Measurement of the Ventilatory Response to Hypoxia
A Step Hypoxia Three-minute Test*

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We should begin with a complete physiologic description of the normal response to CO₂ and oxygen in terms of a fan of CO₂ response curves. This, of course, is the classic Oxford approach,¹ with isopleths of oxygen plotted at increasing CO₂ tensions. The procedure required to generate the entire series of lines requires one to two hours of continuous or discontinuous exposure and is, therefore, considered impractical for the ordinary evaluation of patients. The same data can be displayed alternatively as a function of PO₂ with isopleths of CO₂. The physiologic variables which are involved in these tests need enumeration. They are: a) the possible change in brain tissue Pco₂ at constant arterial Pco₂ due to the increase in cerebral blood flow; b) the uncertain alveolar-to-arterial PO₂ and Pco₂ differences, assuming that the test is done by continuous monitoring of alveolar or end-tidal gases. These differences can be corrected ultimately by sampling arterial blood and, of course, will vary with the quality of the patient's pulmonary function; c) central nervous system depression from hypoxia is due to unknown mechanisms. It is not always seen, but may alter the shape of the response to hypoxia. Also, it is believed, but not certain, that it takes some time to develop and that the time-course of response is the function of this secondary effect; d) central nervous system activation from secondary effects of hypoxia can alter the total response. Such activation can occur through the reticular activating system, the autonomic nervous system, secretion of epinephrine, general CNS excitement, local intracerebral lactic acid generation from hypoxia and its effect on the central CO₂ chemoreceptors; and e) the impact of systemic hypertension resulting from the hypoxic drive at the peripheral chemoreceptors. This hypertension may secondarily depress the peripheral chemoreceptor response to hypoxia, presumably because of an increased blood flow through the receptors or the increased washout of transmitter agent.

The implications of the above slow changes are that it would be desirable to determine the response to hypoxia within seconds after a sudden change of PO₂ to a measured level at the carotid chemoreceptors and then to follow this stimulus as a function of time to determine whether in fact one has observed a steady-state response promptly or whether a long period is required. If indeed slow changes are observed, it would be desirable to identify the source of these.

METHODS AND MATERIALS

The methods which are available assume the use of end-tidal gas indication and some sort of feedback system, whether human or otherwise, to monitor and control the end-tidal gases. It also assumes the need for arterial blood gas correlation, especially in disease states. There are at least three fast methods which we need to discuss. The first is nitrogen breathing as exemplified by Edelman et al² which is useful for distinguishing between subjects who have zero response and those who have a response, but this cannot provide quantitative information. The general procedure is for the subject to take six breaths of nitrogen and then switch to oxygen. The second rapid response test was that of Kronenberg and associates³ in which the subjects were instructed to take vital capacity breaths of nitrogen with either 5 percent CO₂ or 15 percent CO₂. Control was air with 5 percent CO₂. The 2nd and 3rd spontaneous breaths after the vital capacity were measured as a quantitative

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*From the University of California Medical Center, San Francisco.

Supported in part by grants HL06285, GM00063, 5K06 HL 19412.

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expression of the response to hypoxia. The end-tidal \( P_O_2 \) recorded after the inspiration was a measure of the stimulus. The problems with this test were, first of all, that the response was rather slight, and secondly that the blood-hypoxia pulse in the carotid chemoreceptors appeared not to reach a \( P_O_2 \) as low as the end-tidal \( P_O_2 \) and therefore the stimulus was uncertain. Furthermore, we now suspect that the central nervous system response to a step of hypoxia may not reach its maximum until one to two minutes after a steady level of hypoxia, and if so, the single breath test certainly is an incomplete description of the sensitivity to hypoxia.

Intermediate or slow methods which have been used include the standard steady-state methods, such as those originally by the Copenhagen school and recently by the Oxford school which were described above, and the rebreathing methods which have been attempted, particularly the Head rebreathing method. This, unfortunately, cannot be used during hypoxia since a sudden rise in arterial \( P_CO_2 \) produces a much greater peripheral chemoreceptor stimulus than a central response. Therefore, in ventilating normal subjects, when made simultaneously hypercapnic and hypoxic, they reach their ventilation limit too soon and it therefore is very difficult to quantitate. It is also difficult mathematically to justify and to compute from a hypoxic rebreathing response. Progressive hypoxia studies have been the most commonly used; in fact, characteristically, the subject is permitted to reberathe from a system in which the CO2 is held constant perhaps by bypassing the CO2 absorber and the oxygen concentration falls progressively over the course of one to ten minutes from a normal level down to 40 mm Hg. Such tests have been recorded by many authors, for example, Weil et al and Kronenberg and Drage. The only problem with the progressive hypoxia test is that it does not differentiate between the immediate response and the secondary response mentioned above.

We introduce here a third method which we have called step hypoxia in which both the the transient and the steady-state response may be observed following a sudden reduction of alveolar \( P_O_2 \) to 40 mm Hg holding \( P_O_2 \) at this level for at least three minutes.

First, we should like to describe some of the apparatus which has proved useful. A three valve, two reservoir iso \( P_CO_2 \) system has been introduced to facilitate the maintenance of constant \( P_CO_2 \) when ventilation increases (Fig 1).

The principle of this system is that inflow is adjusted to equal the alveolar ventilation of the patient; this inflow is collected in the small reservoir bag separated from the patient by the first inspiratory valve. At the beginning of inspiration, the patient empties this bag into his alveoli and then draws in rebreathed air from beyond the second inspiration valve collected from a rebreathing reservoir which is most conveniently a very large open-ended tubing. Expiration, then, proceeds via a separate valve into this rebreathing reservoir. Increases in total ventilation do not increase the supply of fresh gas and the supply of fresh gas can be controlled by a flowmeter. We have used an analog minute ventilation computer which generates a voltage proportional to the minute ventilation, that is the inspired volume divided by the time interval between two expirations. This device, which is installed within a pneumotachygraph amplifier, has done the same sort of work which can be easily done with large laboratory computers and has been utilized in most of the studies by Weil. There is now available a blending device to mix two gases, for example, air and nitrogen in proportions which can be set with a knob. The output of this blender is a constant high pressure capable of driving a respirator. In this case, the output is used to provide the flow of gas through a needle valve and flowmeter into the rebreathing system. Thus, the concentration of oxygen can be changed from 21 percent to 0 percent continuously without changing the total flow. We now believe that untrained subjects should be tested with mask rather than with mouthpiece, since our evidence suggests that these subjects may hyperventilate more with a mouthpiece than with a mask. Specifically, it seems that the response to both hypoxia and doxapram is about 50 to 100 percent greater in untrained subjects using a mouthpiece. When trained subjects are repeatedly tested, this difference disappears. Finally, we have attempted to test continuous blood \( P_O_2 \) monitoring techniques but have not found any that are, at this time, satisfactory. These include the in-dwelling International Biophysics company’s hydron-coated oxygen catheter, a special membrane-covered oxygen catheter developed by Boyd Coon, and the newly introduced eyelid oxygen electrode invented by Irving Fat and now being tested by Tcena. There is, in addition, a heated oxygen electrode which mounts on the skin (Hoffmann La Roche), but the response time of this is slow and the calibration is in serious doubt because of the need to operate at elevated temperature. We have, therefore, relied on batch arterial blood samples. Our method involves the use of a rapid oxygen (Westinghouse) analyzer, a rapid \( P_CO_2 \) analyzer, the breath-by-breath minute ventilation computer and a graphic pen recorder displaying these three functions for the operator’s use in adjusting gas flows and concentrations. In addition to the blend of air and nitrogen, flowmeters for oxygen and carbon dioxide are available to feed gas into the same small reservoir bag. The procedure is as follows: The subject breathes air (without the reservoir bag). Ventilation and \( P_CO_2 \) are recorded to estimate the level of \( P_CO_2 \) for this subject. A bag is then added and the inflow is adjusted to the expected alveolar ventilation (about 4 L/min). This is then decreased to find the threshold of increased ventilation as \( P_CO_2 \) rises. At an arbitrary endpoint, we set the inflow such that the minute inspiratory ventilation will equal two times the inflow: \( V_i = 2V_a \). This will be a ventilation of about 8 L/min. To begin the test, the blender is switched from air to nitrogen until the end-tidal oxygen has reached 40 mm Hg and the blender is then continuously adjusted by the operator to hold the end-tidal at 40 mm Hg for three or more minutes, as shown in Figure 2. At the second minute, blood pressure should be measured. Blood is sampled between the second and third minute. At the end, the blender is either switched to air, or is turned off and an equal flow of oxygen is substituted to obtain the off transient response. One may compute from the record a delta-V-40 at both one and three

![Figure 1. Step hypoxia test with three-valve rebreathing system.](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/20982/ on 04/07/2017)
minutes to obtain a steady state response to CO₂ at several PO₂ values. Repeat with V₁ = 4 Va and V₁ = 6 Va, waiting for steady-state CO₂ responses at each higher level before beginning the hypoxia test.

**RESULTS**

We have examined the question of alveolar-arterial oxygen tension differences as a function of time after a step change. In anesthetized dogs, with arterial samples drawn rapidly from a cannula in the arch of the aorta, the alveolar-arterial gradient reached its final equilibrium within 20 seconds after a step change in PO₂. It is probable that during this time, the washout of the pulmonary veins and left heart introduced a major share of the delay. Thus, there was no evidence for pulmonary delay in the normal dog due to changing venous oxygen saturation. One probable reason for this is that the alveolar gas chosen during the step closely approximates the mixed venous blood PO₂ and, therefore, little further change would be expected.

The response with mouthpiece and mask was compared in 41 subjects, 15 of whom are high altitude natives (Table 1). In the sea level natives, the response tested with mouthpieces exceeded the response tested with masks. Our efforts to document differences due to such things as temperature of gas passing the nose, CO₂ or O₂ concentrations in the nose, the clamping of the nose under a mask, and pressure differences in the airway due to the presence of a clamp, all failed in the sense that the trained subject in which the tests were done over and over again did not show the differences seen in untrained subjects. We assume that the least stimulating method (the mask) should be used for such tests.

The observed responses to hypoxia in most cases rise gradually over the first two minutes and plateau during the third minute. In some instances we have observed a progressive decline in the ventilatory response during the second and third minutes, suggestive of a central hypoxic depression and in others the response is essentially a square wave. The experience with the three-valve, two reservoir system suggests that CO₂ constancy is not complete, but that its constancy is easier to maintain by the addition of small amounts of CO₂ (Fig 2). Hyperventilation of the same alveolar gas appears to be capable of improving the clearance of CO₂ from the lungs.

Mitchell showed last year the doxapram has its effect in the anesthetized cat entirely via the carotid chemoreceptors. It appears to stimulate ventilation in man primarily through chemoreceptors as well. We have attempted to determine whether a standardized slug injection of 0.4 mg doxapram per kg body weight can be used as a substitute test for hypoxic sensitivity. The high altitude natives (Table 1) showed response to doxapram about 75 percent of the sea level natives' response even though the hypoxic response was 28 percent of normal. On the other hand, two subjects in whom inadvertent carotid chemoreceptor denervation was done in the course of bilateral carotid endarterectomy postoperatively showed no ventilatory response to doxapram.

**Table 1—Ventilation Response to Hypoxia and Doxapram**

<table>
<thead>
<tr>
<th>Stimuli</th>
<th>Hypoxia L/M ± se</th>
<th>Doxapram L/M</th>
<th>Dox/Hyp ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sea level</td>
<td>Mouthpiece n=14</td>
<td>36.8±4.3</td>
<td>32.7±4.2</td>
</tr>
<tr>
<td>Sea level</td>
<td>Mask n=12</td>
<td>12.7±2.8</td>
<td>20.6±3.1</td>
</tr>
<tr>
<td>Altitude</td>
<td>Mouthpiece n=15</td>
<td>10.4±2.2</td>
<td>23.9±1.8</td>
</tr>
<tr>
<td>All</td>
<td>n=41</td>
<td>19.3±0.8</td>
<td>25.1±0.9</td>
</tr>
</tbody>
</table>

Stimuli: Hypoxia PO₂ = 40 mm Hg, PCO₂ = control
Doxapram: 0.4 mg/kg IV bolus

**Figure 2. Example of response to step hypoxia at constant PA CO₂.**
Safety Considerations

It should be possible to put a subject either on a bed or floor and a bag and mask with a large flow of oxygen should be immediately at hand. We keep airways, endotracheal tubes, and laryngoscopes handy. We monitor the state of consciousness and the presence of cyanosis. It is probably a good idea to measure the arterial cuff pressure during the hypoxia run both as for safety and also to monitor whether the patient’s hypoxic chemosensitivity includes a pressor response. It may be a good idea to display the electrocardiogram with oscillographic monitor in patients, but I see no direct indication for this. Cardiac arrhythmias are not induced by hypoxia and cardiac arrest from hypoxia would occur long after central nervous system depression. There are special problems involved in the testing of hypoxic response in the presence of depressants, anesthetics, and narcotics. Presently, we do not feel justified in undertaking direct measures of hypoxic response in man. This would be desirable since it is now established that anesthetics such as halothane selectively depress the hypoxic response even more than the CO₂ response. In particular, the interaction of these two is eliminated. Weiskopf et al showed that the response to CO₂ which is usually steepened by hypoxia is completely flattened by hypoxia in the presence of 1 percent halothane (just sufficient to produce surgical anesthesia). On the other hand, our evidence suggests that narcotics do not depress the response to hypoxia as much as they depress the response to CO₂. In the dog, ventilation in the presence of large amounts of narcotic is initiated by the falling arterial Po₂.

To summarize, a step hypoxia method for testing response of patients has been described. It involves a well-trained operator who must observe the patient while monitoring and adjusting alveolar oxygen and CO₂ tensions. The advantages of the step test are that the time effects can be examined and that quantitative information in a steady-state can be obtained in a relatively short period of time. It can be done at several different levels of CO₂.

Assessment of Ventilatory Response to Hypoxia

Methods and Interpretation*

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Study of the ventilatory response to hypoxia in man is contributing important information concerning the physiology of ventilatory control and providing new insights concerning the pathogenesis of respiratory failure. Assessment of ventilatory responses to hypoxia in man may be carried out using a variety of procedures. Most commonly, such responses are measured under conditions in which arterial carbon dioxide tension remains unchanged so that the response of ventilation to hypoxia may be examined independent of inhibiting effects which hyperventilation-induced hypocapnia would have on such a response. Several techniques are used, but methods employed generally fit into one of four categories. Steady-state techniques involve measurement of ventilation during stepwise decrement of inspired O₂ tension where each step is of several minutes' duration.1 Second is the technique of progressive hypoxia. Because the ventilatory response to hypoxia has a relatively short time constant of approximately 18 seconds, the ventilatory response can be described as a continuous function while the oxygen tension of the gas being breathed is gradually lowered.2 This technique yields data comparable to steady-state method. There is concern that these first two methods entail relatively persistent hypoxia which may in time result in depression of ventilation. Hence, a number of investigators have used a third technique—rapid tests involving hypoxic periods lasting no more than a few breaths. The increase in tidal volume of subsequent breaths is used to gauge the response.3 These latter tests in general suffer from the disadvantage that the stimulus is so rapidly changing and so transient that its precise magnitude cannot be accurately assessed. In addition, the response is also fleeting and it is not certain that the response has become fully developed. Although some investigators have shown reasonably good agreement between transient and steady-state results,4 transient tests are generally considered less quantitatively rigorous. A fourth method for measuring hypoxic responses depends upon the fact that hypoxia augments the ventilatory response to hypercapnia. The ventilatory response to carbon dioxide is measured at high and low oxygen tensions5,6 and the change in slope of the hypercapnic response is used as a measure of the hypoxic drive.

No matter what method is used, suitable transducers must be available for measurement of minute ventilation as well as oxygen and carbon dioxide tensions. For each measurement, several current possibilities exist. Minute ventilation may, of course, be measured using discrete

REFERENCES


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CHEST, 70: 1, JULY, 1976 SUPPLEMENT