Ventilatory response to helium-oxygen breathing during exercise: effect of airway anesthesia

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Ventilatory response to helium-oxygen breathing during exercise: effect of airway anesthesia. J. Appl. Physiol. 83(1): 82–88, 1997.—The substitution of a normoxic helium mixture (HeO₂) for room air (Air) during exercise results in a sustained hyperventilation, which is present even in the first breath. We hypothesized that this response is dependent on intact airway afferents; if so, airway anesthesia (Anesthesia) should affect this response. Anesthesia was administered to the upper airways by topical application and to lower central airways by aerosol inhalation and was confirmed to be effective for over 15 min. Subjects performed constant work-rate exercise (CWE) at 69 ± 2 (SE)% maximal work rate on a cycle ergometer on three separate days: twice after saline inhalation (days 1 and 3) and once after Anesthesia (day 2). CWE commenced after a brief warm-up, with subjects breathing Air for the first 5 min (Air-1), HeO₂ for the next 3 min, and Air again until the end of CWE (Air-2). The resistance of the breathing circuit was matched for Air and HeO₂. Breathing HeO₂ resulted in a small but significant increase in minute ventilation (V˙I) and decrease in alveolar PCO₂ in both the Saline (average of 2 saline tests; not significant) and Anesthesia tests. Although Anesthesia had no effect on the sustained hyperventilatory response to HeO₂ breathing, the V˙I transients within the first six breaths of HeO₂ were significantly attenuated with Anesthesia. We conclude that the V˙I response to HeO₂ is not simply due to a reduction in external tubing resistance and that, in humans, airway afferents mediate the transient but not the sustained hyperventilatory response to HeO₂ breathing during exercise.

THE SUBSTITUTION OF A NORMOXIC helium-oxygen mixture (HeO₂) for room air (Air) during exercise causes an increase in minute ventilation (V˙I) that is evident in the first breath (11, 15, 35). The mechanisms underlying the ventilatory response to HeO₂ breathing are unclear. Because of its reduced density, HeO₂ reduces turbulence and therefore flow resistance in the airways, especially in the upper airways (25). It has been suggested that the respiratory adaptations to HeO₂ breathing may indicate a reflex effect (15). Ward et al. (35) have suggested that the altered activation of irritant or other airway receptors might contribute to the hyperventilation with HeO₂. Afferent information arising from numerous receptors (sensitive to flow, pressure, temperature, and CO₂) in the larynx (33) and the tracheobronchial tree (31) has been shown to influence ventilatory control, in both humans (10, 22) and animals (31). Both topical (10, 21) and inhaled aerosol anesthesia (10, 22) have been used effectively in humans for reversible blockade of these vagally mediated afferents. We therefore examined the effects of airway anesthesia (Anesthesia) on the transient and sustained V˙I response to HeO₂ breathing during exercise in normal humans. Because the reduction in turbulent flow with HeO₂ breathing during exercise is most marked in the upper (extrathoracic) and major intrathoracic airways (25), we combined two methods of Anesthesia administration (10, 21, 22) to target these sites, as has been done in previous studies (18).

We also examined the effects of external tubing resistance on the response to HeO₂ breathing because HeO₂ reduces external tubing resistance, as well as internal airway resistance. With Air breathing, an increase in external resistance causes a decrease in V˙I during exercise (9). It is therefore possible that the V˙I response to HeO₂ breathing is a consequence of the change in external resistive load rather than the change in internal load. The external equipment resistance was therefore matched for both Air and HeO₂ in this study (8).

MATERIALS AND METHODS

Subjects. Eleven active men [age 25 ± 2 (SE) yr] with no history of cardiorespiratory or other diseases and no known hypersensitivity to local anesthetics were studied. Informed written consent was obtained after each subject underwent a physical examination and a 12-lead electrocardiogram (ECG). The study was approved by the institutional ethics committee for human experimentation. All subjects reported to the laboratory at least 2 h in the postprandial state and were specifically instructed not to undertake any strenuous exercise on the days of exercise testing.

Study design. This study was designed to examine whether Anesthesia affected the transient and sustained hyperventilatory response to HeO₂ breathing during exercise. Each subject was tested on five separate days: day 1, to establish the effectiveness and duration of Anesthesia; day 2, maximal incremental exercise to exhaustion; and days 3–5, constant work rate exercise (CWE) breathing Air and HeO₂ after either Saline (days 3 and 5, Control studies) or Anesthesia inhalation (day 4).

Administration of Anesthesia. Each subject gargled 5 ml of 4% lidocaine solution for 2–3 min, attempting to get the solution as far back in the oropharynx as possible without swallowing. To achieve good laryngeal anesthesia, cotton pledgets (held by laryngeal forceps) soaked in 4% lidocaine were then applied directly to the piriform recess for 1 min on each side. This technique has been validated in animals to provide effective blockade of the internal branch of the superior laryngeal nerve and thus block sensory feedback from the larynx (21). The subject then inhaled 200 mg of nebulized lidocaine [5 ml of 4% solution with no preservatives for ophthalmic injection (USP)] with a fixed breathing pat-
tern [a 5-s inspiration to total lung capacity, breath hold for 5 s, and a slow (—5-s) relaxed expiration], which has been shown to promote uniform deposition of heterodisperse aerosols throughout the proximal tracheobronchial tree (1, 28, 29). Lidocaine was nebulized only during inspiration to maximize aerosol delivery, and the process was completed in ~6 min. This combined method of upper and lower airways anesthesia administration has been used previously in this laboratory and has been found to provide reliable airway anesthesia for over 15 min (18).

All aerosols used in the study (lidocaine, Saline) were generated by Devilbiss-646 (Somerset, PA) jet nebulizers, run by a regulated compressed-air source (35 lb./in.2) at a flow rate of 7–8 l/min. Particle size information was obtained from the manufacturer, who determined that, operating under identical conditions to those in our laboratory, these nebulizers produced a heterodisperse normal saline aerosol with a mass median aerodynamic diameter (1) of 5 μm (range of particle size, 2–8 μm). Both the size and distribution of the aerosol and the breathing pattern were chosen to maximize deposition in the larynx and in the central airways (trachea, hilum, and the large bronchi) (28, 29). Particles of this size seldom deposit in the peripheral bronchioles or alveoli (1, 28).

Another subject (Saline-2) did not perform CWE, due to both the insensibility of effective anesthesia for over 15 min was confirmed in each subject in the following manner. Before anesthesia was administered, the baseline subjective responses such as sensation (baseline score = 5), response to blunt pharyngeal probing (baseline score = 5), gag reflex (baseline score = 5), and difficulty in swallowing (baseline score = 0) were graded on a 0—5 (least—most) scale in each subject. The single-breath vital capacity inhalation (at 1 l/s) maneuver (34) was then used to assess the subjects’ cough threshold for nebulized citric acid solutions of doubling concentration (0, 1, 2, 4 . . . 32%). At the end of every 2 min after anesthesia was administered by using the technique described above, each subject was asked to grade these same sensations on the same scale as before. At the end of every 5 min after anesthesia administration, each subject underwent a nebulized citric acid inhalation challenge (34) at the previously determined threshold concentration.

Exercise protocol. On day 2, each subject performed maximal incremental exercise to exhaustion while breathing Air, to measure peak work rate (Wmax; 325 ± 16 W). On days 3—5 (Control studies), each subject performed CWE at ~69 ± 2% Wmax (range 160—290 W, 64—77% Wmax) for 13 min. The CWE protocol on all occasions consisted of a brief warm-up exercise at 75 W (range 19—30% Wmax) for 1 min, after which the work rate was abruptly increased to the predetermined level for each subject. The inspirate was Air during both the warm-up period and the first 5 min of CWE (Air-1), at the end of which the inspirate was abruptly switched (during expiration) to HeO2. The subject breathed HeO2 for the next 3 min, and the inspirate was then switched back (during expiration) to Air. Each subject continued to exercise while breathing Air for the next 5 min (Air-2) or until exhaustion (which ever came first). On days 3 and 5 (Control studies), the subjects inhaled lidocaine nebulized normal saline (5 ml of 0.9% solution, no pressurization) just before the start of CWE (Saline-1, Saline-2) by using the same inhalation pattern as that used with Anesthesia administration. On day 4, Anesthesia was administered just before the start of CWE in a fashion identical to that described earlier. An identical CWE protocol was used on all three (Saline-1, Saline-2, Anesthesia) occasions. One subject completed the first minute of exercise in the Air-2 period on all three occasions, and another subject stopped exercise immediately after the start of the Air-2 period on the Anesthesia (day 4) test day. However, 9 of the 11 subjects completed the 13 min of CWE (Air-1, HeO2, Air-2) on all the three days.

Exercise equipment and measurements. Both the incremental and constant work rate exercise tests were conducted on an electrically braked cycle ergometer (Godart, Bilthoven, Holland). The breathing apparatus consisted of a two-way non-rebreathing Y valve (dead space 115 ml, Hans Rudolph 2700, Kansas City, MO) connected by short tubing (1½" inner diameter) to inspiratory and expiratory pneumotachographs (Fleisch no. 3), each of which was connected to a two-way (switching) valve. These silent valves were used to manually switch the inspiratory and expiratory limbs from Air to HeO2 and vice versa, without any disturbance to the exercising subject. Because it was possible that the hyperventilatory effects of HeO2 breathing may be due, in part, to its unloading of the external tubing resistance, we took care to match the flow resistance of the breathing circuit for both Air and HeO2 before the study by using methods employed by DeWeese et al. (8) at rest. By adding appropriate fixed resistances to the HeO2 ports of the switching valves (on both the inspiratory and expiratory limbs), we were able to match the flow resistances of both the inspiratory and expiratory limbs of the breathing circuit for Air and HeO2. Table 1 summarizes the flow ranges through which the resistances of the inspiratory and expiratory limbs of the breathing circuit (in both Air and HeO2) were matched. Both Air and HeO2 were warmed and humidified and delivered from large meteorological balloon reservoirs that were concealed from the subjects’ direct view. With the aid of inspiratory and expiratory flow sensors, one investigator was able to switch the inspirate from Air to HeO2 (and back again) at the appropriate phase of the breathing cycle and exercise periods. None of the subjects was aware of any of these switches, which were made from behind a screen.

Inspiratory and expiratory flows, measured by two pneumotachograph-transducer (Fleisch no. 3, Validyne MP-45, 2 ± cmH2O) assemblies on either side of the breathing valve, were added electronically to provide flow and volume throughout the breathing cycle. The inspiratory and expiratory pneumotachographs were calibrated (at 4 l/s) with both Air and HeO2 before the start of each test and checked immediately after the end of each exercise test. Measurements were also made in both Air and HeO2, at flow rates of 2 and 8 l/s to assess the linearity of the flow resistance of the breathing circuit through the range of possible flow rates during exercise. The individual flow signals (inspiratory) and (expiratory) were monitored on a breath-by-breath basis throughout exercise for any zero drift (14).

A mass spectrometer (Airspec, MGA 2000) was used to measure gases at the mouth. Pilot studies revealed that when the mass spectrometer was calibrated with an Air standard gas mixture (carrier N2), the measurements of CO2 in HeO2 were inaccurate, probably because of the physical properties of HeO2. For accurate CO2 measurements, therefore, the mass spectrometer was calibrated at the start of each gas period (Air-1, HeO2, Air-2) during CWE, with the gas stan-

<table>
<thead>
<tr>
<th>Flow, l/s</th>
<th>Inspiratory Resistance, cmH2O·l·s−1</th>
<th>Expiratory Resistance, cmH2O·l·s−1</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>0.79</td>
<td>0.75</td>
</tr>
<tr>
<td>4</td>
<td>0.87</td>
<td>0.77</td>
</tr>
<tr>
<td>6</td>
<td>1.06</td>
<td>0.98</td>
</tr>
<tr>
<td>8</td>
<td>1.18</td>
<td>0.98</td>
</tr>
</tbody>
</table>

HeO2, heliox mixture.
standard (carrier N2 or He) appropriate for the inspirate being used (Air or HeO2). A pulse oximeter (Nellcor) recorded both fingertip O2 saturation (SaO2) and a standard three-lead ECG during exercise.

Data analysis. Inspiratory and expiratory flow (V), volume (VT), CO2, SaO2, and ECG were recorded continuously on an 8-channel strip-chart recorder (Gould) and digitized. Data analysis was performed on a computer that measured inspiratory (T1), expiratory (T2), and total (TT) breath durations and tidal volume (VT) for all valid breaths during exercise (those interrupted by cough and/or swallowing were identified and not included). Vt was derived from averaged VT and breathing frequency (f). Appropriate flow correction factors based on calibrations before and after exercise were used to correct during the HeO2 periods. Because the mass spectrometer was being calibrated (with the appropriate gas standard) during the first 15 s of the minute immediately after the gas transitions (HeO2, Air-2), the CO2 data during these periods were unavailable for analysis. However, all other variables were analyzed during these periods. All the other data were collected on a breath-by-breath basis throughout exercise and were used in data analysis. With the use of previously described techniques (36), time-weighted mean alveolar PCO2 (Pa,CO2) was estimated from the averaged breath-by-breath airway PCO2 signal for each minute of exercise. Pa,CO2 thus derived has been shown to accurately estimate arterial PCO2 during exercise (36).

Data from the two Saline tests (Saline-1, Saline-2; not significant) were averaged (Saline) in each subject for comparison with Anesthesia data. To study steady-state effects, data from the first minute of Air were averaged with data from the first minute of Air-2 for comparison with the average data from the second minute of HeO2. A paired t-test (2-tailed) was used to detect differences between Air and HeO2, as well as between Saline and Anesthesia. To study the effects of Anesthesia on the breath-by-breath effects of HeO2, Vt data from the last 10 breaths in Air-1, first 6 breaths in HeO2, and average Vt data from the second minute of HeO2 were analyzed with a two-factor (gas, Anesthesia) repeated-measures analysis of variance design. Significant breath-by-breath effects of HeO2 on Vt (in both the Saline and Anesthesia tests) were then compared with Air in a Dunnett’s comparison procedure (Control group, Air-1). A P < 0.05 was accepted as significant.

RESULTS

Evidence of Anesthesia. On the initial assessment day (day 1), subjects reported significant numbness in the mouth and oropharynx and a noticeable difficulty in swallowing immediately after Anesthesia administration. The cough response to inhaled citric acid aerosol was abolished for over 15 min in all subjects, and it took longer (>20 mins) for subjective sensations to return to baseline levels. After a brief warm-up period at the end of CWE on day 4 (Anesthesia), all subjects reported significant residual Anesthesia, as shown by their grading (0–5, least—most) of the subjective sensations in the mouth (2.8 ± 0.2), in the throat (2.5 ± 0.2), increased tolerance to blunt pharyngeal probing (2.2 ± 0.3), and gag reflex (2.5 ± 0.4), as well as persistent difficulty in swallowing (2.5 ± 0.2). These results are consistent with those from another study in this laboratory, in which subjects showed significant residual Anesthesia after exercise (18).

Effect of Anesthesia on hyperventilatory response to HeO2. Figure 1 shows group mean (± SE) Vt, VT, f, and Pa,CO2 data during warm-up exercise [baseline values (0)] and during the Air-1, HeO2, and Air-2 periods during CWE. Each point represents all valid data averaged over 1 min. As shown in previous studies during CWE (6, 20), VI increased rapidly in the first 3–4 min at the start of CWE and continued to increase slowly throughout CWE. Most of the increase in Vt was as a result of an increase in f because VT leveled off after the initial increase in the first 2 min of CWE. There was a significant increase in Vt and a fall in Pa,CO2 after the switch to HeO2 as the inspirate, and this hyperventilation persisted throughout the HeO2 period. On the switch back to Air (Air-2), however, there was a fall in Vt and an increase in Pa,CO2 after which Vt increased (and Pa,CO2 fell) gradually until end exercise. The magnitude of increase in Vt (~4 l/min; Table 2) and fall in Pa,CO2 (~1.5 Torr) with HeO2 breathing, although small, was significant (2-tailed t-test) in both the Saline and Anesthesia tests (Table 2). This modest increase in Vt with HeO2 breathing was due to a significant increase in f because HeO2 breathing did not alter VT significantly. HeO2 breathing also resulted in a small but significant fall in the inspiratory duty cycle (Ti/Tt) and a small but significant increase in SaO2. However, as shown in Fig. 1 and Table 2, Anesthesia had no effect on the hyperventilatory response to HeO2 breathing during CWE. Effect of Anesthesia on Vt transients with HeO2. The effect of Anesthesia on the immediate increase in Vt on the switch to HeO2 is shown in Fig. 2. The averaged data from the last 10 breaths in Air-1 period (Saline vs. Anesthesia; not significant) represent the baseline (0) values. Data are shown as the increase in Vt (ΔVt in Fig. 2; see also Fig. 3) in the first six breaths of HeO2 and in the second minute of HeO2 breathing. In the Saline test, Vt increased immediately with HeO2 breathing, and almost all the increase in Vt occurred by the second breath. With Anesthesia, there was a noticeable attenuation of this transient increase in Vt in the first five to six breaths of HeO2, but this effect was not present in the second minute of HeO2.

Figure 3 summarizes the effects of Anesthesia on the transient increase in Vt in the second breath of HeO2 and in the second minute of HeO2 in all subjects. Increases in Vt (HeO2 – Air) data in the Saline test are compared with those in the Anesthesia test in each subject. Ten of the 11 subjects had a smaller increase in Vt in the second breath of HeO2 after Anesthesia than with Saline, and this difference was statistically significant. This effect of Anesthesia, however, did not continue into the second minute of HeO2 breathing.

DISCUSSION

The major findings of this study are 1) the immediate but not the sustained hyperventilation due to HeO2 is attenuated by airway anesthesia; and 2) HeO2 causes hyperventilation when the reduction in tubing resistance due to HeO2 is prevented; therefore, the HeO2
hyperventilation is not simply due to a change in external resistive load.

Previous studies have shown that the substitution of HeO2 for Air results in an immediate and sustained increase in V˙I (11, 15, 35). The magnitude of the HeO2-induced hyperventilation during exercise varies significantly among different studies but is greatest at high levels of V˙I (2, 7, 30). As emphasized by Ward et al. (35) and Pan et al. (27), this increase in V˙I is attenuated by the resulting fall in arterial PCO2. The increase in V˙I with HeO2 has been attributed to its physical properties; because of its lower density than air, HeO2 reduces turbulence in airways, primarily large airways, where airflow is turbulent (25).

Table 2. Steady-state exercise variables

<table>
<thead>
<tr>
<th></th>
<th>Saline</th>
<th>HeO2</th>
<th>Δ</th>
<th>Effect of AA</th>
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<tbody>
<tr>
<td>V˙I, l·min⁻¹</td>
<td>89.6 ± 5.4</td>
<td>93.6 ± 6.6</td>
<td>4.0 ± 1.6*</td>
<td>NS</td>
</tr>
<tr>
<td>VT, l</td>
<td>2.66 ± 0.14</td>
<td>2.58 ± 0.13</td>
<td>-0.08 ± 0.12</td>
<td>NS</td>
</tr>
<tr>
<td>f, breaths/min</td>
<td>34.0 ± 1.9</td>
<td>34.0 ± 2.0</td>
<td>2.3 ± 0.6*</td>
<td>NS</td>
</tr>
<tr>
<td>Tt/Ti, Torr</td>
<td>0.49 ± 0.00</td>
<td>0.48 ± 0.00</td>
<td>-0.01 ± 0.00*</td>
<td>NS</td>
</tr>
<tr>
<td>PtcO2, Torr</td>
<td>34.4 ± 0.6</td>
<td>32.9 ± 0.9</td>
<td>-1.5 ± 0.4†</td>
<td>NS</td>
</tr>
<tr>
<td>HR, Beats/min</td>
<td>155 ± 4</td>
<td>156 ± 5</td>
<td>1.0 ± 0.3*</td>
<td>NS</td>
</tr>
<tr>
<td>SaO2, %</td>
<td>96.6 ± 0.4</td>
<td>96.9 ± 0.5</td>
<td>0.3 ± 0.1†</td>
<td>NS</td>
</tr>
</tbody>
</table>

Data are means ± SE; n = 10 subjects. Saline, averaged data from 2 saline tests; Air, averaged data from last minute of 5 min of air breathing after warm-up (Air-1) and 1st minute of air breathing after 3 min of HeO2 breathing (Air-2) periods; HeO2, averaged data from 2nd minute of HeO2 breathing; Δ = HeO2 − Air; AA, airway anesthesia. V˙I, minute ventilation; VT, tidal volume; f, breathing frequency; Tt/Ti, inspiratory duty cycle; PtcO2, estimated mean alveolar PCO2; HR, heart rate; SaO2, O2 saturation; NS, not significant. *P < 0.05, †P < 0.01 (paired 2-tailed t-test).
changes the distribution of resistance among different parts of the airways, reduces total airway resistance (23), and results in respiratory muscle unloading, i.e., respiratory muscles have to generate less pressure for a given \( V_i \) (15, 23). However, respiratory muscle unloading by pressure-assist at the mouth (38) causes little or no increase in \( V_i \) during heavy exercise (12, 20). Therefore, as reviewed elsewhere (6, 12, 20), the hyperventilation with HeO2 is probably not a consequence of respiratory muscle unloading per se. This is supported by the finding that the \( V_i \) response to HeO2 is unaffected by diaphragm deafferentation (11). The hyperventilation may be related to the airway effects of HeO2 (6, 11, 15, 35). The average rate of rise of the diaphragm EMG falls immediately when HeO2 is substituted for room air in exercising humans and ponies (11, 15). It has therefore been suggested that the respiratory responses to HeO2 may involve “a reflex effect” (15). Ward et al. (35) have suggested that changing from Air to HeO2 may activate irritant or other airway receptors, and this might contribute to the \( V_i \) response to HeO2 breathing.

Airway anesthesia and the ventilatory response to HeO2. The methods of Anesthesia used in this study were chosen to cause anesthesia of the large airways where the effects of HeO2 on turbulent airflow are greatest (25). The method of aerosol anesthesia has been shown to cause deposition of most of the anesthetic in the upper airways (oro-, hypopharynx, larynx) and in the central intrathoracic airways (trachea, hilum, large bronchi) (1, 28, 29). Aerosols of the particle size (5 µm) used in our study seldom deposit in the peripheral lung regions or in the alveoli (1, 28). This method has been already shown to cause large-airway anesthesia in previous studies in resting (10, 22) or exercising (18) humans. Additionally, the method of topical laryngeal anesthesia administration used in this study has been shown to block afferents in the superior laryngeal nerve (21). The technique of laryngeal anesthesia differed somewhat between this study and that of Kuna et al. (21). Pledgets soaked in 4% lidocaine were held in each piriform recess for 1 min in our study and for 2 min in their study. Also, 10% cocaine was dropped onto the epiglottis and vocal cords in their study. Could the persistence of the HeO2-induced sustained hyperventilation with Anesthesia in our study be due to the shorter duration of lidocaine application or the fact that cocaine was not used? While this possibility cannot be completely excluded, we feel that it is unlikely because we demonstrated the presence of Anesthesia. Anesthesia of the upper and lower (central) airways was shown to be present for over 15 min, as evidenced by the loss of gag reflex and the cough response to inhaled citric acid, respectively, in all our subjects. It has been shown previously that this method.

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**Fig. 2.** Group mean (n = 11) increase in \( V_i \) (\( \Delta V_i \); HeO2 – Air) at Air–HeO2 transition in Saline (○) and Anesthesia (●) tests. Data from first 6 breaths in HeO2 and averaged data from 2nd minute of HeO2 are shown. Averaged data from last 10 breaths in Air-1 period represent baseline Air (□) values. *Significantly different from Air (analysis of variance [ANOVA]), P < 0.05.

**Fig. 3.** \( \Delta V_i \) in 2nd breath of HeO2 (A) and in 2nd minute of HeO2 breathing (B) in Saline compared with Anesthesia tests. ○, Individual subject (n = 11) responses; bar, group mean responses. Group mean data (±SE) are indicated in parentheses below labels. *Data significantly different from 0. A, Saline vs. Anesthesia, P < 0.05 by ANOVA; B, Saline vs. Anesthesia, NS.
of Anesthesia administration results in persistence of airway anesthesia during and after exercise (18).

Anesthesia caused attenuation of the transient V₂ response to HeO₂ but did not affect the steady-state V₂ response. The attenuation of the transient V₂ response supports the notion that the respiratory adaptations to HeO₂ are related to its airway effects. It also supports the hypothesis that airway reflexes are involved (15, 35).

While this study indicates that airway receptors are involved in the immediate V₂ response to HeO₂, it provides no information as to which receptors may be involved. There are a large number of receptors in the pharynx, larynx, and tracheobronchial tree, the activation of which could be altered by HeO₂. For example, the activation of tracheal and bronchial irritant receptors, which respond to flow, might be altered by HeO₂ (31). Because of their dynamic properties, tracheobronchial stretch-receptor activation is influenced by flow rate (32). The larynx has a rich supply of submucosal and mucosal receptors, some of which are sensitive to pressure and flow (33). Activation of these receptors may have been altered by HeO₂ breathing. Jammes et al. (16) noted greater activation of laryngeal receptors by HeO₂ than by air, but this occurred at 18°C, which is lower than the normal laryngeal temperature. Because of its noninvasive nature, the present study provides no information as to which of these receptors were activated (or inhibited) by HeO₂.

Although the transient V₂ response to HeO₂ was attenuated by Anesthesia, the steady-state response was unaffected. The reasons for this are unclear. This suggests that, although the initial V₂ response to HeO₂ is at least partly dependent on airway receptors, activation of these receptors is not necessary for the sustained response. It has recently been shown that increasing inspiratory flow rate in mechanically ventilated subjects causes a tachypneic hyperventilation, which is not sensitive to airway anesthesia (13). It is possible that the initial HeO₂-induced increase in inspiratory flow rate activates mechanisms not sensitive to Anesthesia, which cause the sustained tachypneic hyperventilation and override the resulting hypocapnia. It should be noted that the HeO₂-induced transient increase in V₂ in our subjects was attenuated, not abolished, by Anesthesia; it is possible that the attenuated initial increase in flow rate was enough to trigger the sustained hyperventilation. This hypothesis is speculative but merits further study.

Is it conceivable that the effect of Anesthesia on the transient but not the sustained hyperventilatory response to HeO₂ was due to a time-dependent reduction in the intensity of Anesthesia during exercise? However, the chances of that having occurred in this study are remote because there was evidence of residual Anesthesia at end exercise in these subjects. These results are similar to those from an earlier study (18), in which the subjects had evidence of significant Anesthesia after exercise. Furthermore, it was ascertained on an initial occasion that each subject in this study had evidence of airway anesthesia for at least the duration of exercise (i.e., 15 min).

HeO₂ increases the maximum expiratory, flow-volume curve (24). Therefore, for the same V₂ and breathing pattern, HeO₂ reduces flow limitation when it is present during Air breathing. We did not assess the presence of flow limitation in the present study. It is possible that the V₂ response to HeO₂ may be related to its effect of reducing expiratory flow limitation (6). This is supported by the observation that the V₂ response to inhaled CO₂ during heavy exercise falls, at levels of V₂ where expiratory flow limitation develops (4).

Ventilatory control during HeO₂ breathing may be further influenced by its effects on gas exchange. Some (3, 37), but not all (26), studies have found that a decrease in carrier gas density increases the alveolararterial Po2 gradient. This, in itself, would cause a small fall in arterial Po2 if nothing else changed. However, this could not have contributed to the HeO₂-induced increase in V₂ in this study because there was a small but significant increase in SaO₂ with HeO₂ breathing (Table 2).

Equipment resistance and helium hyperventilation. HeO₂ reduces external tubing resistance, as well as internal airway resistance. To our knowledge, previous studies of helium breathing during exercise did not match equipment resistance for Air and HeO₂, although DeWeese et al. (8) matched external resistance in their studies with HeO₂ at rest. Forster et al. (11) noted a 47% fall in external resistance with HeO₂ breathing, compared with room air breathing. This fall was almost the same as the fall in pulmonary resistance in their studies. Increasing the resistive load at the mouth causes a reduction in V₂ during exercise with room air breathing (9). It was therefore possible that the HeO₂-induced hyperventilation is related to the reduction in external resistive load, not the change in internal load. Therefore, we matched the external tubing resistance during HeO₂ to that during room air breathing (Table 1). Despite this, HeO₂ caused significant hyperventilation. Therefore, the hyperventilation with HeO₂ is not simply due to a change in tubing resistance, although this may have accentuated the hyperventilation in previous studies.

In conclusion, this study indicates that the transient, but not the sustained, hyperventilation with HeO₂ is dependent on airway afferents sensitive to topical anesthesia. The hyperventilation with HeO₂ breathing is not simply due to a change in external equipment resistance.

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