Sustained isocapnic hypoxia suppresses the perception of the magnitude of inspiratory resistive loads

R. S. ORR, A. S. JORDAN, P. CATCHESIDE, N. A. SAUNDERS, and R. D. McEVOY. Sustained isocapnic hypoxia suppresses the perception of the magnitude of inspiratory resistive loads. J Appl Physiol 89: 47–55, 2000.—The sensation of increased respiratory resistance or effort is likely to be important for the initiation of alerting or arousal responses, particularly in sleep. Hypoxia, through its central nervous system-depressant effects, may decrease the perceived magnitude of respiratory loads. To examine this, we measured the effect of isocapnic hypoxia on the ability of 10 normal, awake males (mean age = 24.0 ± 1.8 yr) to magnitude-scale five externally applied inspiratory resistive loads (mean values from 7.5 to 54.4 cmH2O · l−1 · s). Each subject scaled the loads during 37 min of isocapnic hypoxia (inspired O2 fraction = 0.09, arterial O2 saturation of ~80%) and during 37 min of normoxia, using the method of open magnitude numerical scaling. Results were normalized by modulus equalization to allow between-subject comparisons. With the use of peak inspiratory pressure (PIP) as the measure of load stimulus magnitude, the perception of load magnitude (Ψ) increased linearly with load and, averaged for all loaded breaths, was significantly lower during hypoxia than during normoxia (20.1 ± 0.9 and 23.9 ± 1.3 arbitrary units, respectively; P = 0.048). Ψ declined with time during hypoxia (P = 0.007) but not during normoxia (P = 0.361). Our result is remarkable because PIP was higher at all times during hypoxia than during normoxia, and previous studies have shown that an elevation in PIP results in increased Ψ. We conclude that sustained isocapnic hypoxia causes a progressive suppression of the perception of the magnitude of inspiratory resistive loads in normal subjects and could, therefore, impair alerting or arousal responses to respiratory loading.

AROUSAL FROM SLEEP IS CONSIDERED one of the most important protective respiratory responses (24), and it has particular significance in disease states such as obstructive sleep apnea. In most instances, arousal terminates an obstructive sleep apnea with an abrupt shift in electroencephalograph (EEG) frequency (1, 23). Research in normal subjects indicates that within-subject arousal occurs at the same threshold of respiratory effort, regardless of the type of respiratory stimulus [i.e., hypoxia, hypercapnia, or resistive loading (13)]. It has been postulated (1) that subjects “sense” the increased work of breathing associated with these stimuli and respond by arouses from sleep. Sleep apnea patients require much greater respiratory effort to arouse during an obstructive event than normal subjects (1, 2). Increased sleep drive secondary to the persistent sleep fragmentation experienced by sleep apnea patients may in part explain this difference. Hypoxia may also contribute to increased arousal threshold. Acute isocapnic hypoxia (arterial O2 saturation (SaO2) = 80–90%) has been shown to depress central respiratory neural drive (9, 22) and produce decrements in neurocognitive function (3). Furthermore, sleep apnea patients with associated severe hypoxemia demonstrate a higher level of cognitive impairment than those with little hypoxemia (12).

In the present study, we examined the effects of isocapnic hypoxia on the ability of normal subjects to interpret the magnitude of inspiratory resistive loads while awake. If hypoxia reduces load perception during wakefulness, it may also increase the threshold of respiratory effort at which arousal occurs in sleep and thus may help explain the high arousal threshold observed in sleep apnea patients during airway occlusion. If hypoxia depresses load perception, there may be implications for other respiratory diseases in which perception of increased respiratory load is important in enabling corrective behaviors (16).

METHODS

Subjects

Informed consent was obtained from 10 normal male nonsmokers (mean age = 24.0 ± 1.8 yr) who participated in the study as paid volunteers. Subjects had no history of cardiac or respiratory problems and were free of medication at the time of the experiment. No subject had been born, or had spent any extended time, at altitude. Pulmonary function measurements were normal in every case (forced expiratory volume was 117 ± 4% of predicted; forced vital capacity was 107 ± 3% of predicted). Subjects were recruited from the general student population with the assistance of the Flinders University recruitment agency and by word of

Address for reprint requests and other correspondence: Address for reprint requests and other correspondence: R. D. McEvoy, Sleep Disorders Unit, Repatriation General Hospital, Daw Park SA 5041, Australia (E-mail: doug.mcevoy@rgph.sa.gov.au).

The costs of publication of this article were defrayed in part by the payment of page charges. The article must therefore be hereby marked “advertisement” in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.
mouth from nonmedical or research personnel within the hospital. Of the 10 subjects used, three had participated in a previous experiment to evaluate the impact of inspired gas on threshold load detection. The remaining subjects had no experience of respiratory load magnitude estimation. Subjects were not informed of the hypothesis and remained blind to the inspired gas at all times.

General Procedure

Subjects arrived in the laboratory after a light breakfast without caffeine. Data were collected on each subject in a single morning session. Each session involved two 17-min practice runs and two experimental periods (an isocapnic hypoxic and a normoxic period). Each experimental period had a 37-min duration. During each experimental period, suprathreshold inspiratory resistive loads were presented to and magnitude-scaled by the subjects. The apparatus and psychophysical techniques of open magnitude scaling of inspiratory loads used were similar to those described in studies by Burdon et al. (4) and Killian et al. (17). Finger tapping was conducted during the experimental periods in an attempt to independently measure the effects of hypoxia on cortical function (3).

Measurements

All measurements were conducted with the subjects sitting comfortably on a bed with back support. EEG monitoring from two surface electrodes (C3-A2, Compumedics S-series, Abbotsford, Victoria, Australia) was used during data collection solely to confirm that wakefulness was maintained for the duration of the study. No analysis of the recorded EEG was undertaken, although the data were retained for future reference. Electrocardiograms (ECG) were continuously recorded (Hewlett Packard 78342, Andover, MI). A full face mask with unidirectional valves (8900 series, Hans-Rudolph, KS) was fitted to the face with a silicone seal (Ultimate Seal, Hans-Rudolph). The mask was held in place by an adjustable retaining cap and checked for leaks by having the subject exhale with moderate force against a closed expiratory port. In addition, a perforated tube encircling the perimeter of the mask and attached to a CO2 analyzer (Poet II, 602–3, Criticare Systems) served as a leak detector throughout each experiment. Subjects were asked to choose their preferred route of breathing (mouth, nose, or a combination) and then was measured breath-by-breath tidal volume. Mask pressure (DTX transducer, Spectramed) and inspiratory flow were used to calculate inspiratory resistance. Gas was continuously sampled from a port in the mask, and end-tidal PCO2 (PetCO2) and inspired O2 fraction were determined using CO2 and O2 (Medgraphics, MN) analyzers. The output from a peizo-electric transducer (Leg Movement Sensor, Compumedics) provided data on finger tapping frequency. All data were acquired on a 486 IBM laptop computer using an acquisition system (DATAQ Instruments) with a sampling rate of 150 Hz per channel.

Resistive Loading Apparatus

The apparatus used to provide resistive loading was similar to that described previously (4, 17) for inspiratory resistive scaling. Briefly, two concentric tubes were constructed from PVC pipe. The inner tube [80 mm (ID)] had panels removed, and the cleared areas were replaced with filter paper (Whatman International). The position of an internal plunger determined the area of paper that the subjects inspired through and, therefore, the inspiratory resistance. Five plunger settings were chosen for the experiment to give a wide range of inspiratory resistances (see Fig. 1). The inspiratory resistive circuit was housed in an outer PVC tube connected to a Hans-Rudolph two-way tap. This allowed the resistive loading apparatus to be bypassed or included in the inspiratory circuit. Loads were introduced during expiration and remained in place throughout the inspiratory phase of the following breath (i.e., the loaded breath). A buzzer and light were activated two breaths before the introduction of a load to cue the subject. For the purposes of magnitude scaling, loads were presented every three to four breaths, with the load remaining in place for one breath only.

Calibration of resistance apparatus. The flow vs. pressure relationship for each setting of the resistance circuit was determined by using a suction device to produce a wide range of flows. Negative pressure and the corresponding flow were graphed, and the resistance was calculated at a flow of 0.5 l/s for background (resistive apparatus bypassed) and each of the five resistor settings (Fig. 1). The third resistor setting (R3 in Fig. 1) was used as the reference resistor for the duration of the experiment. The curves generated demonstrate that our circuit had similar characteristics to that used by Burdon et al. (4).

Protocol

The protocol is represented diagrammatically in Fig. 2, and an explanation of each of the components is detailed in this section.

Finger tapping practice run. Subjects were instructed to tap as rapidly as they could with the index finger of their dominant hand for 10-s periods until they felt comfortable with the technique and were instructed to retain this technique for all subsequent tests.

Magnitude scaling practice session. Before each experimental period (isocapnic hypoxia or normoxia), a random sequence of the five loads was presented while the subject breathed room air with the mask in place. Subjects were informed that these loads were typical of what they would likely experience and were then given the following verbal instructions, modified from a text used by Stevens (32).

“We are going to present a series of loads to your breathing, and we want you to put a number on the loads according
to their size. Write the numbers down as you go. No two loads will be exactly the same; however, you may not be able to tell the difference between some of them. First, we will give you a reference load, and we want you to write down the number of your choice that represents how big you think this load is. We will then give you a series of loads, and we want you to put numbers on them, in proportion to their size. If you feel that the second load is twice as big as the reference, then put a number twice as big as your reference number. If you feel it is two and a bit times greater, then put a number two and a bit times bigger. You can use whole numbers, fractions, or decimals, just as long as you are comfortable with the numbers you use.”

Subjects were then presented with and were required to assign a numeric value to the reference load (~20 cmH2O · 1−1 · s). Thirty loads were then magnitude-scaled by the subject. For this and every subsequent presentation of 30 loads, the same five plunger settings were used on six occasions, using a random sequence. A new random sequence of loads was generated for each series of 30 load presentations. The magnitudes assigned to these loads during both practice runs were not used in subsequent analyses. With the presentation of the reference load during the second practice session, subjects were reminded of the quantity they had assigned to that load during their first session and asked to write that same value down. This enabled the subjects to reinforce their earlier quantification of the reference.

Experimental periods. There were two experimental periods: normoxia (breathing from a reservoir bag filled from a compressed air source) and isocapnic hypoxia (FIO2 = 0.09, SaO2 ~ 80%). Before the introduction of the experimental gas, subjects spent 5 min quietly breathing room air without intervention but with all respiratory signals recorded. Isocapnia was maintained in both normoxia and hypoxia experiments by a manual bleed of CO2 into the inspiratory line. After the 5-min quiet breathing period, the reference load was presented again, and the subjects were reminded of the number they had previously assigned to this load and instructed to write that number down on the paper provided.

Subjects were then switched to the experimental gas (9% O2 in N2, or medical air), and a new, random 30-load sequence (5 loads, each presented 6 times) was given over ~15 min. Subjects recorded their estimation of magnitude after every load presentation. After the first series of loads, a finger tapping set (five periods: two 10-s periods followed by 10-s gaps, then 10 s of finger tapping and a 1-min break, followed by two additional 10-s periods with a 10-s break) was performed. This finger tapping sequence is similar to that described by Lezac (20). This was followed by another 30-load sequence and further finger tapping. Consequently, each experimental period of isocapnic hypoxia and normoxia consisted of 60 load presentations.

The experimental periods varied from 37 to 43 min, but the duration of the normoxic and isocapnic hypoxic period did not differ by more than 3 min for each subject. The order of presentation of the experimental gases was alternated among subjects. Consequently, one-half of the subjects breathed a normoxic mixture during the first experimental period, and the remaining subjects breathed a hypoxic mixture during the first experimental period. Each experimental period was separated by 45 min of rest, with the mask and seal removed. After the 45-min rest period, the mask was refitted, and the entire sequence of events was repeated with the alternate gas. The rest period plus the time required to refit the mask, amounted to a minimum of 60 min between experimental periods, thereby allowing the subjects to fully recover from any depressant effects of hypoxia on ventilation (10).

Analysis of Data

Individuals were free to place whatever value they thought appropriate on the reference load and scaled all subsequent loads relative to this reference. Values for perceived magnitude of the inspiratory resistive loads (Ψ) varied considerably with the choice of scales between subjects. To ensure that each subject’s data provided equal weighting to the group results, individual values were transformed by the method of modulus equalization (31). Briefly, the geometric mean of all perception values recorded throughout the study was calculated (grand modulus) along with the geometric mean of all values recorded for each subject (individual modulus). Perception values for each subject were then divided by the appropriate individual modulus and multiplied by the grand modulus, thereby adjusting individual perception values to a common scale (31, 34).

Peak inspiratory pressure (PIP), peak inspiratory flow (PIP, inspired minute ventilation (Vi), inspiratory time (Ti), expiratory time (Te), and total breath time (Ttot) were calculated for every breath, and mean values were derived for the 5-min rest period (i.e., baseline) and over early (1–5 min), mid (5–13 min), and late (20–32 min) periods of isocapnic hypoxia and normoxia. SaO2 and PETCO2 were sampled continuously and averaged for the same time periods. Inspiratory resistance (R) was calculated as the slope of the linear regression of pressure vs. flow for loaded breaths only.

Relationships between Ψ, R, and PIP were assessed according to conventional methods described for the perception of inspiratory resistive loads (5, 17, 19). Mean R, PIP, Ti, and Ψ values for each resistance setting were calculated for the early (1–5 min), mid (5–13 min), and late (20–32 min) periods of isocapnic hypoxia and normoxia.

Values of Ψ for each individual were determined at the group mean values of R and PIP (isocapnic hypoxia and normoxia data combined) for each resistance setting. Group mean R and group mean PIP for each load setting were calculated from the arithmetic mean R and mean PIP for all presentations of the given load setting (i.e., all subjects, normoxia and hypoxia, and repeated presentations in each subject combined). This enabled statistical comparisons of Ψ.
for isocapnic hypoxia and normoxia at identical values of R and PIP. The equations and reasoning for using linear equations to express the relationship between Ψ and PIP are given below.

Finger tapping data were analyzed by a Fourier analysis of the frequency and amplitude characteristics of the record. Preliminary analysis showed that finger tapping frequency vs. the frequency and amplitude characteristics of the record.

**Results**

**Ventilatory Parameters During Baseline Rest Periods, Isocapnic Hypoxia, and Normoxia**

There were no significant differences in any of the ventilatory parameters in the 5-min baseline room air-breathing periods before the experimental runs (Table 1). During isocapnic hypoxia, SaO₂ decreased significantly over the first 8 min to ~80% and remained at that level for the remainder of the experimental period (Fig. 3, Table 1). Isocapnia was maintained throughout the study (Fig. 3, Table 1). During isocapnic hypoxia there was an increase in PIP, PIF,
was elevated during the late period of normoxia. PIP during isocapnic hypoxia was significantly elevated at all times compared with during normoxia (Table 1). PIF, VT, and V̇I were also elevated during hypoxia compared with during normoxia, but differences only reached statistical significance at 1–5 and 5–13 min. There were no differences in T₁, Tₑ, or Tₜₒₜ between hypoxia and normoxia.

Perceived Magnitude of Added Loads

The group mean values of R experienced by the subjects for each setting on the apparatus were calculated from the pressure/flow values for all presentations (isocapnic hypoxia and normoxia combined). For each of the five resistance settings used, the experienced group mean R was 7.53 ± 0.03, 10.47 ± 0.05, 19.66 ± 0.11, 38.20 ± 0.30, and 54.44 ± 0.47 cmH₂O · l⁻¹ · s⁻¹.

Relationship between Ψ and R. The Ψ of added loads increased curvilinearly with R and was well described by Stevens’ power function (r² = 0.942 ± 0.006, SS = 43.33 ± 9.11; see Table 2 and Fig. 4). Values for the exponent n and the intercept k that best fit the equation Ψ = kRⁿ are shown in Table 2. During 1–5 min of hypoxia, n was significantly lower and k was significantly higher than during the same time in normoxia (P < 0.05). After 20–32 min of hypoxia, k was significantly lower compared with 1–5 min of hypoxia. The overall mean value of Ψ, calculated at the group mean values of R, was not significantly different between hypoxia and normoxia (20.09 ± 1.02 vs. 19.78 ± 1.05, respectively). During hypoxia, however, Ψ computed at the group mean values of R declined with time (P = 0.007) and was significantly lower after 20–32 min (17.71 ± 4.22) compared with 1–5 min (22.71 ± 4.51) of hypoxia. By contrast, Ψ did not change across the early, mid, or late periods of normoxia.

Relationship between Ψ and PIP. Although the relationship between Ψ and PIP (see Table 2 and Fig. 4) was well described by Stevens’ power function (r² = 0.937 ± 0.011, SS = 34.09 ± 8.013), the exponents

Table 2. Exponents, intercepts, and coefficients of determination for relationships between perceived magnitude, inspiratory resistance, and PIP at 1–5, 5–13, and 20–32 min of normoxia and hypoxia

<table>
<thead>
<tr>
<th></th>
<th>ψ = kRⁿ</th>
<th></th>
<th>ψ = aPIP + b</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>k</td>
<td>r²</td>
</tr>
<tr>
<td>Normoxia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1–5 min</td>
<td>0.77 ± 0.12</td>
<td>2.38 ± 0.56</td>
<td>0.942 ± 0.015</td>
</tr>
<tr>
<td>5–13 min</td>
<td>0.67 ± 0.11</td>
<td>3.36 ± 0.78</td>
<td>0.954 ± 0.010</td>
</tr>
<tr>
<td>20–32 min</td>
<td>0.71 ± 0.11</td>
<td>2.97 ± 0.79</td>
<td>0.950 ± 0.012</td>
</tr>
<tr>
<td>Overall</td>
<td>0.72 ± 0.06</td>
<td>2.91 ± 0.41</td>
<td>0.949 ± 0.007</td>
</tr>
<tr>
<td>Hypoxia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1–5 min</td>
<td>0.59 ± 0.12*</td>
<td>4.86 ± 1.14*</td>
<td>0.903 ± 0.024</td>
</tr>
<tr>
<td>5–13 min</td>
<td>0.68 ± 0.12</td>
<td>3.39 ± 0.80</td>
<td>0.948 ± 0.014</td>
</tr>
<tr>
<td>20–32 min</td>
<td>0.69 ± 0.12</td>
<td>3.18 ± 0.87†</td>
<td>0.954 ± 0.012</td>
</tr>
<tr>
<td>Overall</td>
<td>0.66 ± 0.07</td>
<td>3.81 ± 0.55</td>
<td>0.935 ± 0.011</td>
</tr>
</tbody>
</table>

Values are group means ± SE (N = 10); Ψ, Perceived magnitude; R, inspiratory resistance; n, exponent; k, intercept; r², coefficient of determination; a, slope; b, intercept. *P < 0.05 compared with corresponding time in normoxia. †P < 0.05 compared with 1–5 min of hypoxia.
were not different from unity \((n = 1.079 \pm 0.068; P = 0.249)\). Furthermore, a linear model provided a significantly better fit to the data \((SS = 21.37 \pm 3.48)\) than Stevens' power function \((P = 0.040)\) and was therefore retained for the remaining analyses.

Values for the slope \(a\) and the intercept \(b\) that best fit the equation \(\Psi = a(\text{PIP}) + b\) are shown for both hypoxia and normoxia in Table 2. There were no differences in \(a\) between hypoxia and normoxia. However, \(b\) was higher during 1–5 min of hypoxia compared with the same period in normoxia and declined after 20–32 min of hypoxia. The overall group mean value of \(\Psi\), calculated at the group mean values of PIP, was significantly lower during hypoxia than during normoxia \((20.10 \pm 0.91 \text{ vs. } 23.88 \pm 1.27; P = 0.048)\), and, furthermore, \(\Psi\) declined with time during hypoxia \((P = 0.007)\) but not during normoxia \((P = 0.361)\).

\(\Psi\) and T\text{I}. Although Ti on the loaded breath increased with R \((\text{from } 2.29 \pm 0.11 \text{ s at } 7.53 \text{ cmH}_2\text{O} \cdot \text{l}^{-1} \cdot \text{s to } 2.99 \pm 0.17 \text{ s at } 54.44 \text{ cmH}_2\text{O} \cdot \text{l}^{-1} \cdot \text{s}; P = 0.003)\), there were no differences in Ti between hypoxia and normoxia \((P = 0.376)\), no changes with time \((P = 0.538)\), and no time or resistance interactions between hypoxia and normoxia. Furthermore, the conventional expression \(\Psi = k\text{PIP}^m\text{T}_i^n\) \((\text{overall } n = 1.004 \pm 0.076, m = 0.451 \pm 0.234)\) did not improve the fit over that of the linear model \(\Psi = a(\text{PIP}) + b\), despite an additional curve parameter \((\text{curvilinear SS } = 24.59 \pm 7.15; \text{linear SS } = 21.37 \pm 3.48; P = 0.576)\).

Finger Tapping

Fourier analysis of the finger tapping data demonstrated no significant differences in the dominant frequency and associated amplitude between the isocapnic hypoxia and normoxia periods or within either of these periods. The mean frequency of finger tapping during isocapnic hypoxia and normoxia was \(5.97 \pm 0.21\) and \(5.86 \pm 0.23\) taps/s, respectively \((P = 0.177)\).

DISCUSSION

The main finding of the present study was that, in normal, healthy, male subjects, the \(\Psi\) of externally applied inspiratory resistive loads decreased progressively during sustained isocapnic hypoxia but remained unchanged during normoxic breathing. This finding held when either R or PIP of the loaded breath was used to quantify the magnitude of the stimulus provided by the externally applied resistive loads. The result is all the more remarkable because PIP was significantly elevated at all times during hypoxia compared with normoxia. Previous studies (4) have shown that an increase in respiratory drive \(\text{i.e., PIP}\) generally results in an increase in the \(\Psi\) of inspiratory resistive loads.

Some differences existed in our results when measured R vs. measured PIP was used to define the magnitude of the applied load. There was no overall difference in \(\Psi\) between hypoxia and normoxia when R
was used as the measure of load, but $\Psi$ was lower during hypoxia than during normoxia when PIP was used to define respiratory stimulus arising from load application. Killian et al. (17) demonstrated that PIP bears a closer relationship to what is perceived as load than $R$ and probably better represents the stimulus provided by external resistive loads. We consider that the reduction observed in load estimation by subjects during hypoxia, using PIP as the independent variable, is strong evidence for an effect of hypoxia on the mechanisms subserving load evaluation.

Previous researchers (4, 5, 17) have investigated the impact of adding loads to breathing on $\Psi$ using a range of inspiratory loads extending from just above background to $>75$ cmH$_2$O $\cdot l^{-1} \cdot s$. To our knowledge, there have been no previous studies that have systematically investigated the effects of hypoxia on the perception of resistive respiratory loads. However, in the study of Burdon et al. (4), one of the stimuli used to increase respiratory drive was isocapnic hypoxia. The relationship between $R$ and $\Psi$, derived from their data using hypoxia to increase respiratory drive, shows considerable scatter. This was not the case for the other two respiratory stimulants used in that study, exercise and hypercapnia. The authors observed that “Following the hypoxic experiment many subjects complained of difficulty in maintaining cognitive ability” (4) and offered this as a possible explanation for their findings. Our data also imply that the sensory mechanisms used to assess the magnitude of inspiratory resistive loads are impaired during hypoxia. Whether this is due to a “cognitive” (i.e., cortical) deficit or to an interruption of afferent information in sensory pathways at another level remains unclear.

The time course of the ventilatory response to sustained isocapnic hypoxia is bimodal: early stimulation of respiration is followed, in a few minutes, by a decline in respiratory neural drive (9, 22, 26). Each of the neuroeffectors shown to be associated with hypoxic ventilatory depression (i.e., endogenous opioids, adenosine, and GABA) has been shown to be capable of blocking sensory pathways involved in pain perception (6–8, 11, 15, 27, 28, 29). It has been suggested by Killian and Campbell (18) that the model for the processing of pain is equally valid for the processing of the proprioceptive information necessary for inspiratory load evaluation. Thus the same neuroeffectors that depress respiration during continuing hypoxia may also diminish the $\Psi$ of inspiratory resistive loads.

Although we postulate that the reduction in $\Psi$ observed during hypoxia may involve the same neuroeffectors associated with hypoxic ventilatory depression, our data did not show a statistically significant decline in ventilation across the hypoxic period. However, ventilation was elevated above quiet breathing during the normoxic period, with the difference reaching statistical significance by 20–32 min. We hypothesize that the changes in ventilation observed during normoxia were a consequence of the tasks subjects had to perform. Because the tasks were identical during the hypoxic period, they would probably have induced similar increases in ventilation, and these increases may have been sufficient to mask hypoxic ventilatory rolloff.

Another potential explanation for our finding of reduced $\Psi$ during sustained hypoxia is that hypoxia induced cerebral arterial dilatation and increased cerebral blood flow, resulting in cerebral hypocapnia. However, this is an unlikely explanation because we observed that the $\Psi$ of inspiratory resistive loads progressively decreased during 32 min of isocapnic hypoxia. In contrast, previous studies in humans (35) show that sustained isocapnic hypoxia produces a sudden reduction in internal jugular PCO$_2$ (i.e., in the first minute) that remains unchanged over 15 min. Previous animal studies (22) suggest that local metabolic regulation of cerebral blood flow counteracts, within 30–120 s, the effects of any cerebral overperfusion induced by hypoxia. Thus, in the same way that these authors argue that cerebral hypocapnia is unlikely to explain the progressive ventilatory rolloff during sustained isocapnic hypoxia, we suggest it is also unlikely to explain the progressive decline in sensory $\Psi$ of respiratory loads during hypoxia.

Our results show that hypoxia altered perceptual interpretation of inspiratory stimuli but did not change finger tapping frequency. Finger tapping was originally used as a test of manual dexterity and was not designed to specifically assess the impact of hypoxia. However, it has been shown by one group (3) to decrease with acute hypoxia, and the relative simplicity of the test enabled us to incorporate it into the experimental protocol. Berry et al. (3), using linear trend analysis, demonstrated a reduction in tapping speed at levels of hypoxia similar to those used in our experiments. However, these trend differences were shown between rather than within subjects. Although considerable efforts were made to match experimental and control groups, intersubject differences may have contributed to their results. Our study, which failed to demonstrate differences in finger tapping frequency, used a more rigorous statistical approach. Finger tapping is a simple motor task and, as such, may be relatively immune to minor degrees of central nervous system depression in contrast to more complex tasks involving cognitive evaluation. Alternatively, the hypoxia in our experiments may have had relatively little effect on this motor function, whereas it may still have affected the sensory pathways involved in respiratory proprioception.

In our study, the equation describing the power relationship between $\Psi$ and PIP that included a $T_i$ component [$\Psi = k(PIP)^{b(T_i)}$] did not improve the fit of the data provided by the simple linear equation relating $\Psi$ and PIP [$\Psi = a(PIP) + b$]. This should not be taken to imply that $\Psi$ is unaffected by changes in inspiratory duration. Previous researchers have manipulated $T_i$ across a wide range of values and shown that as $T_i$ increases, $\Psi$ increases (17). The reason why it did not appear to contribute to $\Psi$ in our experiments is probably due to the fact that $T_i$ varied little both during and between the experiments.
Possible relevance of results to respiratory arousals in sleep. How respiratory loading is perceived to induce an arousal in sleep is still poorly understood. We believe it is possible that the $\Psi$ or respiratory effort during wakefulness is related to the sensing of the respiratory load during sleep. If we accept this premise, it is possible to obtain some idea of how hypoxia might elevate the sensory threshold required for arousal in sleep. Gleeson et al. (13) found a threshold of respiratory effort for arousal in sleeping normal male subjects equivalent to ~16.7 cmH$_2$O of peak-negative esophageal pressure equivalent, in our study, to a mask PIP of ~15.3 cmH$_2$O (transpulmonary pressure at PIP). We calculated from our data that, to reach the level of $\Psi$ associated with a PIP of 15.3 cmH$_2$O during normoxia, a 20–33% increase in PIP would be required after 15–32 min of hypoxia. These data imply that hypoxia during sleep could delay arousal until the level of respiratory effort is increased by as much as one-third above that necessary to produce arousal under normoxic conditions.

Clinical implications for sleep apnea, asthma, and chronic obstructive pulmonary disease. The impact of hypoxia on load evaluation is potentially significant for patients suffering from obstructive sleep apnea. This clinical population has been shown to arouse from sleep at much higher levels of respiratory effort than normal subjects (2). A possible contributor to this elevated arousal threshold is the depressant effect of hypoxia on the central nervous system. The perception of loaded breathing is reduced in asthmatic children (16) and adults (25) who suffer nearly fatal attacks and in chronic obstructive pulmonary disease patients (14). Our data suggest that such patients, apparently already at risk from a relative inability to perceive and react to an inspiratory challenge, may have perception distorted further during times of increased airway obstruction if hypoxia is present.

In summary, this study has shown that, in healthy, male subjects, sustained isocapnic hypoxia leads to a progressive decline in the $\Psi$ of externally applied inspiratory resistive loads. This finding has implications for defensive arousal responses from sleep (e.g., in obstructive apnea) and for disorders such as asthma and chronic obstructive pulmonary disease, in which the reduction in the perception of inspiratory load, due to hypoxia, may cause delays in patients accessing appropriate treatment.

Support for research was provided by The National Health and Medical Research Council (Australia) and the Asthma Foundation of South Australia.

REFERENCES


