Editorial Commentary

Ventilatory inefficiency: a key physiopathological mechanism increasing dyspnea and reducing exercise capacity in chronic obstructive pulmonary disease

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Lin *et al.* (1), remembers an essential principle of physiology, which states that one objective of alveolar ventilation is to clear CO_2 production (VCO_2), maintain an adequate arterial CO_2 pressure ($PaCO_2$), and control acid-base balance. The central PCO_2 set point regulated by the respiratory centers, govern the ventilatory response to depurate CO_2. In absence of fixed acids, the disproportionate increment in minute ventilation (VE) for VCO_2, indicates inefficiency of ventilation (VI). This mechanism exists particularly in chronic obstructive pulmonary disease (COPD) (1-5), where VI raise subrogated to physiological dead space (VDphys/VT), due to waisted ventilation and the need to control the $PaCO_2$. In consequence, the VE/VCO_2 ratio also increase. As example, a normal individual in moderate exercise requires 20–25 L of ventilation to clear 1 L of CO_2, and patient with COPD frequently overpass 35 L.

This unbalanced ventilation (6-8) diminish exercise capacity (EC), and is closely related to the magnitude of dyspnea (1-3,9,10). With the magnified demand of VE imposed by VI, associated with more expiratory resistance, and less time available for deflation, the pulmonary hyperinflation is potentiated. In their investigation, and performing different measurements of the VE/VCO_2 ratio, in the slope, nadir and intercept, authors describe adequately the correlation between VI and hyperinflation. It is the rule, that COPD patients with greater bronchial obstruction, hyperinflation, mechanical restrictions, and less physical conditioning, present greater functional limitation and major dyspnea. However, from the point of view of gas exchange, VI is also a key physiological alteration, enhancing dyspnea and limiting EC (3,4,11,12).

The mechanical restriction imposed by dynamic hyperinflation is a disadvantageous situation, since the loss of the area of apposition and the flattening of the diaphragm, induce less efficiency in their length/tension relationship. In this way, the pressure/volume relationship is unfavorable, and the work of breathing augment (1,2,6,7,9). During exercise, VI means more ventilatory demand and boost dynamic hyperinflation. As this mechanism progresses, the high central neuronal impulse is dissociated with the depressed response of the respiratory musculature, or neuromechanical uncoupling, bringing the patient closer to ventilatory fatigue (2,6,7,9). In association with dynamic hyperinflation, it also reduces venous return, and the capacity of the right ventricle for pulmonary perfusion, enhancing VD/VTphys and VI (3,4,6,7,9).

During an exercise test, the behavior of the VE/VCO_2 slope (*Figure 1*) shows that its lowest level (nadir) corresponds to the optimization of the ventilation/perfusion (V/Q) ratio by alveolar recruitment. After this stage, more VE is required to compensate the increased VCO_2, due to the buffer effect of H_2CO_3 over the rise in lactate. Particularly in COPD, the VE/VCO_2 value at nadir exceeds that of a normal individual, and supposedly it would be magnified in relation to severity, however, this behavior is not directly related (4,10).

In a patient with severe COPD, during exercise, and when hyperinflation and mechanical restrictions do not allow the ventilatory pump to maintain the high demand for VE, the nadir does not overpass that of less severe patients

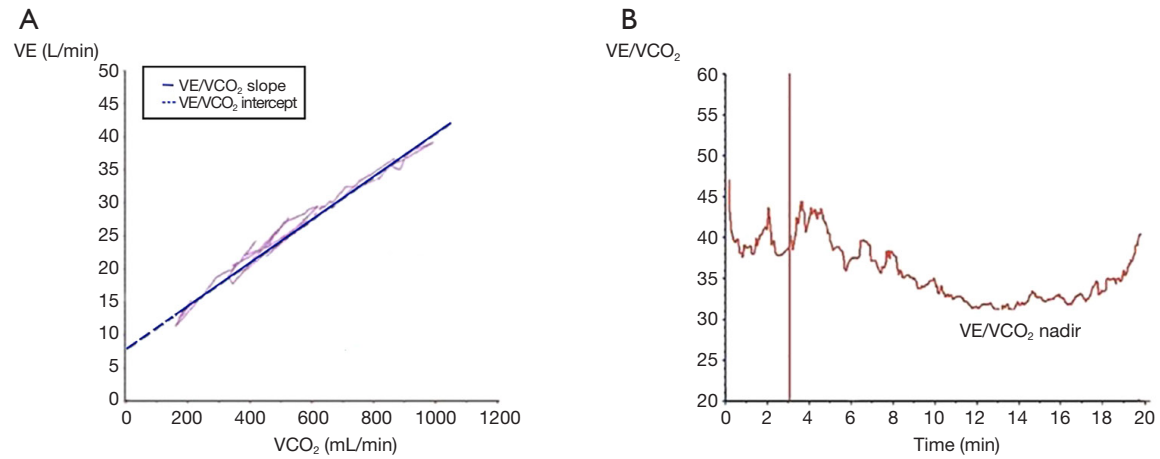

Figure 1 A 55-year-old male with COPD is represented. His FEV1 and DLCO were 47% and 41% of their predicted values. At the end of the exercise, he reached a VO_2max and a Wmax of 60% and 65% of their reference values, his inspiratory capacity decreased by 600 mL, and the VE/VCO_2 measured in the slope was 38. (A) The VE/VCO_2 slope and the VE/VCO_2 intercept are showed. (B) The nadir of the VE/VCO_2 slope is presented. VO_2max, maximal oxygen consumption; Wmax, maximal power; VE, minute volume; VCO_2, CO_2 production; FEV1, forced expiratory volume in 1 second; DLCO, carbon monoxide diffusion capacity.

(1,3,4). Furthermore, it is likely that the PCO_2 set point will also be altered, and the tight control of $PaCO_2$ will be lost. The study of Lin *et al.* (1) provides more information to these concepts, showing that the intercept of the VE/VCO_2 slope (prolongating its linear part to the y-axis) (*Figure 1*), is significantly correlated with static and dynamic hyperinflation. In this context, VE/VCO_2 determinations at the intercept seems to better interpret VI and COPD severity (1,3,4).

The elimination of CO_2, and the efficiency of ventilation, intertwine respiratory and cardiac function. In heart failure, when pulmonary perfusion decline, VD/VTphys, VE/VCO_2 ratio and dyspnea increases, and EC diminish. In some studies, the prognostic value of VO_2 max, or the VE/VCO_2 slope adds valuable information to the left ventricular ejection fraction to discriminate the risk of mortality, left ventricular support, and heart transplantation (13-15). In fact, the American Heart Association and their European counterpart describes 4 levels of severity, according to the grade of VI (16).

The effect of COPD treatments on VI are encouraging and under investigation. As an example, lung volume reduction surgery (LVRS) improves mechanical restrictions and ventilatory efficiency. Armstrong *et al.* compared 55 patients undergoing LVRS with 25 controls from the National Emphysema Treatment Trial, comparing EC at baseline and at 6 months after surgery. They revealed that patients undergoing LVRS improved maximal Oxygen consumption (VO_2max), maximal power, and tidal volume, concomitantly with a decline in the VE/VCO_2 ratio (17). Consequently, studies in lung volume reduction with endobronchial valves are expected. Additionally, by their action in hyperinflation, long acting bronchodilators can attenuate VDphys/VT alterations, and it is assumed that by ameliorating the mechanics of the ventilatory pump, diminish the demand for VE and VI, and delay the pattern of ventilatory fatigue (3,4). It is well known, that the administration of oxygen during exercise, lowers the sympathetic impulse of the respiratory centers, and reduce VE and dyspnea, also suggesting an VI improvement (3,4).

As the authors describe, prognostic studies have been performed with the VE/VCO_2 index as an independent parameter. In a 4-year follow-up of 288 COPD patients, it was demonstrated that the enhanced VE/VCO_2 ratio at nadir, was the only variable related to respiratory and all-cause mortality. When was associated with the inspiratory fraction, its performance as a predictor of mortality grew (4,12). In lung cancer surgery in COPD patients, the increased VE/VCO_2 ratio has exceeded VO_2max, as a predictor of mortality. Shafiek *et al.*, in a 1-year prospective study in 83 patients, showed that the raise in the VE/VCO_2 ratio was associated with 41% of complications and 4% of deaths, overpassing VO_2max as a predictor (18). Torchio *et al.*, in a retrospective study of 145 patients, the 30-day mortality was studied, and

revealed that the elevated VE/VCO_2 slope prior to surgery, was an independent predictor of mortality, even with an acceptable VO_2max for surgery (19).

The conclusions of Lin *et al*. (1) reinforce these concepts, remarking the relevance of the VE/VCO_2 ratio at the intercept. Even more, the importance of the VE/VCO_2 ratio at rest has been described. In a retrospective study of 284 COPD patients, Neder *et al.*, demonstrated that an enhanced VE/VCO_2 ratio at rest, is associated independently, or with hyperinflation, with the magnitude of dyspnea during exercise (20). Considering that many patients with severe COPD are not in a position to carry out a walking test, new studies analyzing determinations of the VE/VCO_2 ratio at lower exercise intensity, or in the intercept, or at rest, are needed to include these parameters, in the evaluation of lung function (1,20,21).

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