Physiological Observations During Induced Dyspnea

By ALBERT J. WASSEMAN, M.D., and JOHN L. PATTERSON, JR., M.D.

Dyspnea may be defined as a sense of need for increased breathing. As a symptom, it must be presumed to have a neurophysiological basis, including stimuli, receptors, and pathways of mediation. This report presents studies in which dyspnea was produced by exercise and added airway resistance in normal individuals. These observations were concerned with the measurement of physiological parameters which might serve as stimuli. No attempt was made to define the receptors or the physiological pathways through which the stimuli might be mediated in the development of this symptom.

Other workers have reported physiological studies of individuals who at one time or another had been dyspneic. Since dyspnea is most often a transient symptom, it was considered important to obtain relevant physiological measurements at the time of onset and disappearance of this symptom. Because the experimental method precluded oral communication, hand signals, the meaning of which was later described by the subject in detail, were utilized to indicate the appearance and abatement of symptoms. It was expected that the alterations in the measured phenomena occurring between the control period and the onset of dyspnea and those occurring between the onset of the symptom and its disappearance would provide the most important clues to the identity of the essential stimuli. The studies herein reported focused on these two time intervals. The observations reported were made before, during, and after controlled, measured exercise and were concentrated on alterations in blood gas tensions and ventilatory volumes. The receptors for alterations in these areas (chemoreceptors and pulmonary stretch receptors) have been extensively studied, and, while some review and revision of older concepts is in order, the importance of these neurophysiological systems is established.

Methods

The 17 subjects of these experiments were untrained normal adult male volunteers with a mean age of 34 and an age range of 21 to 51. All studies were made in the forenoon. The subjects were informed of the experimental procedure and, in addition, were told that, during the time of exercise, symptoms might ensue. They were instructed that, if this occurred, they were to signal, with the fingers of the free hand, the development of any symptoms considered significant, such as headache, dizziness, weakness, feeling of fatigue, or difficulty in breathing. Should any of these symptoms change or should new symptoms develop, a second signal was to be given. They were told that with the free hand, they might, by removing the breathing apparatus, halt the experiment at any time they deemed it wise or necessary.

Following this orientation of the subject, a latex balloon, 15 cm. in length, was passed nasally into the esophagus. The balloon was passed 5 cm. less than the combined nose-to-ear and ear-to-xyphoid distances. A pressure tracing showed in each case that the inspiratory maneuver produced negative pressure and expiration positive pressure. Differential esophageal oral pressure was recorded by means of a PR23-2D-300 Statham transducer and a Sanborn polyviso recorder.

A Cournand needle was inserted into the right brachial artery under local anesthesia, and pressures recorded from a Statham 23G strain gauge were calibrated against a mercury manometer. Air flow was recorded by means of a 400 mesh/inch screen pneumotachograph calibrated daily with Fischer and Porter flowmeters. Planimetric integration was utilized to determine air volumes. A plastic, constricted resistor to breathing was placed just distal to the mouthpiece in all the experiments herein reported. This resistor at its minimum internal diameter had a cross-sectional area of 42 mm.2 A nose clip occluded the nasal passages but...
did not alter the transmission of esophageal pressure via the nasal catheter.

Exercise was accomplished on a recording, calibrated, bicycle ergometer built into a tilting table. Heavy fly wheels facilitated maintenance of constancy of the grade of exercise. A voltmeter placed on the control panel allowed the investigator to monitor the rate of working, and the output in volts was recorded directly on the Sanborn recorder. Since, at any given voltage, the amperage output was constant, the work output in watts could be calculated, and the work input could be derived from the ergometer calibration curve.

Arterial oxygen tension and carbon dioxide tension were determined by the bubble equilibration technique of Riley. Arterial pH was determined by a Cambridge glass electrode with corrections to body temperature.

Following each experimental period, the subject described in his own words in detail the symptoms which had caused him to signal. Further questioning by the investigators was used to clarify any details of the symptoms. Some few experiments were terminated because of weakness or fatigue, and, on a few occasions, the signals represented headache. These experiments are not included in this report. In most instances, the symptom noted was dyspnea, almost invariably described by the subjects in terms which indicated a feeling of insufficient or inadequate breathing. Little or no distinction between difficulty on inspiration and difficulty on expiration was made by the subjects.

The statistical significance was calculated by the analysis of variance as described by Snedecor.

### Experimental Procedure

In the first section of the experiments, after the esophageal balloon and arterial needle were in place, the subject was placed either supine or 65 degrees upright for a period of at least 10 minutes. The mouthpiece-resistor-pneumotachograph assembly was then put in place, and the subject breathed through this assembly for a period of at least two minutes before the control blood gases and pH were obtained. The inspired gas was varied as the protocol dictated. At command, the subject began exercising at a rate of 500 Kg.-M. per minute input (3,000 foot-pounds per minute or 0.11 horsepower per minute). At the time of the first signal, arterial blood samples were again obtained and the exercise terminated. The subject continued to breathe the original gas mixture, and then, at the second signal, arterial

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**Table 1**

<table>
<thead>
<tr>
<th>Subjects Breathing Air in the Supine Position</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
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<tr>
<td>---------</td>
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<tr>
<td>Subj.</td>
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<tr>
<td></td>
</tr>
<tr>
<td>1</td>
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<td>2</td>
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<tr>
<td>3</td>
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<tr>
<td>4</td>
</tr>
<tr>
<td>Mean</td>
</tr>
<tr>
<td>5-9</td>
</tr>
<tr>
<td>Mean</td>
</tr>
</tbody>
</table>

**pO2:** &gt; 80.0 mm. Hg

**pCO2:** &gt; 45.0 mm. Hg

**pH:** &gt; 7.30

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*p1-4: Vent. increased between dyspnea and end dyspnea.*

15-9: Vent. decreased between dyspnea and end dyspnea.
INDUCED DYSPNEA

SUBJECTS WITH INCREASED VENTILATION AT END DYSPNEA
BREATHING AIR IN SUPINE POSITION

SUBJECTS WITH DECREASED VENTILATION AT END DYSPNEA
BREATHING AIR IN SUPINE POSITION

Figure 1
On the left are the scales for arterial oxygen tension (solid line) and arterial carbon dioxide tension (dashed line) and on the right is the scale for ventilation (dotted line). The points represent the mean values for the group. Time is on the abscissa with the arrows indicating the mean time at which dyspnea appeared or disappeared.

blood was again drawn and the experiment terminated.

In a second set of experiments, with the subjects in the supine position breathing air, exercise was accomplished as in the preceding section. Esophageal balloons and arterial needles were not utilized. At the time of the first signal, however, the inspired gas was immediately changed from air to 100 per cent oxygen, and a second signal was awaited. The subjects continued to exercise between the first and second signals.

Results

In 11 experiments, with the subjects breathing air in the supine position (table 1), dyspnea developed after an average of 102 seconds of exercise. At the onset of dyspnea, the arterial oxygen tension had fallen in each subject, the mean values being 92 mm. Hg in the control state and 79 mm. Hg at the time of dyspnea (P < 0.01). Carbon dioxide tension had increased in all, the mean change being from 42 to 53 mm. Hg (0.01 < P < 0.05). Average minute ventilation increased from 9.2 to 26.0 L. per minute (P < 0.01). Dyspnea disappeared after the termination of exercise in an average of 95 seconds. At this point, the arterial oxygen tension had returned to or toward control levels in every subject, but arterial carbon dioxide tension and minute ventilation were not significantly different from the levels noted at the time of dyspnea.

The above subject groups could be subdivided into those four individuals (table 1, subjects 1 to 4) in whom minute ventilation increased (fig. 1) and those five individuals (table 1, subjects 5 to 9) in whom minute ventilation decreased (fig. 2) between the onset and the disappearance of dyspnea. These figures demonstrate that, while arterial carbon dioxide tension and minute ventilation either increased or decreased between the onset and abatement of dyspnea, arterial oxygen tension invariably was reduced at the time of dyspnea and rose again between the onset and disappearance of this symptom. Figure 3 illustrates the mean changes in arterial oxygen and carbon dioxide tensions and in minute ventilation in five subjects who developed dyspnea on exercise while breathing air in the 65-degree head-up position. At the time of dyspnea (mean of 113 seconds after beginning exercise), the arterial oxygen tension had decreased in all (P < 0.01), and the arterial carbon dioxide tension and minute ventilation had increased in all (0.01 < P < 0.05).
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Table 2

<table>
<thead>
<tr>
<th>Subject</th>
<th>Control</th>
<th>Vent. (L./min.)</th>
<th>pH (units)</th>
<th>End dyspnea</th>
<th>Vent. (L./min.)</th>
<th>pH (units)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>pCO₂ (mm. Hg)</td>
<td>pO₂ (mm. Hg)</td>
<td>Time</td>
<td>pCO₂ (mm. Hg)</td>
<td>pO₂ (mm. Hg)</td>
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</tr>
<tr>
<td>2</td>
<td>50</td>
<td>10.4 88.4 41.3</td>
<td>7.39</td>
<td>18.6 77.2 49.2</td>
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</tr>
<tr>
<td>3</td>
<td>51</td>
<td>7.4 90.4 44.4</td>
<td>7.38</td>
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<td>1'18&quot;</td>
</tr>
<tr>
<td>4</td>
<td>42</td>
<td>11.0 93.2 40.0</td>
<td>7.38</td>
<td>26.2 75.9 66.9</td>
<td>7.31</td>
<td>1'30&quot;</td>
</tr>
<tr>
<td>5</td>
<td>37</td>
<td>4.2 89.8 42.2</td>
<td>7.35</td>
<td>10.6 78.8 50.1</td>
<td>7.31</td>
<td>1'40&quot;</td>
</tr>
<tr>
<td>Mean</td>
<td>43</td>
<td>8.2 89.3 42.0</td>
<td>7.38</td>
<td>19.4 75.9 55.4</td>
<td>7.30</td>
<td>1'53&quot;</td>
</tr>
</tbody>
</table>

The disappearance of dyspnea was signaled an average of 81 seconds after the termination of exercise. In the interval between the onset and disappearance of dyspnea, the arterial carbon dioxide tension and minute ventilation were not significantly altered (P > 0.05), but the arterial oxygen tension rose in all subjects (P < 0.01).

In contrast were the changes in seven subjects breathing air supine or in the 65-degree head-up position (table 3) who did not develop dyspnea despite longer periods of exercise (mean of 278 seconds), larger minute ventilation values (mean of 29 L. per minute), and significant (although less severe) elevations of arterial carbon dioxide tension (mean of 49 mm. Hg) (fig. 4). In these subjects, however, the arterial oxygen tension did not fall, as it did in those who developed dyspnea (figs. 1, 2, and 3), but actually rose slightly.

Exercise was carried out in the supine position by nine subjects while they breathed 100 per cent oxygen (fig. 5, table 4). These subjects exercised for 143 seconds, significantly longer (0.01 < P < 0.05) than the subjects who exercised in the supine position while breathing air. At the time of dyspnea, the arterial carbon dioxide tension and minute ventilation had increased in each subject (P < 0.01), but, again, the decrease in carbon dioxide tension between the onset of dyspnea and disappearance of dyspnea was insignificant (P > 0.05). The oxygen tensions, as indicated by the bubble equilibration technique, were greater than 100 mm. Hg and, therefore, beyond the limits of accuracy of this technique.

It is evident that even under the conditions of these experiments, dyspnea could develop in the absence of arterial hypoxemia, although longer periods of exercise were required to produce the symptom. To substantiate further the importance of arterial hypoxemia, eight individuals were exercised with the airway resistance in place until dyspnea was signaled. Without their knowledge, the inspired gas was immediately changed from air to 100 per cent oxygen. Temporary but definite abolition or marked diminution of dyspnea occurred in six of these eight individuals despite continuance of exercise and maintenance of the added airway resistance.

Although the transpulmonary pressure records contained considerable cardiac artifact with the subjects in the supine position, inspection of these records disclosed no consistent difference between these pressures during the respiratory cycle at the times of dyspnea and end of dyspnea.

Discussion

In interpreting the data herein presented, it is vital that the experimental design be kept in mind, for the combination of the following features distinguishes these experiments: (1) normal subjects, (2) added airway resistance and exercise, (3) data derived at the time of the development of dyspnea (not merely at some time during a given level of exercise), (4) stress on the alterations of the measured phenomena at the three points of each experi-

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INDUCED DYSPNEA

SUBJECTS DEVELOPING DYSPNEA
BREATHING AIR IN UPRIGHT (65°) POSITION

SUBJECTS NOT DEVELOPING DYSPNEA
BREATHING AIR IN SUPINE AND UPRIGHT (65°) POSITION

Figure 3
For explanation, see figure 1.

Figure 4
For explanation, see figure 1.

dyspnea could not be regularly produced by exercise on the bicycle ergometer alone. Too frequently, the subjects first experienced fatigue or weakness. Cherniack and Snidel demonstrated that normal individuals with a significant reduction in the maximal breathing capacity produced by an obstruction to breathing had a diminished ventilatory response to the inhalation of 7 per cent carbon dioxide. The relationship between this reduced response to carbon dioxide and the maximal breathing capacity was quite similar to that found in patients with obstructive pulmonary emphysema. Thus, a reduced ventilatory capacity altered the ventilatory response to a known strong respiratory stimulant. In the present subject group, the added airway resistance reduced the average maximal breathing capacity by about one-third. It is unlikely, therefore, that these individuals breathing through added external airway resistance were able to effect a "normal" ventilatory response to the existing respiratory stimuli.

In the past, investigators have often attempted to study dyspnea by making various measurements on subjects who had experienced this symptom. Usually, the subject was...
not dyspneic at the time of the study. It is possible, therefore, that such measurements reflected the physiological alterations produced by the disease process but were not directly related to the symptom itself. The importance of critically studying the changes occurring not only between the control state and the time of development of dyspnea but also between the appearance and disappearance of dyspnea is emphasized by the results described.

In these experiments, the correlation of the onset and abatement of dyspnea with the development and disappearance of arterial hypoxemia was so striking that it demands analysis. On each occasion when the subject was breathing air at the time of appearance of dyspnea, the arterial oxygen tension had fallen, and at the time of disappearance of dyspnea, the arterial oxygen tension had risen to or near normal. Negative correlation was also present, in the sense that when dyspnea could not be induced, hypoxia was absent. No such correlation with minute ventilation, arterial carbon dioxide tension, or arterial pH was found. Further evidence suggesting the importance of hypoxemia in the pathogenesis of dyspnea in these experiments is afforded by the observations during 100 per cent oxygen inhalation, in which the subjects tolerated exercise for longer periods before developing dyspnea. Finally, the abolition or definite diminution of the symptom when the subject was given 100 per cent oxygen to breathe despite continuance of the exercise with the added airway resistance in place is further evidence of the importance of hypoxemia.

It is well established that if, during the course of exercise-induced hyperventilation, the subject is switched from inhalation of air to oxygen, the minute ventilation is reduced. Since studies of simple, acute arterial hypoxemia have shown the oxygen chemoreceptors to be relatively insensitive until rather marked hypoxemia (less than 65 mm. Hg) exists, alleviation of dyspnea by oxygen requires some further explanation. The possibility of an oxygen chemoreceptor on the venous side of the circulation or even in the area of the exercising muscles has been suggested, but its existence has not been established. Such a mechanism would help to explain the level of hyperpnea which accompanies exercise, this level being greater than can be accounted for by the combination of alterations in arterial blood gases, pH, and temperature and also probably by the neurally transmitted influences of motion in the exercising region. The possibility of a venous chemoreceptor responding to the exercise-augmented mixed venous carbon dioxide tension has been suggested and is being explored by Dutton, Nath, and Riley, but this mechanism would not explain the correlations obtained between dyspnea and arterial hypoxemia in our study.

Bannister and Cunningham suggested two
possibilities in an attempt to explain the arterial hypoxemia which they assumed to be present during exercise: (1) an inadequate increase in the diffusing capacity of the lung and (2) physiological shunting due to imperfect ventilation-perfusion relationships—a shunt of 6 to 11 per cent of the cardiac output would have had to be postulated to explain the greater decrease in ventilation with 66 per cent oxygen than with 33 per cent oxygen in their experiments. They further postulated a state of relative cardiac insufficiency secondary to anoxia that, in turn, produced elevation of right heart pressures, which have been shown experimentally to lead to hyperpnea. Heymans and Neil19 feel that the latter two factors are unlikely to be of importance but, rather, that the arterial hypoxemia of exercise is due to the excessively deoxygenated pulmonary arterial blood moving through the pulmonary capillaries at a rate in excess of that at which normal equilibration of blood with alveolar air can occur.

While Mitchell et al.,16 Galdston and Wollock,20 and Richards1 have not found arterial hypoxemia during exercise, their observations and the present studies are not entirely comparable. Mitchell did not exercise his subjects to the point of severe dyspnea, since this was not his object. Galdston and Wollock20 obtained blood samples 45 to 60 seconds after exercise was concluded, probably long enough, in the absence of airway obstruction, for any hypoxemia to have disappeared. On the other hand, Lilienthal and his co-workers21 reported the development of mild arterial hypoxemia during exercise. The additional influence of the external airway resistance in our experiments, by inducing hypoventilation in relation to the strength of the combined respiratory stimuli, may well have been the critical factor in the consistent development of arterial hypoxemia and dyspnea in our subjects. More recent studies by Holland and Blacket22 have also indicated that arterial hypoxemia can be an important factor in the development of dyspnea. In each of their patients with the Hamman-Rich syndrome, they found that significant arterial hypoxemia developed during exercise and that breathing 100 per cent oxygen significantly reduced the exercise-induced dyspnea.

Since dyspnea developed in the present experiments while the subjects were breathing 100 per cent oxygen, arterial hypoxemia could not have been the sole stimulus for the symptom. Other factors must be considered. Arterial carbon dioxide tension, arterial pH, the actual level of minute ventilation, and changes in transpulmonary pressures did not correlate with the development of dyspnea in our subjects. Furthermore, since, in some of our subjects (fig. 1), minute ventilation actually increased from the development of dyspnea until its disappearance, the ratio of actual ventilation to the maximal breathing capacity cannot be correlated with this symptom in our study. For the same reason, there can be no strict correlation between dyspnea and the work of breathing in these experiments, since it is known that the coefficients of elastic and nonelastic work decrease during exercise.23 In our subjects, these coefficients probably increased during the period between the appearance and disappearance of dyspnea, for during that time they ceased exercising. Thus, in some subjects, during the interval between the onset of dyspnea and its disappearance, the minute ventilation increased, the transpulmonary pressure remained unaltered, and the elastic and nonelastic work probably increased. The work
Subjects Breathing 100 Per Cent Oxygen in the Supine Position

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age (years)</th>
<th>Vent. (L./min.)</th>
<th>pO₂ (mm Hg)</th>
<th>pH (units)</th>
<th>Time</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>51</td>
<td>8.7</td>
<td>38</td>
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<tr>
<td>2</td>
<td>42</td>
<td>9.9</td>
<td>45</td>
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<tr>
<td>3</td>
<td>42</td>
<td>10.6</td>
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<tr>
<td>4</td>
<td>31</td>
<td>12.2</td>
<td>40.9</td>
<td>7.40</td>
<td>2'19&quot;</td>
</tr>
<tr>
<td>5</td>
<td>38</td>
<td>13.4</td>
<td>42</td>
<td>7.38</td>
<td>2'50&quot;</td>
</tr>
<tr>
<td>6</td>
<td>37</td>
<td>9.9</td>
<td>43.7</td>
<td>7.40</td>
<td>1'12&quot;</td>
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<tr>
<td>8</td>
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<td>6.7</td>
<td>40.0</td>
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<tr>
<td>9</td>
<td>33</td>
<td>6.2</td>
<td>40.0</td>
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<tr>
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<td>9.5</td>
<td>41.3</td>
<td>7.38</td>
<td>2'28&quot;</td>
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</table>

The data presented, together with the above considerations, suggest the possible existence of a relationship between dyspnea and the summated load of respiratory stimuli. The relative weights to be assigned to the individual stimuli in this physiological summation process cannot, of course, be determined on the basis of present knowledge. It has been suggested by Cornroe that the normal stimuli, when in excess, may spill over into areas of consciousness and result in appreciation of the symptom dyspnea. Among known direct or indirect respiratory stimuli are the following: (1) arterial hypoxemia, (2) arterial hypercapnia, (3) arterial acidemia, (4) limb motion, (5) increased pressure in the right heart and superior vena cava, (6) increased central temperature, (7) decreased systemic blood pressure, (8) pain, (9) emotional factors, and (10) certain pharmacological agents. Other factors have been suspected as being of importance, the stimulus of most recent interest being the mixed venous carbon dioxide tension. While others have suggested that some unique receptor system is related to the development of dyspnea, no such receptors have yet been identified.

Since oxygen tension appears to have been so critical a variable in our experiments, an attempt to explain the mechanisms of these changes is in order. If, as suggested by Heymans and Neil, cited previously, the arterial hypoxemia results from the excessively rapid transit of severely desaturated blood through the pulmonary capillaries, cessation of exercise would very rapidly cause reversion of the hypoxemia. Mitchell, Sproule, and Chapman found that the oxygen saturation of femoral venous blood had returned to levels above control within one to two minutes after cessation of treadmill exercise. The suggestion of Heymans and Neil implies a reduced pulmonary diffusing capacity for oxygen. Although oxygen consumption determinations were not done in the present studies, it appears unlikely that levels of oxygen consumption were attained which would lower end-capillary blood oxygen saturation in the presence of the diffusing capacities possessed by healthy young men. The elevation of arterial carbon dioxide tension at the time dyspnea appeared can be explained on the basis of hypoventilation induced by the added airway resistance. The depression of arterial oxygen tension was of considerably greater magnitude than can be accounted for by the increased alveolar carbon dioxide tension alone, and the additional effect of an increased venous admixture may be postulated to account for this depression. The reasons for the production of uneven distribution of inspired air by the addition of an external resistance are, however, not immediately clear. At the disappearance of
dyspnea, the maintenance of the mean arterial CO2 tension at the previous level indicates that the hypoventilation had become less severe. The rise in arterial O2 tension which had simultaneously taken place could be explained if the oxygen tension of mixed venous blood had increased during persistence of the increased venous admixture. Support for this hypothesis is received from the studies of Mitchell and colleagues,16 who found an increase in the oxygen tension of femoral venous blood in the early stages of recovery following heavy exercise.

Summary

In 17 normal subjects, dyspnea was induced by exercise at 500 Kg.-M. per minute, with added external airway resistance. Arterial blood gas tensions and pH, transpulmonary pressure, and pulmonary ventilation were measured in the control period, at the onset of dyspnea, and at the disappearance of dyspnea, which followed cessation of exercise. Close correlation of the symptom with the functions measured was obtained through the use of hand signals by the subject to denote the onset and disappearance of any unpleasant sensation. The meaning of the signals was later obtained by description. Except for a difference in time required for the development of dyspnea, the results were similar whether the subject was exercised in the supine or in the 65-degree head-up position. In every instance, while the subjects were breathing air, at the time of appearance of dyspnea, the arterial oxygen tension had fallen below control levels, and at the disappearance of the symptom, the oxygen tension had returned to or near the control value. No such correlation was obtained between the symptom and the other variables measured. Subjects who did not develop dyspnea showed no fall in arterial oxygen tension. The subjects exercising while breathing 100 per cent oxygen required longer periods for the development of dyspnea, and six of eight subjects who developed dyspnea while breathing air experienced partial or complete relief of dyspnea despite the continuance of exercise when, unknown to them, the inspired gas was switched from air to 100 per cent oxygen. These results
suggest that dyspnea, under the conditions of these experiments, was related to the summed load of respiratory stimuli. In these experiments, the arterial oxygen tension apparently was the critical variable.

Acknowledgment
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References
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