Contribution of respiratory muscle oxygen consumption to breathing limitation and dyspnea

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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...
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 (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 such as the respiratory muscles. 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 (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 imply 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).
select a number tagged to descriptive phrases that reflect respiratory discomfort: 0 denotes no appreciable dyspnea and 10 denotes maximum discomfort in breathing. Rating was performed during the last minute of each load.

**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, VO2 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 hence, if the load was not completed the values of the previous load were used for calculation of VO2.

**Analysis of results:** Oxygen consumption of the respiratory muscles (VO2 resp) was derived by subtraction of basal oxygen consumption from the measured maximal oxygen consumption. Maximam oxygen consumption of the respiratory muscles (VO2 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 estimated. The measured values at maximal resistance versus maximal dead space (P<0.01); §Maximal resistance versus maximal dead space (P<0.05); §§Maximal resistance versus Maximal dead space (P<0.01); ns Not significant.

**TABLE 1**

| Patient | Sex | Age (years) | Weight (kg) | Height (cm) | Forced expiratory volume in 1 s (L) | Maximal inspiratory pressure (cm H2O) |
|---------|-----|-------------|-------------|-------------|------------------------------------|--------------------------------------|
| 1       | Female | 28          | 61          | 162         | 3.05                               | 135                                |
| 2       | Female | 29          | 60          | 168         | 3.26                               | 80                                 |
| 3       | Female | 33          | 61          | 159         | 3.16                               | 88                                 |
| 4       | Male   | 28          | 66          | 175         | 3.98                               | 100                                |
| 5       | Male   | 35          | 70          | 168         | 3.76                               | 140                                |
| 6       | Male   | 42          | 70          | 178         | 3.93                               | 160                                |
|         | Mean   | 33±5.5      | 65±4.6      | 168±7.3     | 3.52±0.415                         | 117±32.3                           |

**TABLE 2**

|                     | Inspiratory resistance (cm H2O×s/L) | Added dead space (mL) |
|---------------------|------------------------------------|-----------------------|
|                     | Rest mean (SD)                     | Maximal mean (SD)     |
|                     |                                    | Maximal mean (SD)     |
| Peak inspiratory pressure (cm H2O) | 9.1 (1.94) (ns)                  | 64.0 (12.4)††         |
|                     |                                    | 9.6 (1.55)††         |
|                     |                                    | 44.8 (13.9)††         |
| Pressure time product (cm H2O×s)    | 144 (37.9) (ns)                   | 1918 (608.0)††       |
|                     |                                    | 156 (33.1)††         |
|                     |                                    | 808 (277.5)††         |
| Inspiratory work (W)             | 0.08 (0.030) (ns)                 | 0.55 (0.210)††       |
|                     |                                    | 0.09 (0.031)††       |
|                     |                                    | 4.47 (3.17)††         |
| Mouth pressure (cm H2O)           | 1.5 (0.84) (ns)                   | 52.0 (9.57)††         |
|                     |                                    | 1.0 (0) (ns)          |
|                     |                                    | 3.0 (2.28)‡§§         |
| Ventilation (L)                | 7.4 (1.81)††                     | 6.8 (1.57) (ns)       |
|                     |                                    | 8.6 (1.64)‡‡         |
|                     |                                    | 75.1 (29.79)§§         |
| Tidal volume (Vt) (L)            | 0.62 (0.120)*                     | 1.04 (0.505) (ns)     |
|                     |                                    | 0.70 (0.133)‡‡         |
|                     |                                    | 2.71 (0.55)§§         |
| Frequency of breathing (breaths/min) | 12 (2.3) (ns)                | 7 (3.0)††            |
|                     |                                    | 12 (2.3)††            |
|                     |                                    | 27 (7.7)§§            |
| Mean inspiratory flow Vt/Ti (L/s) | 0.33 (0.098) (ns)               | 0.18 (0.043)††       |
|                     |                                    | 0.35 (0.043)††       |
|                     |                                    | 3.06 (1.261)§§        |
| Duty cycle             | 0.37 (0.056) (ns)                 | 0.66 (0.142)††       |
|                     |                                    | 0.41 (0.046) (ns)     |
|                     |                                    | 0.42 (0.034)§§        |
| Arterial oxygen saturation (%)  | 97 (1.7) (ns)                     | 97 (1.8) (ns)         |
|                     |                                    | 98 (1.4)‡            |
|                     |                                    | 85 (9.4)§§           |
| End tidal carbon dioxide (mmHg)  | 36 (8.4) (ns)                     | 41 (4.7) (ns)         |
|                     |                                    | 37 (3.1)‡            |
|                     |                                    | 50 (3.7)§§           |
| Oxygen uptake (mL/min)          | 239 (38.2)*                       | 299 (62.3) (ns)       |
|                     |                                    | 270 (20.2)††         |
|                     |                                    | 426 (81.9)§§         |
| Heart rate (beats/min)          | 65 (10.5) (ns)                    | 75 (12.1) (ns)        |
|                     |                                    | 70 (12.6)††          |
|                     |                                    | 92 (8.3)§§           |
| Borg score               | 0 (ns)                             | 7.5 (1.55)††         |
|                     |                                    | 0††                  |
|                     |                                    | 7.1 (0.66) (ns)       |

*Resting resistance versus resting dead space (P<0.05); ††Resting resistance versus maximal resistance (P<0.01); †Resting dead space versus maximal dead space (P<0.05); ‡Resting dead space versus maximal dead space (P<0.01); §Maximal resistance versus maximal dead space (P<0.05); §§Maximal resistance versus Maximal dead space (P<0.01). ns Not significant.
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: 

$$192 \cdot \frac{V_t}{T_i} + 0.52 \cdot (\frac{V_t}{T_i})^2$$

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:

$$P_{\text{insp peak}} = P_m + 0.8 \cdot V_t + 14.92 \cdot \frac{V_t}{T_i} + 0.52 \cdot \left(\frac{V_t}{T_i}\right)^2$$

The contributions of viscoelasticity 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 x s/L (SD=66.4). There was a small decrease in Ve from 7.4 L/min to 6.8 L/min, and P insp 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 P insp 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 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 x s/L (SD=66.4). There was a small decrease in Ve from 7.4 L/min to 6.8 L/min, and P insp 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).
related to \( P < 0.0001 \), power output (watts) \( P < 0.0001 \) and \( P_{\text{insp peak}} \) (\( cm \ H_2O \)) \( P < 0.0001 \) (Figure 1). In all four relationships dysnea was greater during resistive loading than during dead space loading \( VO_{2 \text{resp}} P < 0.0001 \); PTP \( P < 0.05 \); power output \( P < 0.001 \); \( P_{\text{max insp}} P < 0.10 \). The mechanical variable most closely associated with dysnea was \( P_{\text{insp peak}} \) (Figure 1D).

DISCUSSION

\( VO_{2 \text{resp}} \) 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 \( \text{2 resp max} \) was 156 mL/min (SD=82.4) and power 4.47 W (SD=3.17). The difference in \( VO_{2 \text{resp max}} \) 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 dysnea, 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 dysnea was similar at limitation with both types of loading, a case can be made for sensory limitation expressed through the generation of dysnea.

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 FeO2 lead to large errors in calculated oxygen consumption. Because of these concerns FeO2 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 FeO2 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:

\[
VO_{2 \text{resp}} = 0.12 \cdot V_E^{0.12} \quad (r = 0.95, P < 0.0001)
\]

This relationship indicates that \( VO_{2 \text{resp}} \) 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 \( VO_{2 \text{resp}} \) 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\textsubscript{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\textsubscript{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

1. Wagner PD, Hoppeler H, Saltin B. Determinants of maximal oxygen uptake. In: Crystal RG, West JB, eds. The Lung. Scientific Foundations, vol II. New York: Raven Press, 1991:1585-93.
2. Andersen P, Saltin B. Maximal perfusion of skeletal muscle in man. J Appl Physiol 1985;66:233-49.
3. Rowell LB, Saltin B. Maximal perfusion of skeletal muscle in man. J Appl Physiol 1985;66:233-49.
4. Astrand P, Rodahl K. Physical performance. In: Van Dalen DB, ed. Textbook of Work Physiology. Physiological Bases of Exercise. New York: McGraw-Hill International Editions, 1986:295-353.
5. Lange Andersen K, Shephard RJ, Denolín H, Varnańskas E, Masironi R. Fundamentals of Exercise Testing. Geneva: World Health Organization, 1971:119-23.
6. Glassford RG, Baycroft GYH, Sedgewick AW, MacNab RBJ. Comparison of maximal oxygen uptake values determined by predicted and actual methods. J Appl Physiol 1965;20:509-13.
7. Bellemare F, Wight D, Lavigne CM, Grassino A. Effect of tension and timing of contraction on the blood flow of the diaphragm. J Appl Physiology 1983;54:1598-606.
8. Harrison TR, Harrison WG, Calhoun JA, Marsh JP. Congestive heart failure. XVII. The mechanism of dyspnea on exertion. Arch Intern Med 1972;130:690-720.
9. McLory MB. Dyspnea and the work of breathing in diseases of the heart and lungs. Prog Cardiovasc Dis 1958;1:284-97.
10. Black LF, Hyatt RE. Maximal respiratory pressures: Normal values and relationship to age and sex. Am Rev Respir Dis 1969;99:696-702.

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11. Cipriano RO, Morris AH, Gardner RM. Reference spirometric values using techniques and equipment that meet ATS recommendations. Am Rev Respir Dis 1981;123:659-64.
12. Killian KJ, Bucens DD, Campbell EJM. Effect of breathing patterns on the perceived magnitude of added loads to breathing. J Appl Physiol 1982;52:578-84.
13. Jones NL. Evaluation of a microprocessor controlled exercise testing system. J Appl Physiol 1984;57:1312-8.
14. Borg GAV. Psychophysical bases of perceived exertion. Med Sci Sports Exerc 1982;14:377-81.
15. Kleinbaum DG, Kupper LL, Muller KE. Dummy variables in regression. In: Payne M, ed. Applied Regression Analysis and Other Multivariable Methods. Boston: PWS-Kent Publishing Co, 1988:260-81.
16. D’Angelo E, Calderini E, Torri G, Robatto F, Bonod M, Milic-Emili J. Respiratory mechanics in anesthetized paralyzed humans: effects of flow, volume, and time. J Appl Physiol 1989;67:2556-64.
17. Laforstrua CL, Minetti AE, Mogiini F. Inspiratory flow pattern in humans. J Appl Physiology 1984;57:1111-9.
18. Kearon MC, Summers E, Jones NL, Campbell EJM, Killian KJ. Breathing during prolonged exercise in man. J Physiol 1991;442:477-87.
19. Liljestrand G. Studies of the work of breathing. (Untersuchungen über die Atmungsarbeit. Scand Arch Physiol 1918:35:199-203). Reprinted in West JB, ed. Translations in Respiratory Physiology. Pennsylvania: Dowden, Hutchinson & Ross Inc, 1975:438-513.
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20. Bartlett RG, Brubach HF, Specht H. Oxygen cost of breathing. J Appl Physiol 1958;12:413-24.
21. Campbell EJM, Westlake EK, Cherniack RM. Simple methods of estimating oxygen consumption and efficiency of the muscles of breathing. J Appl Physiol 1957;11:303-8.
22. Campbell EJM, Westlake EK, Cherniack RM. The oxygen consumption and efficiency of the respiratory muscles of young male subjects. Clin Sci 1959;18:55-64.
23. Jones GL, Killian KJ, Summers E, Jones NL. Inspiratory muscle forces and endurance in maximum resistive loading. J Appl Physiol 1985;58:1608-15.
24. Milic-Emili J. Work of Breathing. In: West JB, Crystal RG, eds. The Lung. Scientific Foundations, vol I. New York: Raven Press, 1991:1065-75.
25. Milic-Emili J, Petit JM. Mechanical efficiency of breathing. J Appl Physiol 1960;15:359-62.
26. Collett PW, Perry C, Engel LA. Pressure-time product, flow, and oxygen cost of resistive breathing in humans. J Appl Physiol 1985;58:1263-72.
27. Carlson FD. Kinematic studies in mechanical properties of muscle. In: Remington JW, ed. Tissue Elasticity. Washington: American Physiological Society, 1957.
28. Fenn WO. The relation between the work performed and the energy liberated in muscular contraction. J Physiol 1923;58:373-95.
29. Fenn WO, Marsh BS. Muscular force at different speeds of shortening. J Physiol 1935;85:277-97.
30. Hill AV. The heat of shortening and the dynamic constraints of muscle. Proc R Soc Lond (Biol) 1938;126:136-95.
31. Shepherd JT. Circulation to skeletal muscle. In: Anonymous Handbook of Physiology. The Cardiovascular System. Peripheral Circulation and Organ Blood Flow. Bethesda: American Physiology Society, 1983:319-70.
32. Altose MD, Cherniack NS, Fishman AP. Respiratory sensations and dyspnea: Perspectives. J Appl Physiol 1985;58:1051-4.
33. Killian KJ. Breathlessness – The sense of respiratory muscle effort. In: Prilch G, Ottoson D, eds. The Perception of Exertion in Physical Work. Wenner-Gren International Symposium Series. London: The Macmillan Press Ltd, 1986:71-82.
34. Killian KJ. The Nature of Breathlessness and its Measurement. In: Jones NL, Killian KJ, eds. Breathlessness 1991. Proceedings of the Campbell Symposium held in Hamilton, Ontario, May 1991. Hamilton: Decker Medical Publications, 1992:74-87.
35. Killian KJ, Campbell EJM. Mechanisms of dyspnea. In: Mahler DA, ed. Dyspnea. Mount Kisco: Futura Publishing Co, 1990:55-73.
36. Killian KJ, Campbell EJM. Dyspnea. In: Crystal RG, West JB, eds. The Lung: Scientific Foundations. New York: Raven Press Ltd, 1991:1433-43.
