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EDITORIAL

Clinical relevance of autonomic nervous system disturbances in pulmonary arterial hypertension

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Pulmonary arterial hypertension (PAH) is a rare dyspnoea-fatigue syndrome defined by an isolated increase in pulmonary vascular resistance (PVR) and eventual right ventricular failure [1]. In spite of progress achieved during the last two decades, the condition remains severe, with a median survival limited to 5–6 yrs and persistent functional limitation in approximately half of the survivors [1]. Further improvement is needed, and this involves a better physiopathological understanding of the PAH ''phenotype''.

In the present issue of the *European Respiratory Journal*, WENSEL *et al.* [2] add argument to the notion of PAH as a right heart failure with associated autonomic nervous system disturbances. These authors investigated heart rate variability and baroreflex sensitivity using a spectral analysis of ECG and blood pressure recordings, and correlated the results to aerobic exercise capacity. The spectral power of heart rate variability in their patients was decreased at all frequencies and the baroreflex sensitivity was blunted. These changes were correlated with decreased peak oxygen uptake, very much as previously reported in severe congestive heart failure.

Patients with PAH hyperventilate during exercise, at rest and even during sleep, and this is related to disease severity and survival [3–7]. The cause of hyperventilation in PAH is often assumed to be an increased physiological dead space related to extensive vascular remodelling and obliteration decreasing perfusion with respect to ventilation [4, 6, 7]. However, end-tidal and arterial carbon dioxide tensions (P_{ET,CO_2} and P_{a,CO_2}, respectively) are consistently found to be lower than normal, suggesting an additional component of increased chemosensitivity [3–7]. The respective contributions of physiological dead space and chemosensitivity to hyperventilation in PAH are difficult to assess from reported expired and arterial blood respiratory gases. Studies using the independent multiple inert gas elimination technique have shown that the distribution of ventilation/perfusion (V'_A/Q') relationships in PAH patients is actually close to normal, with a low-to-normal arterial oxygen tension explained by a low mixed venous oxygen tension, a consequence of a low cardiac output, at rest [8, 9] as well as during exercise [10]. A proportion of patients with PAH present with a cardiac right-to-left shunt, which causes more consistent hypoxaemia [9], and also a peripheral chemoreflex-mediated additional increase in ventilation at exercise [11]. However, the recovered inert gas gradients and derived distributions have not been suggestive of an increased physiological dead space, as there was a shift of both ventilation and perfusion modes to higher V'_A/Q' with no disproportionate increase in ventilation, at rest and during exercise [8–10]. The most soluble gases used to derive the distributions of ventilation and perfusion for the high V'_A/Q' relationships are difficult to measure accurately, but quality control including residual sum of squares calculations have been reassuring in these studies. Hyperventilation in PAH is therefore mainly attributable to an increased chemosensitivity.

Hyperventilation at rest and during exercise is also typically observed in congestive heart failure, albeit to a lesser degree than in PAH, and is related to disease severity and prognosis as well [12–14]. The increased ventilatory response to exercise in heart failure has been found to be correlated with autonomic nervous system disturbances, including the central and peripheral chemoreceptor control of ventilation, the ergoreceptor drive to ventilation, and autonomic and baroreflex control of the circulation [14]. However, there has been a report of increased arterial-to-alveolar carbon dioxide tension gradients and preserved P_{a,CO_2} at rest and during exercise in heart failure patients, suggesting that increased physiological dead space accounted for hyperventilation [15]. Only very limited inert gas data have been reported to help enlighten the debate [16]. Opposing points of view could nevertheless be reconciled by a recalculation of peak exercise ventilatory equivalent for carbon dioxide (V'_E/V'_{CO_2}) *versus* arterial P_{a,CO_2} relationships from previously published individual data [17]. The results showed an inverse correlation between V'_E/V'_{CO_2} and P_{a,CO_2}, suggestive of chemosensitivity, but also an upward shift of the relationship to ventilation, suggestive of an increased physiological dead space. It has since been possible to confirm that both increased chemosensitivity and physiological dead space explain the increased ventilation during exercise in heart failure, with, however, a relatively more important impact of chemosensitivity to the measured V'_E/V'_{CO_2} and the prognostic impact of this variable [18].

We revisited our own database and plotted peak exercise V'_E/V'_{CO_2} as a function of P_{ET,CO_2} in 33 patients with PAH, 27 patients with congestive heart failure and 17 healthy controls. Some of these data have previously been reported [19].

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As shown in figure 1, the best adjustment of the data points with the alveolar ventilation equation rearranged as

$$V'E = 863 \times V'CO_2 / PET,CO_2 \times (1\text{-}VD/VT)$$

where $V'E$ is the minute ventilation and $V'CO_2$ is the carbon dioxide production, corresponded to mildly increased dead space volume (VD)/tidal volume (VT) in heart failure and PAH patients. These patients also presented with markedly higher ventilation and lower PET,CO_2, suggestive of a predominant increase in chemosensitivity.

It must be underscored that the building of such a relationship using PET,CO_2 instead of Pa,CO_2 may lead to a considerable underestimation of dead space and consequent overestimation of increased chemosensitivity, although, as already discussed, increased chemosensitivity appears to be dominating both conditions on the basis of previously reported studies. This being said, it might be worth re-exploring these important aspects of PAH and heart failure symptomatology with adequate arterial blood gases and exercise measurements. For those centres still with available ''savoir faire'' of the multiple inert gas elimination technique, it would certainly be worthwhile to re-apply it to heart failure and compare the results with those obtained in similar severity PAH, at rest and during exercise.

Overactive chemoreflexes and ergoreflexes shown to contribute to heightened ventilatory responses are major sympathoexcitatory reflexes. Circulating catecholamines are increased in heart failure, but have been reported variably in PAH [2, 20]. This may not be surprising, as circulating catecholamines are imperfect markers of sympathetic nervous system activity, being affected by a variety of processes including changes in synthesis, metabolism and facilitation of release and reuptake by nerve endings. However, microneurographic recordings in these patients clearly disclose a sympathetic hyperactivity, with an increase in bursts that looks very similar to those previously reported in heart failure (fig. 1b) [20, 21]. Microneurographic bursts in patients with PAH have been correlated to functional class [20], and decreased after an atrial septostomy in spite of expected associated decrease in arterial oxygenation, suggesting a role for right atrial distension (the inverse ''Bainbridge reflex'') [22]. Sympathetic hyperactivity in heart failure has been tentatively explained by increased filling pressures, decreased cardiac output and impaired baroreflex [23, 24]. According to WENSEL *et al.* [2], an impairment of the baroreflex probably adds to cardiac distension to increase sympathetic activity in PAH.

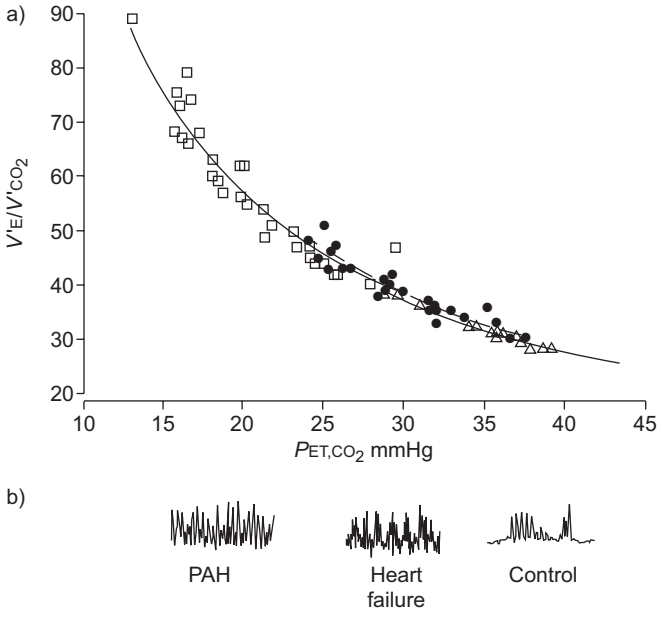

FIGURE 1. a) Peak exercise ventilatory equivalent for carbon dioxide ($V'E/V'CO_2$) as a function of end-tidal carbon dioxide tension (PET,CO_2) in 17 control subjects (△), 27 patients with heart failure (●) and 33 patients with pulmonary arterial hypertension (PAH; □) from previously reported studies [19]. Dead space volume/tidal volume values were 33, 35 and 36%, for controls, heart failure patients and PAH patients, respectively. b) Representative resting muscle sympathetic nerve activity neurograms from previously reported studies [20, 21] are also shown.

Further studies are needed for a better understanding of autonomic nervous system disturbances in PAH. WENSEL *et al.* [2] show that much can be learned from straightforward spectral analysis of short 20-min ECG and blood pressure recordings. Their findings pave the way for further exploration, which would benefit from reinforcement with microneurographic recordings of ventilatory responses to isocapnic hypoxia (peripheral chemoreflex), hyperoxic hypercapnia (central chemoreflex) and muscle ischaemia (metabolic or ergoreflex). Therapeutic implications may emerge, although it would be premature to consider β-blocker therapies. These agents are poorly tolerated in PAH [25], probably because of the critical importance of maintained right ventricular systolic function adaptation to increased afterload [26] overriding possible improvement in systemic neurohumoral desequilibrium in this particular form of right heart failure.

The pathophysiology of PAH remains largely unexplored. WENSEL *et al.* [2] are to be commended for showing us that important steps forward can be achieved through clever use of simple methods and provocative thinking.

STATEMENT OF INTEREST

None declared.

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