Hypoxic and hypercapnic drives to breathe generate equivalent levels of air hunger in humans

S. H. MOOSAVI,1,2 E. GOLESTANIAN,2,3 A. P. BINKS,1,2 R. W. LANSING,1,4 R. BROWN,2,5 AND R. B. BANZETT1,2,5
1Physiology Program, Harvard School of Public Health, 2Pulmonary/Critical Care Medicine, Brigham and Women’s Hospital, and 5Department of Medicine, Harvard Medical School, Boston 02115; and 2Pulmonary Department, Veterans Affairs Boston Healthcare System, West Roxbury Campus, Massachusetts 02132; and 4Department of Psychology, University of Arizona, Tucson, Arizona 85721

Submitted 3 July 2002; accepted in final form 3 September 2002

Moosavi, S. H., E. Golestanian, A. P. Binks, R. W. Lansing, R. Brown, and R. B. Banzett. Hypoxic and hypercapnic drives to breathe generate equivalent levels of air hunger in humans. J Appl Physiol 94: 141–154, 2003. First published September 6, 2002; 10.1152/japplphysiol.00594.2002.—Anecdotal observations suggest that hypoxia does not elicit dyspnea. An opposing view is that any stimulus to medullary respiratory centers generates dyspnea via “corollary discharge” to higher centers; absence of dyspnea during low inspired PO2 may result from increased ventilation and hypocapnia. We hypothesized that, with fixed ventilation, hypoxia and hypercapnia generate equal dyspnea when matched by ventilatory drive. Steady-state levels of hypoxic normocapnia (end-tidal Po2 = 60–40 Torr) and hypercapnic hypoxia (end-tidal PCO2 = 40–50 Torr) were induced in naive subjects when they were free breathing and during fixed mechanical ventilation. In a separate experiment, normocapnic hypoxia and normoxic hypercapnia, “matched” by ventilation in free-breathing trials, were presented to experienced subjects breathing with constrained rate and tidal volume. “Air hunger” was rated every 30 s on a visual analog scale. Air hunger–PETCO2 curves rose sharply at PETCO2 <50 Torr. Air hunger was not different between matched stimuli (P > 0.05). Hypercapnia had unpleasant nonrespiratory effects but was otherwise perceptually indistinguishable from hypoxia. We conclude that hypoxia and hypercapnia have equal potency for air hunger when matched by ventilatory drive. Air hunger may, therefore, arise via brain stem respiratory drive.

visual analog scale; perception; adverse electrocardiogram effects; steady state; shortness of breath; breathlessness

There is a commonly held notion, prevalent in the altitude literature, that dyspnea does not accompany hypoxia. For example, the Handbook of Physiology states that, “Unfortunately man is not endowed with any conscious sensory perception of hypoxia that might alert him to impending danger, such as the marked dyspnea caused by an excess of carbon dioxide” (33). Subjects experiencing high-altitude decompression for training purposes typically express surprise at the absence of unpleasant breathing sensations, for example, “Breathing feels perfectly normal, with no gasping or shortness of breath. That’s what makes hypoxia so dangerous: It sneaks up on you.” (13). “Air hunger” or “breathlessness” is not induced by ascent to altitude, although there is an accentuated sense of “rapid breathing” (36) and improved detection of external resistive loads (17).

The absence of dyspnea during altitude hypoxia may result from other factors that concomitantly reduce or abolish dyspnea. Studies of respiratory sensations during low inspired PO2 (1, 16, 17, 29, 36, 37, 47) have invariably allowed subjects to breathe freely, thereby accentuating pulmonary mechanoreceptor afferent activity. Some also allowed PCO2 to fall, causing chemoreceptor afferent activity to decrease. Both factors will relieve dyspnea (3, 4, 24, 35, 40). Furthermore, hypoxia is associated with a general depression of cerebral function (10, 11, 21, 27) that could mask unpleasant sensations. Reduced cerebral blood flow secondary to hypocapnia may accelerate cognitive impairments, although blood flow reduction might be counteracted by cerebral vasodilation caused by hypoxia itself (25).

In contrast to the lack of sensations at altitude, dyspnea is a prominent sensation during breath holds and in cardiopulmonary disease. To what extent does this dyspnea arise from hypoxia? In these situations, hypoxic and hypercapnic stimuli may act in concert with reduced pulmonary mechanoreceptor activity to accentuate dyspnea. It has been suggested that ventilation, dyspnea, and other signs and symptoms of hypoxia are too variable to be useful in assessment of chronic obstructive pulmonary disease patients (41). The variability in dyspnea among hypoxic chronic obstructive pulmonary disease patients may reflect the sum of discomfort from hypercapnia, increased work of breathing, and the relief that arises from pulmonary stretch receptor activation. Hypoxia may contribute to

http://www.jap.org

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.
the generation of dyspnea in these situations (16, 30). No previous studies have determined the stimulus-perceptual response to steady-state hypoxia while ventilation and PCO_2 are held constant. Studies involving steady-state hypoxia in awake humans are mostly concerned with ventilatory control without comment on perceptual outcome (9, 34).

Air hunger, perception of an uncomfortable urge to breathe, may arise from projection of brain stem respiratory drive (2, 8, 14, 22, 39). If hypoxia is less potent than hypercapnia in generating air hunger when stimuli are matched by reflex ventilatory drive, it would disprove the hypothesis that projection from brain stem respiratory drive is the sole source of air hunger. Several previous studies addressed this issue. Two of these did not detect a systematic difference in potency of hypoxia and hypercapnia for air hunger at equivalent ventilations (1, 29). One indicated that hypoxia may directly generate an “uncomfortable need” to breathe independent of ventilatory drive (16). These studies allowed subjects to breathe freely, and two included a background of exercise.

In two separate experiments, we determined air hunger responses to steady-state hypoxia during fixed rate, tidal volume (VT) and end-tidal PCO_2 (PETCO_2). To compare the potency of hypoxia and hypercapnia, we matched the stimuli on the basis of ventilatory responses in prior free-breathing trials. The data show that hypoxia elicits air hunger when the hypoxia is severe enough to increase ventilation and that hypoxia and hypercapnia are equipotent in generating air hunger. The quality of air hunger during hypoxia was remarkably similar to that during hypercapnia. This is consistent with the hypothesis that air hunger depends on increased drive to breathe rather than the direct effects of the respiratory stimulus.

METHODS

Subjects

Before participation, all subjects were interviewed and examined by a physician. A diagnostic 12-lead electrocardiogram (ECG) was recorded to confirm absence of underlying heart abnormalities. Other exclusion criteria included history of significant respiratory or cardiovascular disease. Informed consent was obtained from all subjects. Experiments were performed in the Pulmonary Section of the Veterans Affairs Boston Healthcare System Medical Center and approved by the Human Subjects Committees of the performance site and of the Harvard School of Public Health.

A total of 16 subjects were studied (Table 1). Of the 11 subjects studied in experiment 1, only subjects 1 and 9 had previously participated in research involving hypoxic or hypercapnic stimulation. Subject 1 was a research assistant, and subjects 2, 3, and 4 were clinical fellows associated with a pulmonary department. The remaining seven subjects had little or no knowledge of respiratory physiology. All subjects studied in experiment 2 had previously participated as subjects in research involving hypoxic or hypercapnic stimulation. Subjects 9 and 13 had little or no knowledge of respiratory physiology. Subjects 12, 14, RBB, and APB were investigators or other respiratory physiologists, aware of the protocol design but blinded to timing and type of intervention.

<table>
<thead>
<tr>
<th>Table 1. Anthropometric data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subject No.</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>4</td>
</tr>
<tr>
<td>5</td>
</tr>
<tr>
<td>6</td>
</tr>
<tr>
<td>7</td>
</tr>
<tr>
<td>8</td>
</tr>
<tr>
<td>9</td>
</tr>
<tr>
<td>10</td>
</tr>
<tr>
<td>11</td>
</tr>
<tr>
<td>12</td>
</tr>
<tr>
<td>13</td>
</tr>
<tr>
<td>14</td>
</tr>
<tr>
<td>RBB</td>
</tr>
<tr>
<td>APB</td>
</tr>
</tbody>
</table>

Note: subject 10 was not included in data analysis.

Experimental Setup

Subjects sat in a comfortable chair (model 6500, Backsaver Products, Holliston, MA) in a semirecumbent position and breathed through a mouthpiece (experiment 1) or through a face mask (experiment 2) that allowed breathing through nose and mouth (model 5710, Hans Rudolph, Kansas City, MO). For tests involving free breathing, the mouthpiece was attached, via a pneumotachograph (Fleisch no. 2), to a breathing circuit that automatically maintained end-tidal gasses to within ±1 Torr of set levels, despite increases in ventilation (6). For tests involving mechanical ventilation, the breathing circuit was replaced with a mechanical ventilator (Servo Ventilator 900C, Siemens-Elema).

Various mixtures of O_2, CO_2, and N_2 from three medical gas cylinders were blended by using a stack of three air-oxygen mixers (Puritan-Bennett, Los Angeles, CA). The arrangement provided 1) various hypoxic mixtures (to a minimum of 7% inspired O_2) while ensuring isocapnia (i.e., fixed PETCO_2) and 2) various hypercapnic mixtures while ensuring isoxia [i.e., fixed end-tidal P_O_2 (PETO_2)]. Blended output was heated and humidified (model SCT 3000, Marquest Medical Products, Englewood, CO) before being supplied to the fresh gas reservoir of the breathing circuit via a flowmeter (Air Oxygen Flow Meter). During constrained ventilation, the output of the blenders was sent directly to the gas input of the ventilator.

Mechanical Ventilation (Experiment 1)

Subjects were instructed to relax and let the ventilator breathe for them. They were informed that swallowing or coughing was easiest during expiration. Ventilation was initially set at 0.16 l·min\(^{-1}\)·kg\(^{-1}\) with respiratory frequency (f_R) set at 12 breaths/min. A small amount (3 cmH_2O) of positive end-expiratory pressure was also imposed to aid relaxation. Subjects were given time and coaching to learn to relax respiratory muscles at these settings. Minor adjustments were made, if necessary, to improve comfort. Average settings used during subsequent hypoxic or hypercapnic challenges were 0.15 ± 0.02 l·min\(^{-1}\)·kg\(^{-1}\) for ventilation, 25–33% of the breathing cycle for inspiratory time, and 10–20% for pause time. (Pause time was the time between end of expiration, detected by return of flow to zero, and start
of the next inspiration.) At regular intervals, subjects were reminded to remain relaxed.

Alternative Method for Constraining Ventilation (Experiment 2)

Ventilation was constrained by the breathing circuit: all inspired gas was delivered from a high-impedance source into an anesthesia bag, and expired gas exited via a one-way valve. Minute ventilation (Vt), therefore, could not exceed the flow rate of fresh gas into the bag. To control Vt, subjects breathed to a metronome (because Vt was fixed, as long as subjects continued to empty the bag with each breath, this also controlled Vt). The following script was read to the subjects: “At times you will feel that your breath suddenly stops; you will not be able to take in more than a certain amount of air with each breath. You should not worry about this because it is part of the test (we will set the amount of air you will be able to take in before it stops). Remember to continue to breathe in time with the metronome when this starts to happen.” This method requires less training of subjects than mechanical ventilation and reduces leakage when a face mask is used, because positive airway pressures are avoided. Hypercapnic air hunger response curves were tested with both methods in two subjects and were indistinguishable (Fig. 1).

Physiological Measurements and Recordings

Airflow at the mouth was measured by a pneumotachometer (Fleisch no. 2) and pressure transducer (2 cmH2O, Validyne MP45); this signal was integrated on-line to provide VT (FV156 Integrator module, Validyne Engineering, Northridge, CA). Airway pressure was measured by using a pressure transducer (56 cmH2O, Validyne MP45) via a 1.5-mm catheter inserted into the mouthpiece or face mask. When subjects breathed from the anesthesia bag, collapse of the bag resulted in peak inspiratory pressures that were used as a loose index of respiratory drive. During mechanical ventilation, inspiratory and expiratory airflow, airway pressure, and volume signals were derived from calibrated transducers internal to the ventilator.

A clinical monitoring device (Datex Cardiocap II CG-2GS) measured tidal PCO2 and PO2 in gas sampled continuously at the mouth via a second catheter inserted into the mouthpiece. Instruments were calibrated before each use with known gas concentrations. The device had a 90% measurement rise time of <270 ms for CO2 and <430 ms for O2. The device also monitored blood O2 saturation via a finger transducer and recorded blood pressure at 3-min intervals. All analog signals were digitized (Dataq Di-220 PGH/PGL) for computer storage and analysis.

Perceptual Measurements of Air Hunger

Subjects were instructed to “pay attention to your breathing sensations” and to “notice the discomfort caused by your urge to breathe, which we call air hunger, in other words, a feeling of being short of breath, starved for air, or out of breath.” Subjects were informed that the sensation “will come and go throughout the experiment; it may change quickly or slowly or stay the same for a long time.” Subjects were specifically instructed not to rate the amount of breathing even though “you may notice that the ventilator is giving you more or less air” or that, during free-breathing trials, “you may notice that you are breathing more at times.”

Air hunger ratings were made by using a 10-cm visual analog scale (VAS). The ends of this scale were labeled “none,” defined as zero air hunger, and “extreme,” defined as an intolerable level requiring immediate reduction of stimulus. Before the experiment, subjects placed three other verbal anchors (“slight,” “moderate,” and “severe”) alongside the scale where they felt it was semantically appropriate. Such verbal anchors improve the consistency of ratings among subjects and of ratings over time within subjects (23, 44). Subjects were told not to restrict ratings to locations indicated by the anchors. Ratings were visually cued at 30-s intervals by a light that signaled subjects to rate air hunger using a sliding potentiometer to control the position of a marker light along the scale. After each rating, subjects returned the marker to an off position. Subjects were permitted to volunteer extra ratings between requests. If extreme was selected, we immediately reduced the stimulus. The smallest possible increment in ratings was 2.5% of scale, the width of one light in the array of 40 making up the 100-mm scale. We defined a threshold increase in air hunger as a 10% (1 cm) rise above baseline; this is well below the position on the scale where our subjects normally place the slight verbal anchor (at 20% of scale on average).

Protocol for Experiment 1

On day 1 (practice session), subjects trained to relax their respiratory muscles during mechanical ventilation. When comfortable ventilator settings were established, subjects were exposed to progressive hypercapnia (increases in PETCO2 of 2–3 Torr every 3 min) to help them recognize and rate changes in air hunger. The practice session was followed by four experimental sessions on separate days (days 2–5). On days 2 and 4, subjects breathed freely on the circuit, whereas on days 3 and 5 ventilation was constrained to a comfortable resting level by mechanical ventilation. Each experimental session involved three test periods of 30-min duration sepa-

![Fig. 1. Air hunger (AH) stimulus response curves obtained with graded steps of steady-state end-tidal PCO2 (PETCO2) while minute ventilation (Vt) was constrained close to the resting level by relaxing breathing muscles during mechanical ventilation (•) and by breathing at a fixed frequency from a bag with a limited supply of fresh gas (○). Data are shown for 2 individuals: S11, subject 11, and S9, subject 9. Despite different methods of constraining ventilation, the response curve for each individual is unchanged.](http://jap.physiology.org/10.1152/jappl.2002.94.1.143)
rated by 15- to 30-min periods during which subjects rested off the circuit or ventilator (Fig. 2A).

Air hunger response to hypoxia. Five-minute periods of various levels of hypoxia (PetCO2 between 40 and 60 Torr; arterial O2 saturation from pulse oximetry [SpO2] between 75 and 90%) were imposed in random order during fixed mechanical ventilation [VE = 10.4 ± 1.5 (SD) l/min]. Each period of hypoxia was separated by 5 min of near normocapnia (PETCO2 = 37.5 ± 1.7 Torr). For safety, inspired PO2 was raised immediately if SpO2 fell <75% at any time or if ECG parameters were altered by hypoxia. Each subject received a total of six steps of hypoxia during constrained ventilation (3 steps on each of days 3 and 5).

Air hunger response to hypercapnia. Five-minute periods of hypercapnia (PetCO2 between 40 and 50 Torr) were imposed in random order with mechanical ventilation fixed at the same level of VE as for the hypoxic tests. Periods of hypercapnia were separated by 5 min of near normocapnia (PetCO2 = 37 ± 2.1 Torr on average). A background of hypoxia (PetO2 = 187 ± 10 Torr) was maintained throughout exposure to hypercapnia. Each subject received a total of six grades of hypercapnia during constrained ventilation (3 levels on each of days 3 and 5).

Ventilatory responses to hypoxia and hypercapnia. Ventilatory responses to hypoxia and to hypercapnia were obtained from the first two test periods of days 2 and 4. The range of gas levels administered during these tests was the same as during the tests of the perceptual responses, but subjects breathed freely on the circuit.

Hypoxia-hypercapnia switchover tests. This additional test was performed at the end of the day 5 protocol by subjects 4, 5, 9, and 11 (Table 1). A 20-min test was performed in which the stimulus was switched every 5 min between normocapnic hypoxia (PetO2 = 44 ± 6 Torr; PetCO2 = 39 ± 3 Torr) and hyperoxic hypercapnia (PetCO2 = 48 ± 6 Torr; PetO2 = 183 ± 7 Torr).

Protocol for Experiment 2

This experimental protocol (Fig. 2B) was optimized to match hypoxic and hypercapnic stimuli on the basis of ventilatory response. After an initial baseline steady state, a 4-min period of normocapnic hypoxia was imposed. This was followed by successive 4-min periods of normoxic hypercapnia until a level was found that produced the same ventilation as the initial period of hypoxia. Mean steady-state levels of respiratory variables during the initial baseline, and “matched” free-breathing stimuli are listed in Table 2.

Ventilation was then constrained (group average: VE = 9.5 ± 1.8 l/min). Three further periods of the matched hypercapnic stimulus were presented separated by 4 min of normocapnia. After a break of 15–30 min, a second trial was performed in which three 4-min periods of the matched hypoxic stimulus were presented while ventilation was constrained to the same level as before. In some subjects, the order of hypoxic and hypercapnic trials was reversed. Be-
Table 2. Respiratory variables for matched stimuli during free and constrained breathing

<table>
<thead>
<tr>
<th></th>
<th>( \text{PETCO}_2 )</th>
<th>( \text{PETCO}_2 )</th>
<th>( V_r )</th>
<th>( V_{E} )</th>
<th>( f_r )</th>
<th>( \text{Peak inspiratory} )</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Torr</td>
<td>Torr</td>
<td>liter</td>
<td>l/min</td>
<td>breaths/min</td>
<td>( \text{P}<em>{\text{m}} ), \text{mH}</em>{2}\text{O}</td>
</tr>
<tr>
<td>Baseline</td>
<td>41.6 ± 2.2</td>
<td>108 ± 9</td>
<td>0.69 ± 0.2</td>
<td>8.2 ± 2</td>
<td>11.5 ± 2</td>
<td>-1.6 ± 0.7</td>
</tr>
<tr>
<td>Hypoxia (free breathing)</td>
<td>41.4 ± 1.4</td>
<td>47 ± 8</td>
<td>0.94 ± 0.3</td>
<td>13.7 ± 7</td>
<td>14.3 ± 3</td>
<td>-2.2 ± 0.9</td>
</tr>
<tr>
<td>Hypercapnia (free breathing)</td>
<td>45.8 ± 1.7</td>
<td>125 ± 27</td>
<td>1.16 ± 0.4</td>
<td>17.5 ± 8</td>
<td>14.9 ± 3</td>
<td>-2.4 ± 1.0</td>
</tr>
<tr>
<td>Hypoxia (constrained)</td>
<td>43.3 ± 1.3</td>
<td>49 ± 8</td>
<td>0.74 ± 0.1</td>
<td>8.8 ± 1</td>
<td>11.8 ± 1</td>
<td>-9.1 ± 2.3</td>
</tr>
<tr>
<td>Hypercapnia (constrained)</td>
<td>45.5 ± 1.8</td>
<td>115 ± 6</td>
<td>0.85 ± 0.2</td>
<td>9.6 ± 2</td>
<td>11.2 ± 1</td>
<td>-11.7 ± 2.9</td>
</tr>
</tbody>
</table>

Values are means ± SD. \( \text{PETCO}_2 \), end-tidal \( \text{PCO}_2 \); \( \text{PETCO}_2 \), end-tidal \( \text{PO}_2 \); \( V_r \), tidal volume; \( V_{E} \), minute ventilation; \( \text{P}_{\text{m}} \), mask pressure.

tween periods of stimulation, the ventilatory constraint was removed briefly to allow subjects to take a sigh.

Debriefing Protocol

Subjects were first asked to describe freely their experience during the trial just completed, with particular attention to their breathing sensations when sensory ratings were elevated. They then picked the two most applicable respiratory descriptive phrases from a list of 12 (experiment 1) or a list of 20 (experiment 2). Subjects also indicated any nonrespiratory sensations they had experienced. The third phase involved asking subjects to rate their anxiety on a scale of 0–5 and to tell us whether they thought that they had missed any ratings, whether they had experienced similar sensations in other circumstances (e.g., during exercise), and whether they had detected experimental manipulations from external cues.

Data Analysis

Processing of ventilatory and psychophysical data. Periods of interest within a trial were the 2 min before the first epoch of stimulation (prestimulation level) and the last 2 min of each epoch of stimulation (steady-state hypoxic or hypercapnic levels). The start and end of each epoch of stimulation was identified as the time of onset of inspiratory flow of the breath in which a discernible change in \( \text{PETCO}_2 \) or \( \text{PETCO}_2 \) was seen by visual inspection of the signal after changes to the fresh gas mix were implemented. Average air hunger ratings were determined for periods of interest. The average of respiratory variables was determined from the last 15 s before each rating request.

Ventilatory responses to hypoxia. A hyperbolic function, \( V_{E} = V_o + A_{AH}(\text{PETCO}_2 - C_{AH}) \), where \( V_o \) is the horizontal asymptote, \( C_{AH} \) is the vertical asymptote, and \( A_{AH} \) is the area constant of hyperbolic function for ventilatory response, was fitted to each individual’s plot of steady-state \( V_{E} \) vs. \( \text{PETCO}_2 \) during unrestrained breathing. The \( V_o \), \( C_{AH} \), and \( A_{AH} \) were adjusted by iteration for the minimum residual sum of squares.

Air hunger responses to hypoxia. A hyperbolic function, air hunger = \( A_{AH} + A_{AH} \) (\( \text{PETCO}_2 - C_{AH} \)), where \( A_{AH} \) is the horizontal asymptote, \( C_{AH} \) is the vertical asymptote, and \( A_{AH} \) is the area constant of the hyperbolic function of the air hunger response, was fitted to each individual’s plot of steady-state air hunger vs. \( \text{PETCO}_2 \) during constrained breathing. The \( A_{AH} \), \( C_{AH} \), and \( A_{AH} \) were adjusted by iteration to find minimum residual sum of squares. We chose to employ a hyperbolic model because it parallels the established method of describing ventilatory responses to hypoxia.

Ventilatory response to hypercapnia. For each individual, a linear regression of steady-state \( V_{E} \) on \( \text{PETCO}_2 \) was fitted to data from trials in which breathing was unrestrained. Baseline normocapnic data points were included. slopes and \( \text{PETCO}_2 \) intercepts are reported for regressions with significant regression coefficients (\( P < 0.05 \)).

Air hunger response to hypercapnia. For each individual, a linear regression of steady-state air hunger on \( \text{PETCO}_2 \) was fitted to data from trials in which breathing was constrained by mechanical ventilation. Baseline normocapnic data points were included. slopes and \( \text{PETCO}_2 \) intercepts are reported for regressions with significant regression coefficients (\( P < 0.05 \)).

Comparison of matched levels of hypoxia and hypercapnia (experiment 2). Changes in air hunger and respiratory variables between prestimulus baseline and stimulus steady state were calculated for each individual. Univariate repeated-measures ANOVA was performed (SPSS statistical software version 10) on the calculated changes for each variable using a design with two within factors. The within factors were condition (2 levels: free or constrained breathing) and stimulus (2 levels: hypoxia or matched hypercapnia). Only five of the six subjects studied in experiment 2 provided data for this analysis; subject 4 was excluded because we could not establish steady-state levels of hypoxic or hypercapnic stimulation before intolerable air hunger was generated (extreme ratings).

Rating response times (experiment 2). For a simple indication of the subjects’ alertness, we measured the time between each rating request (indicated by the voltage driving the “rating request” light) and the onset of the rating (indicated by the voltage signal from the rating control). A rating occurring just before, within 0.1 s after, or >10 s after a rating request was treated as an extra rating and was not included in the analysis of rating response times (this occurred for <5 per 1,000 rating requests). The total number of “missed” ratings, including those classed as “extra” ratings, amounted to 1 per 100 rating requests.

RESULTS

Experiment 1: Stimulus-Response Relationships

Air hunger response to hypoxia. Individual air hunger responses to various levels of steady-state hypoxia are shown in Fig. 3. Below a \( \text{PETCO}_2 \) of 60 Torr, a sharp increase in air hunger ratings was evident in most subjects. However, at our ethical limit of 40 Torr, only four subjects had rated higher than 40% VAS. Failure to find statistically significant hyperbolic functions can be attributed to low statistical power because of a lack of data points between \( \text{PETCO}_2 \) of 60 and 160 Torr.

Air hunger response to hypercapnia. The average slope of linear regression of air hunger on \( \text{PETCO}_2 \) was 7 ± 4 %VAS/Torr with an average \( \text{PETCO}_2 \) intercept of 38 ± 4 Torr. The average \( r^2 \) was 0.96. Similar air
hunger responses to \( \text{PCO}_2 \) have been reported in previous studies (4, 7, 31).

**Effect on air hunger of switching between hypoxic and hypercapnic reflex drives.** A typical “switchover” trial is shown for one individual in Fig. 4. Air hunger ratings did not change significantly when stimulation was switched between hyperoxic hypercapnia and normocapnic hypoxia (Fig. 5). There were small fluctuations in air hunger between adjacent stimulation periods, but these can be explained by differences in the expected level of ventilation for each period (shown by the dotted line in Fig. 5, top). The expected level of ventilation was calculated for each stimulus from individual hyperbolic and linear functions listed in Table 3.

**Quality of air hunger perception during hypoxia and hypercapnia.** Subjects chose “an urge to breathe” and “air hunger” most often as best descriptors of hypoxia and chose “an urge to breathe” and “felt like holding my breath” most often as best descriptors of hypercapnia (Fig. 6). Hypercapnia was also frequently associated with other descriptors (“starved for air,” “air hunger,” and “size of breaths felt too small”). As expected, free-breathing trials were more frequently associated with increased selection of the term “breathing required work/effort” (Fig. 6, right). Because hypoxic and hypercapnic stimuli were not precisely matched in experiment 1, differences in choice of best descriptors between stimuli may be confounded by the strength of

---

**Fig. 3.** Individual AH responses to hypoxia with \( \dot{V}_E \) constrained to a resting level by mechanical ventilation. A sharp increase in AH is seen below end-tidal \( \text{PO}_2 \) (\( \text{PET}_{\text{CO}_2} \)) of 50 Torr in most cases. Best-fit hyperbolic functions are drawn (solid lines) through individual data points for those subjects in whom the fits achieved statistical significance (S1 and S5). Each data point is the average rating of AH during the last 2 min of a step of hypoxia. The mean \( \pm \) SD level of \( \text{PET}_{\text{CO}_2} \) throughout each trial of hypoxia is indicated for each individual. S1–S11, subjects 1–11. VAS, visual analog scale.
sensation. After trials in which hypoxia and hypercapnia were alternated, all subjects indicated, in response to a specific query, that they had not perceived any changes in quality of sensation during the trial.

**Experiment 2: Equivalent Reflex Drives**

Air hunger potency. An individual raw data set for experiment 2 is shown in Fig. 7. Equal potency of the different respiratory stimuli for air hunger is demonstrated by nearly equal air hunger rating between matched stimuli for the constrained ventilation condition (Fig. 8, bottom left). Ventilatory drives were well matched between hypoxic and hypercapnic stimuli during the fixed-breathing condition. This is indicated by similar peak inspiratory mask pressure during fixed breathing, similar V5 during free breathing, and almost identical corresponding end-tidal gas levels between free and constrained breathing conditions for the two stimuli (Table 2). Accordingly, the only significant differences detected by ANOVA between stimuli were for changes in end-tidal gases (main effect of stimuli for change in PETCO2 and for change in PETO2; \( P = 0.007 \) and \( P < 0.001 \), respectively). This was “equally true” for both free- and fixed-breathing conditions (no significant interaction effects between stimulus and condition).

Rating response times. Subjects were prompt in responding to the rating signal; they responded on average within 1–1.5 s. Neither hypoxia nor hypercapnia significantly affected the response times (\( P > 0.2 \); paired \( t \)-test, df = 4). The mean response time was 0.97 ± 0.3 s during hypoxia and 1.12 ± 0.3 s during hypercapnia. The mean response time was 1.31 ± 0.7 s during normocapnic or normoxic/hyperoxic baseline.

Quality of sensation. When subjects were asked immediately after an experimental trial to describe their breathing sensations, the most frequently volunteered comments for both the hypercapnic and hypoxic condi-

---

**Table 2**

<table>
<thead>
<tr>
<th>Condition</th>
<th>PETCO2 (torr)</th>
<th>PETO2 (torr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoxia</td>
<td>40</td>
<td>100</td>
</tr>
<tr>
<td>Hypercapnia</td>
<td>40</td>
<td>100</td>
</tr>
</tbody>
</table>

**Fig. 4.** Alternating hypoxic and hypercapnic stimuli in 1 individual during mechanical ventilation. The ventilator delivered a constant inspired tidal volume (\( V_{IN} \)) of 765 ml at a fixed rate of 12 breaths/min (ventilation constrained to 9.2 l/min). Vertical bars indicate steady-state regions that were analyzed (PRE, 2 min baseline; HC1, HC2: hyperoxic hypercapnia; HX1, HX2: normocapnic hypoxia). Paw is the airway pressure measured at the mouth during inspiration; increased variability of peak Paw indicates failure of the subject to keep respiratory muscles as relaxed during the stimulation periods as during the baseline period. SpO2, arterial O2 saturation from pulse oximetry.
tions related to the desire for more air. These included the following: “couldn’t get deep enough breaths,” “wanted deeper breaths, breaths weren’t deep enough,” “urge to breathe,” and “shortness of breath.” The respiratory descriptors that subjects selected as the best can be seen in Fig. 9, left. The selections were the same for hypercapnic and hypoxic conditions and closely matched their volunteered comments.

When asked at the end of the experimental session, “if you had to go on at ‘moderate’ (air hunger) for a long period of time, which of the trials would you prefer?” all subjects said that they would prefer the hypoxic trial. The nonrespiratory effects (Fig. 9, right) may have contributed to this preference. Subjects reported more nonrespiratory side effects for the hypercapnic condition; the most common being “restlessness,” “irritability,” and “flushed/warm.” Ratings of anxiety ranged from 0 to 4 out of a maximum of 5, with slightly higher mean ratings for hypercapnia (average 2.9 vs. 2.1).

Subjects reported that they were unable to distinguish hypoxia from hypercapnia, despite three of them having expert knowledge of respiratory physiology and extensive prior experience of breathing hypoxic and hypercapnic gas mixtures in laboratory settings. Out of a total of 10 occasions where these subjects were specifically queried about whether they thought they had been given a hypoxic or a hypercapnic trial in the run just completed, they guessed correctly on 40% of occasions (50% of correct guesses would be expected due to chance).

Occurrence of Adverse Effects

Changes in the T-wave and ST-segment of the ECG were noted during hypoxia trials in subjects 4 and 10. The trials were discontinued, and ECG changes were reversed on return to normoxia. Both subjects were excluded from further study, but subject 4 had completed enough of the study to contribute data for analysis. Subject 10 also experienced pronounced nausea coincident with global T-wave inversions. Both subjects were referred to a cardiologist for assessment, including exercise stress testing. Subject 10 additionally underwent echocardiographic evaluation and myocardial perfusion scan. No underlying abnormality of cardiac function was found.

### Table 3. Ventilatory stimulus-response relationships for hypoxia and hypercapnia

<table>
<thead>
<tr>
<th>Subject No.</th>
<th>$V_0$, l/min</th>
<th>C, Torr</th>
<th>A, l·min$^{-1}$·Torr$^{-1}$</th>
<th>$R^2$</th>
<th>Slope, l·min$^{-1}$·Torr$^{-1}$</th>
<th>x-Intercept, Torr</th>
<th>$R^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>8.3</td>
<td>0.0</td>
<td>245</td>
<td>0.43</td>
<td>0.90</td>
<td>31.2</td>
<td>0.51</td>
</tr>
<tr>
<td>2</td>
<td>8.9</td>
<td>29.3</td>
<td>142</td>
<td>0.90*</td>
<td>1.42</td>
<td>33.3</td>
<td>0.86*</td>
</tr>
<tr>
<td>3</td>
<td>6.5</td>
<td>0.1</td>
<td>284</td>
<td>0.62*</td>
<td>1.21</td>
<td>29.4</td>
<td>0.63*</td>
</tr>
<tr>
<td>4</td>
<td>10.5</td>
<td>33.0</td>
<td>43</td>
<td>0.39</td>
<td>1.49</td>
<td>37.2</td>
<td>0.98*</td>
</tr>
<tr>
<td>5</td>
<td>9.7</td>
<td>37.3</td>
<td>34</td>
<td>0.82*</td>
<td>1.28</td>
<td>35.8</td>
<td>0.72*</td>
</tr>
<tr>
<td>6</td>
<td>6.0</td>
<td>32.0</td>
<td>171</td>
<td>0.97*</td>
<td>0.62</td>
<td>20.4</td>
<td>0.30</td>
</tr>
<tr>
<td>7</td>
<td>7.6</td>
<td>9.9</td>
<td>213</td>
<td>0.24</td>
<td>0.72</td>
<td>31.3</td>
<td>0.86*</td>
</tr>
<tr>
<td>8</td>
<td>12</td>
<td>0.5</td>
<td>12</td>
<td>1.38</td>
<td>24.2</td>
<td>0.81*</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>4.7</td>
<td>27.0</td>
<td>63</td>
<td>0.77*</td>
<td>0.62</td>
<td>25.9</td>
<td>0.51</td>
</tr>
<tr>
<td>10</td>
<td>15.5</td>
<td>26.3</td>
<td>71</td>
<td></td>
<td>2.01</td>
<td>33.0</td>
<td>0.92*</td>
</tr>
</tbody>
</table>

$V_0$, horizontal asymptote of hyperbolic decay function for ventilatory response; C, vertical asymptote of hyperbolic decay function; A, area function of hyperbolic decay function (describes the sharpness of response onset). * Significant regression coefficient ($P < 0.05$). Note: mean values are for significant regression coefficients only.
DISCUSSION

The stimulus-response relationship for the perceptual response to hypoxia resembled the ventilatory response to hypoxia. The threshold for air hunger with hypoxia was well below normal Po2. Even when ventilation and PCO2 were held near normal, Po2 had to be reduced to \(60\) Torr to induce air hunger; this threshold was similar to that required for a ventilatory response to hypoxia. Greater stimulation produced a sharp increase in air hunger, but strong air hunger (greater than \(50\%\) VAS) was not present in one-half of the subjects within our ethical limit of stimulation. The present study also provides the first direct comparison of air hunger generated by normocapnic hypoxia and by normoxic hypercapnia with constrained ventilation. We, thereby, assert that chemoreceptor and mechanoreceptor afferent feedback were kept constant. When the stimuli were matched for ventilatory drive, both the quality and intensity of air hunger were the same. These data provide new support for
the hypothesis that air hunger depends on respiratory "drive" and not on the particular respiratory stimulus.

**Critique of Methods**

**Perceptual response to hypoxia using steady-state methods and fixed breathing.** Previous studies of respiratory sensation during hypoxia in normal subjects have used progressive hypoxia (1), an oscillating stimulus (2), or long periods of hypobaric hypoxia (17, 36). Others derived perceptual sensitivity to hypoxia from its effect on perceptual response to hypercapnia or exercise (16, 26, 29, 37, 47). No previous studies have directly determined a stimulus-perceptual response relationship for steady-state hypoxia per se. Moreover, ours is the only experiment in which subjects were not allowed to breathe freely; thus it is comparable with breath holding and disease states, rather than with healthy persons at altitude. With a steady-state stimulus, ratings can be unambiguously associated with levels of stimulation. When the stimulus is changing, air hunger ratings do not immediately reflect the prevailing stimulus; this is the case for a hypercapnic stimulus (5). With free breathing, tidal expansion of the lungs will relieve air hunger, and other respiratory sensations such as "awareness" of increased \( V_r \) or \( f_r \) and a sense of work or effort may be introduced. The latter are qualitatively different from air hunger (i.e., not necessarily unpleasant) and may arise from different afferent sources (31). Our instructions directed subjects to focus on air hunger, a specific, particularly unpleasant form of dyspnea.

**Use of the hyperbola model.** The hyperbola model is commonly used to relate the variable sensed by peripheral chemoreceptors, \( P_{O_2} \), to ventilatory responses and provides a “goodness of fit” through individual data comparable to other popular models (32, 43, 46). Our analysis of perceptual response can be criticized for insufficient data points between \( P_{E O_2} \) of 60 and 160 Torr. A disadvantage of steady-state protocols is the limited number of data points obtainable from a single trial, because subjects begin to tire after 0.5 h, and ratings become less reliable. Thus in two trials per individual, we collected no more than eight data points (a prestimulation level and 3 levels of hypoxia per trial). We assumed that appreciable air hunger would not have occurred above \( P_{E O_2} = 60 \) Torr; this is supported by the data. The existing data points for most subjects (Fig. 3) suggest that extra points above \( P_{E O_2} = 60 \) Torr would not have occurred above baseline air hunger, and statistical power would have increased for testing hyperbolic fits.

---

**Fig. 8.** Change in group means ± SE levels of \( V_E \), \( P_{ETCO_2} \), \( P_{ETO_2} \), and AH from a baseline steady-state period to steady-state periods of respiratory stimulation during the hypoxic (●) and matched hypercapnic (○) trials under conditions of constrained ventilation (left) and of free breathing (right). Respiratory-stimulated levels during the constrained ventilation condition are derived from the average of 3 epochs of stimulation.
Possible influence of CO₂ level during hypoxic challenges. In experiment 1, background PCO₂ during fixed ventilation was 2–3 Torr below that during free breathing. At slightly higher PCO₂ (e.g., 40 Torr), hypoxia might have generated stronger air hunger responses. An effective increase in ventilation by severe hypoxia appears to occur only when background PCO₂ exceeds 39 Torr (38). Background PCO₂ exceeded this threshold only in one subject (Fig. 3; subject 11).

Protocols for testing matched hypoxia and hypercapnia. Experiment 1 was not definitive because “expected” V̇E was based on sparse data and background PCO₂ was held a little below normocapnia. In experiment 2, with the benefit of hindsight, we maintained PCO₂ >40 Torr and closely matched the stimuli by actual measurements of V̇E in immediately prior free-breathing trials. Matched stimuli were tested for perceptual response in separate trials. Experiment 2 thus provides stronger evidence that the potency of the stimulus to produce air hunger is tied to its potency to stimulate V̇E. The use of experienced subjects is unlikely to have biased our data. Despite prior experience of both stimuli, subjects did not distinguish hypoxia from hypercapnia in this “side-by-side” comparison.

Stimuli were matched, assuming that corollary discharge for a given ventilatory drive would not be affected by differences in breathing pattern. This is consistent with the observation that the tolerable limit of hypercapnia is a function of V̇E, independent of the particular combination of fR and VT (42). In any case, matched hypoxic and hypercapnic stimuli did not produce substantially different breathing patterns when our subjects were free to breathe (see Table 2). Thus when the same levels of stimulation were presented with constrained ventilation, the pattern of breathing would have deviated from that generated by the respiratory controller by an equal amount for both stimuli.

Effect of respiratory efforts against ventilatory constraint. Respiratory efforts (as measured by peak inspiratory pressures associated with collapse of the anesthesia bag) were not significantly different between hypercapnic and hypoxic periods. Air hunger has been shown to be independent of respiratory muscle contraction and “fictive” efforts to breathe (7, 8, 22). In some subjects in the present study, respiratory efforts correlated with air hunger ratings; this is possibly because of their common dependence on increased medullary discharge produced by chemoreceptor afferent input.

Apparent absence of cognitive depression. We found no evidence that the levels of hypoxia and hypercapnia used in this experiment altered subjects’ cognitive or psychomotor functions or their ability to sense and report air hunger. Their manual ratings were executed promptly in response to visual cues, they provided detailed descriptions of respiratory and other body sensations during debriefing, and, when asked, none reported disorientation or changes in vision and hearing. This is consistent with previous reports that subjects can reliably rate breathlessness with O₂ saturation as low as 65% at a constant CO₂ (1). Only modest
and inconsistent changes in mental performance have been demonstrated with the levels of hypoxia used in our study (10, 11, 21). Furthermore, our study design prevented hypocapnia (and its attendant cerebral vasconstrictions) that usually accompanies hypoxia.

**Equipotency of Hypoxia and Hypercapnia for Air Hunger**

**Comparison with other studies.** The notion that breathlessness would be the same for any given level of reflex stimulation of ventilation, regardless of the source of ventilatory stimulus, is not new (see Refs. 1, 29, 47). However, previous studies are not conclusive, and each is beset with varying confounds. In one, the equipotency of hypoxia and hypercapnia was inferred indirectly from lack of a systematic difference in breathlessness associated with progressive normocapnic hypoxia and by progressive normoxic hypercapnia among subjects breathing freely at the same ventilation (1). A more direct, within-subject comparison was made in two other studies (29, 47), but both included a background of exercise, introducing other putative drives to breathe, and controversy exists because they produced different results despite similar protocols.

The results of our study are consistent with those in which subjects were instructed to rate “an uncomfortable urge to breathe” and care was taken to exclude a sense of “breathing more” (1, 29). In contrast, hypoxia may be less potent than hypercapnia for generating “breathing difficulty” (47) in which case ratings probably include sensations of work, effort, and increased VE as well as air hunger (18, 45). The present study is the only one in which breathing was restricted (eliminating the confound of mechanoreceptor activity associated with changes in breathing). Steady-state methods were employed, and matching of hypercapnic and hypoxic stimuli was based on actual measurements of ventilation in prior free-breathing runs. A direct within-subject comparison of hypercapnia and hypoxia was possible, without the presence of exercise drives to breathe, allowing a more definitive conclusion.

**Implications for hypothesized neural mechanisms of air hunger.** We have interpreted the equipotency of matched hypoxic and hypercapnic stimuli as a failure to disprove the notion that corollary discharge of brain stem respiratory drive is the sole source of air hunger. There are two important caveats. First, it is possible that other potential sources of influence on perception may differ between matched hypoxic and hypercapnic stimulation. For example, brain tissue hypoxia may have direct influence on the neural “seat” of air hunger perception in the brain. However, the contribution of such influences would not be expected to result in the same level of air hunger between matched stimuli as we have found.

Second, the peripheral and central chemoreceptors may have a common central pathway to the respiratory controller (19, 20). The present protocol cannot distinguish between projection of this common central pathway of combined chemoreceptor activity and projection of brain stem respiratory output as the source of air hunger. Several lines of indirect evidence support the contention that air hunger arises from projection to the cortex of “corollary discharge” from brain stem respiratory motor output. For example, air hunger follows the time course of ventilation more closely than the time course of chemoreceptor stimulation during oscillating hypoxic or hypercapnic stimulation (2). Animal studies have demonstrated that a copy of brain stem respiratory motor output is transmitted to the midbrain and thalamus (14, 15).

**Significance of the “High” Threshold for Hypoxic Air Hunger**

In many instances, a reflex increase in ventilation from the brain stem is adequate to prevent hypoxia. In other instances, such as submersion, a more complex behavioral response is needed, driven by conscious awareness of inadequate ventilation. When PETO2 is controlled experimentally in humans, pronounced ventilatory responses are rarely seen until PETO2 falls below 60 Torr (9, 38). A similar “threshold” for air hunger, as suggested by our data, is physiologically appropriate as there is little to be gained from a ventilatory or behavioral response until the oxygen saturation of hemoglobin begins to fall. Although arterial PO2, rather than arterial O2 content, drives carotid body activity (28, 32), chemoreceptors appear to have evolved to match characteristics of hemoglobin; it is hypothesized that this matching occurs through incorporation of heme molecules in the chemoreceptive mechanism (12).

**Conclusions**

1) When ventilation and PCO2 are held constant, hypoxia severe enough to generate a ventilatory drive will elicit air hunger. 2) The quality and intensity of the sensation are similar to that generated by hypercapnia. 3) The perception of air hunger correlates with reflex respiratory drive, regardless of whether this arises from central or peripheral chemoreceptor afferent activity, supporting the hypothesis that air hunger arises from reflex respiratory drive. 4) Although low inspired PO2 does not generate air hunger in healthy subjects who can increase ventilation and lower arterial PCO2, hypoxemia should not be discounted as an important underlying source of dyspnea in the clinical setting.

Technical assistance of Ronald Garcia in preparation and performance of the experiments as well as with extensive data analysis is greatly appreciated. Further technical assistance during experiments was provided by Dr. Abigail Hafer and by Rebecca Wells. Dr. Hafer also assisted in analysis of subject debriefings. Efficiency of data analysis was greatly aided by computer programs written by Dr. Ben Fabry. We also acknowledge the help of Emil Millet and Dr. Jim Butler with modeling individual air hunger response data. Drs. Lewis Adams and Jim Butler also provided critical appraisal of the manuscript that was greatly appreciated.

This study was funded by National Heart, Lung, and Blood Institute Grant HL-46690. E. Golestanian was funded by the Harvard Training Fellowship Program in Pulmonary/Critical Care Medicine.
REFERENCES


44. Scott J and Huskisson EC. Graphic representation of pain. 
45. Simon PM, Schwartzstein RM, Weiss JW, Lahive K, Fencl V, Teghtsoonian M, and Weinberger SE. Distinguishable 
46. Van Klaveren RJ and Demedts M. A mathematical and 
47. Ward SA and Whipp BJ. Effects of peripheral and central 
    chemoreflex activation on the isopnoeic rating of breathing in 