Hypoxia augments apnea-induced peripheral vasoconstriction in humans

URS A. LEUENBERGER, J. CULLEN HARDY, MICHAEL D. HERR, KRISTEN S. GRAY, AND LAWRENCE I. SINOWAY

Division of Cardiology, The Pennsylvania State University College of Medicine, The Milton S. Hershey Medical Center, Hershey 17033; Lebanon Veterans Affairs Medical Center Lebanon, Pennsylvania 17042; and Keesler Medical Center, Keesler Air Force Base, Mississippi 39534

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Leuenberger, Urs A., J. Cullen Hardy, Michael D. Herr, Kristen S. Gray, and Lawrence I. Sinoway. Hypoxia augments apnea-induced peripheral vasoconstriction in humans. J Appl Physiol 90: 1516–1522, 2001.—Obstructive apnea and voluntary breath holding are associated with transient increases in muscle sympathetic nerve activity (MSNA) and arterial pressure. The contribution of changes in blood flow relative to the contribution of changes in vascular resistance to the apnea-induced transient rise in arterial pressure is unclear. We measured heart rate, mean arterial blood pressure (MAP), and femoral artery blood velocity (VFA, Doppler) in humans during voluntary end-expiratory apnea while they were exposed to room air, hypoxia (10.5% inspiratory fraction of O2), and hyperoxia (100% inspiratory fraction of O2). Changes from baseline of leg blood flow (Q) and vascular resistance (R) were estimated from the following relationships: Q \( \propto \) VFA, corrected for the heart rate, and R \( \propto \) MAP/Q. During apnea, MSNA rose; this rise in MSNA was followed by a rise in MAP, which peaked a few seconds after resumption of breathing. Responses of MSNA and MAP to apnea were greatest during hypoxia and smallest during hyperoxia (P < 0.05 for both compared with room air breathing). Similarly, apnea was associated with a decrease in Q and an increase in R. The decrease in Q was greatest during hypoxia and smallest during hyperoxia (25 \( \pm \) 3 vs. 6 \( \pm \) 4%, P < 0.05), and the increase in R was the greatest during hypoxia and the least during hyperoxia (60 \( \pm \) 8 vs. 21 \( \pm \) 6%, P < 0.05). Thus voluntary apnea is associated with vasoconstriction, which is in part mediated by the sympathetic nervous system. Because apnea-induced vasoconstriction is most intense during hypoxia and attenuated during hyperoxia, it appears to depend at least in part on stimulation of arterial chemoreceptors.

obstructive sleep apnea; muscle sympathetic nerve activity; arterial chemoreflex

OBSTRUCTIVE APNEA IN PATIENTS with the sleep apnea syndrome and voluntary apnea in healthy humans are associated with surges of muscle sympathetic nerve activity (MSNA) and transient increases in arterial pressure (7, 9, 13, 27). Because these responses are attenuated by O2 administration, stimulation of arterial chemoreceptors is thought to play an important role (7, 9, 13, 26, 33). However, when hypoxia is induced during spontaneous breathing, vasodilation occurs in skeletal muscle, despite an increase in MSNA (12, 14, 22). Furthermore, the MSNA responses to obstructive and voluntary apneas are greatest at end apnea, whereas arterial pressure reaches its peak several seconds after resumption of breathing (7, 9, 13). Moreover, heart rate (HR) falls during apnea and rises on resumption of breathing (4, 9, 36). For these reasons, the relative contributions of transient changes in cardiac output and vasoconstriction to the transient pressor response to apnea are unclear.

Previous investigations of the peripheral vascular responses to obstructive apnea produced different conclusions. Using the thermodilution technique, Guilleminault et al. (5) found a decrease in cardiac output at end apnea and a 15% rise above baseline when breathing resumed and arterial pressure reached its peak. However, the temporal resolution of the thermodilution technique is limited and precludes a precise timing of changes in cardiac output associated with apnea. Similarly, measurements obtained with an electrical impedance method suggest that cardiac output decreased during apnea (29). However, for technical reasons, the immediate postapnea phase of the apnea-hyperventilation cycle could not be evaluated with this technique. More recently, Garpestad et al. (3) used a nuclear vest technique to estimate beat-by-beat changes in left ventricular stroke volume during and after obstructive apnea. Their data suggested that cardiac output decreased during obstructive apnea and was lowest a few seconds after apnea termination, i.e., during the arterial pressure peak. This suggested substantial transient vasoconstriction.

In the present study we examined the neurocirculatory changes that occur in awake healthy humans during voluntary end-expiratory apnea maneuvers (breath holds). To determine the effects of apnea on

Address for reprint requests and other correspondence: U. A. Leuenberger, Div. of Cardiology, MC H047, The Pennsylvania State University College of Medicine, The Milton S. Hershey Medical Center, PO Box 850, Hershey, PA 17033 (E-mail: uleuenberger@psu.edu).

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Peripheral vascular resistance, we estimated femoral arterial blood flow with the Doppler technique. We reasoned that voluntary apnea leads to hypoxic chemoreceptor stimulation but, unlike episodes of obstructive apnea, is not confounded by effects of arousal and transient swings in intrathoracic pressure typical of spontaneous obstructive apnea. Our hypothesis was that the increase in MSNA at end apnea resulted in peripheral vasoconstriction. Furthermore, we postulated that if the apnea-induced vasoconstriction was augmented by hypoxia and attenuated by hyperoxia, stimulation of peripheral chemoreceptors was likely to be an important determinant of this response.

METHODS

Subjects. Ten healthy men, age 26 ± 1 (SE) yr (range 22–31 yr), who had no significant medical history and were on no medications participated in the studies. The study protocol was approved by the Institutional Review Board of The Milton S. Hershey Medical Center. Informed written consent was obtained.

Blood pressure and HR measurements. Beat-by-beat arterial blood pressure was determined with a finger photoplethysmographic device (Finapres, Ohmeda) (19). This device has been shown to reliably register transient blood pressure changes induced by physiological maneuvers (19). Mean arterial pressure (MAP) was calculated as diastolic pressure plus one-third of pulse pressure. The electrocardiogram was monitored to determine HR.

Microneurography. MSNA was determined via peroneal microneurography (32). The general procedures for this technique have been described previously (7, 13). Briefly, a tungsten microelectrode was inserted into the peroneal nerve below the fibular head to record activity in efferent sympathetic fascicles carrying skeletal muscle vasconstrictor nerve traffic to the distal lower extremity (32). The nerve traffic signal was filtered, amplified, rectified, integrated, and recorded (model TA 4000, Gould, Valley View, OH). Standard techniques were used to demonstrate that the nerve signal, in fact, represented MSNA (7, 13, 32). The recordings were analyzed by hand, and MSNA was expressed as burst incidence (bursts/min) and total units per minute (average burst height × bursts/min).

Femoral arterial blood flow and vascular resistance. Blood flow in the femoral artery was estimated with the Doppler technique (6, 10, 31, 35). A 5-MHz custom-made continuous-wave ultrasound probe with an angle of insonation of 45° (Hokanson, Issaquah, WA) was placed over the femoral artery below the inguinal ligament. The spectral signal (i.e., the maximal instantaneous Doppler frequency shift) was displayed on a light indicator, fed through a loudspeaker, and inscribed on the multichannel recorder. By manual adjustments, the highest arterial flow signal was sought, and the Doppler probe was stabilized.

With the assumption of a flat, nonturbulent velocity profile, perfect cylindrical shape, and constant diameter of the artery, the flow volume per heartbeat is proportional to the time-velocity integral of the flow signal (6, 10, 31, 35). For simplicity, we determined the peak blood velocity measured over the femoral artery (V_{FA}) as an index of flow per heart-beat. This was converted to an index of flow per minute (Q) by multiplying V_{FA} by the instantaneous HR (calculated as 60/R-R interval of the corresponding cardiac cycle). Thus, Q = V_{FA} × HR. To validate that V_{FA} was a reliable index of mean flow velocity, in three subjects V_{FA} was correlated with the time-velocity integral of the flow signal, which was determined electronically. In these studies we found a good correlation (r = 0.84–0.88) between V_{FA} and the corresponding time-velocity integral over the range of Q and HR studied. To exclude changes of vessel size during the experimental interventions, in three subjects, femoral artery diameter below the inguinal ligament was determined with a cardiovascular scanner (Interspec XL, Conshohocken, PA; 7.5-MHz pulsed-wave transducer).

Because we did not attempt to measure absolute flow rates, flow was expressed as a change compared with the preapnea baseline in each respective condition. The relationship R = MAP/Q was used to estimate changes in leg vascular resistance (R), which was expressed as a change compared with the preapnea baseline in each respective condition.

Respiratory measurements. Minute ventilation (V_{E}, l/min), end-tidal CO_{2} (%), and arterial O_{2} saturation (S_{a}O_{2}, %) were measured with a respiratory gas monitor (model 5250, Ohmeda). Respiratory movements were monitored via a pneumograph.

Protocol. The studies were performed in a temperature-controlled human research laboratory with the subjects in the supine position. Once a suitable site for MSNA in the peroneal nerve was found, the Doppler probe was positioned over the ipsilateral femoral artery. A facemask with separate inlet and outlet valves was positioned securely and checked for leaks. The inspiratory line was connected to a reservoir bag containing the experimental gas mixture. The expiratory line was connected to the respiratory gas monitor. After a 10-min rest period, MSNA, MAP, HR, V_{E}, end-tidal CO_{2}, and V_{FA} were measured over a 5-min period of room air breathing (control). The subjects were then asked to perform two to five maximal end-expiratory apnea maneuvers, each separated by a 1-min recovery period. The subjects were instructed to avoid Valsalva and Müller maneuvers. After recovery, the inspiratory gas mixture was changed at random to 10.5% O_{2} in N_{2} or to 100% O_{2}. MSNA, MAP, HR, V_{E}, end-tidal CO_{2}, and V_{FA} were measured during minutes 6–10 of exposure to hypoxic or hyperoxic gas, and the apnea maneuvers were repeated. After a 30-min rest period, the control measurements during room air exposure were repeated, and the exposure to the other non-room air gas mixture began. After 10-min of hypoxia or hyperoxia, voluntary apnea maneuvers were repeated.

Data analysis and statistics. Measurements during spontaneous room air breathing (control) reflect the average values obtained over 5 min, and values for hypoxia (10.5% O_{2}) and hyperoxia (100% O_{2}) were the averages obtained during minutes 6–10 of exposure to the respective condition. The apnea responses were analyzed as follows: MAP, HR, and V_{FA} were averaged over three representative cardiac cycles immediately before apnea (preapnea baseline) as well as at 5-s intervals during the last 10 s of apnea (late and end apnea, respectively) and during the first 20 s of recovery after apnea (R5, R10, R15, and R20, respectively). Correspondingly, the MSNA response to apnea was measured at 5-s intervals over the last 10 s of apnea and the first 20 s after resumption of breathing. For MSNA, all 5-s averages were extrapolated to 1 min for comparison with the respective preapnea baseline.

Statistical comparisons of room air control and hypoxia or hyperoxia during spontaneous breathing were made with the two-tailed paired t-test. Comparisons of apnea responses under the three different experimental conditions (room air, hypoxia, and hyperoxia) were made by ANOVA for repeated measures. Where the F value indicated a difference, post hoc analysis was performed with Tukey’s test. For multiple com-
Comparisons, the P value was adjusted by the Bonferroni method. P < 0.05 was considered statistically significant. Values are means ± SE; n = 10, except for muscle sympathetic nerve activity (MSNA), where n = 9. MAP, mean arterial pressure; HR, heart rate; SaO2, arterial O2 saturation; Ve, minute ventilation; NS, not significant.

RESULTS

Effects of hypoxia and hyperoxia on MAP, HR, Ve, end-tidal CO2, MSNA, femoral blood flow, and vascular resistance. The effects of hypoxia and hyperoxia on hemodynamic parameters, Ve, end-tidal CO2, and MSNA are shown in Table 1. As expected, during hypoxia, HR and MSNA rose, while end-tidal CO2 decreased. A small rise in MAP was of borderline statistical significance. During hyperoxia, we found no significant changes in HR, MAP, end-tidal CO2, and MSNA, whereas Ve increased mildly. Compared with room air control, during hypoxia, femoral blood flow increased by 28 ± 8% (P < 0.01, single-sample t-test) and decreased by 4 ± 5% during hyperoxia (not significant). Accordingly, vascular resistance decreased by 15 ± 5% during hypoxia (P < 0.01) and increased by 8 ± 5% during hyperoxia (P < 0.01).

Table 1. Effects of hypoxia (FiO2 10.5%) and hyperoxia (FiO2 100%) on MAP, HR, SaO2, Ve, end-tidal CO2, and MSNA

<table>
<thead>
<tr>
<th></th>
<th>MAP, mmHg</th>
<th>HR, beats/min</th>
<th>SaO2, %</th>
<th>Ve, l/min</th>
<th>End-Tidal CO2, %</th>
<th>MSNA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>93 ± 3</td>
<td>67 ± 3</td>
<td>98 ± 0.3</td>
<td>7.6 ± 0.3</td>
<td>5.9 ± 0.1</td>
<td>14 ± 2</td>
</tr>
<tr>
<td>Hypoxia</td>
<td>98 ± 4</td>
<td>85 ± 4</td>
<td>80 ± 2</td>
<td>9.5 ± 0.4</td>
<td>5.4 ± 0.1</td>
<td>20 ± 3</td>
</tr>
<tr>
<td>P</td>
<td>0.05</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.01</td>
<td>0.2</td>
</tr>
<tr>
<td>Control</td>
<td>92 ± 3</td>
<td>64 ± 3</td>
<td>97 ± 0.3</td>
<td>7.7 ± 0.3</td>
<td>5.9 ± 0.1</td>
<td>13 ± 2</td>
</tr>
<tr>
<td>Hyperoxia</td>
<td>94 ± 4</td>
<td>62 ± 2</td>
<td>99 ± 0.2</td>
<td>8.7 ± 0.4</td>
<td>5.8 ± 0.1</td>
<td>17 ± 3</td>
</tr>
<tr>
<td>P</td>
<td>NS</td>
<td>&lt;0.01</td>
<td>0.05</td>
<td>NS</td>
<td>NS</td>
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</tr>
</tbody>
</table>

Values are means ± SE; n = 10, except for muscle sympathetic nerve activity (MSNA), where n = 9. MAP, mean arterial pressure; HR, heart rate; SaO2, arterial O2 saturation; Ve, minute ventilation; NS, not significant.

DISCUSSION

In this study we examined the effects of hypoxia and hyperoxia on the sympathetic neural and peripheral blood flow responses to voluntary apnea in humans. There are two main findings: 1) the transient apnea-induced surges of MSNA and arterial pressure are associated with transient peripheral vasoconstriction, and 2) hypoxia accentuates and O2 administration attenuates the sympathetic and vasoconstrictor responses to apnea. This suggests that hypoxia-induced blood velocity was used to estimate apnea-induced changes in leg blood flow and vascular resistance. The effects of apnea on femoral blood flow and vascular resistance are displayed in Fig. 3. The simultaneous and opposite changes in MAP (which increased) and blood flow (which decreased) translated into a transient increase in peripheral resistance that was most pronounced at the time of the blood pressure peak. The apnea-induced rise in resistance was most pronounced during hypoxia and least pronounced during hyperoxia.

Fig. 1. Muscle sympathetic nerve activity (MSNA), arterial blood pressure (AP), femoral artery blood velocity (Ve), O2 saturation (SaO2), and respiration in response to voluntary apnea during exposure to inspiratory O2 fractions of 10.5 and 100% from 1 subject. Arrows indicate the end of apnea and the resumption of breathing.
sympathoexcitation plays an important role in the transient apnea-induced vasoconstrictor responses. Marked oscillations of arterial pressure and surges in sympathetic nerve activity are characteristic features of obstructive sleep apnea (9, 13, 27). It has been shown in these patients that arterial pressure rises immediately on apnea termination and that the pressure rise is preceded by surges in sympathetic nerve activity directed to skeletal muscle (9, 13, 27). Furthermore, experiments with ganglionic blockade in normal humans suggest that the pressor response to apnea is sympathetically mediated (11). However, the precise trigger of these transient pressure elevations has been debated. Intermittent stimulation of arterial chemoreceptors (7, 9, 13), arousal from sleep (17, 23), and transient changes in intrathoracic pressure (30) have each been postulated to play a role. In the present study we intended to examine the role of chemoreceptor activation during apnea while excluding the confounding influences of arousal and intrathoracic pressure changes on sympathetic nerve activity and vascular resistance. Thus the studies were performed in awake healthy volunteers during voluntary nonobstructive apneas.

In agreement with a previous study, we found sympathetic neural outflow to skeletal muscle and arterial pressure to rise in response to voluntary apnea, and these effects were accentuated by hypoxia and attenuated by O₂ administration (7). In the present report, apnea-induced changes in peripheral vascular resistance were estimated from changes in \( V_{FA} \) and arterial pressure. Our data suggest that, during hypoxic apnea, sympathetic vasoconstrictor nerves targeted to skeletal muscle were activated to a greater degree and the associated fall in femoral blood flow and the rise in vascular resistance were greater than when apnea-induced chemoreceptor activation and sympathetic activation were attenuated by prior exposure to 100% O₂. In our subjects, during hyperoxic, room air, and hypoxic apneas, we estimated maximal decreases of blood flow in the femoral artery at the time of the postapnea blood pressure peak of \(-6, -11, \) and \(-25\%, respectively. The decrease in femoral blood flow during hypoxic apneas in our study was remarkably similar to the \(-26\%\) drop in cardiac output noted by Garpestad et al. (3) in the immediate postapnea period in patients with obstructive apnea events of \(\geq 30\)-s duration and \(S_{A}O_{2}\) nadirs to \(<82\%. These investigators used a radionuclide technique to estimate apnea-related beat-by-beat changes in cardiac stroke volume (3). In contrast, measurements obtained with the thermodilution technique suggested a decrease in cardiac output during apnea and an increase above baseline in the immediate postapnea phase (5). However, because thermodilution output measurements reflect the average of many consecutive
heartbeats, the timing of these measurements is less precise to quantify changes related to apnea.

One major strength of the Doppler technique is its excellent time resolution, which permits a beat-by-beat assessment of blood flow. Several studies have reported excellent correlations between Doppler-derived volumetric flow in the aorta and peripheral arteries and thermodilution, venous occlusion plethysmography, or electromagnetic flow measurements (6, 10, 31). However, rather than absolute blood flow, we determined blood velocity, an indirect index of volumetric flow. Therefore, we cannot comment on absolute changes of blood flow between conditions or during apnea but, instead, expressed apnea-induced changes in blood flow and resistance as percent changes from the preapnea baseline.

An important aspect of our study was that our subjects were awake and did not attempt to breathe against an obstructed airway. Therefore, arousal and the characteristic transient intrathoracic pressure swings associated with obstructive apnea did not occur. In healthy humans it has been shown that transient negativity of intrathoracic pressure induced by a Müller maneuver does not contribute significantly to the sympathetic neural activation induced by (voluntary) apnea (18).

Under all experimental conditions (room air, hypoxia, hyperoxia), our subjects performed maximal tolerated end-expiratory apneas rather than apneas of fixed duration. This ensured that the net respiratory drive and vigor of breathing at apnea termination (“breaking point”) and potential mechanical effects of breathing in the immediate postapneic phase were similar in all experimental conditions (16). However, because for a given lung volume and metabolic rate, CO2 accumulation is a direct function of apnea duration (16), the arterial Pco2 at end apnea was likely very different between room air, hypoxic, and hyperoxic apneas. In contrast to the hypoxic stimulus, the CO2 stimulus was likely smallest during the short apneas performed during hypocapnic hypoxia and greatest during the prolonged hyperoxic apneas. Because of the synergistic effects of hypoxia and hypercapnia on sympathetic activity (28), the pressor and vasoconstrictor effects of hypoxic apnea might even have been greater if we had controlled CO2. Thus our data strongly suggest that apnea-induced hypoxia independent of hypercapnia can explain, at least in part, the neurocirculatory effects of apnea. Of course, these considerations do not exclude the possibility that arousal or other factors may modify the neural and vasomotor responses to obstructive apnea independent of hypoxia (17, 23). In addition to sympathoexcitation, the myogenic response may also contribute to the transient apnea-related pressor responses (15). This reflex may be enhanced by apnea-related surges of sympathetic nerve activity (21).

The relative time courses of the responses of blood pressure, sympathetic nerve discharge, and vasoconstriction to apnea also deserve consideration. Whereas progressive discharges of vasoconstrictor nerve traffic (MSNA) occur during apnea, nerve activity decreases abruptly on apnea termination (7, 9, 13, 27, 34), yet blood pressure and vascular resistance during apnea are similar in the three conditions and do not peak until several seconds after apnea termination. We believe the most plausible explanation for the discrepancy in the time courses of these parameters is the “onset” and “offset” delay for the vascular response to the neural vasoconstrictor signal. This is supported by findings in a dog hindlimb preparation where the time constant for the rise in vascular resistance after the onset of sympathetic activation was ~9 s and the delay between the end of the sympathetic discharge and the onset of vasodilation was 2–5 s (24).

The effects of hypoxia or hyperoxia on peripheral blood flow during spontaneous ventilation (rather than during apnea) in humans are well established (12, 22). During levels of hypoxia similar to those achieved in this study, forearm vascular resistance based on plethysmography flow measurements decreased by ~24 and ~31% (12, 22). Vasodilation during hypoxia with spontaneous breathing but vasoconstriction during apnea at first may appear counterintuitive, because under both conditions, vasoconstrictor nerve traffic is increased. On the one hand, during spontaneous breathing, hypoxia is accompanied by mild sympathetic activation (12, 28) and peripheral release of vasodilator substances, resulting in net vasodilation (14, 25). On the other hand, our data and previous reports (1, 25) suggest that, during apnea, intense sympathetic activation overpowers peripheral vasodilator mechanisms, resulting in net vasoconstriction. In addition to chemoreceptor stimulation, the absence of lung inflation (lung inflation reflex) during apnea is thought to contribute importantly to the marked sympathetic discharges served during hypoxic apnea (1, 25).

As expected, during spontaneous ventilation, hypoxia produced an increase in MSNA, HR, and ventilation, whereas an increase in MAP was of borderline statistical significance (7, 12). On the other hand, hyperoxia was associated with no significant change in MAP, HR, and MSNA (7). However, V̇E rose during hyperoxia, a phenomenon that has been attributed to the Haldane effect (2).

Our conclusions rest on several assumptions, which deserve to be discussed. One major assumption is that V̇fa is indeed proportional to blood flow in the femoral artery. A motion artifact of the transducer relative to the underlying vessel could mimic transient changes in blood flow. However, for several reasons, this appears unlikely. First, we were careful to stabilize the transducer over the femoral artery, and the subjects were instructed to avoid straining and movement during these apnea maneuvers. Second, if the velocity changes were artifactual, we would not have expected to find differences in the responses between room air, hypoxic, and hyperoxic conditions. Third, if changes in velocity were related to changes in the transducer position over the femoral artery, we would not have expected that the decrease in velocity during apnea was reproducible. Finally, our femoral artery diameter measure-
ments make it unlikely that the observed changes in blood velocity were due to an apnea-induced change in vascular dimension.

Our measurements of blood velocity were made in the leg; therefore, extrapolations to stroke volume and cardiac output should be made with caution. It is conceivable that sympathetic neural activation during apnea-induced hypoxia is highly differentiated, leading to vasoconstriction in skeletal muscle, while vasoconstriction may occur in other organs such as the heart and the brain. Such a differentiated pattern of the vascular responses would be consistent with a protective effect of these reflex changes similar the diving reflex seen in aquatic mammals (25).

Despite these limitations, we believe our data are relevant to obstructive sleep apnea. The coincidence during apnea of hypoxia, transient hypertension, and increased vascular resistance suggests that chemoreceptor stimulation such as may occur during obstructive apnea is associated with transient increases in left ventricular afterload at a time of decreased O₂ supply to the myocardium. It is therefore conceivable that repetitive hypoxic/hypertensive insults over time may contribute to the increased cardiac morbidity and mortality observed in patients with obstructive sleep apnea (8, 20).

In conclusion, we found that voluntary apnea in humans was associated with transient vasocostriction that was preceded by a transient rise in vasoconstrictor nerve traffic to skeletal muscle. Because vasoconstrictor nerve traffic and vasoconstriction were greatest during hypoxic apnea and were attenuated during hyperoxic apnea, the magnitude of apnea-induced vasoconstriction appears to be related in part to stimulation of arterial chemoreceptors.

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REFERENCES


