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DOI: 10.1183/09031936.00165509

From the authors:

Our editorial [1] about the report of WENSEL *et al*. [2] on autonomic nervous system disturbances in severe pulmonary hypertension discussed possible links between sympathetic activation, chemosensitivity, and hyperventilation in (right) heart failure. According to B. Raffestin and M. Leroy, this is too much speculation. They believe that hyperventilation in (right) heart failure is simply explained by an increased dead space, and that the report by WENSEL *et al*. [2] is nothing more than a description of heart rate variability.

The figure illustrating our editorial was not meant to support the notion that plots of ventilatory equivalents for carbon dioxide (V'_E/V'_{CO_2}) *versus* end-tidal carbon dioxide tension (P_{ET,CO_2}) in pulmonary arterial hypertension (PAH) and in congestive heart failure (CHF) demonstrate an increased chemosensitivity in both conditions. Of course arterial carbon dioxide tension (P_{a,CO_2}) instead of P_{ET,CO_2} measurements are needed to prove the point, because an increased physiological dead space increases the gradient between arterial and alveolar (end tidal) carbon dioxide tension. Thus, an increase in V'_E/V'_{CO_2} at a given P_{ET,CO_2} could theoretically be observed in the presence of a normal V'_E/V'_{CO_2} to P_{a,CO_2} relationship. However, as already discussed by JOHNSON [3] some years ago, this is not the case in CHF. The available data in PAH are more limited, but point into the same direction, as summarised in our editorial [1].

Dead space should not be confused with physiological dead space. Dead space is anatomic, with a ventilation/perfusion (V'_A/Q') equal to the infinite. It is measured as a $V'_A/Q' > 100$ by the multiple inert gas elimination technique. Physiological dead space corresponds to abnormally high V'_A/Q', >3.3, and therefore includes anatomic dead space and alveolar dead space. Inert gas elimination studies have shown that dead space is normal or near normal in pulmonary vascular diseases. The same studies have demonstrated that physiological dead space is increased, implying an increase in inefficient or ''wasted'' ventilation. However, wasted ventilation cannot be a cause of hypocapnia. Alkalosis at rest and at exercise in PAH patients is a consequence, not a cause, of hyperventilation.

What is the cause of decreased heart rate variability in severe pulmonary hypertension [1]? Heart rate is indeed predominantly under parasympathetic control in healthy subjects. However, there is strong evidence of increased sympathetic nervous system activity related to an increased heart rate in PAH [4], as well as in CHF [5, 6]. B. Raffestin and M. Leroy point to possible pitfalls of the determination of spontaneous baroreflex function. Alternative techniques rely on the administration of vasoactive substances, which, as they acknowledge, is unsafe in PAH, or the neck chamber technique, although this would only explore carotid baroreflex sensitivity.

We agree that more studies are needed to address the complex relationships between the autonomic nervous system, chemosensitibility and high V'_A/Q' gas exchange in severe pulmonary hypertension and in heart failure. There is a lack of data on ventilatory responses to hyperoxic hypercapnia (central chemoreflex) and isocapnic hypoxia (peripheral chemoreceptors), correlated to ventilatory responses to exercise with V'_E/V'_{CO_2} plotted as a function of P_{a,CO_2}. This is clinically relevant, as out of proportion ventilation in (right) heart failure is a major cause of deteriorated functional state and exercise-induced dyspnoea.

Original papers require conclusions supported by data. Editorials are for clarification of concepts and formulation of new hypothesis, allowing for reasonable speculation and a bit of provocation.

We thank B. Raffestin and M. Leroy for this interesting debate, which we hope will help trigger further exciting research in still largely unexplored areas of heart–lung interaction pathophysiology.

R. Naeije and P. van de Borne
Dept of Cardiology, Erasme University Hospital, Brussels, Belgium.

Correspondence: R. Naeije, Dept of Cardiology and Physiology, Erasme Hospital, Université Libre de Bruxelles, 808 Lennik Road, 1070 Brussels, Belgium. E-mail: rnaeije@ulb.ac.be

Statement of Interest: None declared.

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DOI: 10.1183/09031936.00196709