Time course of air hunger mirrors the biphasic ventilatory response to hypoxia

S. H. Moosavi, R. B. Banzett, and J. P. Butler

Physiology Program, Harvard School of Public Health, and Department of Medicine, Harvard Medical School, Boston, Massachusetts 02115

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Moosavi, S. H., R. B. Banzett, and J. P. Butler. Time course of air hunger mirrors the biphasic ventilatory response to hypoxia. J Appl Physiol 97: 2098–2103, 2004.—Determining response dynamics of hypoxic air hunger may provide information of use in clinical practice and will improve understanding of basic dyspnea mechanisms. It is hypothesized that air hunger arises from projection of reflex brain stem ventilatory drive (“corollary discharge”) to forebrain centers. If perceptual response dynamics are unmodified by events between brain stem and cortical awareness, this hypothesis predicts that air hunger will exactly track ventilatory response. Thus, during sustained hypoxia, initial increase in air hunger would be followed by a progressive decline reflecting biphasic reflex ventilatory drive. To test this prediction, we applied a sharp-onset 20-min step of normocapnic hypoxia and compared dynamic response characteristics of air hunger with that of ventilation in 10 healthy subjects. Air hunger was measured during mechanical ventilation (minute ventilation = 9 ± 1.4 l/min; end-tidal PCO2 = 37 ± 2 Torr; end-tidal PO2 = 45 ± 7 Torr); ventilatory response was measured during separate free-breathing trials in the same subjects. Discomfort caused by “urge to breathe” was rated every 30 s on a visual analog scale. Both ventilatory and air hunger responses were modeled as delayed double exponentials corresponding to a simple linear first-order response but with a separate first-order adaptation. These models provided adequate fits to both ventilatory and air hunger data (r2 = 0.88 and 0.66). Mean time constant and time-to-peak response for the average perceptual response (0.36 min−1 and 3.3 min, respectively) closely matched corresponding values for the average ventilatory response (0.39 min−1 and 3.1 min). Air hunger response to sustained hypoxic air hunger tracked ventilatory drive with a delay of ~30 s. Our data provide further support for the corollary discharge hypothesis for air hunger.

visual analog scale; human; perception; hypoxic ventilatory drive; shortness of breath

HEALTHY SUBJECTS REPORT an uncomfortable urge to breathe (“air hunger”) during hypoxia if the hypoxia is severe enough to evoke a ventilatory drive and if ventilation and PCO2 are constrained to normal levels (22). The dyspnea generated is quantitatively and qualitatively equal to that generated by normoxic hypercapnia if the stimuli are matched for respiratory drive (2, 22). One hypothesis that is consistent with these observations is that air hunger arises from projection (corollary discharge) of brain stem respiratory motor drive and does not depend on the nature of the excitatory stimulus (2, 5, 8, 14, 23). This hypothesis predicts that the air hunger response to sustained hypoxia would be biphasic, increasing in the acute phase and then progressively declining. In healthy adults, sustained hypoxic stimulation produces a sharp increase in ventilation in the acute phase followed by a slower ventilatory decline beyond 5 min (7, 11, 28).

A previous study found that the sensation of “difficulty of breathing” and ventilation both decreased after 7 min of a 20-min period of isocapnic hypoxia (arterial oxygen saturation = 80%) (9). However, the perceptual and the ventilatory responses were both derived from the same period of hypoxic stimulation, during which subjects breathed freely. Although the subjects’ descriptions of the sensations were not reported, it is likely that increased respiratory muscle afferent activity would have generated sensations of work or effort of breathing (15, 17, 18, 23). Conversely, pulmonary afferents sensing lung inflation relieve air hunger (12, 13, 16, 20). [This would also account for the absence of breathlessness and increase in sense of rapid breathing on ascent to altitude (21).] Thus it is not surprising to us that, in the study by Chonan et al. (9), the peak level of difficulty of breathing averaged <15% of the visual analog scale.

In the present study, we determined the time course of the air hunger response to sustained isocapnic hypoxia, while ventilation was constrained, and the time course of ventilatory responses to the same stimulus in the same subjects during separate trials with free breathing. We ensured that subjects specifically rated air hunger. The dynamics of the air hunger response were analyzed using a mathematical model previously applied to ventilatory responses to hypoxia. We reasoned that if the air hunger response did not follow the ventilatory response (e.g., if air hunger did not decline after the initial peak), this would undermine the brain stem corollary discharge hypothesis for air hunger perception. The degree to which air hunger response matches the ventilatory response would be a measure of the directness of the connection between brain stem motor activity and perception.

METHODS

Subjects

Before participation, all subjects were interviewed and examined by a physician. A diagnostic 12-lead ECG was recorded to confirm absence of underlying heart abnormalities. Other exclusion criteria included a 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 Human Subjects Committees of the performance site and of the Harvard School of Public Health.

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A total of 10 subjects were studied (Table 1). These subjects were part of a larger group of volunteers who had participated in a previously reported study from our laboratory involving hypoxic and hypercapnic stimulation (22). Subjects 1 and 9 had, in addition, participated in hypoxic and hypercapnic stimulation experiments before attending our laboratory. Subject 1 was a research assistant, and subjects 2–4 were clinical fellows, all of whom were associated with a pulmonary department. The remaining subjects had little or no knowledge of respiratory physiology.

**Experimental Setup**

Subjects sat in a comfortable chair (model 6500, Backsaver Products, Holliston, MA) in a semi-recumbent position and breathed through a mouthpiece. For tests involving free breathing, the mouthpiece was attached via a pneumotachograph (Fleisch no. 2) to a breathing circuit that automatically maintained end-tidal gases to within ±1 Torr of the desired levels despite increases in ventilation (Ve) (4). For tests involving mechanical ventilation, the breathing circuit was replaced with a mechanical ventilator (Servo Ventilator 900C, Seimens-Elema).

Various mixtures of oxygen, CO2, and N2 from three medical-gas cylinders were blended using a stack of three air-oxygen mixers (Puritan-Bennett, Los Angeles, CA). The arrangement provided various hypoxic mixtures to a minimum of 7% inspired oxygen, while ensuring isocapnia, i.e., fixed end-tidal PCO2 (PETO2). Blended output was heated and humidified (model SCT 3000, Marquest Medical Products, Englewood, CO) before supplying the fresh gas reservoir of the breathing circuit via a flowmeter (air-oxygen flowmeter). During constrained ventilation, the output of the blenders was sent directly to the gas input of the ventilator.

**Mechanical Ventilation**

Subjects were instructed to relax and let the ventilator breathe for them. They were informed that swallowing or coughing would be easiest during expiration. Ventilation was initially set at 0.16 l·kg⁻¹·min⁻¹ with respiratory frequency set at 12 breaths/min. Positive end-expiratory pressure of 3 cmH2O was imposed to aid relaxation. Subjects were given time and coaching to relax respiratory muscles at these settings. Minor adjustments were made, if necessary, to improve comfort. Actual settings used during hypoxic challenges were 0.12 ± 0.02 l·kg⁻¹·min⁻¹ for ventilation, 25% of the breathing cycle for inspiratory flow, and 10% for inspiratory pause time.

**Physiological Measurements and Recordings**

Airflow at the mouth was measured by a pneumotachometer (Fleisch no. 2) and a pressure transducer (2 cmH2O Validyne MP45); this signal was integrated online to provide tidal volume (FV156 dynes MP45) via a 1.5-mm catheter inserted into the mouthpiece or facemask. During mechanical ventilation, inspiratory and expiratory airflow, airway pressure, and volume signals were derived from transducers internal to the ventilator. Ventilator transducers were calibrated daily, according to the manufacturers’ procedure. 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 oxygen. The device also monitored blood oxygen 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 using a 10-cm visual analog scale. 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 semantically appropriate. Verbal anchors were provided to help subjects remember the scales between rating requests. Subjects were told not to restrict ratings to locations indicated by the anchors. This scaling method provides results comparable to our laboratory’s earlier ordinal scaling method (19). Ratings were visually cued by a light at 30-s intervals. When the light was illuminated, subjects operated a sliding potentiometer to control the position of a marker light along the 100-mm scale. After each rating, subjects returned the marker to an off position. If extreme was selected, we immediately reduced the stimulus.

**Protocol**

From a baseline of mild hyperoxia [end-tidal PO2 (PETO2) = 186 ± 9 Torr], we imposed a sharp-onset, 20-min step of isocapnic hypoxia (PETO2 = 37 ± 2 Torr, PETO2 = 45 ± 7 Torr) during mechanical ventilation (9 ± 1.4 l/min). On a separate day, a similar exposure (PETO2 = 40 ± 3 Torr, PETO2 = 49 ± 14 Torr) was imposed during free breathing. Respiratory and perceptual recordings during each presentation of hypoxia are shown for subject 9 to illustrate the protocol (Fig. 1). Subjects were unaware of the onset or offset of hypoxic steps; when asked, subjects denied receiving any extraneous cues or sensing any changes in air quality (such as temperature, taste, or “dryness”).

**Data Analysis**

Changes in PETO2 associated with hypoxic stimulation were identified by visual inspection of tidal PO2 recordings. Onset of the hypoxic step (time 0) was defined as end expiration of the last breath preceding the fall in PETO2. The end of the 20-min step of hypoxia was defined as end expiration of the last breath preceding the rise in PETO2. The first rating request after time 0 occurred at 17 ± 5 s. The average of respiratory variables was determined from the 15 s before each rating request. Corresponding respiratory measurements and air hunger ratings associated with each rating request were averaged across

### Table 1. Anthropometric data

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</table>

*Note that subject identification numbers match those used in a previous study (22). *No fixed mechanical-ventilation trial. †No free-breathing trial.
We analyzed the average VE response and average air hunger response curve (Fig. 2). The level of noise in the data precluded analysis of individual subject data. The average baseline VE in the minute before hypoxia was subtracted from the average VE at each time point of the free-breathing hypoxic step. Likewise, average baseline air hunger before was subtracted from the average air hunger at each time point of the constrained ventilation hypoxic step. We modeled the average VE response curve (free-breathing condition) and the average air hunger response curve (constrained-ventilation condition) to a double exponential with nonzero asymptote using the fitting function:

$$y = A[1 - e^{-a(t-\tau)}] + B[1 - e^{-b(t-\tau)}]$$

for times greater than the delay time ($\tau$), where $t$ is time and $A$, $B$, $a$, and $b$ are independent parameters, discussed below.

This is a generic form of a second-order system beginning at zero, with a potentially nonzero asymptote at large times. It does not correspond physically to a two-compartment system. Rather, it is the solution to two first-order systems, one resulting from the change in ventilation or air hunger at a given gain and the other for the decrease or adaptation in the gain itself. These ideas follow directly those of Painter et al. (26). Although convenient for the numerical analysis, the above form of the fitting function obscures the potential physiological implications. We therefore transform the four independent parameters $A$, $B$, $a$, and $b$ to an equivalent set of four, namely: transform 1) asymptotic response, given by $A + B$ (this is the level of response that would be approached for indefinitely prolonged stimulus); transform 2) interval from initial delay time to time of peak response ($\Delta t_{max}$), given by $\Delta t_{max} = [\ln(-bB/aA)]/(a - b)$; transform 3) peak response given by $y = A[1 - \exp(-a\Delta t_{max})] + B[1 - \exp(-b\Delta t_{max})]$; and transform 4) simple mean time constant of the response itself, given as $(a + b)/2$. Note that the term time constant has two common definitions: 1) the constant multiplying time in the exponent, with dimensions of inverse time, and 2) the reciprocal of this, with dimensions of time and which denotes the time required to achieve $1/e$, ~63% of full response. In this paper, we use the former definition for time constants $a$ and $b$.

Besides the utility in physiological interpretation using these new parameters, such a transformation has the advantage of substantially reducing the covariance in their statistical estimates and makes the comparison between the ventilatory and air hunger responses correspondingly easier. The delay parameter $\tau$ was not transformed.

We analyzed the data by minimizing the sum of squared residuals between the data and the fitting function with respect to the five parameters $A$, $B$, $a$, $b$, and $\tau$; these were then transformed to the physiological parameters as described above. For statistical purposes, the variance/covariance matrix was computed from the Hessian model. We were particularly interested in several specific features of the ventilatory and air hunger response curves.

1) What, if any, time difference exists in the ventilatory and air hunger time delays?
2) What are the characteristic time scales for reaching peak response?
3) How do the magnitudes of the adaptive ventilatory and air hunger responses to hypoxia compare?
RESULTS

The average $V_E$ and air hunger response curves are presented together in Fig. 3 after each data point was divided by an estimate of that variable's peak response (i.e., the peak of the best fit arising from the double-exponential fitting function for each average response curve). Several features stand out immediately. First, the similarity in overall shape of the $V_E$ and air hunger response curves is striking. The rise times to peak, the time course of adaptation (or falloff), and the magnitude of the falloff are virtually identical. The only difference appears to lie in the time delay, which is roughly $42 \pm 10$ s for $V_E$ and $68 \pm 36$ s for air hunger. We found the mean response time constant and time to peak response to be $0.39 \pm 0.09$ min$^{-1}$ and $3.1 \pm 0.42$ min, respectively, for the ventilatory response and $0.36 \pm 0.29$ min$^{-1}$ and $3.3 \pm 1.5$ min for the air hunger response. We found that the asymptotic or plateau ventilatory response at large times (roughly 7–10 min, corresponding to 95% adaptation for time constants of $\sim 0.4$ min$^{-1}$) approached the modest value of $1.68 \pm 1.0$ l/min above baseline; the peak response over baseline was $9.36 \pm 0.36$ l/min. For the air hunger response, we found visual analog scale values of $9.6 \pm 5.4$ and $23.4 \pm 2.8\%$ for the asymptotic and peak values, respectively.

The similarity of shape can be further displayed by plotting the fit of the air hunger response as a function of the fit of the $V_E$ response. This is shown in Fig. 4 along with the line of identity: each curve has been shifted by its own time delay. Note two important features here. First, there is essentially no hysteresis; this means that (apart from the time delay) the level of air hunger at a given level of $V_E$ is the same in the rising response or adaptive response phase of the hypoxic stimulus. Second, the plot is linear, i.e., air hunger and $V_E$ responses were essentially proportional to one another.

DISCUSSION

We have verified and refined the observations in an earlier report (9) by showing that the ventilatory rolloff or adaptation to sustained isocapnic hypoxia is mirrored in the time course of the air hunger response when ventilation is constrained. The similarity in the overall shape of the modeled air hunger and ventilatory responses is remarkable considering that the responses were obtained from separate trials in the same subjects. Our data fail to disprove the brain stem corollary discharge hypothesis for air hunger perception but do suggest that forebrain processing, involved in perception and reporting, may significantly delay the onset of the perceptual response relative to the onset of the ventilatory response.

![Fig. 2. Levels of respiratory variables and corresponding 30-s ratings of AH during a 20-min step of isocapnic hypoxia while subjects breathed freely (○) and while subjects were ventilated mechanically at fixed ventilation (●). The average of 15 s of breath-by-breath measurements per subject contributes to each data point for respiratory variables. One AH rating per subject contributes to each AH data point. Values are means ± SE; n = 9 subjects per condition; 1 subject did not perform the fixed-ventilation trial, and a different subject did not perform the free-breathing trial.](http://jap.physiology.org/)

![Fig. 3. Average AH response to 20 min of isocapnic hypoxia during mechanical ventilation superimposed on the average ventilatory response to the same stimulus during a separate free-breathing session. Data of each response curve are divided by the peak of the best-fit double exponential. ○, $V_E$ response; dotted line, $V_E$ curve fit; ●, AH response; solid line, AH curve fit.](http://jap.physiology.org/)

![Fig. 4. Best-fit double exponential for the AH response to 20 min of isocapnic hypoxia plotted as a function of the best-fit double exponential for the ventilatory response to the same stimulus on a separate occasion. The delay in onset of the AH response relative to the ventilatory response (evident in Fig. 3) has been removed. Note that the curve closely follows the line of identity (dotted line) on the ascending as well as the descending directions.](http://jap.physiology.org/)
Validity of Curve-Fitting Function

The temporal characteristics of the ventilatory response to hypoxia and the air hunger response to hypoxia were analyzed in a fashion similar to that of Painter et al. (26). Thus we specified that ventilation satisfy a first-order differential equation, where the (multiplicative) gain is itself subject to adaptation through its own first-order behavior. Each of these parameters (ventilatory response and gain) was allowed to have independent time constants. In the particular case of a step change in \( P_{O_2} \), the Painter model reduces to a double-exponential behavior. This is mathematically equivalent to a two-compartment model of the response, but this is potentially misleading because there are not two independent compartments. Rather, the double-exponential characteristic is the coincidental result of the coupling of a first-order response with a first-order adaptive gain, which, in fact, is obtained only for step changes in \( P_{O_2} \). In general, the Painter equations are nonlinear and do not admit such a simple description. Figures 1 and 2 show that the changes in \( P_{O_2} \) did approximate step changes, and so we adopted the double-exponential solution of the nonlinear equations of Painter et al. (26).

Significance of the Adaptive Decline in Air Hunger

The striking similarity in the shape of the biphasic ventilatory and air hunger responses suggests that there is a common origin of the signal driving \( V_{E} \) during voluntary free breathing and the signal driving air hunger during fixed ventilation, because these pathways are parallel and arise most likely from the brain stem. We view this as further support for the notion that a copy of brain stem respiratory drive projecting to the forebrain is implicit in the perceptual process for air hunger.

The authors of a recent study (25) have suggested that sustained hypoxia may result in impaired alerting or arousal responses. They observed a progressive suppression in the perceived magnitude of inspiratory-resistive loads. The level and duration of hypoxia was similar to that which we employed. However, in our laboratory’s prior study (22), no evidence was found indicating that the hypoxic stimulus altered subjects’ cognitive or psychomotor abilities or their ability to sense or report air hunger. Other laboratories have also reported the reliability of subjective ratings at oxygen saturations as low as 65% (1). Nevertheless, we cannot discount the possibility that sustained hypoxia is associated with a nonspecific cortical depression that accounts for the falloff in air hunger perception and that hypoxia independently inhibits brain stem processing to produce the falloff in ventilatory drive. It seems unlikely to us that the shape of the ventilatory and perceptual responses could be so similar on the basis of this explanation.

Significance of Delayed Onset of Perceptual Response

We can be confident that the air hunger response to hypoxia is significantly delayed relative to the almost instantaneous ventilatory response. It would be interesting to compare the delay in air hunger response to hypoxia with the delay in air hunger associated with hypercapnia. If the delays are similar despite a faster ventilatory response to hypoxia than to \( CO_2 \) (generally attributed to greater speed of response of peripheral chemoreceptors that dominate the hypoxic response), this would suggest that forebrain processing rather than chemoreceptor input or brain stem processing limits response speed. The only previous publication to report the response dynamics of hypercapnic air hunger did not estimate delay (3). In that study, a delay was assumed on the basis of published ventilatory data and physiological principles (circulation times). The forebrain processes involved in perceptual ratings of air hunger are thought to include 1) a comparison of a copy of the brain stem respiratory motor output projected to the forebrain, with afferent information reporting the prevailing ventilation, and 2) subsequent forebrain processes involved in reporting perception.

Factors Influencing Measurement of Dynamic Response

Time delays. Time delays reported include transmission delays due to circulatory delay from alveolus to chemoreceptor, neural synaptic and axonal transmission delays, and neural processing delays. There is an additional apparent delay averaging 15 s due to the 30-s sampling interval (points are plotted at the end of each interval). In addition to the foregoing, there is a less obvious source of delay: the time required for the stimulus to reach the minimal level at which the response rises above zero. Thus there is an initial time during which alveolar \( P_{O_2} \) falls from the baseline level (mean 170 Torr) to the level that stimulates the arterial chemoreceptors [\( \sim 60 \) Torr (10)]. The air hunger response is further delayed by the time required for the medullary respiratory center activity to rise to the point at which it generates air hunger. Chen et al. (8) have shown that respiratory center activity must exceed a threshold level above resting before corollary discharge is generated, and there may be an additional threshold of cortical activity required to exceed the subject’s decision threshold to increase air hunger rating.

Time constants. The model analysis we used required the assumption that onset of the hypoxic stimulus was instantaneous. A true step change in hypoxic drive would have produced a faster ventilatory and air hunger response than that produced by the slower rising actual stimulus (e.g., Fig. 2). This means that our quantitative estimates of the response time constants are underestimated (our time constants are reported in units of inverse minutes; see transform 4 in METHODS). We assessed the magnitude of this effect by using the measured fall times in \( P_{O_2} \) stimulus to approximate a first-order drive. We then used that drive as input to the double-exponential model, simulated the resulting ventilation and air hunger, and recomputed the best-fitting parameters. This analysis showed that the mean response time constants we have reported here (0.39 min\(^{-1}\) for ventilation and 0.36 min\(^{-1}\) for air hunger) are approximately one-half of the actual values. A more exact analysis using our linear model is precluded by the known nonlinear steady-state response to hypoxia (10).

Effect on conclusions. The main objective of our modeling approach was to test the correspondence of air hunger response to the onset and falloff of ventilatory response. The above considerations affect both air hunger and ventilatory responses; thus our main conclusion that the ventilatory and air hunger responses essentially track one another remains valid, and the pure time offset observed is probably due to the phenomena above that affect air hunger alone.
Mechanism of Hypoxic Ventilatory Decline

The mechanism of the adaptive phase of the ventilatory response (hypoxic ventilatory decline or rolloff) remains controversial (24, 27). In awake humans, some studies point to peripheral chemoreceptors as the source of hypoxic ventilatory decline (6), whereas others implicate central nervous system effects (29). The latter is supported by animal studies in which phrenic efferent activity is diminished by sustained hypoxia while carotid afferent activity remains elevated (30). If change in sensitivity of peripheral chemoreceptors is the source of hypoxic ventilatory decline, the present study cannot reject the possibility that direct projection of chemoreceptor afferents gives rise to air hunger perception.

In conclusion, the strikingly common features of the dynamic ventilatory and air hunger responses to sustained isocapnic hypoxia provide further support for the hypothesis implicating corollary discharge of ventilatory drive from the brain stem as the most likely afferent source for air hunger. Also, the significant delay in onset of the air hunger response to sustained hypoxia most likely reflects a need for a threshold increase in medullary drive for corollary projection to the cortex, additional forebrain processing associated with perception (e.g., comparison of ascending information about the prevailing ventilation and information about ventilatory drive from the brain stem), and further downstream mental processes associated with reporting of the perception.

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Present address of S. H. Moosavi: National Heart and Lung Institute, Imperial College London, Guy Scadding Bldg., Dovehouse St., London SW3 6LY, UK.

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