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EDITORIAL COMMENT

Exercise ventilatory inefficiency in heart failure: some fresh news into the roadmap of heart failure with preserved ejection fraction phenotyping

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This article refers to 'Physiological dead space and arterial carbon dioxide contributions to exercise ventilatory inefficiency in patients with reduced or preserved ejection fraction heart failure', by E.H. Van Iterson *et al.*, published in this issue on pages 1675–1685.

A progressive increase in exercise ventilation (VE) is vital to the efficiency of gas exchange and its related abnormalities have been long recognized as a matter of concern in heart failure (HF).[1]

At sea level (normobaric normoxia) VE is regulated by the carbon dioxide production (VCO_2), the dead space to tidal volume ratio (VD/VT), and the CO_2 partial pressure ($PaCO_2$), which are the final bioproduct of muscle activity, waste VE, and chemoreflex regulation, respectively. Accordingly, VE increases during exercise due to the progressive release of CO_2 and their relationship is determined by two sources based on the modified alveolar equation (*Figure 1A*): the increased VE, which is required to overcome a large dead space to maintain a normal $PaCO_2$, and the enhanced neural drive to VE which yields $PaCO_2$ levels below what is normally expected. In healthy individuals, for low to moderate intensity of work, the VE response is tightly regulated by the $PaCO_2$, whereas at higher work intensities, VE is more affected by the amount of VD/VT and by the development of lactic acidosis and H^+ production from anaerobic prevailing metabolism. In its turn, VD/VT is highly dependent on respiratory rate. Thus, VD/VT ratio and $PaCO_2$ are the two reference variables for exploring the pathways involved in a deranged ventilatory response.[2]

The physiological increase in exercise VE during a ramp exercise protocol to maximum is defined by four distinct phases: the first up to the ventilatory threshold, also called the anaerobic threshold; the second between the 1st ventilatory threshold and the respiratory compensation point (2nd ventilatory threshold); the third up to peak exercise. In a few highly performing subjects a fourth phase is observed around peak exercise (*Figure 1B*). The mediators of these phases are VO_2, VCO_2, unbuffered acidosis, and thermal dispersion, respectively. All these factors are, at least in part, under the control of the sympathetic nervous system.

The net result of changes in VE during exercise is defined by the VE/VCO_2 relationship that in normal conditions is characterized by an intercept at 4–5 L and for an approximately 1 L of VCO_2 by 23–25 L/min VE (*Figure 1B*). Overall, VE/VCO_2 reflects VE efficiency, which is similarly described when assessing the ratio at determined points (1st ventilatory threshold or lower ratio) or the slope.[3]

In HF, there are a number of factors that may mutually and negatively interact impairing this relationship during exercise: intrinsic pulmonary vascular[4] and non-vascular disease,[5–7] impaired neural[8] control of VE, and early incurrence of acidosis (*Figure 1C*).[7] Overall, it is now well established that an excessive VE during exercise, i.e. steep VE/VCO_2 slope, is the net result of the deregulated cardiorespiratory reflex control and a manifestation of structural changes in the lung that impair ventilation (*V*)/perfusion (*Q*) matching. In their pioneering report, Wasserman *et al.*[5] showed that in HF with reduced ejection fraction (HFrEF) VE is increased for a given work rate, even double than in normal subjects.

What are the reasons and related interpretations? Again, from a physiological standpoint, it is relevant to define 'hyperpnoea' (increase in VE response at normal $PaCO_2$) compared with 'hyperventilation' (increase in VE at $PaCO_2$ levels below normal). In the former case, VD/VT is the cause of the increased VE for a given VCO_2 while reflex, sympathetic-induced, increase in VE is present, alone or combined with VD/VT increase, in the second case. In HFrEF it has been shown that 8%, 47%, and 45% of VE increase is due to $PaCO_2$, VCO_2, and VD/VT, respectively.[5] This,

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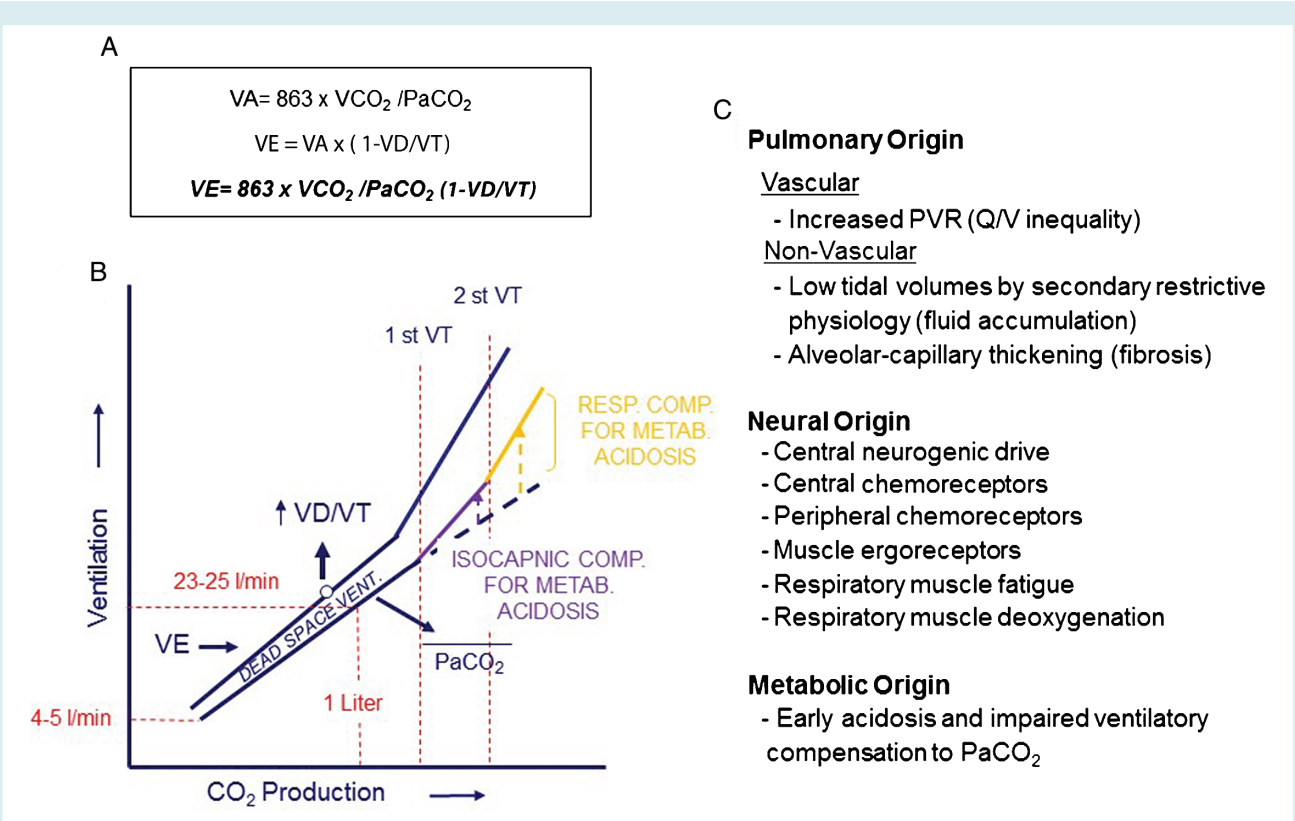

Figure 1 (*A*) The modified alveolar equation and its determinants. (*B*) Description of ventilation vs. carbon dioxide production increase during exercise. Ventilation increments are driven by CO_2 changes in the deoxygenated blood. A difference between alveolar ventilation and effective ventilation increase is mediated by the extent of dead space. After a linear increase in the initial and intermediate phases, a change in slope occurs due to isocapnic compensation for incoming acidosis. At the end of exercise, a further steepening occurs as a result of respiratory compensation. Adapted with permission from *Principles of Exercise Testing and Interpretation*, Wasserman *et al.*,[30] Lippincott Williams & Wilkins ©2011. (*C*) Mechanisms responsible for the increase in ventilation/carbon dioxide production slope during exercise in heart failure. $PaCO_2$, CO_2 partial pressure; PVR, pulmonary vascular resistance; VA, alveolar ventilation; VCO_2, carbon dioxide production; VD, dead space; VE, ventilation; VT, tidal volume.

along with other evidence, has made it axiomatic that HF patients display a sort of mixed response due to either hyperpnoea or hyperventilation.

Ultimately, an increased VE/VCO_2 slope has long been recognized as a major determinant of exercise limitation in HF and one of the most powerful predictors of outcome available.[9] Unequivocal evidence on this parameter has yielded to the formulation of a subdivision of four classes to be used and integrated in a multiparametric process of clinical decision-making.[10–12] Thus, the precise knowledge about what factor disturbs the exercise VE/VCO_2 slope translates into a better potential for treatment.[13]

Of note, most of the findings regarding the pathophysiological and clinical insights on VE/VCO_2 slope have been obtained in a population of HFrEF.[14]

In the present issue of the Journal, Van Iterson *et al.*[15] report an elegant set of observations on the two pathophysiological contributors to impaired VE efficiency during exercise, extending the evidence to HF with preserved ejection fraction (HFpEF) patients. Interestingly, a comparative evaluation of HFrEF vs. HFpEF by cardiopulmonary exercise testing with $PaCO_2$ sampling via radial arterial catheterization showed an impaired VE efficiency in both groups, despite a higher level of VE/VCO_2 slope in HFrEF, and a different pattern in VD/VT and $PaCO_2$.

At rest, HFrEF, compared with HFpEF, displayed an end-tidal CO_2 ($PETCO_2$) significantly lower (for the same respiratory rate), consistent with a tendency toward a lower $PaCO_2$ and a higher VD/VT, which is indicative of more ventilated but not perfused lung areas. The same was observed at peak exercise with the new finding that HFpEF is accompanied by a predominant impairment of VD/VT and a quite normal $PaCO_2$, suggestive, from a physiological point of view, of hyperpnoea. This pattern clearly differentiates HFpEF from HFrEF whose abnormal VE response is also driven by a low $PaCO_2$ and increased chemoreflex activity (hyperventilation).[16–18] The unquestionable strength of the paper is the reliable measurement of VD/VT by incorporating into the formula the invasively obtained $PaCO_2$ and avoiding the underestimation when calculated by $PETCO_2$.[19]

Some considerations are necessary to better highlight the present findings. Is there enough evidence for abnormal VE to play a critical role in HFpEF? How could the differences in VE

determinants be convincingly explained and what are the potential reasons for a prevailing VD/VT-related mechanism in HFpEF?

HFpEF definition applies to a garden-variety of clinical phenotypes. Previous studies have reported lower levels of inefficient VE compared with the present population.[20,21] Nonetheless, the actual population appears to be in a quite peculiar advanced stage of the syndrome as suggested by the high rate (74%) of Weber peak VO_2 class D.

As VD/VT depends on *V*/*Q* mismatch, valid measures of *V*/*Q* matching are helpful for the identification of underlying mechanisms and provide clear implications in terms of interventions. Actually, measures of alveolar gas diffusion would have been of help in this respect. Nonetheless, the authors make a strong argument on the minimal effect that a mild reduction in alveolar gas diffusion (around 20% based on a previous case series) would have on CO_2 transfer even in the presence of a low perfusion, while impacting the alveolar–arterial O_2 difference. Thus, a lung vascular disease, potentially induced by the systemic proinflammatory state[22], may be suspected to play the major role in the present HFpEF population. Very likely, this assertion would have been less speculative in the case of a direct lung *V*/*Q* assessment[23] along with a thorough definition of the underlying pulmonary haemodynamics and right ventricular function to pulmonary circulation coupling.[24]

Considering the different underlying pathophysiology, with a prevailing higher reflex-induced inefficiency of VE in HFrEF as the major reason for exercise hyperventilation and a high VD/VT as the major cause of hyperpnoea in HFpEF, should we start to consider ventilatory abnormalities during exercise a more focused target of therapy and treat them accordingly? Evidence is lacking but some speculation may derive from the observed physiological ventilatory adaptations obtained at high altitude, where hypoxia (and the associated high VE/VCO_2 slope) can be partially corrected by a voluntarily imposed high tidal volume at low VE frequencies.[25] This way of breathing is typical of some relaxing activities such as rosarium, yoga, and listening to music that might overall benefit VE efficiency, at least in HFrEF.[26,27] In HFpEF, the recent greater molecular understanding of endothelial damage and oxidative stress due to the proinflammatory state would imply the concept of a pulmonary microvessel vasculopathy susceptible to benefits by interventions targeting the impaired nitric oxide–cGMP bioavailability pathway by improving the regional lung perfusion and, for instance, the VD/VT pattern during exercise.[28,29]

In conclusion, evidence provided by Van Iterson *et al.*[15] refreshes some knowledge on the ventilatory mediators of exercise intolerance and remarkably enriches the picture, especially prospecting for new insights on patients with HFpEF. Findings support the hypothesis that HFpEF and HFrEF may be two distinct entities also in terms of ventilatory response to physical challenge. The roadmap of HFpEF phenotyping is intriguingly moving forward, hopefully in the right direction.

Conflict of interest: none declared.

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