Contribution of respiratory muscle oxygen consumption to breathing limitation and dyspnea

PERE CASAN MD, CARLOS C VILLAFRANCA MD, CLIVE KEARON MB BCH, EDWARD JM CAMPBELL MD PhD, KIERAN J KILLIAN MB FRCPC FRCPI
Department of Medicine, McMaster University Medical Centre, Hamilton, Ontario

During exercise, the sustainable activity of large muscle groups is limited by oxygen delivery. The purpose of this study was to see whether the oxygen consumption of the respiratory muscles reaches a similar critical value under maximal resistive loading and hyperventilation. A secondary objective was to see whether dyspnea (estimated discomfort experienced with breathing using the Borg 0-10 scale) and the oxygen consumption of the respiratory muscles are closely related across conditions. This would be expected if intramuscular sensory nerve fibres stimulated as a consequence of metabolic events contributed to this sensation. In six normal subjects the respiratory muscles were progressively activated by the addition of incremental inspiratory resistive loads to a maximum of 300 cm H2O×s/L (SD=66.4), and incremental dead space to a maximum of 2638 mL (SD=452), associated with an increase in ventilation to 75.1 L/min (SD=29.79). Each increment was maintained for 5 mins to allow the measurement of oxygen uptake in a steady state. During resistive loading total oxygen consumption increased from 239 mL/min (SD=38.2) to 299 mL/min (SD=52.3) and dyspnea increased to ‘very severe’ (Borg scale 7.5, SD=1.55). During dead space loading total oxygen consumption increased from 270 mL/min (SD=20.2) to 426 mL/min (SD=81.9) and dyspnea increased to ‘very severe’ (7.1, SD=0.66). Oxygen cost of inspiratory muscle power was 25 mL/watt (95% confidence limits 16.7 to 34.3) with dead space loading and 91 mL/watt (95% confidence limits 54 to 128) with resistive loading. Oxygen consumption did not reach a critical common value in the two types of loading, 60 mL/min (SD 22.3) during maximal resistive loading and 156 mL/min (SD 82.4) during maximal dead space loading (P<0.05). Physiological factors limiting the respiratory muscles are not uniquely related to oxygen consumption and appear to be expressed through the activation of sensory structures, perceptually manifested as dyspnea.

Key Words: Borg scale, Dead space loading, Hyperventilation, Resistive loading

Contribution de la consommation d’oxygène des muscles respiratoires au manque de souffle et à la dyspnée

RÉSUMÉ : Pendant l’exercice, l’activité soutenue des grands groupes musculaires est limitée par l’apport en oxygène. Le but principal de cette étude était de voir si la consommation d’oxygène des muscles respiratoires atteint une valeur critique similaire au cours d’une épreuve de charge résistive maximale et de l’hyperventilation. Un objectif secondaire de l’étude était de voir si la dyspnée (estimation de la gêne respiratoire avec l’échelle de Borg de 0 à 10) et la consommation d’oxygène des muscles respiratoires sont étroitement liés. On pourrait s’y attendre si les fibres nerveuses sensorielles intramusculaires stimulées à la suite de l’exercice...
Oxygen delivery is believed to limit exercise performance because the mitochondrial capacity of muscle to consume oxygen vastly exceeds the capacity of the cardiorespiratory system to deliver oxygen (1-3). Maximal oxygen uptake ($\text{VO}_2\text{max}$) during exercise with large muscle groups varies to a limited extent with the mode of exercise, and is similar during cycle ergometry, treadmill exercise and stair climbing (4-6). Oxygen delivery is less compelling as a limiting factor to sustained activity with small muscle groups. However, studies of diaphragmatic bloodflow have indicated that a limitation in bloodflow contributes to diaphragmatic fatigue (7). The purpose of the present study was to determine whether oxygen consumption by the respiratory muscles reaches similar limiting values during two different types of maximal sustained breathing manoeuvres. The absence of a common critical value tends to refute a limitation in either oxygen delivery or the metabolic processes stoichiometrically expressed by oxygen consumption. A secondary objective was to see whether the intensity of dyspnea experienced in the two maximal breathing manoeuvres was uniquely related to the oxygen consumption of the respiratory muscles. In 1932, Harrison et al (8) considered dyspnea to be similar to claudication, and McIlroy (9) suggested that dyspnea occurred when the respiratory muscles developed an oxygen debt. Both suggestions implied that the metabolic activity of the respiratory muscles may reach a critical value at the limits of breathing performance and contribute to dyspnea through the direct stimulation of intramuscular sensory nerve fibers.

To measure dyspnea and the oxygen consumption of the respiratory muscles under sustained but close to maximal conditions, we took advantage of respiratory control which serves to preserve arterial gas and pH status substantially in the face of added resistive and dead space loads. Progressive loading was used to drive the respiratory muscles to limitation during high tension and low velocity contractions with imposed resistances, and during both high tension and high velocity contractions with dead space loading.

**PATIENTS AND METHODS**

**Subjects:** Studies were carried out in six normal subjects (three males and three females) ranging from 28 to 42 years of age, who had previous experience with respiratory studies but did not know the purpose of the experiment (Table 1).
**General procedures:** Subjects were seated in a comfortable chair and were requested to relax and to avoid any extraneous muscular activity. A brief period was allowed for adaptation to the circuit. The experiment began with 20 mins of resting ventilation at the end of which VE, VO$_2$, and expired gas composition varied by less than 5%. Following this the respiratory loads, inspiratory resistance or dead space were added in random order. The subjects were not informed before laboratory loads, inspiratory resistance or dead space were added. The mechanical indexes of peak inspiratory pressure (P$_{\text{resp peak}}$), pressure/time product (PTP) and inspiratory work (PTP×VT/TI) were estimated. The measured values at rest and maximal, added dead space at rest and maximal

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age (years)</th>
<th>Weight (kg)</th>
<th>Height (cm)</th>
<th>Rest</th>
<th>Maximal</th>
<th>Maximal</th>
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<td>3.05 ± 3.25</td>
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<td>1.78 ± 1.78</td>
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</table>

**Oxygen cost of breathing and dyspnea**

<table>
<thead>
<tr>
<th>Inspiratory resistance (cm H$_2$O×s/L)</th>
<th>Added dead space (mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rest mean (SD)</td>
<td>Maximal mean (SD)</td>
</tr>
<tr>
<td>Peak inspiratory pressure (cm H$_2$O)</td>
<td>9.1 (1.94) (ns)</td>
</tr>
<tr>
<td>Pressure time product (cm H$_2$O×s)</td>
<td>144 (37.9) (ns)</td>
</tr>
<tr>
<td>Inspiratory work (W)</td>
<td>0.08 (0.030) (ns)</td>
</tr>
<tr>
<td>Mouth pressure (cm H$_2$O)</td>
<td>1.5 (0.84) (ns)</td>
</tr>
<tr>
<td>Ventilation (L)</td>
<td>7.4 (1.81)$^T$</td>
</tr>
<tr>
<td>Tidal volume (Vt) (L)</td>
<td>0.62 (0.120)$^*$</td>
</tr>
<tr>
<td>Frequency of breathing (breaths/min)</td>
<td>12 (2.3) (ns)</td>
</tr>
<tr>
<td>Mean inspiratory flow Vt/Ti (L/s)</td>
<td>0.33 (0.098) (ns)</td>
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<td>Duty cycle</td>
<td>0.37 (0.056) (ns)</td>
</tr>
<tr>
<td>Arterial oxygen saturation (%)</td>
<td>97 (1.7) (ns)</td>
</tr>
<tr>
<td>End tidal carbon dioxide (mmHg)</td>
<td>36 (8.4) (ns)</td>
</tr>
<tr>
<td>Oxygen uptake (mL/min)</td>
<td>239 (38.2)$^T$</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>65 (10.5) (ns)</td>
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<tr>
<td>Borg score</td>
<td>0 (ns)</td>
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**Analysis of results:** Oxygen consumption of the respiratory muscles (VO$_2$ resp) was derived by subtraction of basal oxygen consumption from the measured maximal oxygen consumption. Maximam oxygen consumption of the respiration muscles (VO$_2$ resp max) during maximal resistive loading and maximal dead space loading was compared using Student’s paired t test. The submaximal relationships between oxygen uptake and added resistance, dyspnea and oxygen consumption and other similar variables were analyzed using both linear regression analysis and multiple linear regression analysis. Multiple linear regression analysis was performed following the introduction of dummy variables to identify and treat individual subjects as covariates to control for the variability across subjects (15). Where multiple regression analysis was used following the introduction of the dummy variables, the coefficients associated with each subject were omitted from the reported regression equations. Regression of VO$_2$ resp versus ventilation was performed assuming a resting VO$_2$ resp of 0.5mL oxygen/L ventilation. Both VO$_2$ resp and Ve were logarithmically transformed because the oxygen costs of breathing increase in an alinear manner with increasing ventilation, yielding an equation of the form:

$$\frac{VO_2}{Ve} = \text{constant} \times Ve^n$$

The mechanical indexes of peak inspiratory pressure (P$_{\text{resp peak}}$), pressure/time product (PTP) and inspiratory work (PTP×VT/TI) were estimated. The measured values at 103
the mouth were added to the values calculated to overcome the elastance and resistance of the respiratory system. The elastance of the respiratory system was taken as 14 cm H2O/L and resistive pressure was taken as:

$$192 \cdot VT/TI + 0.52 \cdot (VT/TI)^2$$

These values were taken from D’Angelo et al (16). Inspiratory flow was taken as rectangular assuming a value equal to VT/TI (17). Peak pressure was assumed to occur following 80% of the inspired volume:

$$P_{\text{peak}} = P_m + 0.8 \cdot VT + 14.92 \cdot VT/TI + 0.52 \cdot (VT/TI)^2$$

The contributions of viscoelastance and distortion to pressure, PTP and power were omitted.

**RESULTS**

**Resistive loading:** VO2 increased from a resting value of 239 mL/min (SD=38.2) to 299 mL/min (SD=52.3) with a maximal added resistance of 300 cm H2O×s/L (SD=66.4). There was a small decrease in VE from 7.4 L/min to 6.8 L/min, and Pinsp peak increased from 9.1 cm H2O to 64.0 cm H2O (Table 2). The estimated power output of the inspiratory muscle increased from 0.08 W (SD=0.03) to 0.55 W (SD=0.21) with an oxygen consumption of 60 mL/min (SD=22.3) (Table 2), an oxygen cost of 91 mL/W (95% confidence interval 54 to 8). SaO2 and PETCO2 did not change during resistive loading (Table 2).

**Dead space loading:** VO2 increased from a resting value of 270 mL/min (SD=20.2) to 426 mL/min (SD=81.9) with a maximal added dead space of 2638 mL (SD=451.9). VE increased from 8.6 to 75.1 L/min, and Pinsp peak increased from 9.6 to 44.8 cmH2O (Table 2). The estimated power output of the inspiratory muscles increased from 0.09 W (SD=0.03) to 4.47 W (SD=3.17) with an oxygen consumption of 156 mL/min (SD=82.4) (Table 2). Oxygen cost was 25 mL/W (95% confidence interval 16.7 to 34.3). SAO2 fell from 98% to 86%, and PETCO2 increased from 37 mmHg to 50 mmHg with the highest dead space load (Table 2).

**Dyspnea, oxygen consumption and respiratory mechanics:** Dyspnea increased to a maximal intensity of ‘very severe’, 7.5 during resistive loading (SD=1.55), and to ‘very severe’, 7.1 during dead space loading (SD=0.66) (2638 mL, SD=451.9 mL). The intensity of dyspnea was significantly
related to \( z \) (P<0.0001), PTP (cm H2Oxs) (P<0.0001), power output (watts) (P<0.0001) and \( P_{\text{insp}} \) peak (cm H2O) (P<0.0001) (Figure 1). In all four relationships dyspnea was greater during resistive loading than during dead space loading (\( VO_2 \) resp P<0.0001; PTP P<0.05; power output P<0.001; \( P_{\text{max}} \) resp insp P<0.10). The mechanical variable most closely associated with dyspnea was \( P_{\text{insp}} \) peak (Figure 1D).

**DISCUSSION**

\( VO_2 \) resp max may be determined by a limitation in oxygen delivery to respiratory muscles or merely reflect the sum of unit processes involved in aerobic metabolism in a stoichiometric manner. In the present study the oxygen consumption reached at, or very close to, the point of limitation was not the same during the two types of respiratory loading. Respiratory muscle oxygen consumption was 60 mL/min (SD=22.3) and power output 0.55 W (SD=0.21) during maximal resistive loading was substantially lower than during maximal dead space loading, in which \( 2 \) resp max was 156 mL/min (SD=84.2) and power 4.47 W (SD=3.17). The difference in \( VO_2 \) resp max was so great that it is difficult to regard respiratory muscle oxygen delivery or aerobic metabolism as limiting in both types of respiratory loading. Although both loads were accompanied by similar intensity of dyspnea, dead space loading was associated with a greater capacity to perform work and higher energy expenditure and oxygen consumption. This was most likely due to the higher velocity and extent of respiratory muscle contraction with higher rates of actin and myosin cross bridging in dead space loading.

While oxygen delivery or consumption did not limit, it was also apparent that power output or PTP did not reach similar critical limiting values at limitation. Although a case might be made in favour of peak pressure as limiting, this variable also was not significantly different at limitation (P=0.10). Because the intensity of dyspnea was similar at limitation with both types of loading, a case can be made for sensory limitation expressed through the generation of dyspnea.

Oxygen uptake reflects only aerobic metabolism and at the point of limitation it is difficult to exclude anaerobic metabolism and its consequences as a limiting factor. Short periods of high intensity activity can be performed with selective recruitment of fast twitch motor units, in which intramuscular energy stores of adenosine triphosphate, creatine phosphate and the production of lactate from glycolysis may account for an appreciable proportion of the energy needs. However, the generation of substantial energy from these sources is unlikely to apply to a load maintained for 5 mins, as in the present study. Anaerobic metabolism may have occurred during the final load, which was usually sustained for only a few breaths. Even the contribution of anaerobic processes to limitation are likely to be expressed through the activation of sensory receptors contributing to discomfort, in turn limiting further activity.

The large differences in oxygen uptake observed between resistive and dead space loading in the present study are unlikely to have been due to technical errors, but these should be considered. Oxygen uptake continues to increase with time during high intensity muscular activity (18) such that steady state conditions are only strictly achieved during low intensity activity, but the 5 min duration of each load increment should have ensured a steady enough state for the measurements of oxygen uptake to be valid. Furthermore, this effect and the effect of any extraneous muscle activity would be expected to influence measurements in both types of incremental loading, in which oxygen uptake increased systematically. Liljestrand (19) showed that activation of the normal control processes was essential for reproducible measurement of the oxygen cost of breathing, with voluntary hyperventilation leading to unreliable measurements because of inefficient activation of respiratory and other muscles. Errors in the measurement of the oxygen cost of breathing historically have been a matter of concern (20-25). Reliability has been an issue because with the hyperventilation of ventilatory loading, the inspired to expired oxygen difference is small; errors in the measurement of \( FO_2 \) lead to large errors in calculated oxygen consumption. Because of these concerns \( FO_2 \) was measured simultaneously in the present study by two independent techniques, polarographic electrode and mass spectrometry, both calibrated by the same test gases. The values of \( FO_2 \) were highly correlated, with r=0.98 and a slope close to unity (0.97, intercept 0.003); these results are similar to a previous comparison of these methods during exercise (13). For these reasons, although care with the experimental protocol and precision of analysis are critical, the measurements of oxygen uptake in the present study appear to be valid, and analytical errors are unlikely to have accounted for the large differences in between the two types of loading.

In the present study the oxygen cost of breathing increased in a positively accelerating manner with ventilation:

\[
VO_2 = 0.12 \times V_e^{0.12} \quad (r = 0.95, P < 0.0001)
\]

This relationship indicates that \( VO_2 \) resp increases from 6 mL/min at 10 L/min (0.6 mL/L), to 20 mL/min at 20 L/min (1 mL/L), 63 mL/min at 40 L/min (1.6 mL/L) and 206 mL/min at 80 L/min (2.6 mL/L) of ventilation. With the maximal added dead space the oxygen consumed by the respiratory muscles was 151 mL/min at a ventilation of 75 L/min. These values for the oxygen cost of increased breathing are virtually the same as in the carefully conducted studies of Liljestrand in 1918 (19). With maximal resistive breathing the oxygen consumed by the respiratory muscles was 60 mL/min and ranged from 26 to 79 mL/min at the maximal added resistance tolerated. These results are also similar to those previously reported (23,26). The substantial differences between \( VO_2 \)resp measured under the two types of conditions are probably explained in terms of the differing relationships among tension, length and velocity of muscle contraction. With maximal breathing efforts in resistive loading, tension is high, velocity is low and changes in length are small; in dead space loading, tension is lower, velocity higher and large changes in length accompany the large tidal volumes employed. Power output of muscle is the product of
tension and velocity, and the muscle’s greatest capacity to perform external work occurs in conditions of low tension with high velocity and large changes in length (27-31). Thus, in ventilatory loading imposed by added dead space, the higher maximum $VO_2$ resp is explained by low tension and high velocity contractions of respiratory muscles generating high tidal volumes at high frequency; the lower maximum $VO_2$ resp in resistive loading are associated with the contractile conditions of high tension and low velocity, with small tidal volumes and low breathing frequencies.

The idea that limitation was imposed by the sensory consequences of respiratory muscle activity does not address the physiological processes contributing to sensory receptor stimulation and, thus, contributing to dyspnea. The intensity of dyspnea was the same at discontinuation for the two conditions of loaded breathing. Strictly considered, the final loads were submaximal, and maximal symptom ratings of 10 on the Borg scale were not seen, but submaximal symptom ratings at the limits of human muscular performance are often seen because subjects are unwilling to tolerate maximal discomfort (32,35). Locally produced mediators in the respiratory muscles including potassium ions, adenosine, prostaglandins, lactate and changes in osmolarity effectively achieve a match between metabolism and muscle bloodflow (36-41). These mediators may also stimulate sensory nerve endings and contribute to a sense of muscular discomfort and dyspnea. If mediators released in a stoichiometric relationship to metabolism stimulated free nerve endings and contribute to dyspnea, the sensory intensity of dyspnea might be broadly similar to oxygen consumption across contractile conditions. The results of the present study refute this simple hypothesis. Many other sensory inputs have been postulated to contribute to dyspnea including central motor output that is associated with a sense of effort, afferent activity from muscle spindles and tendon organs that is associated with perceived force and displacement, and chemoreceptor stimulation generating an increased and uncomfortable urge to breathe (42). Central motor output results in a sense of effort and may determine the magnitude of dyspnea. The other sensory structures such as tendon organs, muscle spindles, joint receptors and perhaps chemoreceptors are sentient and may influence the quality of the resulting sensation (43-46). The magnitude of dyspnea in the present study would increase as a function of the motor output (effort) required to generate a ventilation or to maintain ventilation in the face of increasing resistance. Chemoreceptor stimulation appears to generate an unpleasant urge to breathe and may contribute to dyspnea independent of effort. The increased chemoreceptor activity caused by hypercapnia and desaturation may have contributed in part to the dyspnea experienced during dead space loading.

The absence of the simple relationship sought between respiratory muscle oxygen consumption and dyspnea does not exclude an indirect role for respiratory muscle metabolism in contributing to dyspnea. Changes in metabolism affecting membrane polarization, electromechanical coupling and calcium release modify the responsiveness of the respiratory muscle to alpha motor stimulation. Also, the inherent excitability of the alpha motor neurone may itself be reflexly inhibited by free nerve endings stimulated as a consequence of mediator release.

In summary, no finite critical limiting value in oxygen consumption was observed when the respiratory muscles were driven to limitation during resistive and dead space loading. The intensity of discomfort reached a critical and finite limiting value but its relationship to oxygen consumption by the respiratory muscle appears to be variable and indirect.

REFERENCES

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