Exercise Ventilation-CO_2 Output Relationship in COPD and Heart Failure: A Tale of Two Abnormalities

Ventilatory gas exchange measurements have been increasingly accepted as an integral part of cardiopulmonary exercise testing by pulmonologists[1-3] and more recently by cardiologists.[4,5] A particularly useful measure is the total ventilation (minute ventilation [$\dot{V}_E$]) versus metabolic CO_2 output ($\dot{V}_{CO_2}$) relationship obtained with incremental exercise from rest to maximal exercise. In healthy subjects, the $\dot{V}_E$-$\dot{V}_{CO_2}$ relationship from rest to moderate exercise is remarkably linear ($y = mx + b$, where m is the slope and b is the y intercept), with P_{aCO_2} and arterial pH being closely regulated homeostatically within narrow limits. For more severe exercise, the relationship becomes curvilinear when $\dot{V}_E$ increases disproportionately with respect to $\dot{V}_{CO_2}$ as lactic acidosis sets in, resulting in hypocapnia.[6] Patients with chronic heart failure also demonstrate a similar biphasic linear-curvilinear $\dot{V}_E$-$\dot{V}_{CO_2}$ relationship but with an earlier onset of lactic acidosis and a lower peak O_2 uptake attained compared with normal depending on the severity of the disease.[4] Remarkably, the $\dot{V}_E$-$\dot{V}_{CO_2}$ relationship in chronic heart failure is significantly steeper than normal in compensation for the increase in alveolar dead-space fraction (dead-space-to-tidal volume ratio) due to ventilation-perfusion mismatching. The augmentation in the slope of the $\dot{V}_E$-$\dot{V}_{CO_2}$ relationship heightens with increasing alveolar dead-space fraction and is an indicator of poor prognosis in these patients.[7]

By contrast, the scenario for patients with COPD is less well defined except that peak O_2 uptake is typically also reduced. Part of the difficulties in delineating the disease-dependent changes in the exercise $\dot{V}_E$-$\dot{V}_{CO_2}$ relationship in COPD is that the latter is a multidimensional disease affecting not only pulmonary gas exchange but also respiratory mechanics to varying degrees, with potential development of expiratory flow limitation and consequent dynamic lung hyperinflation, which may severely limit exercise $\dot{V}_E$.[8] The attendant ventilation-perfusion mismatching in COPD is likely to predispose these patients to an augmented $\dot{V}_E$-$\dot{V}_{CO_2}$ slope as with chronic heart failure. On the other hand, increasing ventilatory limitation during exercise may constrain the patient's ability to augment $\dot{V}_E$ in compensation for the dead-space ventilation. How these contrasting chemical and mechanical factors play out in determining the resultant exercise $\dot{V}_E$-$\dot{V}_{CO_2}$ relationship may vary greatly depending on the severity of the disease. Indeed, although expiratory flow limitation could also occur in chronic heart failure, it is generally less prohibitive than in severe COPD and can be largely circumvented by switching to a rapid and shallow breathing pattern without compromising ventilation.[9] How do patients with COPD defend exercise $\dot{V}_E$ compared with chronic heart failure in the face of increased ventilatory limitation? In this issue of RESPIRATORY CARE, Teopompi et al[10] report that the slopes of the exercise $\dot{V}_E$-$\dot{V}_{CO_2}$ relationship were similar in subjects with COPD and chronic heart failure provided that

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the peak O_2 uptakes in both groups were > 16 mL/kg/min. However, the exercise $\dot{V}_E$-$\dot{V}_{CO_2}$ slope was significantly diminished in COPD compared with chronic heart failure when the peak O_2 uptakes in both groups were < 16 mL/kg/min.[10] Thus, advancing severity of COPD is accompanied by a corresponding rollback of the exercise $\dot{V}_E$-$\dot{V}_{CO_2}$ slope, in contrast to the monotonic increase in slope with increasing severity of chronic heart failure.

The study by Teopompi et al[10] adds to an emerging body of evidence indicating that the exercise $\dot{V}_E$-$\dot{V}_{CO_2}$ slope is augmented in patients with early-stage COPD compared with normal, but this augmentation may reverse as the disease advances.[11] If ultimately validated in a larger population with refined patient stratification, these new data could provide a noninvasive physiologic measure for assessing the severity of COPD that can be more reliably obtained than traditional indexes such as FEV_1/FVC. To this end, several technical issues in analyzing the $\dot{V}_E$-$\dot{V}_{CO_2}$ relationship remain to be resolved. For example, inclusion of the curvilinear section of the $\dot{V}_E$-$\dot{V}_{CO_2}$ relationship in data analysis could result in a slight overestimation of the exercise $\dot{V}_E$-$\dot{V}_{CO_2}$ slope and underestimation of the y intercept, especially for chronic heart failure and with in-

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creasing severity of the diseases, where the curvilinear section of the $\dot{V}_E$-$\dot{V}_{CO_2}$ relationship may be further magnified by a corresponding early onset of lactic acidosis. This discrepancy may account for the small (albeit statistically significant) differences in the y intercept estimates for COPD and chronic heart failure subjects reported by Teopompi et al.[10] On the other hand, the influence of ventilatory limitation on the $\dot{V}_E$-$\dot{V}_{CO_2}$ relationship is likely to be most pronounced at peak exercise, where $\dot{V}_E$ is highest. Therefore, the $\dot{V}_E/\dot{V}_{CO_2}$ ratio at peak exercise could be a more sensitive measure of the severity of expiratory flow limitation in COPD compared with the slope of the linear section of the exercise $\dot{V}_E$-$\dot{V}_{CO_2}$ relationship per se. Indeed, whether the rollback of the $\dot{V}_E$-$\dot{V}_{CO_2}$ slope with advancing COPD is directly correlated to the increasing influence of expiratory flow limitation remains to be verified. These questions await further studies.

As promising as the exercise $\dot{V}_E$-$\dot{V}_{CO_2}$ slope (or $\dot{V}_E/\dot{V}_{CO_2}$ ratio at peak exercise) appears in providing a useful diagnostic/prognostic test for chronic heart failure and COPD, a thorough understanding of the physiologic determinants underlying the varying $\dot{V}_E$-$\dot{V}_{CO_2}$ relationships in health and disease is ultimately necessary before its clinical relevance can be fully established. Two mechanistic implications from the study of Teopompi et al[10] are noteworthy. First, the similarity of the augmented exercise $\dot{V}_E$-$\dot{V}_{CO_2}$ slope exhibited in early-stage chronic heart failure and COPD further underscores the tantalizing possibility that the brain mechanism for ventilatory control in both these subject groups may be endowed with an intrinsic capability of compensating for the wasted dead-space ventilation in maintaining normocapnia. This self-adaptive brain mechanism of controlling $\dot{V}_E$ not only to match $\dot{V}_{CO_2}$ but also to compensate for increases in dead-space-to-tidal volume ratio that add to the burden of pulmonary CO_2 elimination has been likened to the temperature controller's well-acknowledged cognition and perception capability in compensating for the adverse influences of environmental factors (such as humidity and wind-chill factor) on heat transfer from the body that add to the burden of thermoregulation.[12] On the other hand, the dramatic rollback of the exercise $\dot{V}_E$-$\dot{V}_{CO_2}$ slope (with consequent development of CO_2 retention during exercise[8,11]) in severe COPD vis-à-vis its monotonic increase (without CO_2 retention) in severe chronic heart failure once again reminds us of the often-forgotten fact that ventilatory control is strongly influenced by respiratory mechanical constraints rather than being totally reflex-driven, as commonly assumed. Indeed, reflexogenic drives such as peripheral chemoreflex or skeletal muscle metaboreflex per se are unlikely to be the cause of exercise hyperpnea, as interruption of the corresponding afferent pathways affects only the transient but not the steady-state ventilatory response to exercise (reviewed in Reference 12). How does the respiratory controller in the brain integrate information about chemical and mechanical factors that constrain exercise $\dot{V}_E$ in health and in disease? The answer to this critical question may call for a fundamental paradigm shift in viewing the brain mechanism for ventilatory control not as a simplistic knee-jerk reflex driver but as a self-adaptive intelligent controller capable of balancing such chemical and mechanical constraints in determining the optimal $\dot{V}_E$ that meets the metabolic demand without causing excessive work of breathing.[12-16] In this light, patients with chronic heart failure, COPD, and other diseases may actually be much smarter in optimizing their breathing for self-survival than they have been traditionally given credit for in practice.

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