Resting V'_E/V'_{CO_2} adds to inspiratory capacity to predict the burden of exertional dyspnoea in COPD

To the Editor:

Exertional dyspnoea is a cardinal symptom of patients with COPD [1]. Incremental cardiopulmonary exercise testing (CPET), in particular, might provide useful mechanistic insights into the genesis of this distressing symptom. More recently, there is growing evidence that ventilatory inefficiency (high ventilation (V'_E)/carbon dioxide output (V'_{CO_2}) nadir) coupled with assessment of operating lung volumes (peak tidal volume (V_T)/dynamic inspiratory capacity (IC_{dyn})) are key to uncover the origins and consequences of exertional dyspnoea in COPD [2].

Unfortunately, however, a sizeable fraction of patients with COPD are either not referred to CPET or, if referred, they are unable (or unwilling) to exercise minimally in order to expose the underlying physiological abnormalities [3]. Indeed, an audit of our hospital and referring physicians indicated that about one-third of dyspnoeic COPD patients are deemed too disabled (due to overwhelming dyspnoea at rest, severe cardiovascular and metabolic comorbidities, extreme obesity, orthopedic/rheumatological issues, severe hypoxaemia and long-term oxygen therapy, among others) to be referred to CPET [3]. Moreover, we found that CPET is not performed in one out of five COPD patients who eventually attended the laboratory (due to the reasons outlined above). This state of affairs indicates that identification of resting variables able to predict exercise ventilatory efficiency and critically high inspiratory constraints is of clinical relevance.

In this context, the most obvious candidates are the same variables used on exercise, *i.e.* V'_E/V'_{CO_2rest} [4] and IC_{rest} [5]. Interestingly, we have observed in several of our previous studies that patients presenting with high V'_E/V'_{CO_2nadir} and higher operating lung volumes on exertion did present, at least based on "mean" data, with high V'_E/V'_{CO_2rest} and IC_{rest} [6–8].These preliminary data ignited our interest in investigating whether the latter variables would indeed be useful predictors of exertional dyspnoea in a large sample of COPD patients with varying disease severity.

We retrospectively analysed data from COPD patients who performed an incremental CPET on a cycle ergometer with serial measurements of IC_{dyn} and exertional dyspnoea (0–10 modified Borg scale) [9] in our laboratory since 2010. Higher dyspnoea burden was defined if the patient reported dyspnoea as the main limiting symptom (alone or in association with leg discomfort) and dyspnoea/work ratio slope was greater than the sample median [2, 10]. Thus, these criteria considered the burden of dyspnoea relative to leg effort in a given subject and its severity comparative to other patients facing a similar challenge (work rate), *i.e.* they provide an index of intra- and inter-subject dyspnoea severity [2, 10]. We included only patients in whom there was no evidence of resting hyperventilation as indicated by a respiratory exchange ratio >0.9 and/or a chaotic breathing pattern (as judged by a gestalt impression of the pattern) during the minute preceding the start of exercise. We did not consider a low end-tidal partial pressure for CO_2 (P_{ETCO_2}) as an exclusion criterion, because this finding might reflect increased areas of high ventilation–perfusion relationship rather than alveolar hyperventilation (low arterial partial pressure of CO_2). In those included, V'_E/V'_{CO_2rest} values were averaged over this time period. We therefore included 284/371 (76.5%) patients (forced expiratory volume in 1 s (FEV_1) ranging from 24% to 107% predicted, aged 44 to 92 years, 178 (62.6%) males). In those excluded, resting hyperventilation was identified in the great majority (71/87, 81.6%) whereas a chaotic breathing pattern was present in isolation in eight subjects (9.7%) and

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associated with hyperventilation in the remaining eight subjects. Based on our previous studies, we *a priori* established the following V'_E/V'_{CO_2nadir} and peak V_T/IC thresholds to define "absent", "mild-moderate" and "severe" ventilatory inefficiency and inspiratory constraints, respectively: <34, 34–44, >44 and <0.7, 0.7–0.9, >0.9 [2, 11, 12].

We found that dyspnoea has a limiting role in 155/284 (54.5%) patients. They presented with worse exercise capacity (and, as expected, high V'_E/V'_{CO_2nadir} and peak V_T/IC_{dyn}; $p<0.05$) than their counterparts who reported only leg discomfort as the limiting symptom (peak work rate 91±37 W *versus* 55±28 W; p<0.001). The areas under the curves (95% confidence interval) obtained from receiver operating characteristics analysis for V'_E/V'_{CO_2rest} against the absence or presence of high V'_E/V'_{CO_2nadir} was 0.859 (0.814 to 0.896) and IC (% predicted) against the absence or presence of inspiratory constraints was 0.886 (0.821 to 0.901). V'_E/V'_{CO_2rest} >44 and >54 (figure 1a) and IC_{rest} <60% predicted and >80% predicted were the best cut-offs associated with "mild-moderate" and "severe" exertional ventilatory inefficiency or inspiratory constraints, respectively (p<0.001 for all). All but 19 patients with V'_E/V'_{CO_2rest} >54 (85/104, 81.7%) had a higher burden of dyspnoea; conversely, 65/77 (84.4%) patients with V'_E/V'_{CO_2rest} <44 have a lower burden (p<0.001) (figure 1a).

Higher dyspnoea burden was found in 37/45 (82.3%) with IC_{rest}<60% (quadrants 1, 2 and 3 in figure 1b) (positive likelihood ratio 4.36 (95% CI 2.10–9.04) and positive predictive value 82.4% (95% CI 69.2–90.6%)). The correspondent values for V'_E/V'_{CO_2rest} >54 (quadrants 1, 4 and 7 in figure 1b) were: 4.16 (95% CI 2.67–6.47) and 81.7% (95% CI 74.1–87.4%), respectively. It follows that IC_{rest} <60% and/or V'_E/V'_{CO_2rest} >54 (quadrants 1, 2, 3, 4 and 7 in figure 1b) had high positive predictive value (80.3%, 95% CI 72.6–84.7%) but only moderate negative predictive value (68.3%, 95% CI 63.1–72.9%) to identify those with higher dyspnoea burden. Conversely, IC_{rest} >80% and/or V'_E/V'_{CO_2rest} <54 (quadrants 9 and 8 in figure 1b) had high negative predictive value (80.4%, 95% CI 66.5–89.5%) to rule out a higher dyspnoea burden (p<0.001 for all analyses). Interestingly, a *post hoc* analysis revealed that, regardless of FEV_1, transfer factor (T_{LCO}) <3 z-scores [13] identified 20/25 (80%) patients with preserved IC_{rest} and V'_E/V'_{CO_2rest} between 44 and 54 (quadrant 8 in figure 1b) (p<0.01 for all analysis).

This is the first study to investigate whether resting markers of excessive ventilation to metabolic demand and/or reduced room for V_T expansion are useful to identify which patients with COPD are more likely to be physically limited by exertional dyspnoea. Overall, whereas severely reduced IC_{rest} (<60%) and/or severely-increased V'_E/V'_{CO_2rest} (>54) were predictive of a higher dyspnoea burden, preserved IC_{rest} (>80%), provided that V'_E/V'_{CO_2rest} was <54, was useful to rule out this finding. These variables should be used in conjunction: whereas a high V'_E/V'_{CO_2rest} predicts heightened ventilatory demands (*i.e.* "how much" V'_E), a low IC_{rest} foresees "how well" (*vis-à-vis* lung mechanics) a given V'_E is obtained on exercise [14, 15]. Further information can be obtained when T_{LCO} (likely reflecting the adding value of impaired gas exchange efficiency) [16] is at least moderately reduced in patients with preserved IC_{rest} but intermediate V'_E/V'_{CO_2rest} (figure 1b).

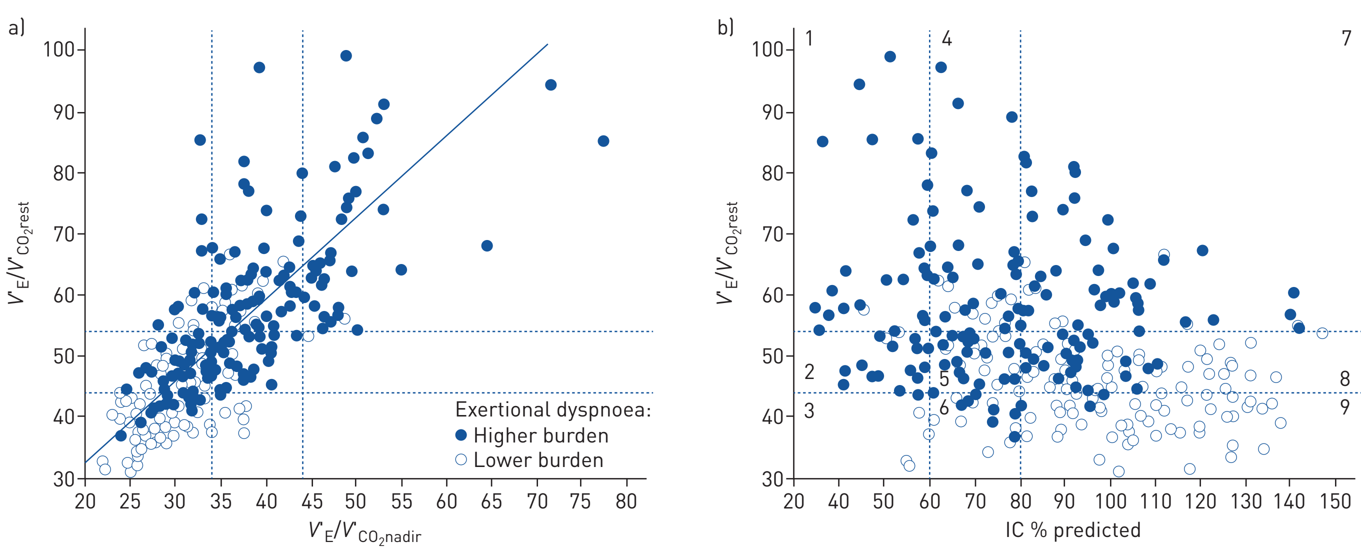

FIGURE 1 Relationship between ventilation (V'_E)/carbon dioxide output (V'_{CO_2}) ratio during incremental exercise: a) lowest value (nadir) and at rest and b) between resting inspiratory capacity (IC) and V'_E/V'_{CO_2rest} in COPD with higher and lower burden of exertional dyspnoea. Dashed lines indicate cut-offs of severity. Letters in (b) indicate specific quadrants (further elaboration in the text).

From a technical standpoint, it is crucial to assure stable V'_E/V'_{CO_2rest}, the absence of hyperventilation and an irregular breathing pattern before exercise. Due to the retrospective nature of this study (*i.e.* V'_E/V'_{CO_2rest} was not a variable deemed relevant at the time of testing), about one-quarter of the readings did not meet these quality criteria. In practice, better results can be obtained if V'_E/V'_{CO_2rest} is averaged over longer periods of time, the patient is familiarised with the setting (including the use of a mask instead of a mouthpiece) and he/she remains seated on a chair (instead of the cycle ergometer seat). Additional studies are required to optimise the protocol to record V'_E/V'_{CO_2rest}.

What are the clinical scenarios in which V'_E/V'_{CO_2rest} plus IC_{rest} might prove to be clinically useful? First of all, it is noteworthy that we are not proposing that resting measurements should "substitute" CPET. Whenever feasible and safe, CPET must be performed as it provides a plethora of clinically useful and mechanistic information on the determinants of exercise intolerance. Exertional dyspnoea is an important outcome in patients with COPD, regardless of the underlying mechanisms [17, 18]. Many patients report poor exercise tolerance, but whether this is indeed secondary to physiological abnormalities, rather than deconditioning, anxiety or patients' over-estimation of their physical limitation, remains frequently unclear in practice [19]. The variables herein reported allows the examiner to estimate the physiological challenges and their perceptual consequences had the patients been able to perform CPET. This approach might also prove valuable in other patient populations in which ventilatory inefficiency and/or inspiratory constraints have been relevant to explain exertional dyspnoea (*e.g.* pulmonary hypertension, heart failure, interstitial lung disease) [20].

In conclusion, we showed, for the first time, that a novel variable (V'_E/V'_{CO_2rest}) adds important information to IC_{rest} in predicting the severity of exertional dyspnoea. Although these resting variables are not deemed to replace CPET in the investigation of the mechanisms and consequences of exertional dyspnoea, our data indicate that useful clinical and physiological can still be obtained from "metabolic carts" in patients unable to safely exercise.

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