# Carotid chemoreceptor modulation of sympathetic vasoconstrictor outflow during exercise in healthy humans

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**Recently, we have shown that specific, transient carotid chemoreceptor (CC) inhibition in exercising dogs causes vasodilatation in limb muscle. The purpose of the present investigation was to determine if CC suppression reduces muscle sympathetic nerve activity (MSNA) in exercising humans. Healthy subjects ($N = 7$) breathed hyperoxic gas ($F_{IO_2} \sim 1.0$) for 60 s at rest and during rhythmic handgrip exercise (50% maximal voluntary contraction, 20 r.p.m.). Microneurography was used to record MSNA in the peroneal nerve. End-tidal $P_{CO_2}$ was maintained at resting eupnoeic levels throughout and breathing rate was voluntarily fixed. Exercise increased heart rate (67 *versus* 77 beats min$^{-1}$), mean blood pressure (81 *versus* 97 mmHg), MSNA burst frequency (28 *versus* 37 bursts min$^{-1}$) and MSNA total minute activity (5.7 *versus* 9.3 units), but did not change blood lactate (0.7 *versus* 0.7 mM). Transient hyperoxia had no significant effect on MSNA at rest. In contrast, during exercise both MSNA burst frequency and total minute activity were significantly reduced with hyperoxia. MSNA burst frequency was reduced within 9–23 s of end-tidal $P_{O_2}$ exceeding 250 mmHg. The average nadir in MSNA burst frequency and total minute activity was $-28 \pm 2\%$ and $-39 \pm 7\%$, respectively, below steady state normoxic values. Blood pressure was unchanged with hyperoxia at rest or during exercise. CC stimulation with transient hypoxia increased MSNA with a similar time delay to that obtained with CC inhibition via hyperoxia. Consistent with previous animal work, these data indicate that the CC contributes to exercise-induced increases in sympathetic vasoconstrictor outflow.**

(Received 29 October 2007; accepted after revision 11 January 2008; first published online 17 January 2008)
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The carotid chemoreceptors (CCs) are the major oxygen sensor in the body and CC stimulation causes a reflex-mediated increase in ventilation (Olson *et al.* 1988; Curran *et al.* 2000). Importantly, however, CC stimulation also elicits increases in sympathetic vasoconstrictor outflow to the skeletal muscle, renal and mesenteric vascular beds (Rutherford & Vatner, 1978; Balkowiec *et al.* 1993; Sun & Reis, 1994*a*; Guyenet, 2000). Previous investigators have demonstrated that carotid chemosensitivity is enhanced with exercise. Forster *et al.* (1974) found, in humans, that the ventilatory response to the CC stimulant doxapram was greater during exercise as compared to rest, and exercise has been shown to greatly potentiate the ventilatory response to hypoxia (Weil *et al.* 1972). Biscoe & Purves (1967) demonstrated, in anaesthetized animals, that passive exercise increased CC activity via feedback from the exercised limb, although subsequent studies failed to confirm this effect (Davies & Lahiri, 1973; Aggarwal *et al.* 1976). Although the steady-state ventilatory response to exercise seems to be unaffected by CC inhibition (Boetger & Ward, 1986; Henson *et al.* 1992), the ventilatory kinetics to incremental exercise are slowed when chemoreceptors are inhibited with dopamine (Boetger & Ward, 1986). Thus, previous research suggests that the CCs are sensitized during exercise.

Exercise significantly increases sympathetic vasoconstrictor outflow, which reduces blood flow to non-contracting muscle and other inactive vascular beds, thereby redistributing the cardiac output to contracting muscle (Buckwalter & Clifford, 1999). Increased sympathetic vasoconstrictor activity also constrains the increase in blood flow in contracting muscle during exercise (Joyner *et al.* 1992; Buckwalter & Clifford, 1999) in order to maintain blood pressure (Rowell & O'Leary, 1990). It is generally assumed that the increased sympathetic nervous system activity during exercise is due to feedforward mechanisms such as central command,

 DOI: 10.1113/jphysiol.2007.147421

feedback from muscle metaboreceptors, muscle mechanoreceptors and/or a resetting of systemic baroreceptors (Rowell & O'Leary, 1990).

Recently we have shown in dogs that specific, transient inhibition of the CC during exercise caused peripheral vasodilatation as demonstrated by increases in hindlimb flow and conductance (Stickland *et al.* 2007). Vasodilatation was not observed when the CCs were inhibited at rest, indicating that tonic CC activity does not influence resting vasoconstrictor tone. In addition, the vasodilatation following CC inhibition during exercise was abolished with $\alpha$-adrenergic blockade, suggesting that vasodilatation was due to a reduction in sympathetic outflow. These results demonstrated an important role for the CC in exercise cardiovascular control and indicate that the CC contributes to the increased sympathetic nerve activity observed with exercise.

It remains to be determined whether the reflex vasodilatation that was observed after CC inhibition in the exercising dog (Stickland *et al.* 2007) was, indeed, the result of withdrawal of chemoreceptor-induced sympathoexcitation. Moreover, it is unclear whether this reflex is functional in exercising humans. Hyperoxia has been shown to rapidly inhibit the CC (Nye *et al.* 1981). Therefore the purpose of the present investigation was to determine if CC inhibition with hyperoxia affects muscle sympathetic nerve activity (MSNA) during exercise in humans. Consistent with our previous animal studies, we hypothesized that the CCs are sensitized with exercise and therefore inhibiting the CCs with transient hyperoxia will reduce MSNA during exercise, while little effect will be observed with CC inhibition at rest.

## Methods

### Ethical approval

Seven healthy men aged $33 \pm 1$ years (range, 28–35 years), of normal weight ($85 \pm 6$ kg) and height ($180 \pm 2$ cm), served as subjects after providing written, informed consent. All subjects were normotensive and free from cardiovascular and pulmonary disease. Experimental procedures and protocols were approved by the University of Wisconsin Center for Health Sciences Institutional Review Board and conformed with the *Declaration of Helsinki*.

### Cardio-respiratory measures

Subjects breathed through a mouthpiece with the nose occluded. Airflow was measured by a heated pneumotachograph (model 5719, 0–100 l min$^{-1}$; Hans Rudolph, Kansas City, MO, USA), tidal volume and breathing frequency were calculated, and end-tidal $P_{O_2}$ ($P_{ETO_2}$) and $P_{CO_2}$ ($P_{ETCO_2}$) were measured using Applied Electrochemistry (Pittsburgh, PA, USA) $O_2$ and $CO_2$ sensors. A single lead electrocardiogram was continuously recorded. Blood pressure was monitored using beat-by-beat photoplethysmography obtained on a toe (Finapres model 2300; Ohmeda, Englewood, CO, USA). In addition, arterial oxygen saturation was obtained from an ear oximetry probe (Biox 3740; Ohmeda). Force output data from two handgrip dynamometers were likewise recorded. Earlobe capillary blood was obtained at rest and immediately following exercise and analysed for blood lactate using an electrochemical analyser (YSI 1500 Sport, OH, USA).

### Sympathetic nerve activity

Postganglionic MSNA in the right peroneal nerve was recorded directly using the microneurography technique (Vallbo *et al.* 1979). The neural signals were passed to a differential preamplifier, an amplifier (total gain, 100 000), a band-pass filter (700–2000 Hz) and an integrator (time constant, 100 ms). Placement of the recording electrode within a muscle nerve fascicle was confirmed by: (1) the presence of muscle twitches, but not paresthesias, in response to electrical stimulation; (2) the pulse-synchronous nature of the nerve activity; (3) the appearance of afferent activity in response to tapping or stretching of muscle, but not gentle stroking of skin, in the appropriate receptive fields; and (4) the absence of neural activation in response to a startle stimulus. Once an acceptable neural recording (signal-to-noise ratio $> 3:1$) was obtained, the subject was instructed to maintain the leg in a relaxed position for the duration of the study. Sympathetic bursts were identified by computer-assisted inspection of the mean voltage neurogram. For purposes of quantification, MSNA was expressed as burst frequency (bursts min$^{-1}$), burst amplitude (arbitrary units) and total minute activity (burst frequency $\times$ mean burst amplitude). MSNA total minute activity during the hyperoxic and hypoxic interventions was also expressed as a percentage of the baseline steady-state level.

### Experimental protocols

Prior to the experimental session, a practice was conducted on a separate day to familiarize each subject with the protocol. The set-up and exercise protocol was similar to the full experimental session; however, MSNA data were not obtained.

Following instrumentation, subjects breathed freely on the mouthpiece for 10 min so that resting eupnoeic data could be obtained. Interventions at rest and during exercise were then performed at a breathing frequency of 20 breaths per minute, with inspiratory time/total breath time $\approx 0.3$, and $P_{ETCO_2}$ was maintained at resting eupnoeic levels by

adding $CO_2$ to the inhaled gas. Hyperoxia interventions ($F_{IO_2}$ ~1.0) were conducted at rest and during steady-state exercise. For exercise interventions, subjects performed rhythmic bilateral handgrip exercise at 50% maximal voluntary contraction at a frequency of 20 contractions per minute, which was coordinated with breathing such that contractions occurred during inspiration (i.e. duty cycle ~0.3). Target handgrip force output was displayed on an oscilloscope to provide visual feedback to the subject. Reported data are of the mean individual response from two to five interventions during each condition (i.e. rest and during exercise). At least two hyperoxia interventions at rest were conducted prior to exercise and additional interventions were conducted at rest several minutes following termination of exercise. No differences in response to hyperoxia were noted between interventions performed prior to *versus* following exercise and therefore resting data were combined.

At the beginning of each condition (i.e. rest or exercise), each subject was permitted to find a comfortable tidal volume at the paced breathing frequency and once a steady state in ventilation and MSNA had been determined, the subject was instructed to maintain this tidal volume during each intervention. Target tidal volume was displayed on an oscilloscope to provide visual feedback. For each intervention, data were collected for 3 min: 1 min of steady-state room air breathing, 1 min of hyperoxia or hypoxia, 1 min of return to control. Interventions were separated by 3–4 min to allow $P_{ETO_2}$ to normalize and a steady state to be established. Between interventions subjects were permitted breaks from paced breathing.

To further characterize the time-course of the MSNA response to varying $F_{IO_2}$ values, transient hypoxic interventions (target $P_{ETO_2}$ ~45 mmHg, $F_{IO_2}$ ~0.1) were also conducted for 1 min, both at rest and during exercise. These interventions were preceded by a normoxic control period and data collection continued during return to normoxia following hypoxia. Hypoxic interventions were performed after the hyperoxia trials so as to avoid any possible hypoxia-induced sensitization of the CC which could confound the hyperoxic trials.

### Data analysis

All signals were digitized and stored on the hard drive of a personal computer for subsequent analysis and on a polygraph as previously described (TA-4000; Gould, Cleveland, OH, USA) (Taha *et al.* 1995). Bursts of MSNA were detected by custom-written computer program (St Croix *et al.* 1999) and confirmed by visual inspection of the integrated neurogram by one investigator (M.K.S.). The amplitude of each burst of MSNA and the beat-to-beat levels of arterial blood pressure were determined by computer.

For all inferential analyses, the probability of type I error was set at 0.05. Group data for each variable are expressed as means ± S.E.M. One minute mean steady-state values for each condition (free breathing, paced breathing, exercise) were compared using a repeated measures ANOVA. The mean 15 s changes from baseline with inhaled gas (hyperoxia or hypoxia) were compared between rest and exercise using a two-way repeated measures ANOVA. Upon detection of an effect, paired *t* test comparisons were made and a Bonferroni correction factor was applied to maintain family wise error rate at 0.05. The nadir 15 s value for burst frequency and MSNA total activity within each hyperoxic intervention was also determined and the nadir at rest was compared to the nadir during exercise using a paired *t* test.

## Results

### Effects of hyperoxia at rest

With paced breathing, breathing frequency was increased (14 *versus* 20 breaths min$^{-1}$), while tidal volume decreased (728 *versus* 511 ml), resulting in small increases in minute ventilation (8.3 *versus* 10.2 l min$^{-1}$) as compared to eupnoeic breathing ($P < 0.05$ for all). End-tidal $P_{CO_2}$ was maintained at spontaneous eupnoeic levels (42 ± 2 mmHg) throughout paced resting and exercise trials via $CO_2$ supplementation of the inspired air. As compared to spontaneous eupnoeic breathing, paced breathing at rest did not change heart rate (68 *versus* 67 beats min$^{-1}$), mean arterial pressure (83 *versus* 81 mmHg), MSNA burst frequency (28 *versus* 28 bursts min$^{-1}$), or MSNA total minute activity (5.2 *versus* 5.7 units, $P > 0.05$ for all).

A representative hyperoxia trial at rest in a subject is illustrated in Fig. 1 (top panel). Mean data are reported in Table 1. Hyperoxia resulted in a rapid increase in $P_{ETO_2}$ such that $P_{ETO_2}$ exceeded 250 mmHg within 2.6 ± 0.4 breaths or 8.2 ± 1.4 s. Hyperoxia did not result in a significant change in burst frequency or MSNA total minute activity from baseline. Blood pressure, heart rate, tidal volume, breathing frequency and $P_{ETCO_2}$ were unchanged with hyperoxia from baseline normoxic steady-state values.

### Effects of exercise and of hyperoxia during exercise

A representative exercise hyperoxic trial in the same subject is illustrated in Fig. 1 (lower panel). Group mean responses are detailed in Table 2. Exercise in normoxia significantly increased heart rate (67 *versus* 77 beats min$^{-1}$), mean blood pressure (81 *versus* 97 mmHg), tidal volume (511 *versus* 719 ml), MSNA burst frequency (28 *versus* 37 bursts min$^{-1}$) and MSNA total activity (5.2 *versus* 9.3 units) above resting values ($P < 0.05$ for all, see Tables 1

and 2 for baseline resting and exercise steady-state data). Blood lactate, however, was not different between rest ($0.7 \pm 0.1$ mM) and exercise ($0.7 \pm 0.1$ mM).

Similar to rest, hyperoxia resulted in a rapid increase in $P_{ETO_2}$ such that $P_{ETO_2}$ exceeded 250 mmHg within $2.3 \pm 0.2$ breaths or $6.9 \pm 0.7$ s. In contrast to rest, transient hyperoxia during exercise resulted in a significant reduction from baseline exercise steady-state values in both burst frequency and MSNA total activity. Mean burst frequency was reduced with hyperoxia beginning at the 16–30 s time-point and continuing through to the 46–60 s time-point. MSNA total activity was significantly reduced at the 31–45 s and 46–60 s time-points (see Fig. 2 and Table 2). Heart rate was reduced with hyperoxia, while blood pressure, tidal volume, breathing frequency and $P_{ETCO_2}$ were unchanged from baseline exercise steady-state values with hyperoxia (see Table 2).

In the return back to normoxic breathing following hyperoxia, $P_{ETO_2}$ remained elevated above the normoxic baseline for 60 s after hyperoxia onset and thereafter returned to $< 120$ mmHg. MSNA burst frequency and total activity were not significantly different from control during the normoxic period following hyperoxia.

The nadir 15 s burst frequency and total MSNA value within each 60 s period of hyperoxia was also determined for each trial and reported in Fig. 3. At rest, on average, the nadir 15 s value occurred during the 30–45 s time-point of hyperoxia. At rest, the nadir values for burst frequency and MSNA total activity were 11% and 15%, respectively,

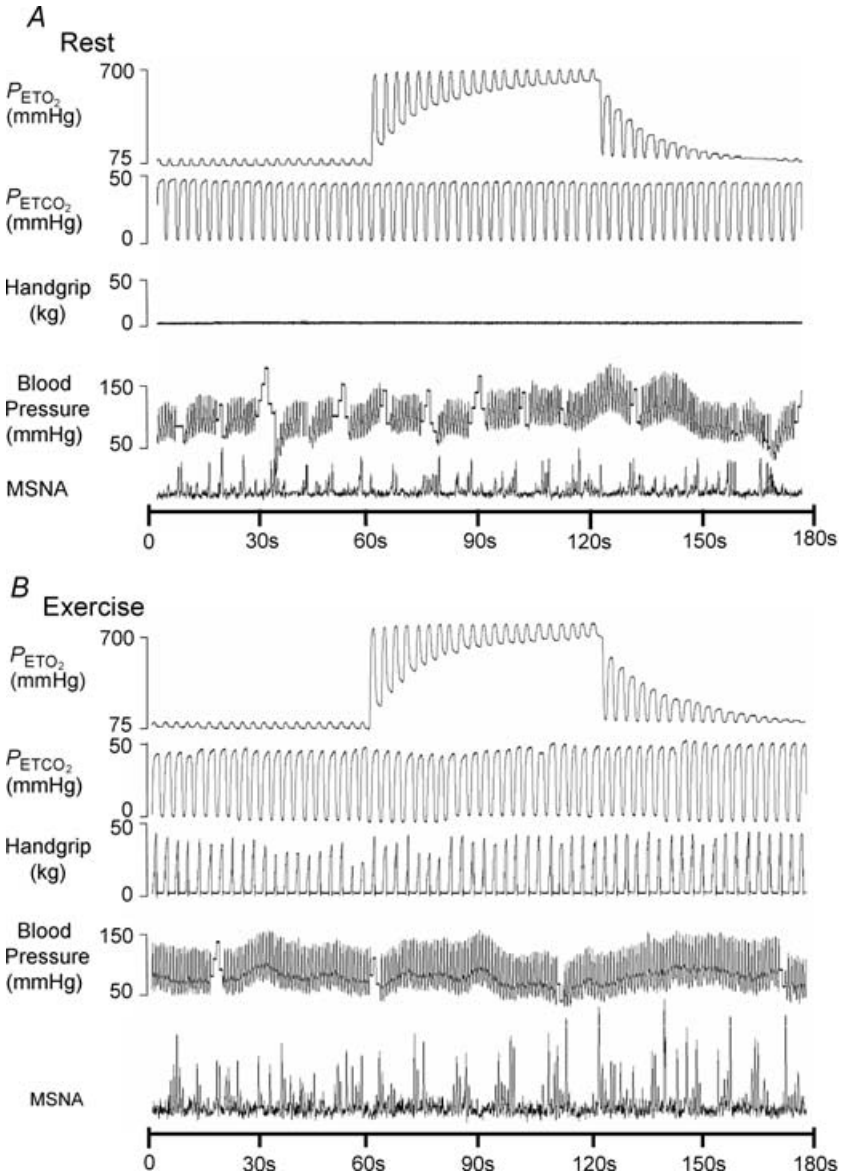


**Figure 1**
Representative trace of a subject receiving hyperoxia at rest (top) and during exercise (bottom).

**Table 1. Cardiorespiratory data during hyperoxia trials at rest ($N = 7$)**

| | Normoxia | Hyperoxia | | | | Return to normoxia | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | 0–15 s | 16–30 s | 31–45 s | 46–60 s | 0–15 s | 16–30 s | 31–45 s | 46–60 s |
| Heart rate | 67 | 67 | 66 | 66 | 66 | 64 | 64 | 64 | 66 |
| (beats min$^{-1}$) | 5 | 5 | 5 | 5 | 5 | 4 | 5 | 4 | 4 |
| Mean arterial pressure | 81 | 80 | 78 | 79 | 78 | 80 | 79 | 79 | 78 |
| (mmHg) | 11 | 10 | 12 | 10 | 11 | 11 | 11 | 11 | 10 |
| Tidal volume | 511 | 524 | 514 | 494 | 517 | 514 | 515 | 484 | 511 |
| (ml) | 40 | 33 | 35 | 35 | 34 | 34 | 39 | 38 | 43 |
| Breathing frequency | 20 | 20 | 20 | 21 | 20 | 20 | 20 | 21 | 20 |
| (breaths min$^{-1}$) | 0.2 | 0.6 | 0.2 | 0.7 | 0.2 | 0.2 | 0.3 | 1.5 | 0.2 |
| Minute ventilation | 10.2 | 10.3 | 10.3 | 9.9 | 10.3 | 10.3 | 10.2 | 9.9 | 10.3 |
| (l min$^{-1}$) | 0.8 | 0.8 | 0.7 | 0.7 | 0.7 | 0.7 | 0.9 | 0.9 | 0.9 |
| End-tidal $P_{O_2}$ | 108 | 290* | 446* | 523* | 556* | 208* | 155* | 153* | 148* |
| (mmHg) | 2 | 17 | 24 | 26 | 22 | 22 | 2 | 1 | 3 |
| End-tidal $P_{CO_2}$ | 41 | 41 | 41 | 41 | 41 | 41 | 41 | 41 | 41 |
| (mmHg) | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| $S_{pO_2}$ | 98 | 98 | 99* | 99* | 100* | 99* | 99* | 99* | 99* |
| (%) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Burst frequency | 28 | 29 | 27 | 30 | 29 | 25 | 27 | 27 | 27 |
| (bursts min$^{-1}$) | 3 | 5 | 4 | 4 | 4 | 4 | 3 | 4 | 3 |
| Total minute actvity | 5.7 | 5.6 | 6.1 | 6.6 | 6.7 | 5.8 | 5.4 | 6.0 | 5.3 |
| (units) | 1.8 | 1.8 | 1.9 | 2.4 | 2.3 | 2.3 | 2.2 | 2.1 | 1.9 |

Values are mean (± S.E.M., value below). Note: *$P < 0.05$ *versus* baseline. $SpO_2$ = arterial $O_2$ saturation.

**Table 2. Cardiorespiratory data during hyperoxia trials during exercise ($N = 7$)**

| | Rest Normoxia | Exercise Normoxia | Exercise Hyperoxia | | | | Exercise Return to normoxia | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | 0–15 s | 16–30 s | 31–45 s | 46–60 s | 0–15 s | 16–30 s | 31–45 s | 46–60 s |
| Heart rate | 67 | 77† | 77 | 75 | 74* | 74* | 73* | 73* | 74* | 75 |
| (beats min$^{-1}$) | 5 | 5 | 4 | 4 | 4 | 4 | 4 | 4 | 5 | 4 |
| Mean arterial pressure | 81 | 97† | 97 | 99 | 100 | 99 | 98 | 100 | 99 | 98 |
| (mmHg) | 11 | 12 | 12 | 11 | 11 | 11 | 12 | 11 | 11 | 11 |
| Tidal volume | 511 | 719† | 731 | 728 | 742 | 748 | 740 | 754 | 749 | 739 |
| (ml) | 40 | 79 | 83 | 88 | 75 | 60 | 84 | 92 | 85 | 91 |
| Breathing frequency | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 |
| (breaths min$^{-1}$) | 0.2 | 0.0 | 0.1 | 0.1 | 0.1 | 0.5 | 0.1 | 0.3 | 0.2 | 0.2 |
| Minute ventilation | 10.2 | 14.5† | 14.6 | 14.7 | 14.4 | 15.0 | 15.0 | 15.0 | 15.0 | 14.9 |
| (l min$^{-1}$) | 0.8 | 1.6 | 1.6 | 1.7 | 1.6 | 1.3 | 1.7 | 1.8 | 1.8 | 1.8 |
| End-tidal $P_{O_2}$ | 108 | 114 | 357* | 523* | 593* | 635* | 271* | 157* | 149* | 145* |
| (mmHg) | 2 | 5 | 26 | 25 | 20 | 8 | 31 | 3 | 2 | 5 |
| End-tidal $P_{CO_2}$ | 41 | 41 | 41 | 41 | 40 | 40 | 41 | 41 | 41 | 42 |
| (mmHg) | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| $S_{pO_2}$ | 98 | 98 | 98 | 99* | 99* | 99* | 99* | 99* | 99* | 99* |
| (%) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Burst frequency | 28 | 37† | 35 | 31* | 29* | 30* | 33 | 32 | 34 | 32 |
| (bursts min$^{-1}$) | 3 | 3 | 3 | 4 | 3 | 3 | 4 | 2 | 3 | 2 |
| Total minute actvity | 5.7 | 9.3† | 8.7 | 8.6 | 7.3* | 7.2* | 8.7 | 8.7 | 8.9 | 9.0 |
| (units) | 1.8 | 2.0 | 1.8 | 2.3 | 1.8 | 1.6 | 2.6 | 2.1 | 1.9 | 2.1 |

Values are mean (± S.E.M., value below). Note: †$P < 0.05$ *versus* steady-state baseline at rest. *$P < 0.05$ *versus* baseline during exercise.

below baseline. The nadir 15 s MSNA value while breathing hyperoxia during exercise also occurred, on average, during the 30–45 s time-point and averaged −28% below normoxic control for burst frequency and −39% for MSNA total activity. The maximum decrease in MSNA was significantly greater during exercise as compared to rest. Blood pressure recorded during the same period at the lowest burst frequency and MSNA total activity was not different from baseline either at rest or during exercise.

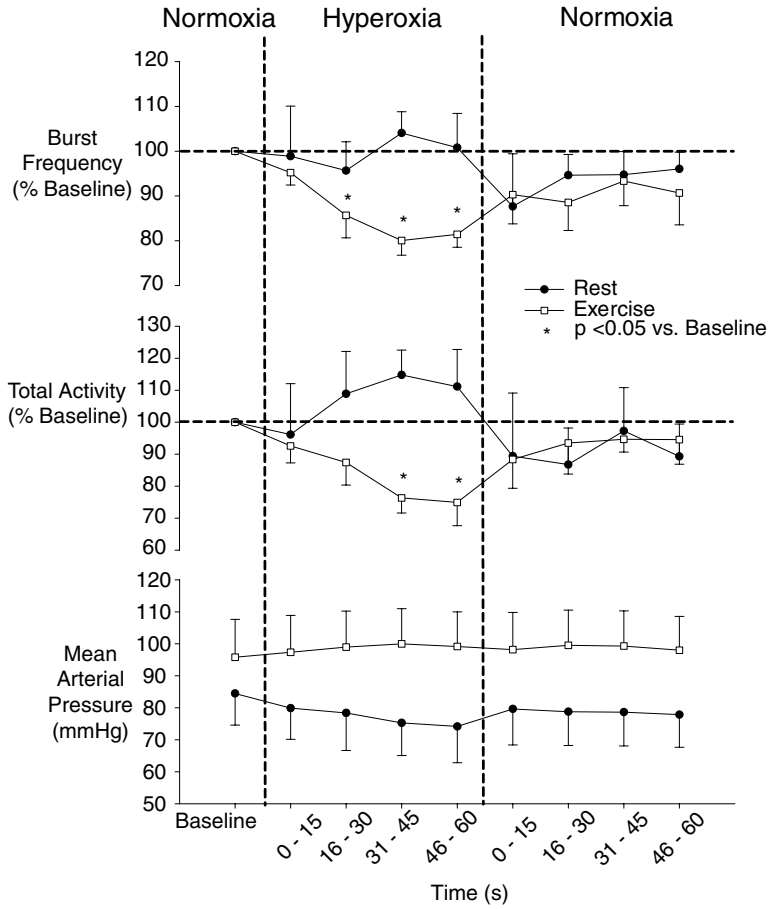


**Figure 2**
Mean (± S.E.M.) MSNA and mean arterial blood pressure response to hyperoxia at rest and during exercise ($n = 7$).

### Effects of hypoxia at rest and during exercise

A representative trace of an exercise hypoxia trial is illustrated in Fig. 4 and mean responses at rest and during exercise are detailed in Tables 3 and 4, and Fig. 5.

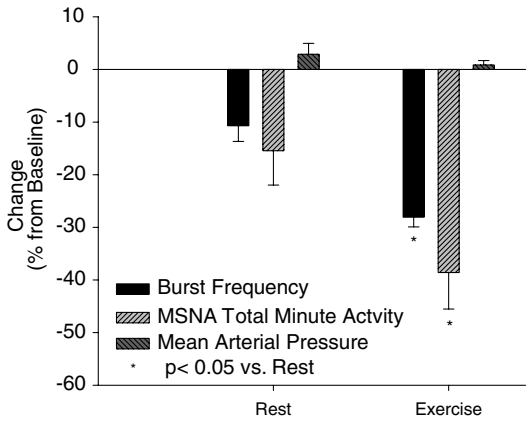


**Figure 3**
Mean nadir burst frequency and MSNA total minute activity with hyperoxia, as a percentage of steady-state baseline ($N = 7$). Note: change in mean arterial pressure is the difference between steady-state baseline and the pressure obtained at the same time as the nadir in MSNA.

Hypoxia reduced $P_{ETO_2}$ below 50 mmHg within $21.7 \pm 1.3$ s ($8.0 \pm 0.4$ breaths) following the switch from room air to hypoxia at rest and within $26.2 \pm 4.3$ s ($10.1 \pm 1.6$ breaths) during exercise. Despite feedback to voluntarily maintain tidal volume, tidal volume and consequently minute ventilation increased with hypoxia both at rest and during exercise. Heart rate was increased during both rest and exercise with hypoxia, while blood pressure increased with hypoxia only during exercise.

Transient hypoxaemia resulted in an abrupt increase in burst frequency and MSNA total activity both at rest and during exercise. Resting values were significantly increased above baseline by the 46–60 s time-point following hypoxia onset, whereas exercise values were significantly increased above steady-state baseline at the 31–45 s and 46–60 s time-points. As a percentage of baseline, there were no differences between rest and exercise in the increase in MSNA from hypoxia (see Fig. 5). For both conditions, $P_{ETO_2}$ returned to baseline after 15 s of breathing room air. At rest, MSNA was not significantly different from control during the normoxic period following hypoxia. However, during exercise MSNA remained elevated above baseline for 30 s during the normoxic period following hypoxia.

## Discussion

Inhibition of the carotid chemoreceptors with hyperoxia resulted in a decrease in MSNA burst frequency and total minute activity during exercise, but not at rest. The MSNA response was rapid and had a similar time-course to chemoreceptor stimulation with hypoxia, indicating the reduction in MSNA from hyperoxia during exercise was secondary to CC inhibition. Consistent with our previous animal experiments (Stickland *et al.* 2007), these results support the hypothesis that the CCs contribute significantly to sympathetic vasoconstrictor outflow during exercise in humans.

### Evidence for carotid chemoreceptor mediation of the MSNA response to transient hyperoxia

The CCs are considered the major oxygen sensor in the body. The aortic chemoreceptors are also sensitive to changes in $P_{O_2}$, although previous work in cats has shown that the aortic chemoreceptor responsiveness to $P_{O_2}$ is substantially smaller than the CC (Lahiri *et al.* 1981). More importantly, carotid body denervation in patients free of pulmonary disease abolishes the ventilatory response to hypoxia (Timmers *et al.* 2003). Similarly, carotid body denervation virtually abolishes the ventilatory (Olson *et al.* 1988; Curran *et al.* 2000) and sympathetic (Balkowiec *et al.* 1993) response to hypoxia in animals. These results support our interpretation that the effects of short-term hyperoxia on MSNA occur as a result of CC inhibition.

However, brain hypoxia *per se*, if sufficiently severe, is known to increase sympathetic outflow (Sun & Reis, 1994*a*). Therefore it is possible that inhibition of central hypoxic sensors in the rostral ventrolateral medulla could play a role in the observed reduction in MSNA with hyperoxia. However, we think our data strongly support a role for the CC as the primary mediator of our observed reductions in MSNA in response to transient hyperoxia. In the current study, $P_{ETO_2}$ exceeded 250 mmHg, a value known to cause substantial suppression of CC activity (Eyzaguirre & Lewin, 1961*a*), within 7 s of breathing hyperoxic gas during exercise. In turn, MSNA burst frequency was reduced by the 16–30 s time period, indicating a reduction in MSNA within 9–23 s of CC inhibition. These delay times coincide with those from the lung to the CC estimated in the healthy human, based on the time to ventilatory response following a step increase in end-tidal $CO_2$ (Sebert *et al.* 1990; Solin *et al.* 2000) or the lung-to-ear circulation time (Xie *et al.* 2006). Carotid body denervation or isolation will increase the delay time 1.5- to 2-fold beyond those in the control animal (Sun & Reis, 1994*b*; Nakayama *et al.* 2003; Smith *et al.* 2006). Furthermore, we think it highly unlikely that transient central hyperoxia, *per se*, would inhibit MSNA relative to normoxia because: (a) substantial levels of hypoxaemia are apparently required to stimulate sympathetic outflow (Sun & Reis, 1994*a*) or ventilation (Curran *et al.* 2000) via central mechanisms; and (b) central hyperoxia, in isolation, causes substantial increases – not decreases – in ventilation (Dean *et al.* 2004) (see further discussion on central hyperoxia below).

Hypoxic trials were also performed at rest and during exercise to examine the time-course of the chemoreceptor response. End-tidal $O_2$ decreased below 50 mmHg within $26.2 \pm 4.3$ s of breathing hypoxia during exercise, and MSNA was increased with hypoxia by the 31–45 s time-point, indicating that MSNA was increased within 21 s of CC stimulation with hypoxic gas. The timing of the sympathetic response to CC stimulation from hypoxia during exercise was virtually identical to the hyperoxic MSNA response, suggesting that both MSNA responses were mediated via CC modulation.

MSNA during exercise can be modulated by muscle metaboreceptors, muscle mechanoreceptors, baroreceptors and/or central command (Rowell & O'Leary, 1990); therefore, an important question is

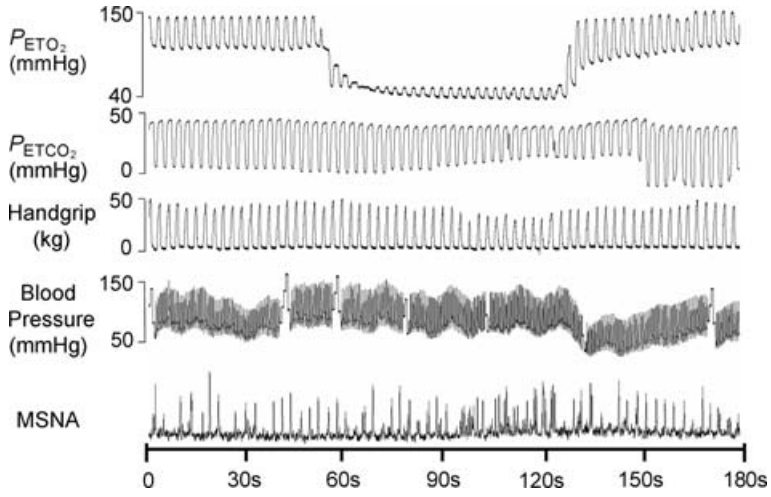


**Figure 4**
Representative trace of a subject breathing a hypoxic gas mixture for ~60 s during exercise.

**Table 3. Cardiorespiratory data during hypoxia trials at rest ($N = 6$)**

| | Normoxia | Hypoxia | | | | Return to normoxia | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | 0–15 s | 16–30 s | 31–45 s | 46–60 s | 0–15 s | 16–30 s | 31–45 s | 46–60 s |
| Heart rate | 66 | 65 | 69 | 74* | 74* | 75* | 71 | 69 | 69 |
| (beats min$^{-1}$) | 5 | 5 | 6 | 7 | 7 | 7 | 6 | 6 | 6 |
| Mean arterial pressure | 79.1 | 75.5 | 75.7 | 79.4 | 86.0 | 82.6 | 81.3 | 80.5 | 78.2 |
| (mmHg) | 6.5 | 7.9 | 8.4 | 6.5 | 4.2 | 3.4 | 3.5 | 3.9 | 5.6 |
| Tidal volume | 491 | 501 | 581 | 636* | 646* | 659* | 547 | 544 | 542 |
| (ml) | 62 | 54 | 42 | 55 | 58 | 69 | 76 | 51 | 56 |
| Breathing frequency | 20 | 19 | 20 | 20 | 20 | 21 | 20 | 20 | 20 |
| (breaths min$^{-1}$) | 0.4 | 1.1 | 0.2 | 0.3 | 0.7 | 0.8 | 1.2 | 0.5 | 0.2 |
| Minute ventilation | 9.7 | 9.7 | 11.7 | 12.8* | 12.9* | 13.1* | 10.9 | 10.7 | 11.0 |
| (l min$^{-1}$) | 1.3 | 1.3 | 0.9 | 1.2 | 1.4 | 1.5 | 1.7 | 1.1 | 1.1 |
| End-tidal $P_{O_2}$ | 101 | 57* | 49* | 44* | 41* | 54* | 74 | 81 | 87 |
| (mmHg) | 6 | 2 | 2 | 2 | 1 | 5 | 4 | 4 | 4 |
| End-tidal $P_{CO_2}$ | 41 | 41 | 40 | 39 | 39 | 40 | 42 | 42 | 42 |
| (mmHg) | 2 | 2 | 2 | 2 | 1 | 1 | 1 | 2 | 2 |
| $S_{pO_2}$ | 96 | 96 | 93* | 89* | 85* | 83* | 88* | 93 | 95 |
| (%) | 1 | 1 | 1 | 2 | 2 | 2 | 2 | 1 | 1 |
| Burst frequency | 26 | 29 | 31 | 37 | 42* | 35 | 35 | 29 | 27 |
| (bursts min$^{-1}$) | 2 | 3 | 3 | 8 | 6 | 7 | 5 | 5 | 5 |
| Total minute actvity | 4.2 | 5.0 | 6.4 | 9.6 | 12.8* | 8.1 | 6.9 | 6.0 | 5.0 |
| (units) | 1.0 | 1.3 | 1.8 | 4.7 | 5.2 | 3.4 | 1.7 | 2.3 | 1.4 |

Values are mean (± S.E.M., value below). Note: *$P < 0.05$ *versus* baseline. Note: blood pressure at rest $N = 4$.

**Table 4. Cardiorespiratory data during hypoxia trials during exercise ($N = 6$)**

| | Rest Normoxia | Exercise Normoxia | Exercise Hyperoxia | | | | Exercise Return to normoxia | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | 0–15 s | 16–30 s | 31–45 s | 46–60 s | 0–15 s | 16–30 s | 31–45 s | 46–60 s |
| Heart rate | 66 | 78† | 79 | 82 | 86* | 87* | 87* | 82 | 79 | 78 |
| (beats min$^{-1}$) | 5 | 5 | 4 | 5 | 5 | 5 | 5 | 5 | 4 | 4 |
| Mean arterial pressure | 79.1 | 99† | 103 | 103 | 105* | 104* | 104 | 103 | 102 | 103 |
| (mmHg) | 6.5 | 16 | 18 | 18 | 17 | 16 | 20 | 14 | 17 | 16 |
| Tidal volume | 491 | 666† | 692 | 762 | 834* | 866* | 860* | 764 | 709 | 713 |
| (ml) | 62 | 69 | 56 | 36 | 65 | 56 | 74 | 82 | 74 | 63 |
| Breathing frequency | 20 | 20 | 20 | 20 | 21 | 21 | 21 | 20 | 21 | 20 |
| (breaths min$^{-1}$) | 0.4 | 0.1 | 0.1 | 0.3 | 0.5 | 0.7 | 0.5 | 0.2 | 0.3 | 0.2 |
| Minute ventilation | 9.7 | 13.3† | 14.0 | 15.4* | 16.9* | 17.9* | 17.2* | 15.3 | 14.3 | 14.2 |
| (l min$^{-1}$) | 1.3 | 1.4 | 1.1 | 0.7 | 1.2 | 1.1 | 1.3 | 1.7 | 1.5 | 1.2 |
| End-tidal $P_{O_2}$ | 101 | 100 | 58* | 48* | 43* | 41* | 60* | 78 | 89 | 94 |
| (mmHg) | 6 | 1 | 1 | 2 | 1 | 1 | 6 | 5 | 3 | 3 |
| End-tidal $P_{CO_2}$ | 41 | 41 | 41 | 40 | 40 | 39 | 40 | 43 | 42 | 42 |
| (mmHg) | 2 | 2 | 2 | 1 | 1 | 1 | 1 | 2 | 1 | 1 |
| $S_{pO_2}$ | 96 | 97 | 97 | 93* | 88* | 85* | 85* | 92* | 95 | 97 |
| (%) | 1 | 0 | 0 | 1 | 1 | 1 | 0 | 2 | 1 | 0 |
| Burst frequency | 26 | 29 | 30 | 37 | 41* | 40* | 36* | 37* | 35 | 26 |
| (bursts min$^{-1}$) | 2 | 3 | 2 | 5 | 7 | 5 | 3 | 3 | 4 | 2 |
| Total minute actvity | 4.2 | 7.5† | 7.8 | 12.6 | 15.5* | 14.8* | 10.1* | 10.2* | 9.3 | 6.3 |
| (units) | 1.0 | 1.7 | 1.8 | 5.3 | 6.6 | 3.7 | 2.0 | 2.0 | 2.0 | 1.9 |

Values are mean (± S.E.M., value below).Note: †$P < 0.05$ *versus* steady-state baseline at rest. *$P < 0.05$ *versus* baseline during exercise.

whether these reflexes were altered by hyperoxia. Blood pressure did not change with transient hyperoxia, indicating that baroreceptor feedback was unaltered with hyperoxia. Subjects maintained steady-state exercise at carefully controlled workloads and thus input from muscle metabo- and mechanoreceptors or central command were unlikely to change substantially within each trial. The increased arterial oxygen content during hyperoxia would increase $O_2$ delivery to working muscle and this may have reduced feedback from muscle metaboreceptor afferents. However, findings in anaesthetized animals have shown that during contraction, afferent nerve traffic is either unaffected in most metaboreceptor afferents (Hill *et al.* 1992), or even demonstrates a decrease in activity (Arbogast *et al.* 2000) in response to severe hypoxia ($P_{a,O_2} = 22$–$38$ mmHg). Furthermore, Sheriff *et al.* (1987) have shown that the metaboreflex is not triggered in exercising muscle until blood flow was reduced to the point where lactic acid was produced. Therefore it is doubtful that a 2–3% transient increase in arterial content as imposed in our study would cause a rapid metaboreceptor-induced reduction in MSNA. Again, the relatively short latency of the reduction in MSNA in response to hyperoxia speaks against an effect of systemic $O_2$ transport on muscle metabolism.

In summary, the previous studies documenting a rapid CC response to a change in $P_{O_2}$, our similar MSNA time-course of response to hypoxia, combined with the unlikely effect of rapid hyperoxia on aortic or central chemoreceptors, muscle metaboreceptors, mechanoreceptors, baroreceptors and central command, support the interpretation that the reduction in MSNA during exercise with hyperoxia is most probably secondary to CC inhibition.

### Effect of hyperoxia on MSNA: previous work

Our finding that inspired hyperoxia applied transiently reduced MSNA during exercise is at odds with previous reports of steady-state hyperoxia (Seals *et al.* 1991*a*; Houssiere *et al.* 2006). We believe the time-dependent effects of hyperoxia are likely explanations for these divergent findings. Houssiere *et al.* (2006), who demonstrated an *increased* MSNA response to exercise with hyperoxia, had subjects inspire a hyperoxic gas mixture for 15 min, while Seals *et al.* (1991*a*), who showed

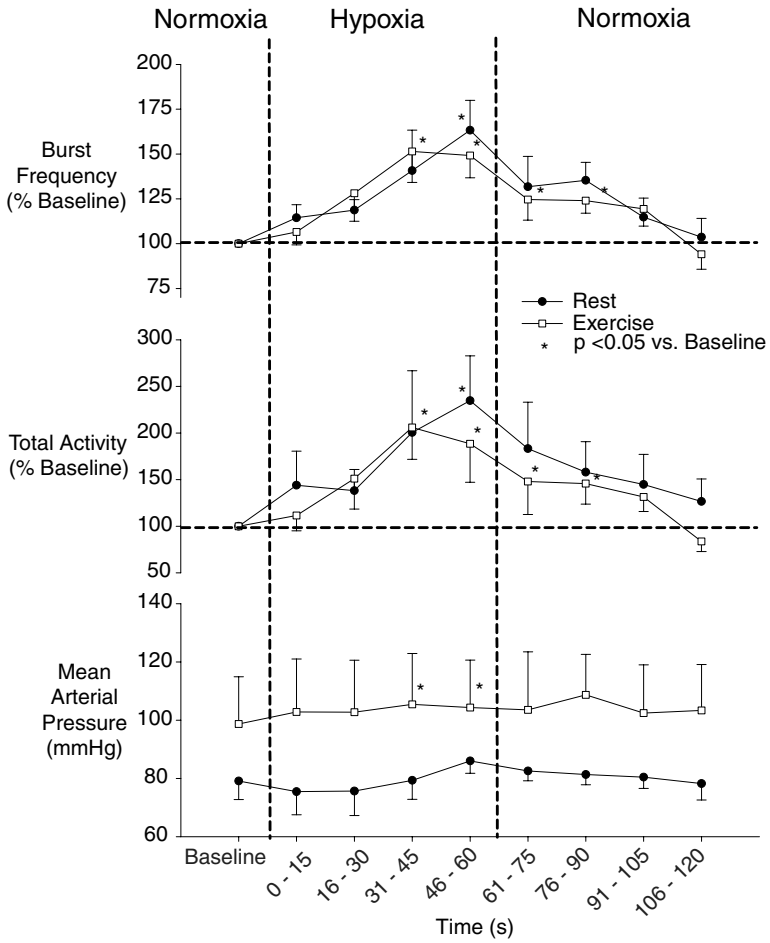


**Figure 5**
Mean MSNA and mean arterial pressure response breathing a hypoxic gas mixture at rest and during exercise ($N = 6$). Note: mean arterial pressure at rest $N = 4$.

a reduction in MSNA at rest with hyperoxia, but no effect during exercise, had subjects breathe hyperoxia for 3–4 min. In contrast, we studied the transient effect of oxygen because we were interested in the influence of the CC alone on MSNA. Examining the transient effects helps to minimize the influence of secondary, time-dependent influences on the steady-state cardiovascular response (Britton & Metting, 1999). Therefore, comparisons to previous reports that used prolonged hyperoxic exposure cannot easily be made because these studies only provide data obtained during steady-state hyperoxia. Importantly, prolonged exposure to hyperoxia can act as a central stimulant (Dean *et al.* 2004), manifested by substantial dose-dependent increases in minute ventilation (Becker *et al.* 1996) following an initial transient reduction in ventilation. Indeed, previous work in humans has shown that minute ventilation begins to increase above baseline after ∼4 min of hyperoxia and continues to increase with further hyperoxic exposure (Becker *et al.* 1995). It was for this reason that we administered hyperoxia for only 1 min in the present study and conducted a time-course analysis of the MSNA response. Thus, is it likely that the secondary central stimulatory effect of prolonged hyperoxia explains why previous studies showed either no effect (Seals *et al.* 1991*a*) or an exaggerated MSNA response to hyperoxia during exercise (Houssiere *et al.* 2006).

### Hypoxia trials

Hypoxia rapidly increased MSNA burst frequency and total minute activity at rest and during exercise. Our findings are consistent with previous animal work demonstrating rapid sympathoexcitation with systemic hypoxia (Sun & Reis, 1994*b*) and are also consistent with the $< 20$ s delay observed in the increases in MSNA induced following apnoea onset in humans (Morgan *et al.* 1993). These rapid, transient increases in MSNA are probably mediated primarily via hypoxia-induced stimulation of the CCs (Balkowiec *et al.* 1993; Guyenet, 2000). Despite subjects being encouraged to maintain breathing frequency and tidal volume, similar proportional increases in both tidal volume and minute ventilation were observed at rest and during exercise beginning after 30 s of hypoxia. This hyperpnoea, by itself, would be expected to reduce MSNA slightly via lung stretch (Dempsey *et al.* 2002); thus, the full effect of hypoxaemia on MSNA was probably underestimated.

We observed that the percentage increase in MSNA with transient hypoxaemia was similar at rest and during exercise. These data are not consistent with the marked increases in ventilatory (Weil *et al.* 1972) and MSNA (Seals *et al.* 1991*b*) responsiveness to hypoxia previously reported during exercise. Our discrepant findings are probably explained by our limited design in which only very transient hypoxia was used at a single dose for the purpose of comparing the time-course of the MSNA excitation with the time-course of inhibition with hyperoxia. To adequately address whether MSNA responsiveness to hypoxia is altered by exercise it would be important to use an adequate dose–response design and to include exposures of sufficient duration to ensure a maximum response to each level of hypoxia.

### Exercise-induced chemosensitization

Blood lactate did not increase with exercise, indicating no metabolic acidosis and therefore no apparent increase in circulating CC stimuli. However, CC inhibition resulted in a reduction in MSNA during exercise, but not at rest, which would suggest an exercise-induced sensitization of the CC reflex, i.e. an increased responsiveness (to transient hyperoxia) during exercise in the face of no apparent change in CC stimuli. This hypothesis, based on MSNA changes in exercising humans, is consistent with the effects of specific CC inhibition on limb vascular conductance in dogs during mild-intensity exercise (Stickland *et al.* 2007). The exact mechanisms for CC sensitization during mild-intensity exercise are unclear, but may occur at the level of the chemoreflex or centrally at the level of integration. For example, exercise-induced sympathoexcitation may increase vasoconstrictor outflow to the CC vasculature, leading to stagnant hypoxia and therefore increased chemoreflex stimulation (Eyzaguirre & Lewin, 1961*b*; Biscoe & Purves, 1967; Acker & O'Regan, 1981; O'Regan, 1981). Increased circulating levels of angiotensin II may also explain the enhanced CC sensitivity, as angiotensin II is elevated with exercise (Maher *et al.* 1975) and is a CC stimulant (Allen, 1998; Li *et al.* 2006). Alternatively, as is the case with exercise-induced resetting of the baroreflex (Raven *et al.* 2006), the somatic inputs from exercising muscle and/or central command might interact at the level of the nucleus tractus solitarius to enhance the effect of a tonic sensory imput from the CC. Given the increases with incremental exercise in both circulating CC stimuli such as $H^+$, $K^+$, norepinephrine (noradrenaline) and temperature, as well as somatic feedback from locomotor muscles and increased central command, we would anticipate an increasing contribution from CC input to sympathoexcitation with increasing exercise intensity.

### Conclusion

When ventilation is tightly controlled, transient CC inhibition with hyperoxia reduces MSNA during exercise. These findings support previous experiments in animals (Stickland *et al.* 2007) demonstrating an important role for the CC in the sympathetically mediated control of vascular

conductance in exercising muscle. The relative importance of the CC to sympathoexcitation and regulation of exercise blood flow in humans both in health and disease remains to be determined, as does the mechanism for the exercise-induced sensitization of the CC.

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## Acknowledgements

This material is based upon work supported, in part, by the Office of Research and Development, Clinical Science R & D Service, Department of Veterans Affairs. This research was also supported by grants from the NHLBI and the American Heart Association. M.K.S. was supported, in part, by a Natural Sciences and Engineering Council of Canada (NSERC) post-doctoral fellowship. We acknowledge the technical assistance of Dominic Puleo and David Pegelow. We are especially grateful to Paul Rutecki, MD for his support.