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EDITORIAL COMMENT

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Ventilatory efficiency slope: an additional prognosticator after lung cancer surgery

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Although maximum oxygen consumption (VO_2max) is still the most widely used parameter to assess global fitness during cardiopulmonary exercise test, in recent years the importance of evaluating minute ventilation alone or in combination with oxygen consumption (VO_2) or carbon dioxide production (VCO_2) has been emphasized.

The most studied parameter in this regard is the relationship between minute ventilation and carbon dioxide output (VE/VCO_2), also called ventilatory efficiency slope.

It is expressed as the slope of the best-fit linear regression line relating VE and VCO_2. The slope is usually calculated from rest to the anaerobic threshold (AT), a period where the relationship between these two parameters is linear. However, it can be calculated up to the peak exercise. The relationship between VE and VCO_2 from AT to peak exercise is, however, usually non-linear and steeper; therefore, if the slope is estimated at peak exercise, its value is generally higher than at AT.

The rise in VE and VCO_2 is strictly linked during aerobic exercise since increased VCO_2 levels due to the increased metabolism drive ventilation. In healthy individuals, the values of VE/VCO_2 slope are usually lower than 30.

PATHOPHYSIOLOGY OF VE/VCO_2 SLOPE

VE/VCO_2 slope can be increased in both pulmonary and cardiac diseases. Patients with lung disease, for instance, have increased ventilatory requirements for a given level of exercise. The ventilatory requirement is determined among others by the CO_2 output (VCO_2). In other words, they require more ventilation for a given workload, being the VE/VCO_2 a measure of the efficiency of CO_2 elimination. In these patients, the VE/VCO_2 slope can be as high as 50.

In patients with heart failure (HF), the increased VE/VCO_2 slope has a multifaceted origin [1–3].

Perhaps, the most important factor is a reduced cardiac output with a subsequent impact on both left and right circulations. A reduced pulmonary perfusion leads to impaired CO_2 exchange, which in turn, determines an increased VE/VCO_2 relationship, due to the ventilation–perfusion mismatch. In addition, a raised pulmonary vascular pressure caused by reduced left ventricle function is associated with increased VE/VCO_2 slope, indicating that an increased right-sided pressure can also contribute to ventilation–perfusion mismatch. Reports have shown a depressed production of nitric oxide during exercise in HF patients, which blunts the pulmonary vasodilatation response to exercise, contributing to V/Q mismatch [4].

Finally, changes in the sensitivity of central and peripheral chemoreceptors appear to influence the abnormal ventilatory response of HF patients to exercise [5].

VE/VCO_2 AND EARLY OUTCOME AFTER LUNG RESECTION

Numerous studies have shown the association between high VE/VCO_2 slope values and poor prognosis in patients with HF. In this group of patients, a VE/VCO_2 >35 is associated with an increased risk of mortality [6] independent of VO_2max. This parameter has been shown to be superior to VO_2max in stratifying the risk of death in HF patients. One of the most important characteristics, which makes it superior to VO_2max is that it is independent of patient effort and can be measured at sub-maximal workload levels.

Torchio *et al.* [7] were the first to demonstrate an association between an increased VE/VCO_2 slope and mortality after lung resection. They found that the VE/VCO_2 was the only predictor of survival after logistic regression analysis when adopting the cut-off of 34 as used in HF patients.

This finding was subsequently confirmed by Brunelli *et al.* [8]. They analysed 225 patients submitted to anatomical lung resection and found that VE/VCO_2 was the strongest predictor of respiratory complications, whereas VO_2max was not associated with complications in this series. Patients with a VE/VCO_2 slope greater than 35 had an incidence of 22% of respiratory complications, 3-fold higher than in patients with lower VE/VCO_2 slope values. In addition, they showed that patients with a VE/VCO_2 slope greater than 35 had a mortality rate of 7.2% compared with that of 0.6%

of those with a lower value ($P = 0.01$). The association between respiratory complications and VE/VCO_2 was present in patients with VO_2max higher and lower than 15 ml/kg/min and in patients with and without chronic obstructive pulmonary disease (COPD).

VE/VCO_2 SLOPE AND SURVIVAL AFTER LUNG SURGERY

In the study by Shafiek *et al.* in this issue of the journal [9], the authors analysed 55 COPD patients deemed fit for surgery according to the existing guidelines.

The authors found that a VE/VCO_2 slope of >35 was a significant predictor of cardiopulmonary complications and of 1-year survival. In particular, only 30% of patients with a VE/VCO_2 >35 at peak exercise survived 1 year compared with 80% of those with lower values of VE/VCO_2.

This is the first report to link long-term prognosis after lung cancer resection to ventilatory efficiency slope. Unfortunately, it was not clear from the study how many patients died of lung cancer recurrence and how many of non-cancer-related causes during that first year of follow-up.

Certainly, this work is a further confirmation of the prognostic role of this ventilatory ergometric parameter.

Several previous papers have shown an association between non-oncological prognosticator and survival after lung cancer surgery.

Parameters such as carbon monoxide lung diffusion capacity, spirometry, coronary artery disease, exercise tolerance and VO_2max in particular have been associated with long-term survival in early-stage lung cancer patients after curative surgery. Fitness has been associated with both cancer- and non-cancer-related mortality. If the association with non-cancer mortality appears intuitive and explained by the occurrence of late cardiorespiratory complications, the link between cancer progression and poor exercise tolerance or poor functional status has been explained by the ensuing inactivity and deconditioning. Poor physical activity seems, in turn, to be able to modify a series of tumour-related or host-related factors linked to cancer progression (angiogenic factors, metabolic or sex steroid hormones, immune surveillance, production of cytokines and inflammatory markers, oxidative status etc.) [10].

Future studies are needed to better define the role of VE/VCO_2 slope in the preoperative work-up of high-risk lung resection candidates. Perhaps, this parameter can overcome the limitations of the most widely used VO_2max and could eventually be included in updated functional algorithms. In addition, larger scale investigations are warranted to explore the association between ventilatory efficiency slope and long-term survival after lung cancer surgery in different subsets of patients (i.e. elderly, COPD, cardiac comorbidity etc.).

The authors should be commended for having contributed to this still novel field of research.

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