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Early View

Research letter

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Ventilatory demand-capacity imbalance during incremental exercise in COPD: An in-silico perspective

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Dear Editor,

Exercise intolerance constitutes a key patient-oriented outcome in chronic obstructive pulmonary disease (COPD).[1] There is mounting evidence that the so-called "ventilatory inefficiency" (as established by the linear ventilation ($\dot{V}E$)-CO_2 output ($\dot{V}CO_2$) relationship during incremental cardiopulmonary exercise testing (CPET)) [2] has an important role in setting the limits of exercise tolerance in this disease. [3] The rationale is straightforward: the faster $\dot{V}E$ increases (i.e., the steeper the $\dot{V}E$-$\dot{V}CO_2$ slope), and the higher its resting value (~ y-intercept), [2] the shorter $\dot{V}E$ is expected to reach a lower compared to a higher maximum breathing capacity (MBC). [4] Recognizing that $\dot{V}E$ close to MBC cannot be sustained for a prolonged period of time without intolerable dyspnea,[5] it can be hypothesized that peak work rate (WR) would change inversely with $\dot{V}E$-$\dot{V}CO_2$ slope and intercept but directly with MBC. Since the first two parameters are influenced by the fraction of $\dot{V}E$ "wasted" in the physiological dead space and the "set-point" for the arterial partial

pressure for CO_2 ($PaCO_2$) [2] whereas MBC is linked to the resting ventilatory capacity [6], it is not surprising that the exertional ventilatory demand-capacity relationship varies markedly among patients with COPD.[7]

Understanding the complex interplay between exertional demand ($\dot{V}E$) and capacity (MBC) in vivo, however, is not a trivial task as several confounders are likely to obscure (or distort) the underlying relationship. For instance, the "qualitative" features of the $\dot{V}E$ response (breathing pattern, operating lung volumes, inspiratory constraints) are also key to exercise limitation, being highly variable at a given $\dot{V}E$ and MBC.[7] The $\dot{V}E$ response may also be curtailed by precocious exercise termination due to symptoms other than dyspnea, such as heightened leg discomfort.[8] Additional sources of $\dot{V}E$ stimuli (e.g., early lactic acidosis, hypoxemia, increased cortical discharge secondary to anxiety) [2] are also common. Considering that an animal study is unlikely to have external validity in this scenario, we reasoned that an in-silico approach would be helpful to shed new light on this conundrum without multiple concomitant confounders.

In order to develop a modelling strategy with biological plausibility, we reviewed our CPET database with 612 patients with mild to end-stage COPD (FEV_1 ranging from 104% to 18% predicted; lung transfer factor for carbon monoxide (TL_{CO}) ranging from 88% to 31% predicted). We identified the most frequent $\dot{V}E$-$\dot{V}CO_2$ slopes which were rounded to multiples of 5: 25 L/min (N= 73), 30 L/L (N= 253), 35 L/L (N= 144), 40 L/L (N= 62), 45 L/L (N= 49) and 50 L/L (N= 31). The estimated (FEV_1 x 40) MBC was rounded to 40 L/min in those with FEV_1 up to 1 L (typically Global Initiative for Chronic Obstructive Lung Disease (GOLD) [1]

category III-IV; N= 216), 60 L/min in those with FEV_1 above 1 L up to 1.5 L (typically GOLD II; N= 273) and 80 L/min in those with FEV_1 above 1.5 L (GOLD I; N= 123). We considered 10 L/min as a representative value of those showing a "high" y-intercept (above 5 L/min; N = 381) and 5 L/min in those showing a "low" y-intercept (up to 5 L/min; N= 231). We then calculated the expected $\dot{V}CO_2$ at $\dot{V}E/MBC= 1$, i.e., the point of ventilatory limitation from a "quantitative" perspective.[6] The work rate (W) at that specific point was calculated based on a $\dot{V}CO_2$-WR slope of 9 mL/min/W starting from unloaded $\dot{V}CO_2$ of 0.4 L/min.

In keeping with our hypothesis, the steeper the slope, the higher the intercept and the lower the MBC, the quicker $\dot{V}E$ reached MBC; accordingly, estimated peak WR varied negatively with the $\dot{V}E$-$\dot{V}CO_2$ parameters but positively with MBC (***Figure 1***, ***left panels***). The effect of $\dot{V}E$-$\dot{V}CO_2$ was large: for instance, a "patient" with only mild disease (MBC_1), but a particularly steep slope (50 L/L), showed a peak WR similar to that observed in moderate (MBC_2) and severe (MBC_3) "patients" provided their slopes were 40 L/L and 25 L/L, respectively (***Figure 1***, ***left upper*** and ***left lower panels*** for 5 L/min and 10 L/min intercepts, respectively). At a given MBC (***Figure 1***, ***right panels***), we observed that, regardless of the intercept, peak WR decreased non-linearly as the slope increased. All curves were well fitted by a two-parameters, quadratic hyperbola ($r^2 \sim 1$, $P<0.0001$; regression equations showed in ***Figure 1***, ***right panels***). Of note, the curvature constant increased significantly from MBC_3 to MBC_1, i.e., less severe "patients" showed a larger variability on peak WR as the slope increased ($P<0.05$ by two-way analysis of variance) (***Figure 1***, ***right panels***). In keeping with what it would be expected from parallel hyperbolas with progressively

higher asymptotes (i.e. MBC_1>MBC_2>MBC_3) (P<0.05), relative (%) decrease in peak WR from MBC_1 to MBC_2 and MBC_2 to MBC_3 at a given slope remained unaltered (being. of course, larger in the latter scenario due to the lower absolute WRs in more severe "patients") (***Figure 1***, ***right panels***).

How to apply our findings to the real world? Firstly, we provided objective evidence that, in the absence of confounders, ventilatory inefficiency has a major effect on the rate at which $\dot{V}_E$ reaches its theoretical "ceiling" during incremental exercise. It should be emphasized that a high $\dot{V}_E$-$\dot{V}CO_2$ is translated into worsening exertional dyspnea, being frequently associated with a low T_{LCO}, higher "wasted" ventilation in the dead space and more extensive emphysema.[3] [9]-[11] There is, therefore, a sound physiological rationale to explain the clinical importance of ventilatory inefficiency in COPD. Secondly, major inter-subject differences in absolute peak WR (W) can be expected from relatively modest variations in the $\dot{V}_E$-$\dot{V}CO_2$ slope and, secondarily, in the intercept. This is even truer the milder the patient, i.e., the higher the MBC (**Figure 1**, ***left panels***). These results might help explaining our previous findings that the ventilatory inefficiency explains a larger fraction of peak WR in mild-moderate than severe-to-very severe COPD.[10] These assertions should be tempered with our previous findings that whereas the slope *increases* from age-matched controls to mild-moderate COPD, it *decreases* in more severe patients as the mechanical constraint progresses. [11] Even considering this important caveat, we previously found that speeding the rate of increase in $\dot{V}_E$ by accelerating $\dot{V}CO_2$ (induced by progressively higher constant WRs) led to a hyperbolic decrease in the time to ventilatory limitation in severe COPD.[5] Similar

considerations were made (on a theoretical basis) by Whipp and Ward as pertaining to the effects of interventions.[12] The corollary is that a lower slope may reflect different phenomena depending on the relative contribution of a low drive (beneficial) versus critical mechanical constraints (deleterious). [7] Thirdly, the major impact of steeper slopes in peak WR is a refreshing call for the key importance of addressing COPD co-morbidities known to heighten exertional $\dot{V}_E$, e.g., pulmonary hypertension, [13] lung fibrosis [14], and heart failure [15]. Finally, despite the fact that no intervention (apart from O_2 supplementation in hypoxemic patients) [3] has so far consistently decreased the $\dot{V}_E$-$\dot{V}CO_2$ slope (or the intercept) in COPD, our results show that this remains an important unmet need to improve patients' exercise tolerance.

As expected from a modelling study with limited degrees of freedom, our study has some limitations. Would the combination of different slopes and intercepts [10] provide a different picture? We firstly looked at the pattern of responses in a large population; thus, model parameters do hold external validity. As mentioned, we did not take into consideration a plethora of other factors affecting the time course of $\dot{V}_E$ during incremental exercise. [4] However, we contend that this is exactly the key advantage of an in-silico study since the fundamental relationship of interest ($\dot{V}_E$-$\dot{V}CO_2$-to-MBC) can be relatively "isolated" from its confounders. The estimated MBC is a crude index of the ventilatory "ceiling", overestimating and underestimating the expected peak $\dot{V}_E$ in milder and severe patients, respectively.[4]

Under the inherent limitations of an in-silico study, we herein provided novel evidence that the $\dot{V}_E$-$\dot{V}CO_2$ relationship during incremental exercise may have a

major impact on peak WR across the range of potential MBCs (COPD "severity"). Considering our limited potential to effectively improve patients' ventilatory capacity (↑MBC), fighting the determinants of a heightened ventilatory demand (↓$\dot{V}_E$-$\dot{V}CO_2$) assumes foremost relevance to mitigate the devastating effects of exercise intolerance in this patient population.

Acknowledgements: *This piece of work is dedicated to the memory of Prof. Brian J Whipp (1937–2011), a pioneer and enthusiast of the concept of ventilatory in(efficiency) as applied to cardiopulmonary diseases.*

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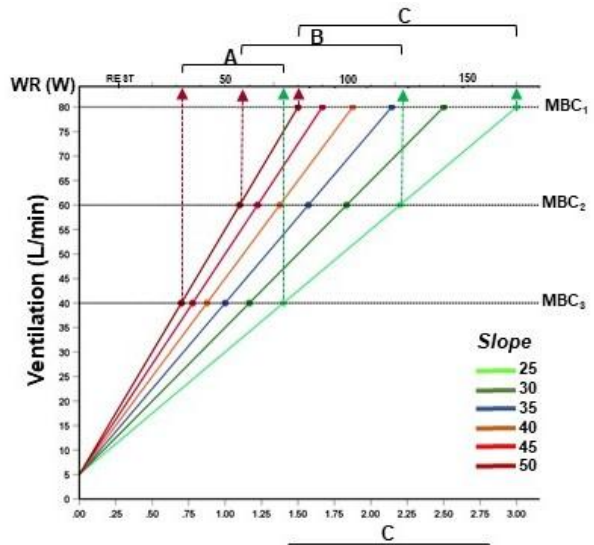
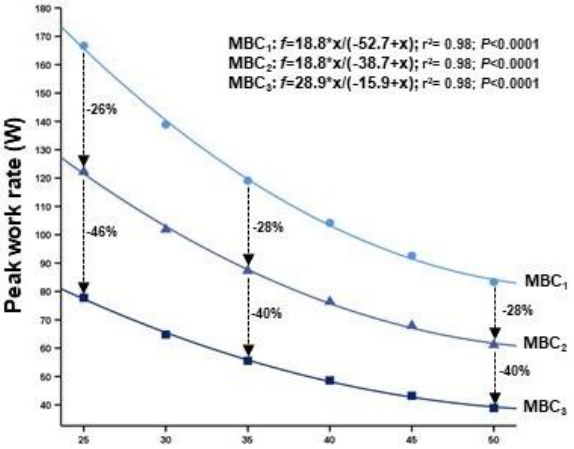
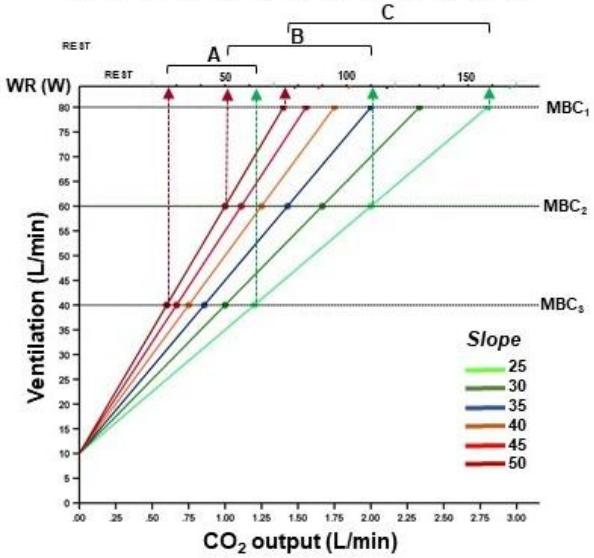
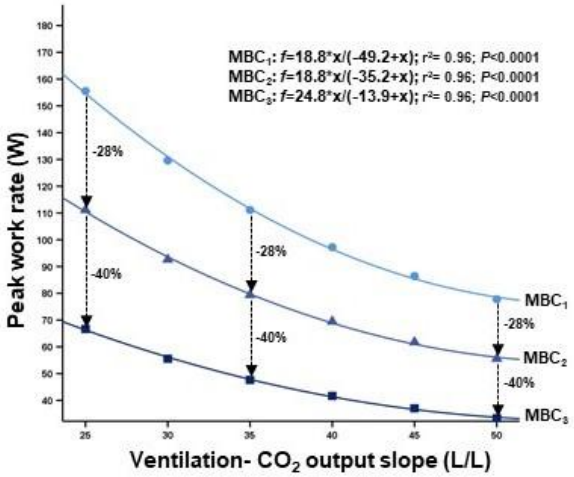
Figure Legend

Figure 1. Modelled exertional ventilation as a function of carbon dioxide (CO_2) output and work rate (WR) (*x* and *z* axis, respectively) (*left panels*) in hypothetical COPD patients presenting with progressively higher ventilation-CO_2 output slopes. Peak WR corresponds to the point at which ventilation reached different maximal breathing capacities (MBC_1-MBC_3). "A", "B" and "C" indicate differences in peak WR between patients showing the highest and the lowest slopes at progressively higher MBCs, respectively. The *right panels* show peak WR as a function of the slopes at a given MBC. Data calculated assuming y-intercepts of 5 L/min and 10 L/min, respectively (*upper* and *lower* panels). See text for elaboration.


C
B
A
WR (W)
REST
50
100
150
MBC1
MBC2
MBC3
Ventilation (L/min)
Slope
25
30
35
40
45
50


MBC1: f=18.8*x/(-52.7+x); r²= 0.98; P<0.0001
MBC2: f=18.8*x/(-38.7+x); r²= 0.98; P<0.0001
MBC3: f=28.9*x/(-15.9+x); r²= 0.98; P<0.0001
-26%
-46%
-28%
-40%
-28%
-40%
MBC1
MBC2
MBC3
Peak work rate (W)


C
B
A
REST
WR (W)
50
100
150
MBC1
MBC2
MBC3
Ventilation (L/min)
Slope
25
30
35
40
45
50
CO2 output (L/min)


MBC1: f=18.8*x/(-49.2+x); r²= 0.96; P<0.0001
MBC2: f=18.8*x/(-35.2+x); r²= 0.96; P<0.0001
MBC3: f=24.8*x/(-13.9+x); r²= 0.96; P<0.0001
-28%
-40%
-28%
-40%
-28%
-40%
MBC1
MBC2
MBC3
Peak work rate (W)
Ventilation- CO2 output slope (L/L)