Possible Mechanism of Augmented Exercise Hyperpnea in Congestive Heart Failure

To the Editor:

Congestive heart failure (CHF) patients demonstrate a significant potentiation of the ventilatory response to muscular exercise under normal PaO₂ and PaCO₂ and normal exercise tolerance, and this important trait has been variously proposed as a predictor of poor prognosis. The augmented exercise hyperpnea is in contrast to the decreased cardiac chaos and blunted baroreflex sensitivity in these patients. In a two-part editorial, Johnson1 emphasizes the remarkable correlation between the increased ventilatory drive and increased pulmonary dead space (Vtd/VVT) in CHF patients, which then leads to an important question: from whence might this increased drive (at normal PaO₂ and PaCO₂) arise? The author argues that this cannot simply stem from an increased chemoreceptor gain, but more likely a decreased chemoreflex threshold (“set point”)—perhaps due to increased sympathetic stimulation or that of skeletal muscle “ergoreceptors”.

Although the validity of these putative mechanisms remains controversial, there are unsettled questions regarding the observed correlation between the augmented exercise hyperpnea and increased Vtd/VVT in CHF. Is such a correlation indicative of causality, or is it fortuitous? How is the change in the apparent chemoreflex threshold linked to an abnormal increase in Vtd/VVT in the lungs? Is such functional correlation unique to CHF or is it suggestive of a general physiological principle?

A body of literature omitted in this1 and all related previous reports may offer some clues to these critical issues. Specifically, a general optimization model of respiratory control2 postulates that ventilatory output is not simply driven reflexively as conventionally presumed—but instead, may be adaptively tuned3 by the brain to minimize a weighted sum of the chemical and mechanical costs of breathing. This model accurately describes the normal ventilatory responses to hypercapnia, hypoxia, and exercise and their interactions, as well as the effects of respiratory mechanical loading and unloading, without invoking putative exercise-specific stimuli, such as ergoreceptor activation. Importantly, this model predicts an increased exercise ventilatory sensitivity under increased Vtd/VVT (with resultant constancy of PaO₂ and PaCO₂), as well as increased ventilatory CO₂ sensitivity—precisely as manifest in CHF patients. These model predictions have been largely confirmed experimentally in healthy subjects exposed to large external dead space.4,5 Thus, the augmented exercise hyperpnea in CHF patients may represent more than a simple prognostic marker: it may shed light on the homeostatic regulation of cardiorespiratory functions and their underlying mechanisms in health and in disease, on which any diagnostic or prognostic procedures should be based.

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Response

I appreciate the interesting questions raised by Dr Poon in his letter. The editorials on which he comments arose from observations that ventilation is abnormally high with respect to CO₂ output during exercise testing of patients with chronic heart failure (CHF) and that the level of increase correlates with prognosis. Because arterial blood gases were not available, it was not clear whether the high exercise ventilation reflects a high alveolar dead space, reduced tidal volume, or increased ventilatory drive. Data from separate studies where arterial blood had been collected indicate that the high ventilation in CHF arises from a combination of increased dead space and increased ventilatory drive, which reduces the PaCO₂ far below normal homeostatic levels in the absence of arterial hypoxemia or acidosis. Dr Poon chastised me for neglecting his own relevant work on ventilatory drive during exercise in my editorial1, and I apologize. Some history may help emphasize the problem, which he addresses.

In 1946, John Gray2 described his multiple factor theory of the chemical control of breathing, which he succinctly stated as follows for subjects with normal lungs at rest:

\[ V_{\text{A}}/V_{\text{AO}} = 0.22[H^+] + 0.262 \text{PaCO}_2 + 105 \times 10^{-0.038 \text{PaO}_2} - 18 \]

where \( V_{\text{AO}} \) is resting alveolar ventilation at normal resting levels of \([H^+]\), PaCO₂, and PaO₂; \( V_{\text{A}} \) is the alveolar ventilation in response to deviations from these levels. Later, Milic-Emile and Tyler3 further showed that chemical feedback was directed primarily at controlling power developed by inspiratory muscles rather than by ventilation per se. A modification of Gray’s equation based on the latter observation effectively describes the ventilatory response to arterial hypoxemia and acid base disturbances at rest even in the presence of altered lung mechanics.4 However, Gray’s equation cannot explain the large increases in ventilation during exercise. Gray argued that reflexes from exercising skeletal muscles must play a major role in mediating exercise response. Dr Poon hypothesizes two interactive feedback signals controlling ventilation: one from chemoreceptors and another from neuromechanical feedback from respiratory muscles sensing ventilatory power requirements.5 Both stimuli augment ventilation: the central controller integrates the responses to tighten homeostatic control of \([H^+]\), PaCO₂, and PaO₂ and at the same time minimizes ventilatory power requirements. His model can effectively explain normal ventilatory response to exercise, added dead space, and acid base derangements but cannot explain the increased ventilatory drive in CHF, lowering PaCO₂ far below normal homeostatic levels. The questions raised in his letter pertaining to this problem are insightful and must be addressed in future studies in an attempt to understand this phenomenon.

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