate; MAP, mean arterial pressure; SBP, systolic blood pressure; MSNA, muscle sympathetic nerve activity; T50, DBP with a 50% likelihood of a burst occurring. *Significantly different from baseline, P < 0.05.
(−3 mmHg in Fig. 1). At baseline, all subjects operated at a DBP that was higher than their T50, resulting in a negative error signal (−3.9 ± 0.8 mmHg; Table 2). Throughout the hypoxia exposure, the DBP error signal became progressively less negative. In the posthypoxia period, the mean DBP was lower than the T50, which resulted in a positive error signal of 0.2 ± 0.6 mmHg (Table 2; Fig. 2B). Regression analysis of the DBP error signal and MSNA burst incidence demonstrated a significant positive relationship during baseline (slope = 2.1; r = 0.62; P < 0.05), hypoxia (20 min; slope = 4.2; r = 0.97; P < 0.05), and posthypoxia (slope = 4.2; r = 0.88; P < 0.05).

**Modified Oxford technique.** Bolus injections of sodium nitroprusside and phenylephrine HCl resulted in similar increases (~13-mmHg increase) and decreases (~16-mmHg decrease) in DBP from baseline (Table 1). There was no difference in the T50 value between the spontaneous baroreflex threshold analysis and the modified Oxford analysis (baseline: spontaneous = 57.5 ± 3.9 mmHg, Oxford = 57.8 ± 2.9 mmHg, P > 0.05; posthypoxia: spontaneous = 64.5 ± 3.5 mmHg, Oxford = 61.7 ± 1.3 mmHg, P > 0.05; Fig. 3 shows data from one subject). Similar to the spontaneous baroreflex threshold curve analysis, there was no change in the slope (baseline = −0.003 ± 0.002, posthypoxia = −0.002 ± 0.001 AU/mmHg, P > 0.05), and three of four subjects demonstrated an upward and rightward shift in the curve, although the group mean baroreflex set point did not reach statistical significance (P = 0.7).

**Continued recordings of MSNA during posthypoxia.** We recorded all physiological measures for 20 min following hypoxia in five subjects. In those subjects, hypoxia increased MSNA burst frequency and the T50 by 9.5 ± 0.9 bursts/min and 5.5 ± 3.8 mmHg (P < 0.05), respectively. There was also an increase in the DBP error signal of 4.6 ± 1.5 mmHg (P < 0.05) from baseline, although there was no change in DBP (1 ± 3 mmHg increase, P > 0.05). The MSNA burst frequency, T50, and DBP error signal remained elevated relative to baseline for 20 min posthypoxia (MSNA burst frequency: 8.2 ± 1.9 bursts/min increase; T50: 8.8 ± 2.2 mmHg increase; DBP error signal: 4.3 ± 1.5 mmHg increase; P < 0.05; Fig. 4); however, there was no significant change in DBP from baseline levels (5 ± 3 mmHg increase, P > 0.05).

**DISCUSSION**

**Main findings.** The purpose of this study was to test the hypothesis that the baroreflex contributes to persistent sympathoexcitation following acute isocapnic hypoxia in humans. We tested the hypothesis using the spontaneous baroreflex threshold analysis technique (13, 38, 42), as well as with the infusion of vasoactive drugs (modified Oxford). Our findings demonstrate a persistent resetting of the baroreflex stimulus-response curve upward and rightward (to higher MSNA and pressures) in acute isocapnic hypoxia, without a change in slope. The primary new finding from this study is that the resetting of the baroreflex that occurs in acute isocapnic hypoxia persists for at least 20 min following the termination of the hypoxic stimulus. This suggests that the resetting of the baroreflex functions to permit the persistent sympathoexcitation following exposure to hypoxia, likely from the peripheral chemoreceptors (31). Our findings provide further insight into the importance of hypoxia for the elevated levels of sympathetic outflow expressed in patients with OSA (24).

**Sympathetic control of blood pressure.** The sympathetic nervous system plays an important role in short- and long-term control of arterial pressure (20, 26). We found an inverse relationship between variations in blood pressure and MSNA because of the baroreflex. However, in most young normotensive subjects, interindividual analysis shows that chronic levels of resting sympathetic nerve activity are not related to resting blood pressure levels (3, 4, 15, 38). This somewhat paradoxical phenomenon is thought to be due to the fact that the pressor effects of sympathetically mediated vasoconstriction are balanced by other factors, such as low cardiac output and possibly high nitric oxide (3, 34). In the present study, an anticipated observation was the modest relationship (r = 0.55; P < 0.05) between MSNA and DBP. Although the reason for the association is not clear, certainly the heterogeneity in sympathetic control mechanisms noted in previous work might contribute to some subsets of subjects exhibiting this relationship when most do not (10).

At baseline, all subjects in the present study had a negative DBP error signal (T50 minus DBP); that is, <50% of the...
cardiac cycles at rest were associated with a sympathetic burst. Also, the DBP error signal was related to MSNA burst incidence \((r = 0.62; P < 0.05)\), where those subjects with the most negative DBP error signal (DBP much higher than T50) also had the lowest MSNA burst incidence. In hypoxia and post-hypoxia periods, the DBP error signal became less negative with a greater likelihood of sympathetic bursts. This occurred even though there was a concurrent increase in DBP, which would normally lower the likelihood of a sympathetic burst \((38)\). The reduction in the error signal reflects a hypoxia-induced shift in the baroreflex curve to higher levels of MSNA and indicates an upward and rightward shift in the setpoint of the baroreflex.

Interaction of the baro- and chemoreflexes. Hypoxia activates peripheral chemoreceptors located in the carotid sinus, which leads to an increase in activity of the chemoafferents in the carotid sinus nerve. The carotid sinus nerve projects to the lower brain stem and is integrated in the nucleus tractus solitarius. Following integration of chemoafferents, there are subsequent increases in ventilation and sympathetic outflow. Sustained hypoxia causes a progressive increase in chemosensory discharge and sensitizes the peripheral chemoreceptors to subsequent hypoxia exposures \((23, 25)\), due to a reactive oxygen species-dependent upregulation of endothelin-1 and endothelin receptor A \((30)\). Accordingly, previous studies have implicated an elevation in chemoafferents from the peripheral chemoreceptors for the persistent sympathoexcitation following hypoxia \((24, 31)\).

The present study, along with others \((6, 11, 22)\), demonstrates modulation of the baroreflex with acute isocapnic hypoxia; however, the mechanisms are unclear. Carotid artery ultrasound imaging in humans shows that baroreflex impairment \((\sim 40–50\%)\) during and following poikilocapnic hypoxia is attributed to the neural component of the baroreflex \((i.e.,\) neural properties in the reflex arc), rather than the mechanical component \((i.e.,\) transduction arterial pressure into baroafferent stretch) \((14)\). Furthermore, studies in rodents show that hypoxia modulates the integration of sensory information in the central nervous system \((16)\). Our study was not designed to directly address where along the baroreflex arc hypoxia-induced modulation occurs; however, medullary integration of baroafferents is likely an important contributor.

It is important to emphasize that the peripheral chemoreflex and baroreflex do not operate in isolation. Rather, in conscious and neurally intact humans, sensory information regarding blood-gas homeostasis and arterial blood pressure regulation converge in an integrative fashion. The persistent sympathoexcitation following acute hypoxia may be the result of a coordinated response from both the baroreflex and chemoreflex. Specifically, neural pathways of the baroreflex and chemoreflex arcs coincide, which permits interaction \((19, 41)\).

In humans, there is a negative relationship between the baroreflex and chemoreflex; that is, baroreflex activation inhibits the chemoreflex and vice versa \((6, 35)\). Therefore, the persistent sympathoexcitation following acute hypoxia may be due to an upregulation of the chemoreflex \((i.e.,\) sustained elevation in chemoreceptor activity) \((23, 31)\) and concurrent resetting of the baroreflex \((reduced\) baroreceptor activity or altered medullary processing from baroafferents) \((11, 16, 22)\) via an increase in endothelin-1 \((27, 28)\). Stated differently, the inhibitory influence of the baroreflex on sympathetic tone may be attenuated.
through central barosensitive neurons, thereby “allowing” increased sympathetic outflow from elevated chemoreceptor accessory activity. The reset baroreflex appears to be functioning on top of the hypoxia-induced increase in vasomotor outflow from the peripheral chemoreceptors.

Persistent effect of hypoxia on baroreflex control. A hypoxia-induced adjustment of the baroreflex could partly explain alterations in blood pressure control inherent to certain pathological conditions. Individuals with OSA have an impaired baroreflex during sleep, as well as throughout the day (1, 2), which suggests that there is a long-lasting effect of night-time exposure to repeated apneas on cardiovascular control. Monahan et al. (22) removed the confounding factors of OSA (e.g., obesity, night-time arousal) and determined the effect of repeated hypoxic apneas (20-s apnea, 1 apnea/min, 30 min) on baroreflex function in otherwise healthy humans (comparable to the subjects in the present study). They found a resetting of the baroreflex to higher pressures and MSNA that persisted for 50 min following the hypoxic apneas. It was concluded that repeated apneas, specifically the exposure to hypoxia, are responsible for persistent resetting of the baroreflex. However, it is important to note that hypoxic apneas are also accompanied with periods of hypercapnia (~6-mmHg increase), which could explain the change in baroreflex set point (6). In the present study, we used an isocapnic hypoxia protocol and also demonstrated a persistent resetting of the baroreflex. Our new findings extend those from Monahan et al. (22) and show a requisite role of hypoxia for a long-lasting resetting of the baroreflex, rather than an effect of concurrent hypercapnia.

Conversely, a study in which CO₂ was permitted to drop from hypoxia-induced hyperventilation has demonstrated different findings. Cooper et al. (6) found a reduction in baroreflex sensitivity in acute poikilocapnic hypoxia that persisted for 10 min posthypoxia with no change in baroreflex set point. There are several important methodological differences that could explain the disparity in results between the present study and those from Cooper et al. (6). First, we used a more severe level of hypoxia (SpO₂ = ~80 vs. ~89%), which could mediate the autonomic control of blood pressure (17). Second, Cooper et al. (6) loaded and unloaded the carotid baroreceptors with the neck chamber technique; thus the results may have been confounded by responses from the other baroreceptors (aortic receptors). Last, we obtained direct nerve recordings to quantify sympathetic vasoconstrictor activity in relation to pressure, whereas Cooper et al. (6) measured vascular resistance responses (carotid sinus minus forearm vascular resistance curves), which is influenced by vasoconstricting and vasodilating factors. Additional study is necessary to fully reconcile the discrepancy.

Methodological considerations. Assessing baroreflex function in anesthetized animals permits larger changes in blood pressure, thereby enabling identification of baroreflex threshold and saturation (29). Our two measures of baroreflex function in humans (i.e., spontaneous baroreflex threshold analysis and modified Oxford technique) allow characterization of the linear portion of the curve and excludes reflex threshold and saturation (11, 13, 32, 38). Although this limitation prevents characterizing the full baroreflex curve, the changes in blood pressure in our study (~10- to 15-mmHg change in DBP from resting levels) are similar to the spontaneous changes in blood pressure experienced by individuals during the activities of daily living. The spontaneous baroreflex analysis relies on the negative relationship between MSNA and blood pressure. The baroreflex slopes become less obvious in subjects with very low nerve activity. Also, the analysis would be less clear in pathologies associated with very high nerve activity (i.e., a sympathetic burst at every DBP). However, we do not feel this potential caveat compromised our analysis, given that our subjects had burst incidences ranging from ~35 to 45 bursts/100 beats.

Three of four subjects demonstrated an upward and rightward shift in the baroreflex curve using the modified Oxford technique; however, the average of the trials demonstrated a nonsignificant effect of hypoxia. Although we consider the data from the modified Oxford technique are a good complement to the spontaneous baroreflex analysis, a subsequent study with multiple measurements using the modified Oxford technique in a larger sample would be useful.

Perspectives and Significance

The control of blood pressure and sympathetic outflow is multifactorial; however, the baroreflex plays an important role in regulating both systems. The present study was designed to address whether the baroreflex was involved in the persistent elevation in sympathetic outflow following exposure to acute hypoxia in humans. We found a resetting of the baroreflex to higher blood pressures and levels of MSNA, which persisted following termination of the hypoxic stimulus. We conclude that baroreflex resetting occurs in parallel with a hypoxia-induced overactivity of the peripheral chemoreceptors. The convergence of inputs and areas of integration result in a coordinated relationship between the baro- and chemoreflexes and provides a complex mechanism for the long-lasting sympathoexcitation following hypoxia exposure. This has implications for explaining, at least in part, the sympathoexcitation and altered blood pressure control in patients with OSA. Future investigations using a reductionist approach would be useful in understanding the neuroanatomic mechanisms of this integrated system.

GRANTS

This study was supported by the Natural Sciences and Engineering Research Council of Canada. J. S. Querido was supported with graduate scholarships from the Heart and Stroke Foundation of Canada, Canadian Stroke Network, Canadian Institutes of Health Research, and Michael Smith Foundation for Health Research.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS


REFERENCES


