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Chronic Alveolar Hypoventilation Helps To Maintain the Inspiratory Muscle Effort of COPD Patients Within Sustainable Limits*

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Abbreviations: Pi = inspiratory pressure; Pmax = maximal inspiratory pressure; Ti/T = inspiratory duty cycle; Tt1 = tension-time index of the inspiratory muscles; VCO2 = carbon dioxide output; VPAT = physiologic dead space ventilation; Z = mechanical impedance

When the load imposed on the inspiratory muscles is excessive relative to the neuromuscular capacity, patients need mechanical ventilation. Patients breathing with a tension-time index of the inspiratory muscles (Tt1) above a threshold value between 0.12 and 0.15 have been found to be difficult to wean from the ventilator. The

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resting TTi of stable patients with COPD and chronic hypercapnia have also been shown to be increased.\(^3\),\(^4\) However, the mechanisms leading to chronic alveolar hypoventilation in COPD are still debated.\(^5\) We reasoned that patients in steady state must maintain their inspiratory effort within sustainable limits and that alveolar hypoventilation might serve that purpose. The concept of a critical TTi value provides a framework to validate our hypothesis.

**Theoretical Considerations**

To assess the relationship between inspiratory muscle load and \(\text{PaCO}_2\), we developed the ventilation equation as to express minute ventilation using its inspiratory mechanical determinants\(^6\):

\[
\text{PaCO}_2 = \frac{\text{VCO}_2 \times Z/(1 - \text{Vd}/\text{VT}) \times K}{\text{Ti}/\text{Tr} \times \text{Pi}}
\]

where \(\text{VCO}_2\) = carbon dioxide output, \(Z\) = mechanical impedance (mean inspiratory pressure [Pi]/mean inspiratory flow), \(\text{Vd}/\text{VT}\) = physiologic dead space ventilation; \(K = 0.863\) mm Hg; and \(\text{Ti}/\text{Tr}\) = inspiratory duty cycle.

The equation predicts that \(\text{PaCO}_2\) is directly related to a combination of metabolic and mechanical loads and, for any given load, is inversely related to the inspiratory muscle effort. To reflect physiologic constraints, one may divide the mechanical load and the inspiratory effort in the above equation by maximal inspiratory pressure (\(\text{Pimax}\)). The \(\text{Z}/\text{Pimax} \times (1 - \text{Vd}/\text{VT})\) expression can then be simplified into the \(\text{TTi}/\text{Vd}/\text{VA}\) ratio, and the \(\text{Ti}/\text{Tr}\) [times] \(\text{Pi}/\text{Pimax}\) into \(\text{TTi}\).

**Materials and Methods**

We reexamined these relationships by comparing gas exchange and pulmonary mechanics in a previously reported\(^1\) population of clinically stable COPD patients with a wide range of airway obstruction (\(\text{FEV}_1/\text{FVC} < 70\%\)). From 304 available charts, we selected patients with body mass index < 35 kg/m\(^2\) whose respiratory acidoses (\(H^+ = 40.7 \pm 3.1\) mmol/L, \(\text{PaCO}_2 = 51.8 \pm 7.3\) mm Hg, \(n = 51\)) or respiratory alkaloses (\(H^+ = 34.8 \pm 1.4\) mmol/L, \(\text{PaCO}_2 = 32.3 \pm 2.0\) mm Hg, \(n = 12\)) were compatible with a primary acid-base disorder,\(^7\),\(^8\) along with patients with \(\text{PaCO}_2\) and \(H^+\) values in the normal 35 to 45 range (\(n = 199\)). To avoid the effect of esophageal balloon on breathing, TTi was corrected for the level of minute ventilation measured during steady-state ventilation.

**Results**

\(\text{PaCO}_2\) was found to be directly related to \(Z\) \((r = 0.55)\), and even more closely to \(Z/(1 - \text{Vd}/\text{VT})\) \((r = 0.64)\) and to the product of this parameter with \(\text{VCO}_2\) \((r = 0.65)\). The \(\text{Ti}/\text{Tr} \times \text{Pi}\) product was also found to be highly related to \(Z\) \((r = 0.90)\), hence to be directly related to \(\text{PaCO}_2\) \((r = 0.44, p < 0.001)\). Multiple regression analysis showed that hypercapnia was associated to a lower inspiratory effort for a given load in the following equation:

\[
\text{Ti}/\text{Tr} \times \text{Pi} = 0.42 + 0.07 \times Z/(1 - \text{Vd}/\text{VT}) + 9.62 \times \text{VCO}_2 - 0.06 \times \text{PaCO}_2
\]

where all are \(p < 0.001; r = 0.97\); \(\text{Pi}\) is expressed in centimeters of water, \(Z\) is expressed in centimeters of water per liter per second, \(\text{VCO}_2\) is expressed in liters per minute, and \(\text{PaCO}_2\) is expressed in millimeters of mercury.

Figure 1 illustrates the relationship between TTi and V\(a\) in hypercapnic (black triangles), normocapnic (open circles), and hypocapnic subjects (open inverse triangles). Hypercapnic subjects are shown to have the highest TTi values along with the lowest V\(a\) values, thus the highest energetic cost of V\(a\). The reverse was found in hypocapnic subjects. All patients were found to develop a TTi value below or within of the critical zone described as a determinant of weaning outcome,\(^2\) and far below the 0.27 to 0.30 threshold value sustained for 1 h by normal subjects during endurance runs.\(^9\) Overall, \(\text{PaCO}_2\) was found to be closely related to the TTi/V\(a\) ratio \((r = 0.62)\).

**Discussion**

Patients with hypercapnia were found to have a TTi value (mean ± SEM) of 0.071 ± 0.037. In these patients, the equation allows to estimate the TTi required to achieve normocapnia at 0.092 ± 0.051, assuming constant V\(\text{CO}_2\) and TTi/V\(a\). However, this calculation most likely underestimates the inspiratory effort needed to normalize V\(a\), since these patients are expected first to develop dynamic hyperinflation when increasing ventilation\(^10\); second, to adopt a rapid and shallow breathing pattern when approaching the critical TTi values; and third, to increase V\(\text{CO}_2\) due to increased work of breathing. Hence, the
mechanical and metabolic loads are expected to increase more than the level of ventilation.

Our results are in keeping with the findings of others, that resting $Paco_2$ in COPD is related to inspiratory work per liter of ventilation$^{11}$ and to peak inspiratory flow (reflecting inspiratory load).$^{12}$ They also show that the fatigue threshold values of inspiratory muscles are not reached in stable hypercapnic COPD patients. Hence, the inspiratory cost of $V_a$ ($TTi/Va$), rather than inspiratory muscle fatigue, appears to be a major determinant of chronic hypercapnia in COPD. The greater the $TTi/Va$ ratio is, the greater the reduction in $TTi$ resulting from alveolar hypoventilation.

**CONCLUSION**

Patients with COPD and chronic alveolar hypoventilation need to develop a higher $TTi$ to fight increased mechanical loads; alveolar hypoventilation helps to maintain the inspiratory muscle effort within sustainable limits.

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**Familial Aggregation of Severe, Early-Onset COPD**

**Candidate Gene Approaches**

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**Abbreviations:** $A_1^{-}$-antitrypsin; $\beta_2$AR = $\beta_2$-adrenergic receptor

Severe $A_1^{-}$-antitrypsin ($A_1 AT$) deficiency is the only proven genetic risk factor for COPD. Asthmatics may develop chronic airflow obstruction, but it is unknown if asthma and COPD share common genetic determinants. To study novel genetic determinants of COPD, we enrolled 44 severe, early-onset COPD probands (FEV$_1 <$ 40%; age, < 53 years, without severe $A_1 AT$ deficiency) and obtained DNA samples from 266 of their relatives. Ongoing work in our laboratory has demonstrated increased risk to current or exsmoking first-degree relatives of early-onset COPD probands for reduced FEV$_1$, chronic bronchitis, and spirometric bronchodilator responsiveness. $\beta_2$-adrenergic receptor (β$_2$AR) polymorphisms have been associated with asthma severity, but the role of variation in the β$_2$AR gene in COPD is unknown. Therefore, we performed linkage analysis and family-based association analysis using the β$_2$AR amino acid 16 polymorphism with categorical phenotypes including the following: mild airflow obstruction (FEV$_1 <$ 50% predicted), moderate airflow obstruction (FEV$_1 <$ 60% predicted), bronchodilator responsiveness (FEV$_1$ increase > 10%), and absolute bronchodilator responsiveness (FEV$_1$ increase > 200 mL). Nonparametric linkage analysis was performed with GENEHUNTER; we found no evidence for significant linkage of β$_2$AR amino acid 16 genotype to mild airflow obstruction (p = 0.7), moderate airflow obstruction (p = 0.5), percent bronchodilator responsiveness (p = 0.4), or absolute bronchodilator responsiveness (p = 0.4). In addition, family-based association studies were performed with the probands and their siblings using the sibship disequilibrium test; no evidence for significant associations between COPD-related phenotypes and β$_2$AR genotype was found. In summary, we found no evidence for significant linkage

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