The apneic threshold during non-REM sleep in dogs: sensitivity of carotid body vs. central chemoreceptors

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Smith CA, Chenuel BJ, Henderson KS, Dempsey JA. The apneic threshold during non-REM sleep in dogs: sensitivity of carotid body vs. central chemoreceptors. J Appl Physiol 103: 578–586, 2007. First published May 10, 2007; doi:10.1152/japplphysiol.00017.2007.—The relative importance of peripheral vs. central chemoreceptors in causing apnea/unstable breathing during sleep is unresolved. This has never been tested in an unanesthetized preparation with intact carotid bodies. We studied three unanesthetized dogs during normal sleep in a preparation in which intact carotid body chemoreceptors could be reversibly isolated from the systemic circulation and perfused. Apneic thresholds and the CO2 reserve (end-tidal PCO2 eupneic — end-tidal PCO2 apneic threshold) were determined using a pressure support ventilation technique. Dogs were studied when both central and peripheral chemoreceptors sensed transient hypocapnia induced by the pressure support ventilation and again with carotid body isolation such that only the central chemoreceptors sensed the hypocapnia. We observed that the CO2 reserve was ≈4.5 Torr when the central chemoreceptors sensed the transient hypocapnia but more than doubled (>9 Torr) when only the central chemoreceptors sensed hypocapnia. Furthermore, the expiratory time prolongations observed when only central chemoreceptors were exposed to hypocapnia differed from those obtained when both the central and peripheral chemoreceptors sensed the hypocapnia in that they 1) were substantially shorter for a given reduction in end-tidal PCO2, 2) showed no stimulus: response relationship with increasing hypocapnia, and 3) often occurred at a time (>45 s) beyond the latency expected for the central chemoreceptors. These findings agree with those previously obtained using an identical support pressure ventilation protocol in carotid body-denervated sleeping dogs (Nakayama H, Smith CA, Rodman JR, Skatrud JB, Dempsey JA. J Appl Physiol 94: 155–164, 2003). We conclude that hypocapnia sensed at the carotid body chemoreceptor is required for the initiation of apnea following a transient ventilatory overshoot in non-rapid eye movement sleep.

hypocapnia; carbon dioxide reserve; carbon dioxide sensitivity; sleep-disordered breathing; non-rapid eye movement sleep

NON-RAPID EYE MOVEMENT (NREM) SLEEP is known to unmask a highly sensitive hypocapnic-induced apneic threshold whereby very small transient reductions in PaCO2 secondary to a brief ventilatory overshoot causes expiratory time (TE) prolongation, ventilatory instability, and sometimes upper airway obstruction in selected patients (10, 11). The relative importance of peripheral vs. central chemoreceptors in causing apnea and periodic breathing during sleep is unresolved. On the one hand, the central chemoreceptors are known to account for most of the ventilatory response to hypercapnia in the steady state (12, 28, 30, 31, 34). On the other hand, the carotid chemoreceptors respond much more quickly to step increases in arterial PCO2 (PaCO2) (7, 36), and the apnea that normally occurs immediately following a transient ventilatory overshoot requires the presence of the carotid chemoreceptors (5, 26). Furthermore, in anesthetized cats, with isolated perfusion of the pontomedullary regions, Berkenbosch et al. (3) found that breathing pattern remains stable until PaCO2 (in the brain perfusate only) was reduced to <10 Torr.

These latter data suggest that the hypocapnic-induced apneic threshold of the peripheral chemoreceptors is much more sensitive than that of the central chemoreceptors. However, both of these types of studies have major limitations, which preclude generalization of these findings to the intact sleeping animal. For example, carotid body denervation is known to markedly reduce baseline eupneic ventilation and cause CO2 retention (13, 33), to upregulate aortic chemoreceptors (4, 20, 29), to reduce the CO2 responsiveness of central chemoreceptors (16, 25, 38), to alter the response of central chemoreceptors to focal acidosis (18), and to decrease cytochrome oxidase activity in the pre-Bötzinger complex of neonatal rats (21), and it can alter responses to systemic hypoxia and cyanide in CO2-sensitive neurons in the retrotrapezoid nucleus (38).

A major advantage of the Berkenbosch et al. (3) study cited above was that peripheral chemoreceptors were intact. However, their animals were also anesthetized and to maintain ventilatory output as brain perfusate Pco2 was lowered, peripheral chemoreceptors had to be stimulated by maintaining systemic PaCO2 >50 Torr and arterial PO2 (PaO2) <45 Torr. It is important, then, that the relative sensitivities of the two sets of chemoreceptors be quantified under physiological conditions in the intact, sleeping animal.

Accordingly, we tested our hypothesis that the central chemoreceptors are less sensitive than are the peripheral chemoreceptors to dynamic reductions in PaCO2 secondary to transient ventilatory overshoots in unanesthetized, carotid sinus-perfused dogs during normal sleep. In this preparation, the carotid chemoreceptors are intact and provide tonic input to the medulla but are unable to sense imposed changes in systemic PaCO2.

METHODS

Studies were performed on three unanesthetized, young (1–2 yr of age) female, mixed-breed dogs (20–25 kg). Two of the dogs were also used in a different study performed concurrently with the present study. To avoid the ventilatory effects of fluctuating ovarian hor-
mones, the dogs were always studied during anestrus, which was confirmed by vaginal smear. All studies were performed during NREM sleep. The dogs were trained to lie quietly in an air-conditioned (19–22°C) sound-attenuated chamber. Throughout all experiments, the dogs’ behavior was monitored by an investigator seated within the chamber and also by closed-circuit television. The Animal Care and Use Committee of The University of Wisconsin-Madison approved the surgical and experimental protocols for this study.

**Chronic Instrumentation**

Our preparation required two surgical procedures performed under general anesthesia and with strict sterile surgical techniques and appropriate postoperative analgesics and antibiotics. In the first procedure, a chronic tracheostomy was created, and a five-lead electroencephalogram-electrooculogram montage was installed. Electroencephalogram leads were tunneled subcutaneously to the cephalic portion of the dog’s back where they were exteriorized.

In the second procedure, the left carotid body was denervated and the right carotid sinus was equipped with a vascular occluder and catheter to permit extracorporeal perfusion of the reversibly isolated carotid sinus-carotid body (see below). Indwelling catheters were also placed in the abdominal aorta and abdominal vena cava via branches of the femoral artery and vein, respectively. Catheters were tunneled subcutaneously to the cephalic portion of the dog’s back where they were exteriorized. Dogs recovered for at least 4 days before study.

**Carotid Body Perfusion**

Dogs lay unrestrained on a bed in an air-conditioned, sound-attenuated chamber. The extracorporeal perfusion circuit was primed with ~700 ml of saline, 120 ml of allogenic blood, and 5,000 U of heparin (derived from beef lung), and it was supplemented with 2,500 U/lhr Pco2, P2 and pH in the perfusion circuit were matched to a given dog’s eupneic values by adjustment of the gas concentrations supplying the circuit and by addition of NaHCO3. The carotid sinus region was perfused at flow rates  100 ml/min, which raised the pressure in the sinus region by <10 Torr. Before data acquisition, a 30-min period of normal perfusion of the carotid sinus region was used to ensure uniformity between systemic and extracorporeal circuit flow. Intravenous boluses of NaCN (~20 mg/kg) were used to confirm isolation of the carotid sinus during perfusion and also served to confirm denervation of the contralateral carotid body. These techniques have been described in detail in previous publications (8, 35, 37).

**Use of unilateral carotid body denervation.** Our method of carotid body perfusion does require unilateral carotid body denervation on the nonperfused side. Although the potential effect on the central ventilatory control system mentioned in the introduction is a concern, we think it is probably not significant. There is evidence using this preparation in both the goat (6) and the dog (37) showing that unilateral carotid body denervation has little effect on ventilation during control, air-breathing conditions or on ventilatory responses. Apparently, there is sufficient redundancy in the control system to compensate for the loss of one carotid body.

**Experimental Setup and Measurements**

The dogs breathed via an endotracheal tube inserted into the chronic tracheostomy. Airflow was measured with a heated pneumotachograph system (model 3700, Hans Rudolph, Kansas City, MO; model MP-45-14-871, Validyne, Northridge, CA) connected to the endotracheal tube. The pneumotachograph was calibrated before each study with four known flows. One-milliliter arterial or perfusion circuit samples were analyzed for pH, P2, and Pco2 on a blood-gas analyzer (model ABL-505, Radiometer, Copenhagen, Denmark). The blood-gas analyzer was validated daily with dog blood tonometered with three different combinations of P2 and Pco2 covering the range encountered in the experiments. Samples were corrected for both body temperature and systematic errors revealed by tonometry. Ventilation and blood pressure signals were digitized (128-Hz sampling frequency) and stored on the hard disk of a personal computer for subsequent analysis. Key signals were also recorded continuously on a polygraph (model K2G, AstroMed). All ventilatory data were analyzed on a breath-by-breath basis by means of custom analysis software developed in our laboratory.

**Experimental Protocols**

When the dogs achieved NREM sleep based on electroencephalogram criteria, the apnic threshold was determined by means of multiple trials of pressure support ventilation (PSV; see below). Any trials in which sleep state changed [arousal or rapid eye movement (REM) sleep] were excluded from analysis. These apneic threshold determinations were performed in the nonperfused side such that both central and peripheral chemoreceptors could sense the imposed hypocapnia (“central + peripheral”) and, on a different day(s), after a stable carotid sinus perfusion status had been achieved with normocapnic and normoxic blood such that the carotid bodies could not sense the imposed hypocapnia (“central only”).

**Use of PSV to Define the Apneic Threshold**

Dogs breathed room air spontaneously through the open port in the balloon valve (see Measurements). PSV was provided by means of a Hamilton Veolar ventilator (Hamilton Medical, Rahaus, Switzerland). The ventilator was set in the pressure support mode and the trigger sensitivity was set as low as possible (approximately −1.5 cmH2O) and the expiratory positive airway pressure was set at 0 cmH2O. The gas supplied by the ventilator was ambient air (inspired O2 fraction ~0.21). When the balloon was inflated and the low-resistance shunt to the room sealed, the ventilator delivered preset levels of inspiratory pressure support whenever the trigger threshold was reached [i.e., the dog set its own frequency; increased pressure support resulted in increased tidal volume (Vt)]. Each pressure support level was maintained for 2 min, and then the balloon was deflated and the dog was allowed to breathe spontaneously again. At least 2 min elapsed before another PSV trial was performed. PSV was varied randomly over a range of 2–20 cmH2O. Te was measured from the end of the inspiratory flow to the onset of the next inspiration.

Under control conditions (in which the carotid chemoreceptors were not isolated, i.e., central + peripheral) the apneic threshold was defined as the end-tidal Pco2 (Petco2) obtained in the breath immediately preceding the first apneic breath. This was defined as a breath with Te prolonged to  >3 SDs beyond the eupneic control Te. In addition, to make our approach more conservative, we further required that this apnea was followed by at least three cycles of alternating hyperpnea and apnea with a consistent cycle length and that the first apnea had to occur ≤60 s after the initiation of PSV (i.e., hypocapnia).

Under conditions in which the carotid chemoreceptor was isolated, perfused, and with normal blood gases and pH maintained at normal sleeping eupneic levels (i.e., central only), periodic breathing was never observed. Thus, during carotid sinus perfusion, to determine the effect of hypocapnia on Te, we chose the longest Te: that occurred in the 20th–60th s following the onset of PSV. We then associated the treset with the lowest Petco2 observed in this interval that also preceded the longest Te. The first 20 s following the initiation of PSV were excluded from analysis. Thus each trial provided one Te value and a corresponding Petco2 value. For each dog, we then regressed the ΔTe (i.e., longest Te minus mean baseline Te) on the change in Petco2 (∆Petco2) using an exponential function model (5–17 trials, i.e., 5–17 points, per dog). Our intent was to estimate the CO2 reserve by determining the point at which the regression line crossed the Te value observed in the trial used for CO2 reserve determination in the central + peripheral condition (but see RESULTS).
of these trials, although isolated, prolonged TE values were noted in about half of the trials. In all central + peripheral trials with >4.3- to 4.7-Torr decreases in PETCO2, produced by ~9 to 13 cmH2O of PSV, clear apnea and periodicity developed (middle panels). Apneas were longer and periodicity became more marked as hypocapnia became more severe (bottom panels). We completed a total of 29 central + peripheral trials in all 3 dogs with a decrease in PETCO2 of >4.3 Torr. In 27 of these 29 trials, significant Tp prolongation occurred (11 of 13, 7 of 7, and 9 of 9 trials in dogs B, C, and D, respectively). In 20 of the 29 trials clear periodic breathing ensued (8 of 13, 7 of 7, and 5 of 9 trials in dogs B, C, and D, respectively). The latency to significant Tp prolongation occurred on average at 14.2, 16.4, and 17.7 s following the decreases in PETCO2 caused by PSV for dogs B, C, and D, respectively.

In contrast, as shown in Figs. 1, A–C, when the carotid bodies were isolated and perfused with normocapnic blood (i.e., central only), significant Tp prolongation was not observed consistently in trials with decreases in PETCO2 comparable to the periodic breathing trials in the central + peripheral condition (i.e., decreases in PETCO2 secondary to PSV >4.3 Torr). Specifically, zero of three, five of six, and two of four trials for dogs B, C, and D, respectively, showed significant Tp prolongation (greater than control mean Tp + 3 SD) following the onset of PSV. The remaining six trials showed no significant Tp prolongation even when the ΔPETCO2 exceeded 4.3 Torr for 2 min. Furthermore, in the seven trials in which Tp was significantly prolonged the prolongations differed in three important respects from those in the central + peripheral trials. 1) On average, the latencies were twofold longer in the Central only condition (36.8 ± 11.8 s) and in three of the seven trials latencies were >45 s. 2) The lengths of the Tp prolongations for any given reduction of PETCO2 were less than half those observed in the central + peripheral condition (also see Fig. 2). 3) There was no clear stimulus-response relation between Tp prolongation and decreases in PETCO2 in the central only condition.

The data from all PSV trials in each of the three dogs are summarized in Fig. 2 A–C, which plots changes in Tp from baseline eupnea as a function of the decrease in PETCO2 caused by PSV (see METHODS). Note that in the central + peripheral condition, marked prolongation of Tp (usually accompanied by periodic breathing) began to occur with PSV-induced reductions in PETCO2 greater than ~4.3–4.7 Torr. During central only conditions, no consistent Tp prolongation-ΔPETCO2 relationship was detected despite ΔPETCO2 of up to 12 Torr, and the magnitudes of Tp prolongations did not approach those observed in the central + peripheral condition for any given ΔPETCO2 when the ΔPETCO2 was >4.3 Torr.

The mean values for eupneic PETCO2, and the apneic threshold PCO2 are shown for each of the three dogs in Fig. 3. Note that the CO2 reserve, i.e., the ΔPETCO2 below
eupnea required to cause apnea, ranges between 4.3 and 4.7 Torr in the three dogs studied under central + peripheral conditions. In contrast, when the carotid chemoreceptors were not involved in sensing transient reductions of PETCO2 during PSV, the CO2 reserve was increased substantially; in fact, we were unable to increase PSV and lower the PETCO2 sufficiently to determine a clear apneic threshold without arousal even when the Te prolongation often occurred beyond 35–40 s of hypocapnia (see dog C, bottom right).

**Neuromechanical Effects on Te**

During PSV, breath timing may be influenced by both the reduction in PaCO2 as well as by the mechanical feedback associated with an increase in VT. The latter so-called neuromechanical effect is reflected in the first breath of PSV, i.e., before the effects of hypocapnia are sensed by the peripheral chemoreceptors (see Fig. 1).

The first breath of PSV tended to prolong the Te of the first breath for all dogs in the central + peripheral condition by 10.2 ± 1.5% relative to control Te. Similarly, the first breath of PSV tended to prolong Te for all dogs in the central only condition by 9.9 ± 1% relative to control Te. These “nonchemical” effects of PSV on Te were always substantially less than the two- to fourfold prolongation of Te observed when PETCO2 was reduced for a few breaths and the apneic threshold was reached. These findings are consistent with the significant but relatively small effects of PSV per se reported by Nakayama et al. (27), who raised the inspired CO2 fraction to prevent hypocapnia during PSV.

**DISCUSSION**

The major finding of our study is that during NREM sleep in the intact, carotid sinus-perfused central only dog, the apneic threshold is reduced and the CO2 reserve widens (i.e., there is
substantially less propensity for apnea following a transient ventilatory overshoot) when the intact but vascularly isolated carotid chemoreceptors are maintained normocapnic, normoxic, and normohydric and prevented from sensing the hypocapnia induced by PSV. Accordingly, our findings support the conclusion that hypocapnia occurring at the carotid body chemoreceptor is required for the initiation of apnea following a ventilatory overshoot in NREM sleep within the time period normally observed in naturally occurring sleep-disordered breathing. In contrast, central chemoreceptors were relatively insensitive, in terms of changes in Te, to even substantial and sustained reductions in P_{ETCO2} accompanying hyperventilation.

Cerebral Blood Flow

The hypocapnia that accompanied PSV may well have caused transient reductions in cerebral blood flow, which in turn would have decreased the fall in brain P_{CO2} relative to that in P_{ACO2}. The majority of the literature does not support a role for carotid body chemoreceptor stimulation affecting cerebral blood flow (1, 17, 19, 32). Accordingly, we do not believe that these hypocapnia-induced decreases in cerebral blood flow would affect our conclusions because we expect this effect to be similar whether the carotid body was or was not held normocapnic.

Determining the Peripheral and Central Chemoreceptor Apneic Threshold in Intact and Carotid Body-Denervated Experimental Models

Our present findings in the intact, isolated, and perfused carotid chemoreceptor model are consistent with the increase in CO2 reserve our laboratory previously reported in the carotid body-denervated animal (26). We compare the results from these two preparations in Fig. 4. In the denervated dog, eupneic P_{ACO2} was elevated significantly (+5.6 to +11.2 Torr eupneic P_{ACO2}). However, in response to transient reductions in P_{ETCO2} via varying levels of PSV, we also found that the CO2 reserve was markedly widened in the carotid body-denervated dogs

Fig. 2. A–C: stimulus-response for pressure support ventilation-induced hypocapnia in dogs B, C, and D. All pressure support trials in each dog are included for the central + peripheral and “central only” conditions. Changes in P_{ETCO2} (ΔP_{ETCO2}) and Te (ΔTe) were determined as described in METHODS. The lines are best-fit regressions using either exponential or second-order polynomial fits. Note the marked increase in ΔTe beyond the apneic threshold value (ΔP_{ETCO2} 4.3–4.7 Torr) in the central + peripheral condition and the limited increase in ΔTe in the central only condition even in the face of large increases in ΔP_{ETCO2}.

Fig. 3. Summary of mean CO2 reserve data for each dog in this study. The top of each P_{ETCO2} bar indicates the mean eupneic P_{ETCO2}, the bottom indicates the mean apneic threshold, and the P_{CO2} difference between the two points is the CO2 reserve. Open bars represent the central + peripheral condition [16, 13, and 10 trials for dogs B (B), C (C), and D (D), respectively], and solid bars represent the central only condition (5, 9, and 6 trials for dogs B, C, and D, respectively). Note the marked widening of the CO2 reserve in the central only condition in all dogs. Indeed, we could not induce sufficient hyperventilation to define an apneic threshold without causing arousal, so the true CO2 reserve values are probably larger. The numbers below the central only bars that are preceded by the “<” symbol indicate the lowest P_{ETCO2} (in Torr) achieved because an apneic threshold could not be detected.

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This widening of the CO2 reserve occurred despite a significantly elevated eupneic PaCO2, which, by itself, would have increased plant gain and markedly reduced the CO2 reserve and rendered the animal much more susceptible (not less susceptible as observed) to ventilatory instability and apnea (see section below on loop gain).

In the intact dog in the central only condition (present study), the CO2 reserve was also markedly widened to a similar or even greater extent than in the carotid body-denervated dogs. However, in this intact model, the tonic sensory input to the medullary ventilatory controller from the carotid chemoreceptors remained intact, and eupneic ventilation and PaCO2 were not altered by normocapnic perfusion of the isolated carotid sinus. Accordingly, the entire increase in the CO2 reserve below eupnea was due to a markedly lowered apneic threshold (also see below). We also note that neither the intact dogs in central only conditions nor the carotid body-denervated dogs demonstrated substantially prolonged apneas or periodic breathing despite PSV-induced reductions in PETCO2 equal to or greater than that required to reach the apneic threshold value in control conditions.

In the central only intact dogs of the present study, even when significant TE prolongations were noted they differed in latency and pattern relative to prolonged TE values observed in central + peripheral conditions. Specifically, TE prolongations in the central only condition were much shorter for any given reduction in PETCO2 than in the central + peripheral condition and a clear stimulus-response relationship of ΔPETCO2 to ΔTE was not obvious. Latencies from the onset of hypocapnia to TE prolongation were longer in the central only, as would be expected, but they were also more variable. In some instances, the latencies were >45 s, a much longer latency than one would predict for central CO2 chemoreception based on our laboratory’s previous work in the same isolated and perfused carotid sinus model in the sleeping dog (36). In these studies, step increases in PETCO2 were used to determine that ventilatory response latencies for central chemoreception averaged 30.9 ± 8.8 s. Accordingly, we speculate that at least some of the TE prolongations we observed in the central only condition may have been random events not specifically attributable to hypocapnia such as one encounters in any long run of breathing and unrelated to central chemoreception. We propose that periodic breathing requires the carotid chemoreceptors to be exposed to the transient reduction in PaCO2 induced by the ventilatory overshoot. Finally, our findings are also consistent with the markedly depressed apneic threshold (<10 Torr PaCO2) reported in the intact, anesthetized cat whose “central” PaCO2 was reduced via isolated pontomedullary perfusion at the same time as breathing rhythm was maintained by a high systemic PaCO2 and low PaO2 (3) (also see the introduction).

Peripheral vs. Central Chemoreceptor Loop Gain and Apnea Susceptibility

According to control system theory, overall loop gain determines ventilatory stability. In turn loop gain is determined by the product of controller gain (conventionally defined by the CO2 response slope above eupnea) and plant gain, which is critically dependent on the position of eupneic PaCO2 on the isometabolic line relating VA to alveolar PCO2. Figure 5 is a theoretical representation of how differences in controller gain below eupnea can be affected by whether or not both peripheral and central chemoreceptors or central chemoreceptors alone sense the hypocapnia resulting from a ventilatory overshoot. Note the marked decrease (down to at most 58% of control; see RESULTS) in the ΔPETCO2/ΔVA response slope (i.e., controller gain) when only the central chemoreceptors can sense the transient hypocapnia. In the absence of any change in plant gain, this change in controller gain accounts for the entire reduction in apneic threshold that we observed for the central only condition.

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Fig. 4. Summary of CO2 reserve data for all dogs in this study and the carotid body-denervated (CBX) dogs studied by Nakayama et al. (26). Data of Fig. 3 are repeated on the left for ease of comparison. On the right, we have replotted the carotid body denervation data of Nakayama et al. Note the similarity of the central only and carotid body denervation CO2 reserve data despite the CO2 retention and corresponding increase in plant gain in the carotid body-denervated dogs. G, J, N, and Ni, dogs G, J, N, and Ni, respectively.
Implications for Sleep Apnea

The findings of the present study together with previous work from our laboratory have established the preeminent role of the carotid body chemoreceptors in initiating apnea following ventilatory overshoots within the time interval observed in essentially all types of unstable/periodic breathing in sleep. We have shown that the carotid body chemoreceptors possess the characteristics required to initiate apnea quickly following a ventilatory overshoot, namely: 1) marked attenuation of $V_t$ when exposed to carotid-body specific hypocapnia (37); 2) a quick response to increases or decreases in $P_{aCO_2}$ (36); 3) a high response gain to reductions in $P_{aCO_2}$ below eupnea that are achieved during transient hyperventilation (Fig. 5). Accordingly, carotid bodies were shown to be required to initiate apnea in the time interval encountered in naturally occurring sleep apnea following a ventilatory overshoot and decreased $P_{aCO_2}$ (26).
These same characteristics might also indicate a role for the carotid body chemoreceptors in the cycling of ventilatory overshoots and undershoots observed in many forms of periodic breathing such as those that occur during sleep in congestive heart failure; in hypoxia; and in central, obstructive, or mixed sleep apnea. For example, they probably play a role in the ventilatory overshoot that inevitably follows apnea/hypopnea not only because of their rapid response and high gain but because they are also the site of hypoxic/hypercapnic interaction (9) and therefore would provide a substantial ventilatory overshoot in response to asphyxial stimuli present during periods of apnea or hypventilation.

Our findings should not be construed to mean that there is no role for the central chemoreceptors in unstable/periodic breathing during sleep. The central chemoreceptors remain the major CO₂/H⁺ chemoreceptor in the steady state. Once an apnea is initiated the delay or phase lag between the peripheral and central CO₂ responses (36) could contribute to prolongation of the apnea and a subsequent additional increase in asphyxial stimuli which, in conjunction with interactive effects at the carotid body, could promote a ventilatory overshoot and repeating episodes of unstable/periodic breathing.

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