Role of Chemoreception in Cardio-Respiratory Acclimatization to and Deacclimatization from Hypoxia

Jerome A. Dempsey\textsuperscript{1}, Frank L. Powell\textsuperscript{2}, Gerald E. Bisgard\textsuperscript{1}, Gregory M. Blain\textsuperscript{3}, Marc J. Poulin\textsuperscript{4} and Curtis A. Smith\textsuperscript{1}

University of Wisconsin – Madison\textsuperscript{1}, University of California – San Diego\textsuperscript{2}, University of Nice Sophia Antipolis\textsuperscript{3} and University of Calgary\textsuperscript{4}

\textbf{Corresponding author:}

Jerome A. Dempsey

University of Wisconsin – Madison

4245 MSC, 1300 University Avenue

jdempsey@wisc.edu

Phone: (608) 263-1732

Fax: (608) 262-8235

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Abstract:

During sojourn to high altitudes progressive time-dependent increases occur in ventilation and in sympathetic nerve activity over several days and these increases persist upon acute restoration of normoxia. We discuss evidence concerning potential mediators of these changes including: a) correction of alkalinity in cerebrospinal fluid; b) increased sensitivity of carotid chemoreceptors; and c) augmented translation of carotid chemoreceptor input (at the level of the CNS) into increased respiratory motor output via sensitization of hypoxic sensitive neurons in the CNS and / or an interdependence of central chemoreceptor responsiveness on peripheral chemoreceptor sensory input. The pros and cons of chemoreceptor sensitization and cardio-respiratory acclimatization to hypoxia and intermittent hypoxemia are also discussed in terms of their influences on arterial oxygenation, the work of breathing, sympathoexcitation, systemic blood pressure and exercise performance. We propose that these adaptive processes may have negative implications for the cardiovascular health of patients with sleep apnea and perhaps even for athletes undergoing regimens of “sleep high : train low”!

Keywords: carotid chemoreceptor; CSF [H+]; chemoreceptor interdependence; CNS sensitization

Running head: Cardiorespiratory Acclimatization and Deacclimatization
During sojourn to the hypoxia of high altitudes a progressive time-dependent hyperventilation occurs over the initial several days of sojourn. Upon return to sea level normoxia, the hyperventilation persists, slowly returning to pre-sojourn levels (Fig 1). This time-dependent ventilatory acclimatization and deacclimatization also occurs during all sleep states (7) and is slightly more pronounced during exercise (24). These features are also present in several mammals including the rat, goat and pony, although these species complete ventilatory acclimatization in a shorter time period than humans, who continue to increase the intensity of hyperventilation even over 10-15 days or more (11; 23; 60). Note in Figure 1 that arterial PO$_2$ increases substantially as ventilatory acclimatization proceeds – which means, by definition, that the ventilatory response to the prevailing hypoxemia is increasing with time. Most of the continued hyperventilation upon return to normoxia is completed within one to three days, although the duration of this continued hyperventilation will depend upon the duration of the stay in hypoxia (25; 48).

How are ventilatory acclimatization and deacclimatization mediated? These processes are complex and multifaceted and to date have been only partly resolved. We now examine hypotheses which include separate, independent contributions from peripheral and central chemoreceptors as originally proposed 50 years ago, as well as current hypotheses which incorporate newer (and controversial) concepts of cardioventilatory control based on plasticity of chemosensitivity, multiple sites of hypoxic sensing, interdependence of central and peripheral chemoreceptors and an upregulation of CNS neurons comprising respiratory and sympathetic regulatory pathways.
Increased central chemoreceptor input from the compensation of CSF [H+]

This concept proposed that acute hypoxia stimulated the carotid chemoreceptors, causing hyperventilation and systemic and cerebral spinal fluid hypocapnia and respiratory alkalosis; and that over time, while arterial pH remained alkaline, CSF and therefore central chemoreceptor pH would be quickly restored to normal, achieved via “active transport” of bicarbonate across the blood:brain barrier. This compensatory process would gradually return the central chemoreceptor drive to breathe back to normal which, when combined with a constant excitatory input from the hypoxic carotid chemoreceptors, would gradually increase ventilation, thereby accounting for time-dependent ventilatory acclimatization. Then, upon acute restoration of normoxia and reduction of peripheral chemoreceptor inputs, the small initial increase in PaCO₂ would acidify the CSF (with an already reduced \[HCO_3^-\]) and maintain hyperventilation at greater than control (chronic normoxic) levels until CSF \[HCO_3^-\] and pH were gradually restored to normal (17; 53; 70). This attractive, integrative hypothesis has been shown to be unlikely for several reasons:

- CSF pH during acclimatization was shown to be incompletely compensated with the same time-course, and to the same extent (i.e., 60-70%) as that in arterial plasma. Thus, CSF alkalinity increased or remained constant as hyperventilation intensified over time (23; 86). Similarly, upon acute re-oxygenation following acclimatization, CSF pH was either equivalent to, or alkaline to, sea level control values in the face of continued hyperventilation (25).

- Equally important, over time during recovery in normoxia or “deacclimatization” from hypoxia, CSF pH changed in an acid direction as the level of hyperventilation was...
gradually reduced and PCO₂ in arterial blood and CSF rose over the first 24 hours of restoration of normoxia (25).

Thus, during either acclimatization to or recovery from chronic hypoxia, CSF pH appeared to be primarily determined by – rather than a determinant of – ventilatory acclimatization and deacclimatization. These data, obtained by measuring lumbar CSF acid-base status in humans were confirmed via cisternal CSF measurements in non-human species (11; 25).

Finally, arterial hypocapnic alkalosis does not appear to be required for ventilatory acclimatization to or deacclimatization from hypoxia. When end tidal PCO₂ was precisely controlled at normocapnic levels (via increased FiCO₂) over several hours of constant hypoxia, a normal, time-dependent ventilatory acclimatization occurred in awake goats (9). Similarly in humans, following many hours of hypoxic exposure, significant hyperventilation continued upon acute restoration of normoxia (or acute hyperoxia) whether PETCO₂ was maintained normocapnic or allowed to fall during the hypoxic exposure (32; 79). Furthermore, spontaneous hyperventilation was shown to persist following 26 hours of voluntarily maintained hypocapnia in humans and the level of this spontaneous, sustained hyperventilation was greater when the day-long hypocapnia was accompanied by hypoxia. This additional sustained stimulatory effect of hypoxemia on ventilation in the post-hypoxic period occurred even though the arterial and CSF pH were identical (and significantly alkaline to normocapnic control levels) at the termination of both the normoxic and hypoxic hypocapnic periods (26).
Carotid chemoreceptor sensitization

There is now substantial evidence showing the critical importance of carotid chemoreceptors and their time-dependent sensitization to ventilatory acclimatization to chronic hypoxia.

- Bilateral carotid body denervation prevents ventilatory acclimatization to high altitude – even in the face of very severe levels of hypoxemia (PaO$_2$ 29-31 mmHg) (75). Even though brain lactic acidosis is greatly augmented and brain intracellular acidosis occurs in these conditions of extreme hypoxia (56), this is not sufficient, in the absence of carotid chemoreceptors, to elicit ventilatory acclimatization.

- Recordings of single unit carotid sinus nerve (CSN) activity in anesthetized goats showed an increase and then a plateau over the initial hour of hypoxia but thereafter increased progressively over the remaining three hours (58). These data demonstrated that CB sensitization occurs relatively early in the time-course of exposure to hypoxia. Cross-sectional studies in anesthetized cats also confirmed that several days of hypoxic exposure elicited increases in CSN activity at any given PaO$_2$ during superimposed acute hypoxia (3; 84). Upregulation of neuromodulators ATP (42), endothelin-1 (16) and angiotensin II (43) have all been implicated in this carotid chemoreceptor-specific sensitization (64).

- When the carotid chemoreceptor of the awake goat was isolated and perfused with hypoxic blood for 6 hours (via an extra-corporeal gas exchanger), ventilatory acclimatization proceeded normally. Time-dependent ventilatory acclimatization did not occur (i.e. beyond the acute response) if the isolated, perfused carotid chemoreceptor was stimulated with hypercapnia, rather than hypoxia (8).
• Increased protein expression occurred in rat carotid chemoreceptors over the first few days of moderate hypoxic exposure (85) and these newly generated type I glomus cells in the carotid body remained for several weeks after return to normoxia (85). Thus, in contrast to the hypoxic-induced apoptosis or cell death often reported in the CNS (2), the carotid chemoreceptor glomus cells appear to thrive and multiply under conditions of sustained oxygen lack.

While the critical role of carotid body sensitization in ventilatory acclimatization to hypoxia seems clear, it is less clear that this sensitization – by itself – accounts for the continued hyperventilation upon acute return to normoxia. On the positive side, in the rat, Chen et al. (16) reported an elevation in carotid sinus nerve activity (above that in chronic normoxia) upon restoration of acute normoxia after the third day (but not during the first two days) of hypoxic exposure. Furthermore, as noted above, new type I glomus cells in the carotid body remained for several weeks after return to normoxia (85). On the negative side, the carotid sinus nerve activity was shown to return immediately to control upon reoxygenation after four hours of rising activity during isocapnic hypoxia in the anesthetized goat (10). Furthermore, even after hypoxic acclimatization was complete in the intact animal, bilateral carotid body denervation reduced but did not eliminate continued hyperventilation upon acute restoration of normoxia (3).

Enhanced CNS translation of carotid chemoreceptor input

Dwinell and Powell used a unique approach in the anesthetized rat to show that one week of hypoxia significantly increased the phrenic nerve response to supramaximal electrical
stimulation of the carotid sinus nerve, as measured in a background of acute hyperoxia following prolonged hypoxic exposure (29). These data suggest that sensitivity is increased at the level of those CNS neurons concerned with translation of carotid sinus nerve input into ventilation (also see below). Indirect findings in humans (36) and rats (87) also showed that chronic hypoxia markedly augmented the ventilatory response to a pharmacologic carotid body stimulus (doxapram HCl) – again when the stimulus was applied in an acutely hyperoxic background following acclimatization to moderate hypoxia (36).

In summary, the available data would attribute ventilatory acclimatization and deacclimatization to both time-dependent sensitization of carotid chemoreceptor sensory input as well as a “central enhancement” of this input. We now discuss two potential means whereby this central enhancement might occur, namely via hypoxic-sensitive neurons in the CNS and/or as a consequence of central/peripheral chemoreceptor interdependence.

**CNS Hypoxia.** Acute CNS hypoxia in anesthetized animals resulted in no change in ventilation or a ventilatory depression (50; 57; 83). In awake, CB denervated animals, physiological levels of hypoxia usually have no significant effect on ventilation (13; 19). In contrast, when awake or sleeping animals with a vascularly isolated, intact carotid chemoreceptor which is perfused with normoxic, normocapnic blood are exposed to hypoxia via reduced FIO2, a dose-dependent mildly tachypneic *hyperventilation* is observed. This response is initiated within 20-25 seconds of hypoxic onset, persists for 25 minutes or longer and amounts to about 20-30% of the total ventilatory response to combined CB and CNS hypoxia (11; 19; 30) (see Fig 4). These findings are consistent with the hypoxic-induced depolarization of many (but not all) cardiorespiratory...
neurons in the ventral-lateral medulla (59; 67). Given the tachypneic nature of the ventilatory response to CNS hypoxia in the awake animal (Fig 4) this hyperventilatory response might also be attributed to depression of cortical neurons which, in turn, would remove the inhibitory influence normally exerted by the cortex on “rate-facilitating” neurons in the diencephalon (80).

So, acute CNS hypoxia, per se, elicits ventilatory stimulation in the unanesthetized animal so long as an intact carotid chemoreceptor provides tonic (normal) input to the medulla. However, use of the isolated carotid chemoreceptor preparation in the goat exposed to 6 hours of systemic hypoxemia (with isolated carotid bodies maintained normoxic and normocapnic) showed that sustained CNS hypoxia, per se – in the absence of increased carotid chemoreceptor stimulation, does not elicit a further time-dependent hyperventilation i.e. beyond that obtained in acute CNS hypoxia (14). These negative findings speak against a time-dependent effect of CNS hypoxia, per se. However, the possibility remains that the sustained increases in carotid sinus nerve activity in chronic hypoxia may enhance the stimulatory effect of CNS hypoxia and possibly other inputs to the autonomic control system as well (also see Summary below).

Peripheral chemoreceptor influences on central CO$_2$ chemosensitivity. Recent evidence points to an interdependence of central medullary chemoreceptor activity on input from several sources. Guyenet and associates (38; 39) have recorded directly from CO$_2$ sensitive neurons in the retrotrapezoid nucleus (RTN) of the rat medulla. They found: a) that a direct glutaminergic pathway exists to the RTN from carotid chemoreceptors via the nucleus tractus solitarius ;b) that central CO$_2$ chemosensitive neurons also increased their activity in response to systemic hypoxia or to sodium cyanide and that this response was eliminated following carotid body denervation;
and c) that inputs to the RTN from other areas such as the hypothalamus and pulmonary stretch receptors from the lung also influence the activity of RTN CO$_2$ sensitive cells. In other words, the responsiveness of the central CO$_2$ chemoreceptors in the RTN is not dependent only on the CO$_2$/H$^+$ in their immediate environment (23; 70). Rather in addition they appear to also be dependent on the magnitude and source of several synaptic inputs that these neurons receive, …and the carotid chemoreceptors are one important source of input affecting central chemoreceptor function.

The functional consequences of these neuronal connections to ventilatory control have been addressed in a variety of experimental preparations. The findings remain highly controversial as summarized recently in a three sided debate with proponents representing additive, hypoadditive or hyperadditive effects on ventilation resulting from carotid chemoreceptor: central chemoreceptor interactions (28; 81; 88). We reasoned that, given the neuronal interconnections (39) the testing of their functional importance would require an experimental preparation wherein chemoreceptors were anatomically separated, major sources of influence on both sets of chemoreceptors were uncompromised and in which chemosensitivity remained in the physiologic range. Accordingly, we used the isolated, perfused carotid body preparation in the awake canine in which we superimposed central hypercapnia (via increased FiCO$_2$) on a background of normal, inhibited or stimulated input from the isolated carotid chemoreceptor. As summarized in Fig. 5 (12) we found a hyperadditive effect of carotid chemoreceptor input on central chemoreceptor CO$_2$ responsiveness, whereby stimulating the isolated CB with hypoxia increased and inhibiting CB input via hyperoxic, hypocapnia markedly reduced the ventilatory response to central CO$_2$. These findings are consistent with the substantial suppressive effect of
bilateral CB denervation on ventilatory responses to focal medullary CO₂-induced acidosis in the awake goat (44), to steady-state hyperoxic CO₂ inhalation in the awake (68) or anesthetized dog (6) and awake human, as well as the so-called “late phase” CO₂ ventilatory response in the human (5; 21; 31). We propose that this hyperadditive effect of carotid chemoreceptor output on central chemoreceptor gain (see Fig. 6) might contribute importantly to time-dependent ventilatory acclimatization as carotid chemoreceptor sensitivity increases over time in hypoxia. Moreover we suspect that the time-dependent increase in carotid chemoreceptor input also elicits changes in elements of the control system itself that might contribute to the continued, gradually diminishing hyperventilation upon return to normoxia (also see Summary below). Of course this possibility awaits resolution of the controversy over the functional nature of peripheral : central interdependence.

**Sympathetic acclimatization/deacclimatization to hypoxia.**

There are many similarities in the ventilatory and sympathetic vasoconstrictor responses to chronic hypoxia (18; 47). Like ventilation, muscle sympathetic nerve activity (MSNA) in humans increases slightly upon acute hypoxic exposure, is substantially further augmented over several days at high altitude and then remains elevated upon return to normoxia – even after up to 3-5 days in normoxia (40)(see Fig 7). As explained above for ventilation, the carotid chemoreceptors are also critical to the acute sympathetic response and carotid chemoreceptor sensitization and its central amplification coincides with the time dependent increase in MSNA. Further, the continued elevation in MSNA upon return to normoxia may rely at least in part on residual, sustained increases in carotid sinus nerve activity (62) (see also Summary below). Other similarities are that only hypoxic and not CO₂-induced increases in MSNA elicited a
persistent after-effect upon normoxic restoration (90) and also that hypoxic receptors in the rostral ventrolateral medulla (RVLM) have been shown to drive a sympathetic response to CNS hypoxia (77). On the other hand, a clear difference between sympathetic vs. ventilatory responses to hypoxia in the human is that a substantial, sustained after-effect of hypoxia on elevating MSNA (upon return to normoxia) occurred after only 20-30 minutes of hypoxic exposure and at a time when ventilation had returned completely to control levels (55; 90).

Summary

Different sets of overlapping mechanisms may account for ventilatory and sympathetic acclimatization to vs. deacclimatization from chronic hypoxia. First, it is likely that CB sensitization, per se, contributes importantly to the time dependent ventilatory acclimatization during the hypoxic exposure. Further, we speculate that this carotid body sensitization in chronic hypoxia also contributes to the “central enhancement” of carotid sinus nerve input by further sensitizing hypoxic sensitive respiratory neurons in the CNS and/or CO₂ sensitive neurons in the retrotrapezoid nucleus. On the other hand, given the continued hyperventilation obtained upon the acute application of normoxia or even hyperoxia we must also conclude that an ongoing raised carotid sinus nerve activity (in the post-hypoxic period) is not required to be present for this continued hyperventilation to occur. Rather, as has been demonstrated recently in rodent models of prolonged intermittent hypoxia with attendant carotid body sensitization (62), the persistent elevation of respiratory motor output and sympathetic nerve activity upon return to normoxia was dependent upon ongoing tonic hyperactivity of neurons at the level of the paraventricular nucleus (PVN) (72) and the RVLM (37; 49; 74). These sustained neuroadaptive responses coincided with upregulation of the renin-angiotensin system (33) and of angiotensin II...
AT1 receptors in the PVN (20). Based on these findings, we predict that chronic constant hypoxia may also elicit chemoreceptor input-dependent long term CNS adaptive responses that induce tonic hyperactivity and acute hyperexcitability of neurons comprising respiratory and sympathetic regulatory pathways with cardiorespiratory effects that outlast the hypoxic stimulus.

Physiological consequences of chemoreceptor sensitization and cardiorespiratory acclimatization

Excessive hyperventilation. The time-dependent increases in ventilation in hypoxia are critical to minimizing the reduction in alveolar PO2 (and therefore SaO2) as PrO2 is reduced with increasing altitude. For example, note the progressive rise in PaO2 over time in Figure 1, amounting to an increase in arterial HbO2 saturation from about 75% on day one to 85% on day 14. The enhanced hyperventilation and accompanying high alveolar PO2 are especially critical during heavy intensity exercise in the sojourner at high altitude in order to minimize the magnitude of exercise-induced arterial hypoxemia in the face of an exercise-induced widening of the alveolar to arterial PO2 difference (24) (see also Fig 8). At the same time, during exercise in chronic hypoxia the “excess” hyperventilation means a markedly increased work of breathing (82), as well as increased susceptibility to expiratory flow limitation, leading to hyperinflation and severe dyspneic sensations. Accordingly, studies using mechanical ventilation to unload the respiratory muscles have shown that this excessive ventilation and work of breathing in hypoxia may contribute significantly to exercise performance limitation because of enhanced respiratory muscle fatigue resulting in a faster rate of development of locomotor muscle fatigue (1). In turn, this link between respiratory muscle work and fatigue and locomotor muscle fatigue may be
explained by a sympathetically mediated redistribution of blood flow from locomotor to respiratory muscles (41).

In contrast to the sojourner, most long-term high altitude residents or natives have blunted (rather than enhanced) hypoxic chemosensitivity at both rest (34; 54) and during exercise (24). Thus, highlanders show only minimal hyperventilation during exercise (i.e. beyond that at rest), in their hypoxic environment. However, they preserve their arterial PO$_2$ and O$_2$ saturation during exercise at about the same level as in the markedly hyperventilating sojourner (24). This highly efficient preservation of arterial oxygenation occurs because – unlike the sojourner – the long-term resident highlander has undergone adaptive morphologic changes in the lung parenchyma which produce a greatly enhanced alveolar-capillary diffusion surface area and therefore minimizes the alveolar to arterial PO$_2$ difference during exercise (15; 24; 45) (See Fig. 8).

Excessive sympathetic vasoconstrictor activity. Theoretically, the enhanced, time-dependent increase in sympathetic vasoconstrictor activity in chronic hypoxia (40; 66) should help maintain systemic blood pressure by opposing the vasodilatory effects of systemic local hypoxemia. In acute hypoxia this balance appears to occur as systemic blood pressure is normally unchanged from control. However after days to weeks at high altitudes the vasoconstrictor effects of excessively high sympathetic outflow in the sojourner appear to dominate, as manifested in the occurrence of systemic hypertension throughout the waking and sleeping hours (66; 89). These dominant vasoconstrictor hypertensive effects also persist for several days upon return to sea-level (71; 89).
Of clinical relevance, a persistent sympatho-excitatory effect in the normoxic recovery period following acute hypoxia has also been observed at sea-level (90). This “carry-over” effect on MSNA has been implicated in the high prevalence of persistent daytime systemic hypertension in patients with severe obstructive sleep apnea (OSA) accompanied by nocturnal intermittent hypoxemia (see Fig 9) (4; 91). Furthermore, when the intermittent hypoxemia normally attending OSA was mimicked (via FIO₂ manipulation) in healthy young adults for 8-10 hours/day over 2-3 week periods, significant increases occurred in daytime (normoxic) MSNA and systemic BP, together with an increased hypoxic ventilatory response, reductions in baroreceptor sensitivity and increased inflammatory markers (63; 78)

Studies in the rodent have shown that chronic intermittent hypoxemia sensitizes carotid chemoreceptors so that carotid sinus nerve activity remains elevated upon acute return to normoxia (65). A contributive role of inflammatory cytokines (46) and an upregulation of angiotensin II AT₁ receptors (52) in this CB sensitization has been proposed. The persistence of elevated sympathetic nerve activity following intermittent hypoxemia also coincides with neuroadaptation at several sites of cardiorespiratory regulation within the CNS (see Summary section above). In the healthy sojourner to high altitude, periodic breathing during sleep is common and attributable to increased carotid chemoreceptor gain effects on sensitizing the hypocapnia-induced apneic threshold (22). It is likely that this nocturnal periodic breathing with attendant intermittent hypoxemia contributes to the sojourner’s daytime hypertension and heightened MSNA.

In addition to OSA and hypoxemia, excessive sympathetic nerve activity has been also shown in both preclinical and clinical experiments to contribute to the development and progression of hypertension present in congenital hypertension, insulin resistance and heart failure (61). Afferent signals from the kidney appear to underlie some of this excess sympathetic drive seen in these states (69). However the carotid chemoreceptors have also been implicated, especially in heart failure and clinical trials are currently underway to determine the efficacy of treating at least some types of sympathetically-mediated diseases via CB denervation (61).
It is important to determine if these same substantial after-effects of intermittent hypoxemia on the cardiovascular system persist at rest and exercise in the athlete repeatedly exposed to intermittent hypoxemia via the popular practice of “live high: train low” training regimens (51). This occurrence is most likely in those who choose exposure altitudes greater than 3000m and who experience periodic breathing and intermittent hypoxemia during the periods of sleep in hypoxia. Perhaps the deleterious effects of this intermittent hypoxemia on endothelial function and the hypersensitization of the carotid chemoreceptors leading to increased sympathetic vasoconstriction – especially during exercise (76) – may counteract the normal benefits of physical training on blood flow distribution and O₂ transport and account for at least some of the marked heterogeneity of changes in exercise performance routinely experienced with live high: train low regimens (51; 73). These hypotheses concerning the potential complex cardiovascular consequences of sleeping in hypoxia remain to be tested. In the meantime we strongly urge those conducting sleep high: train low regimens to routinely measure O₂ saturation as a marker of periodic breathing and intermittent hypoxemia during sleep in the hypoxic environment and to monitor systemic blood pressure in the post-hypoxic periods.
Acknowledgements

The original research reported in this review was funded by NHLBI R01 15469 (Dempsey), 081823 (Powell), 15473 (Bisgard), and 50531 (Smith) and by an American Heart Association Post-Doctoral Fellowship (Blain).
1. Time-course of ventilatory acclimatization to hypoxia (over 11 days) and
deacclimatization from hypoxia (over 24 hours of normoxic restoration) in resting sea-
level natives sojourning at 4300m altitude (Mt. Evans, Colorado). Note the alkalization
of arterial plasma and to a nearly identical extent cerebrospinal spinal fluid (CSF),
throughout the sojourn at high altitude. Changes in PaCO$_2$ reflect the degree of
hyperventilation according to the alveolar gas equation: $\text{PACO}_2 = \frac{863}{([\dot{V}\text{E}} / \dot{V}\text{CO}_2) \times (1 - V_d / V_T)}$. In this example at 4300 m, the 13-15 mmHg total reduction in PaCO$_2$
represents a 35 to 40% increase in alveolar ventilation from chronic normoxia to 10-11
days in hypoxia. Adapted from Forster et al. (35).

2. Perfusion of the isolated carotid chemoreceptor in the intact awake goat showed that a
hypoxic carotid chemoreceptor combined with a normoxic systemic circulation resulted
in a normal ventilatory acclimatization and deacclimatization upon return to normoxia.
Additional studies with this preparation also showed that, unlike CB hypoxemia, CB
hypercapnia increased ventilation acutely but did NOT elicit a time-dependent
hyperventilation (Adapted from Bisgard and Forster, 1996 (11)).

3. Increased response of phrenic nerve activity to carotid sinus nerve electrical stimulation
in anesthetized rats in chronic normoxia and in acute normoxia following seven days in
hypoxia. (From Dwinell and Powell, 1999 (29)).
4. Ventilatory effects of hypoxia presented to both the carotid body chemoreceptors and CNS or isolated to the CNS. Inspired FiO₂ was reduced for 5-7 minutes each at three levels of hypoxemia during quiet wakefulness or NREM sleep in 11 (mean ± SEM) canines under: a) intact, control conditions in which both the carotid chemoreceptors and the CNS were exposed to the hypoxemia (■); and b) with the vascularly isolated carotid body chemoreceptor which was maintained normoxic and normocapnic via extracorporeal circulation (◊), thereby allowing only the CNS to be exposed to the hypoxemia. Note the dose-dependent tachypneic hyperventilatory response to CNS hypoxemia alone, which averaged about one-third the ventilatory response observed in the intact condition where both CB and CNS are hypoxic. Mean inspiratory flow rate (VT/Ti) and rate of rise of diaphragm EMG (not shown) were also increased significantly with CNS hypoxia conditions alone. Normoxic control values from intact and CB isolated conditions, respectively, averaged 3.8 and 4.8 l/min Vt, 42 and 40 mmHg PaCO₂, 10 and 13 bpm f, and 0.4 and 0.4 l VT. Data obtained from ref. (19) combined with additional unpublished observations from the author’s lab.

5. Interdependence of carotid and medullary chemoreceptors. In a canine the carotid chemoreceptor is denervated on one side. The remaining carotid chemoreceptor is vascularly isolated from the systemic and cerebral circulation and perfused extracorporeally. The central chemoreceptor response to CO₂ – by itself – is determined by steady-state inhalation of CO₂ enriched air. Animals were studied during quiet wakefulness. Note that when the isolated CB is inhibited (PcbCO₂=20 mmHg and PcbO₂...
> 500 mmHg), the central CO₂ response was reduced to about one fifth of normal and
when the isolated CB was stimulated (PcbO₂ 40, PcbCO₂ 40 mmHg) the central CO₂
response increased an average of two-fold. The data shown here in one animal was
typical of the hyperadditive responses observed in 8 dogs. The ventilatory response slope
changes shown here were accompanied by comparable changes in VT, fₐ, VT/Ti and
diaphragm EMG. Reproduced with permission from Blain et al. (12).

6. Schematic of central:peripheral chemoreceptor interdependence. Shown are the
traditional concept supporting only separate chemoreceptor functions (solid lines) and the
newer concept of interdependent chemoreceptor function (dashed lines). (NTS = nucleus
tractus solitarius; RTN = retrotrapezoid nucleus; CPG = central pattern generator) (see
Fig. 5 and text for explanation and references to original research).

7. Muscle sympathetic nerve activity recorded via microneurography from the peroneal
nerve in three healthy sea-level natives in chronic normoxia (sea level), after four weeks
at 5260 m altitude, and after three days descent to sea level normoxia. The increase in
MSNA in chronic hypoxia was accompanied by significant increases in systemic mean
arterial blood pressure, reductions in limb blood flow and increase in vascular resistance.
Reproduced with permission from Hansen et al. (40).

8. Contrast of the ventilatory and respiratory gas exchange responses to exercise at 3100 m
altitude in acclimatized sojourners (solid line) vs. native or long-term resident
highlanders (dashed line). (\(\dot{V}O₂ = O₂\) consumption, \(Q_c\) = pulmonary blood flow). Note
the greater hyperventilation (lower PaCO₂) during all exercise levels in the sojourners in contrast to the near isocapnic hyperpnea in the highlander. However, the arterial PO₂ is similar between the groups because the lung diffusion capacity (DLCO) is greater and the alveolar-to-arterial PO₂ difference narrower in the highlander. Shading indicates confidence limits around the mean. Data compiled from (15; 24).

9. Acute effects of cyclical sleep apneas and attendant intermittent hypoxemia on MSNA and systemic blood pressure in a patient with obstructive apnea during sleep at sea-level. Each apneic event terminated with a transient arousal pattern in the EEG (not shown).

Adapted from Dempsey et al. (27).


67. **Reis DJ, Golanov EV, Ruggiero DA and Sun MK.** Sympatho-excitatory neurons of the rostral ventrolateral medulla are oxygen sensors and essential elements in the tonic and reflex control of the systemic and cerebral circulations. *J Hypertens Suppl* 12: S159-S180, 1994.


Carotid Chemos (H^+, CO_2, PO_2) → NTS → RTN Central Chemos (H^+, CO_2) → CPG → Respiratory Sympathetic, Outputs

Hypothalamus → Lung Stretch

[Conventional model of separate peripheral / central chemoreception]
[Interdependent model of peripheral / central chemoreception]