Influence of arterial O₂ on the susceptibility to posthyperventilation apnea during sleep

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Xie, Ailiang, James B. Skatrud, Dominic S. Puleo, and Jerome A. Dempsey. Influence of arterial O₂ on the susceptibility to posthyperventilation apnea during sleep. J Appl Physiol 100: 171–177, 2006. To investigate the role of arterial O₂ in determining of the susceptibility to posthyperventilation apnea, we employed a combination of peripheral arterial O₂ saturation (SaO₂) and central chemoreceptor response to CO₂. Arterial O₂ saturation (SaO₂) was measured using arterial oxygen saturation monitoring (Model 2311, Medical Electronics Co, Inc). During hypoxia, the apneic threshold PETCO₂ was higher (38.9 ± 1.7 Torr; P < 0.05) compared with normoxia (35.8 ± 1.1 Torr); during hyperoxia, it was lower (33.0 ± 0.8 Torr; P < 0.05). Furthermore, the difference between the eupneic PETCO₂ and the apneic threshold PETCO₂ was smaller during hypoxia (3.44 ± 0.63 l.min⁻¹.Torr⁻¹; P < 0.05) compared with normoxia (0.63 ± 0.04 l.min⁻¹.Torr⁻¹; P < 0.05). These findings indicate that posthyperventilation apnea is initiated by the peripherchemical sensors and that the varying susceptibility to apnea during hypoxia vs. hyperoxia is influenced by the relative activity of these receptors.

The relative contribution of peripheral vs. central chemoreception in initiating the posthyperventilation apnea remains an unresolved question. The importance of peripheral chemoreception in mediating the rapid ventilatory response to hypoxia has been supported using animal models. Carotid body denervation either eliminated or prolonged the time course for the development of apnea after the administration of augmented breaths (6, 39). However, carotid body denervation profoundly alters central chemoreception as indicated by the substantial CO₂ retention after denervation. Our laboratory has previously demonstrated the complex effect of hypoxia in the development of posthyperventilation apnea by showing that hypoxia is unique, compared with pure carotid body stimulants such as almitrine, in its failure to reduce the apněic threshold Pco₂ as much as the eupneic Pco₂ (38, 52). As a result, the difference between the eupneic Pco₂ and the apněic threshold Pco₂ is narrowed, causing a greater susceptibility to apnea. However, our laboratory’s previous investigation of the effect of hypoxia on posthyperventilation apnea did not determine the time course between the reduction in Pco₂ and the development of apnea.

Hypoxia is known to increase the responsiveness of the peripheral chemoreceptor to CO₂ (20, 42), and to reduce the Pco₂ and the H⁺ concentration ([H⁺]) at the central chemoreceptors (CC) through its effect of increasing cerebral blood flow (40). In contrast, hyperoxia suppresses peripheral chemoresponsiveness to CO₂ (23) and increases Pco₂ and [H⁺] at the sites of central chemoreceptors through reduction of cerebral blood flow (17, 21). Thus the level of arterial PO₂ (PaO₂) is an important determinant of the relative contribution of the peripheral vs. central chemoreceptor contribution to stable breathing pattern and to the susceptibility to apnea.

The purpose of our present study was to investigate the time to onset of apnea after a transient hyperpnea as an index of peripheral vs. central chemoreception and to investigate the influence of inspired O₂ fraction (FIO₂) on susceptibility to posthyperventilation apnea during sleep. Accordingly, we determined the time course of the posthyperpnea apnea and the preapnea end-tidal Pco₂ (PETCO₂) at different levels of FIO₂.

METHODS

Subjects Nine healthy nonsnoring volunteers (4 men, 5 women) with a mean age of 24 (18–39) yr and body mass index of 22 ± 2 kg/m² served as subjects. Women were studied within 7–10 days of their last menstrual period. All were nonsmokers and free from cardiovascular, pulmonary, and neurological diseases. This study was approved by the University of Wisconsin Health Sciences Institutional Review Board.

Polysomnographic methods. Overnight sleep studies were performed on each subject using standard polysomnographic techniques to identify sleep stage and arousals (44). Ventilation was measured with pneumotachograph (700 series, Hans Rudolph) coupled to a differential pressure transducer (model DP103-10, Validyne). A pressure transducer (model MP45-1 Validyne) monitored airway pressure via mask port. Respiratory effort was monitored by respiratory inductive plethysmography (Ambulatory Monitoring, Respirac), calibrated with an isovolume maneuver. Arterial O₂ saturation (SaO₂) was measured using Nellcor pulse oximetry (N-100, Nellcor, Pleasanton, CA). Arterial O₂ saturation (SaO₂) was measured using arterial oxygen saturation monitoring (Model 2311, Medical Electronics Co, Inc).
measured continuously by a pulse oximeter (Biox 3740, Ohmeda) with a response time of 6 s, placed on the lobe of the right ear for all subjects. PETCO2 and end-tidal P02 (PETO2) were sampled from the nasal mask and measured by gas analyzers (models CD-3A and S-3A/1, AMETEK). All variables were recorded continuously on a polygraph (model K2G, Astromed) and transferred to a computer for analysis.

Apparatus. Subjects slept while breathing through a sealed nasal mask with the mouth being taped shut to prevent air leaks. The mask was attached to a mechanical ventilator (Hamilton Medical, Veolar), which was equipped with air and O2 inlets. The O2 inlet was connected to two tanks with different O2 concentration (100% O2 and 8% O2 balanced with N2) via a Y valve so that the hyperoxia and hypoxia could be easily achieved by switching the valve. For hypoxia trials, subjects inhaled a gas mixture with FIO2 of 8–12% to achieve SaO2 of 78–80%. For hyperoxia trials, subjects inhaled a gas mixture with a FIO2 of 50–53%. The ventilator was set in the pressure support mode, which allowed an independent adjustment of the inspiratory and expiratory pressures. All subjects were initially on continuous positive airway pressure (CPAP) at 2–4 cmH2O to minimize the upper airway resistance. The trigger sensitivity of the ventilator was set at 2 cmH2O below the CPAP level. To facilitate sleep and avoid sleep fragmentation, zolpidem (10 mg) was orally given to all subjects before lights out.

Protocol. During stable non-rapid eye movement (NREM) sleep, after a period of normoxic baseline study, multiple trials of augmented breaths were performed under conditions of normoxia, hypoxia, and hyperoxia in a random order. The baseline values at each FiO2 level were measured during spontaneous breathing with CPAP before pressure support. When a normoxia trial immediately followed a hypoxia or hyperoxia trial, the pressure support protocol was not initiated until the PETCO2 and SaO2 both returned to the normoxic baseline level. In hypoxia or hyperoxia trials, the pressure support protocol was not initiated until the SaO2 stabilized at 78–80% or FiO2 stabilized at 50–53% for at least 5 min to allow subjects to approach a steady state (30).

Augmented breaths were delivered during NREM sleep by abruptly increasing the inspiratory pressure to 20–25 cmH2O at the middle of expiration phase to support the inspiration of the following breath(s) until apnea occurred. The target ventilator pressure level was the maximum pressure that the subject could tolerate without affecting EEG state or provoking arousal and often resulted in an increased tidal volume (VT) by about twice the baseline level. Usually, the same pressure setting was used in all trials under each FiO2 level. However, if this initial ventilator pressure was able to easily trigger apnea after a single large breath as often was seen during hypoxia, the pressure would be decreased by 1-cmH2O decrements in the following trials to find the minimum hyperventilation required to produce an apnea with one or two augmented breaths. Once an apnea was initiated, the ventilator would be turned back to CPAP. Data collection began when the final pressure setting was achieved. Trials that resulted in awakening or arousal were excluded from analysis.

Data analysis. Sleep stages were scored according to standard criteria (44). Heart rate was measured from the ECG. Respiratory parameters, including VT, frequency, minute ventilation (VE), inspiratory time (TI), expiratory time (TE), PETCO2, and PETO2, were measured breath by breath. The baseline values were determined by averaging all breaths during stable, spontaneous breathing on CPAP during each FiO2 level and were compared among the three inspired O2 conditions. Apnea was defined as an absence of airflow and perceptible inspiratory effort on the mask pressure, Respiritrace, and flow signals for a length of at least 10 s. The apneic threshold PETCO2 was measured at the end of expiration of the first breath immediately before apnea (vertical arrow in Fig. 1). The PETCO2 at the second and third breaths before each apnea event was also measured to appreciate the dynamic change of PETCO2 during the transition from stable breathing to apnea. Apnea length was measured from the end of the breath preceding the apnea to the onset of inspiration of the breath ending the apnea (53). Apnea latency was measured from the end inspiration of the first augmented breath to the onset of apnea (horizontal arrow in Fig. 1). The lung-to-ear circulation delay (LECD) was measured from the end of apnea to the subsequent nadir of SaO2, during room air and hypoxia periods (35). The relationship between apnea latency and LECD was examined using least squares linear regression analysis. The mean apnea latency, apnea length, apneic threshold, and the difference between eupneic PETCO2 and apneic threshold PETCO2 (ΔPETCO2) were compared among normoxia, hypoxia and hyperoxia conditions. The ventilatory response to CO2 below eupnea was calculated by dividing the ΔVE (eupneic VE – apneic VE) by the ΔPETCO2. The slopes of ventilatory response were compared among the normoxia, hypoxia, and hyperoxia trials. These comparisons were made using one-way repeated-measures ANOVA, along with Student-Newman-Keuls test if necessary. For those large breath(s) failing to produce apnea, we compared the posthyperventilation breathing pattern (Ti, Te, and VT) with the eupneic breathing pattern during normoxia, hypoxia, and hyperoxia periods, respectively, using paired t-test. Data are reported as means ± SE.

RESULTS

Cardiorespiratory effect of hypoxia and hyperoxia during spontaneous breathing. Compared with normoxia, hypoxia increased breathing frequency (16 ± 1 vs. 15 ± 1 breaths/min; P < 0.05) and VE (7.2 ± 0.4 vs. 6.5 ± 0.4 l/min; P < 0.05) with no significant effect on VT (0.46 ± 0.3 vs. 0.45 ± 0.0 liter; P = 0.76). Hyperoxia did not change any of the breathing parameters compared with room-air breathing (Table 1). PETCO2 was reduced by hypoxia (44 ± 1 vs. 42 ± 1 Torr; P < 0.05), but not by hyperoxia (43 ± 1 Torr; P = 0.20) (Table 1). Heart rate was increased by hypoxia (75 ± 5 vs. 64 ± 3 beats/min; P < 0.01) but not by hyperoxia (61 ± 4 beats/min; P > 0.05). Hypoxia also significantly shortened the LECD compared with normoxia (11.7 ± 0.9 vs. 8.9 ± 0.6 s; P < 0.01). During hyperoxia, apnea-related desaturation was not detectable, making the measurement of the LECD not available.

Effect of FiO2 on posthyperventilation apnea. As shown in Fig. 1, during normoxia, the apnea latency from the first augmented breath (VT = 1.7 ± 0.1 liters) was usually two respiratory cycles (12.2 ± 1.1 s), which was similar to the LECD of 11.7 s in our subjects. The correlation coefficient between the two variables was 0.69 (P < 0.01). Hypoxia advanced the onset of apnea by one respiratory cycle, with significantly shorter apnea latency (6.3 ± 0.8 s; P < 0.05), at an even smaller preapneic VT (1.4 ± 0.1 liters; P < 0.05). In contrast during hyperoxia, multiple augmented breaths with the same VT (1.9 ± 0.1 liters; P = 0.27) were required to eventually induce apnea. One subject failed to produce apnea after undergoing prolonged hyperventilation. In the rest of the subjects, the time delay from the hyperventilation to the onset of apnea was much longer during hyperoxia (71.5 ± 13.8 s; P < 0.01; Fig. 2).

Because of the different number of augmented breath(s) required to produce apnea at each FiO2 level, the PETCO2 on the three breaths preceding the apnea demonstrated a different time course for each FiO2 (Fig. 3). During normoxia, most subjects required only two augmented breaths to produce apnea so that the reduction in PETCO2 occurred consistently on the first two breaths preceding the apnea. During hypoxia, only a single augmented breath was required to produce apnea so that the
reduction in PETCO₂ occurred only on the first breath preceding the apnea. During hyperoxia, more than three breaths were usually required to produce apnea so that PETCO₂ was reduced on all three breaths preceding the apnea.

The apneic threshold PETCO₂, measured at the first preapneic breath (as shown in Figs. 1 and 3), was significantly higher during hypoxia (38.9 ± 1.7 Torr) whereas it was lower during hyperoxia (33.0 ± 0.8 Torr; P < 0.05). The ∆PETCO₂ was smaller during hypoxia (3.0 ± 1.0 Torr; P < 0.001), whereas it was greater during hyperoxia (10.6 ± 0.8 Torr; P < 0.05) compared with normoxia (8.0 ± 0.6 Torr) (Fig. 4). The hypocapnic ventilatory response was greater during hypoxia and less during hyperoxia (Table 1).

**Table 1. Spontaneous breathing during normoxia, hypoxia, and hyperoxia**

<table>
<thead>
<tr>
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<th>Normoxia</th>
<th>Hypoxia</th>
<th>Hyperoxia</th>
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<tbody>
<tr>
<td>PETCO₂, Torr</td>
<td>340±13*</td>
<td>50±1*</td>
<td>430±13*</td>
</tr>
<tr>
<td>SaO₂, %</td>
<td>97±1*</td>
<td>75±1*</td>
<td>99±0*</td>
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<tr>
<td>Vt, ml</td>
<td>455±34</td>
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<td>443±34</td>
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<td>Frequency, breaths/min</td>
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<td>15±1</td>
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<tr>
<td>V̇E, l/min</td>
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<td>6.5±0.4</td>
<td>6.5±0.4</td>
</tr>
<tr>
<td>PETCO₂, Torr</td>
<td>44±1</td>
<td>42±1*</td>
<td>43±1</td>
</tr>
</tbody>
</table>

Values are means ± SE. PETCO₂, end-tidal PCO₂; SaO₂, arterial O₂ saturation; Vt, tidal volume; V̇E, minute ventilation; PETCO₂, end-tidal PCO₂. *P < 0.05 compared with room air.
In trials that failed to produce apnea (Fig. 1), the posthyperventilation breathing was characterized by a small VT (68 ± 8% of baseline during normoxia, P < 0.05; 61 ± 12% of baseline during hypoxia, P < 0.05; and 74 ± 18% of baseline during hyperoxia, P = 0.21). No significant change was noted in either Tt (92 ± 9% of baseline during normoxia, 91 ± 12% of baseline during hypoxia, 106 ± 21% of baseline during hyperoxia; P > 0.05) or Te (81 ± 10% of baseline normoxia, 151 ± 40% of baseline hypoxia, 97 ± 7% of baseline hyperoxia; P > 0.05). In other words, posthyperventilation hypopnea was not associated with any significant change in breathing frequency or duty cycle, regardless of the level of PO2.

**DISCUSSION**

The major findings of this paper are the following. The time course of the occurrence of apnea after transient hyperpnea is consistent with a peripheral chemoreceptor mechanism during normoxia. Hypoxia advanced the onset of apnea, shortened the apnea latency, and narrowed the ∆PETCO2. In contrast, hyperoxia delayed the onset of apnea, prolonged the apnea latency, and widened ∆PETCO2. These observations provide insight about the interaction of peripheral and central chemoreceptors in developing central sleep apnea as well as the influence of PO2 on breathing stability.

**Critique of methods.** The ∆PETCO2 was greater in the present study (8 Torr during normoxia and 3 Torr during hypoxia) compared with our laboratory’s previously reported observations (52). This may have resulted from the different experimental conditions used to identify the apnea threshold. In the previous study, PETCO2 was gradually lowered by small decrements for several minutes to identify the minimum PETCO2 required to produce apnea. In the present study, we dropped the PETCO2 rapidly over a few breaths using the maximum tolerable VT. These large VT values might have resulted in an excessive lowering the PETCO2 to a level below the actual apneic threshold.

When delivering high VT values through a ventilator, neuromechanical inhibition may occur (33, 36). Although approximately the same VT was used under all three conditions, it may not have necessarily caused a comparable degree of neuromechanical inhibition at the three FIO2 levels (8). The influence of neuromechanical inhibition might be exaggerated by hypoxia at a given level of pressure support (1, 45, 52), but no evidence has demonstrated an interaction between central chemoreceptors and stretch receptor inputs. Because the apnea latency was generally longer than one respiratory cycle during normoxia.
and hyperoxia, and because the neuromechanical inhibition only caused a reduction of VT without producing apnea (51), the posthyperventilation apnea more likely results from a chemical rather than neuromechanical inhibition.

To minimize the non-carotid body effects of hyperoxia, we used 50% rather than 100% FIO2. The PETO2 increased to 340 Torr, which was sufficient to reduce the sensitivity of the peripheral chemoreceptor in humans (16). Zolpidem was used to reduce arousability. It has no effect on ventilation or breathing stability (4).

Peripheral chemoreceptor and posthyperventilation apnea. During normoxia, the apnea usually occurred within two respiratory cycles. Because the apnea latency of 12.2 s was similar to the LECD of 11.7 s, we concluded that the apnea latency was the result of the transport delay of the hypocapnia between the lungs and carotid body. Hence, this finding provides evidence that posthyperventilation apnea occurs in a time frame consistent with the responsiveness of the peripheral chemoreceptor. The ability of the carotid body to respond to the abrupt disturbance of blood gases has been tested with a transient increase in alveolar CO2. The maximum increase in VT after CO2 administration was observed during the second or third breath with a latency of 10–12 s (28, 46, 49). In patients with CSA, good agreement between the time from lowest PETCO2 to the onset of apnea and LECD has also been observed (35). Thus the short latency that we observed favors the concept that the peripheral chemoreceptors are the principal site of action of transient hypocapnia in precipitating central sleep apnea (7, 9, 10, 30, 39).

The importance of peripheral chemoreceptors in the rapid onset of posthyperventilation apnea is also supported by the observation that carotid denervation in dogs prevented the development of apnea after acute hypocapnia until the hypocapnia had been present for >30 s (39). However, the role of the peripheral chemoreceptors is more complex because the carotid body hypocapnia by itself was not sufficient to produce apnea as shown by the presence of only reduced VT but not apnea during hypocapnic perfusion of an isolated carotid body preparation in the unanesthetized sleeping dog (48). The delayed posthyperventilation apnea with carotid body denervation and the failure of isolated carotid body hypocapnia to produce apnea raises the possibility that central mechanisms may modulate the primary role of the peripheral chemoreceptors in producing posthyperventilation apnea.

The contribution of the central chemoreceptors to the posthyperventilation apnea has not been well defined. Animal studies indicate that medullary chemoreceptors have a perivascular location (43) and that a decrease in pH of the surface extracellular fluid could be measured only 6 s after CO2 inhalation in anesthetized cats (40). However, human studies suggested a much longer time delay for the central chemoreceptor response to a change in inspired gases, varying from 20 s (18, 24) to ~3 min (2, 13). In fact, our laboratory’s latest study on unanesthetized dog with intact, isolated carotid chemoreceptors shows that the initiation of the ventilatory response to a step increase in PETCO2 was delayed 1.5–2 times when the carotid chemoreceptor was not exposed to the hypoxia (47). Because of the properties of the blood-brain barrier plus the washout equilibration time in brain tissue, the central chemoreceptors may still have a longer response time compared with the intravascularly located peripheral chemoreceptors (18), making their role as the primary source of the initiation of apnea less likely.

Altered peripheral chemoreceptor activity and susceptibility to apnea. Stability of the breathing pattern during sleep is dependent on the background level of O2. Hypoxia has a destabilizing effect, whereas hyperoxia has a stabilizing effect. The present study confirmed and extended our laboratory’s previous observations (52) by showing that the narrowed PETCO2 caused by hypoxia results in shortened apnea latency. Hypoxia also tends to increase cardiac output, which could shorten the transport time by as much as half (37). Added CO2 produced a larger and faster response at the carotid body during hypoxia compared with normoxia (29, 50). In addition, as we discussed above, the influence of neuromechanical inhibition may be exaggerated by hypoxia (45). Taken together, the shorter apnea latency is due to a combination of an easier accessibility to the apnea threshold for CO2 and a hyperdynamic circulation that delivers the inhibitory influence more rapidly to the chemoreceptor site, making subjects more susceptible to apnea and breathing instability.

The cause of the smaller ΔPETCO2 is not just due to nonspecific hypoxic stimulation of the peripheral chemoreceptor because isolated stimulation of the peripheral chemoreceptor with almitrine was not sufficient to enhance the susceptibility to posthyperventilation apnea as has been reported with hypoxia (38). The effect of hypoxia may be related to less central ventilatory drive (40) as result of medullary hypocapnia due to hypoxia-induced hyperventilation and increased cerebral blood flow. Thus hypoxia may enhance periodic breathing and apnea through a combination of its stimulating effect on the peripheral chemoreceptor and its suppressive effect on central respiratory drive (26, 41) and via increased cerebral blood flow (12). In other words, even though peripheral chemoreceptor presence is necessary for the manifestation of a rapid-onset posthyperventilation apnea, additional central influences are required to produce periodic breathing.

In contrast to hypoxia, hyperoxia acts to blunt the carotid body responsiveness to CO2, preventing the rapid transmission of the inhibitory discharge to the respiratory center in response to transient reduction in CO2. The longer latency during hypoxia in our study was consistent with previous investigations that showed the latency of the response to CO2 withdrawal was longer during a hyperoxic background compared with a hypoxic background (37). A longer latency of the response to CO2 bolus was also seen in carotid body-dener-vated dogs (5), which raises the possibility that the central chemoreceptors may contribute to apnea when the peripheral chemoreceptor influence is diminished or no longer present. We, therefore, suspect that hyperoxia reduced the peripheral chemoreceptor response to hypcapnia and resulted in the central chemoreceptor becoming the principal site of action of hypcapnia in precipitating the apnea. A central site of action for the hypcapnic inhibition is supported by our observation that all three of the preapnic breaths during hyperoxia had a similarly low PETCO2. The fact that apnea did not occur despite the presence of a sufficient degree of hypcapnia in the alveoli and presumably in the arterial blood indicates that the delay in the occurrence of apnea was not due to a lower apnea threshold, but rather it was due to the longer time required to reach the requisite chemoreceptors in the central nervous system.
Because the apnea threshold of the central chemoreceptors is lower than the threshold of the peripheral chemoreceptors (15, 31, 32, 39), the involvement of central chemoreceptor would widen the ΔPCO2 and make it more difficult to develop apnea. However, the stabilizing effect of hyperoxia on breathing pattern is not merely the result of suppression of the peripheral chemoreceptor. When a direct inhibitor of the peripheral chemoreceptor, dopamine, was administered to sleeping dogs, the breathing pattern became unstable (11). Therefore, other effects of hyperoxia may also contribute to stabilizing the breathing pattern. For instance, hyperoxia decreases cerebral blood flow, which would tend to increase [H+] in the region of the central chemoreceptor and thereby resist to occurrence of hypocapnic apnea. Furthermore, hyperoxia may cause nonchemical ventilatory stimulation via reactive O2 species (14) or by a direct effect on lung irritant receptors, which, in turn, could reduce the susceptibility to apnea.

Hyperoxia has been demonstrated to stabilize the breathing pattern in humans with central sleep apnea associated with high altitude (3) and, to some extent, congestive heart failure (22, 25, 27). The present study identified several mechanisms for this therapeutic effect, including decreased influence of the peripheral chemoreceptor, widened ΔPCO2, lengthened duration of hypocapnia required to produce apnea, and reduced susceptibility to posthyperventilation apnea. In addition, previous studies have shown that hyperoxia also suppresses the ventilatory response to CO2 above eupnea (16, 23), reducing the ventilatory overshoot after an apnea or other perturbations, making the subsequent hypocapnia less likely. All the aforementioned factors associated with hyperoxia tend to facilitate a stable respiratory pattern.

In summary, during normoxia and hypoxia, the apnea latency correlates with the lung-to-eart circulation time, indicating that the predominant component of the hypocapnic apnea response originates from the fast-acting peripheral chemoreceptor. During hyperoxia, the prolonged onset of apnea and the lowered the apneic threshold support an attenuation of peripheral chemoreceptor influence and a greater contribution of central mechanisms. The dominance of the peripheral chemoreceptor in shortening the apnea latency and narrowing the ΔPCO2 (eupneic PCO2 – apneic PCO2) contributes to breathing pattern instability. Hyperoxia reduces the susceptibility to apnea by reducing the influence of the peripheral chemoreceptor and enhancing the central chemoreceptor function, which results in a wider ΔPCO2 and a longer apnea latency.

GRANTS

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