Correspondence regarding "Ventilatory efficiency in athletes, asthma and obesity": different ventilatory phenotypes during exercise in obesity?

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To the Editor:

COLLINS *et al.* [1] discussed the pathophysiological mechanisms and clinical relevance of ventilatory efficiency in athletes, asthma and obesity in their interesting review article entitled "Ventilatory efficiency in athletes, asthma and obesity". Patients with obesity can display an altered ventilatory response to exercise, which may contribute to functional limitations in this population. We aim to provide a supplementary contribution to the clinical evaluation and pathophysiological interpretation of the ventilatory response to exercise in patients with obesity. This contribution resulted from two papers recently published by our research group.

COLLINS *et al.* [1] described how patients with obesity have higher ventilation at rest and any given work rate due to increased metabolic costs and work of breathing. Reduced chest wall compliance leads to a shallow breathing pattern, which, however, does not seem to significantly affect the ventilatory efficiency of patients, commonly measured by minute ventilation relative to carbon dioxide production (V'_E/V'_{CO_2}), at submaximal exercise intensities [1]. Nonetheless, related scientific knowledge is less clear for severe and morbid obesity patients, particularly at elevated exercise intensities. Indeed, inadequate compensatory hyperventilation at maximal physical exertion has been described due to mechanical ventilatory constraints [2]. The V'_E/V'_{CO_2} at peak exercise has thus been proposed as a clinical marker to evaluate the respiratory response to exercise, since it can provide important information regarding the underlying mechanisms of exercise intolerance [1].

In our recently published paper, entitled "Ventilatory response at rest and during maximal exercise testing in patients with severe obesity before and after sleeve gastrectomy", 46 patients with severe obesity (mean body mass index (BMI) 43.59±5.30 $kg \cdot m^{-2}$) were evaluated 1 month before and 6 months after sleeve gastrectomy. Ventilatory response and efficiency were analysed by incremental, maximal cardiopulmonary exercise testing on a treadmill [3]. It has been shown that patients affected by severe obesity have a shallow breathing pattern but a resulting ventilatory efficiency (*i.e.* V'_E/V'_{CO_2} slope) within the normal range of predicted [3, 4]. Interestingly, after surgery and significant weight loss (BMI 32.27±4.84 $kg \cdot m^{-2}$), reduced ventilation at rest, during submaximal and maximal exercise was revealed by data and an improvement of breathing pattern and V'_E/V'_{CO_2} slope. This might be a suggestion that a significant weight loss can increase ventilatory efficiency, likely because of adaptations in ventilatory mechanics and constraints. A less shallow breathing pattern, enhanced lung expansion and the associated relatively lower dead space ventilation could indeed lead to increased alveolar ventilation and better ventilatory efficiency. These adaptations led to an increased breathing reserve and thus less ventilatory limitation at peak exercise in patients who demonstrated improved exercise capacity and tolerance [3].

Although the pathophysiological adaptations to physical exercise are positively affected by weight loss and fewer mechanical ventilatory constraints, the mechanisms related to the ventilatory response at maximal exercise intensities are still poorly investigated. Only a few studies have specifically addressed this issue in obesity without considering the possible impact of other frequently associated comorbidities [5–8].

Shareable abstract (@ERSpublications)
Patients with obesity may have different ventilatory phenotypes during exercise related to an interaction of expiratory flow limitation, mechanical constraints and adaptations of chemoreception and metabolic setpoints. https://bit.ly/3JBs86S

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Currently, it is suggested by scientific evidence that patients with severe and/or morbid obesity have a blunted ventilatory response during exercise. This condition occurs particularly at vigorous intensities, which has also been associated with exercise intolerance [1, 9, 10]. Expiratory flow limitation and mechanical ventilatory constraint due to fat mass surrounding the chest wall and diaphragm have been discussed as major determining factors [1, 2]. However, the ventilatory response could also be affected by pathophysiological adaptations during exercise, which may depend on chemoreception and metabolic setpoints. Indeed, increased V'_E/V'_{CO_2} at peak exercise was associated with reduced arterial carbon dioxide tension (P_{aCO_2}) and/or end-tidal carbon dioxide tension (P_{ETCO_2}) after bariatric surgery [5, 6]. Although this metabolic adaptation to resting P_{ETCO_2} has been confirmed in our study after sleeve gastrectomy, we would like to emphasise that a significant decrease in the submaximal V'_E/V'_{CO_2} slope has been shown [3]. This improvement in submaximal ventilatory efficiency is a suggestion that the V'_E/V'_{CO_2} slope can also provide important information in the follow-up of subjects undergoing bariatric surgery, which is not in contrast with the previously described increase of V'_E/V'_{CO_2} at peak exercise. The latter could reflect an improved ability to respond to metabolic demands at the highest exercise intensities with adequate compensatory alveolar hyperventilation.

In their review, Collins *et al.* [1] described a divergent ventilatory response at maximal exercise in patients with morbid obesity with inadequate compensatory hyperventilation. Moreover, it is known that P_{aCO_2}/P_{ETCO_2} and ventilatory response can be affected not only by obesity but also obstructive sleep apnoea syndrome (OSA), a frequent obesity-related comorbidity. Our group has recently published a study entitled "Cardiopulmonary exercise testing in patients with moderate-severe obesity: a clinical evaluation tool for OSA?". In this study, we evaluated 147 patients with severe obesity (mean BMI 45.34±6.70 $kg \cdot m^{-2}$) with a cardiorespiratory sleep study and maximal cardiopulmonary exercise testing [9]. To the best of our knowledge, this was the most extensive single study reporting cardiopulmonary exercise testing parameters in patients with obesity affected by OSA. With these results, we provided further evidence for the added value of functional evaluations in the clinical management of these patients. According to the outcomes of the study, we revealed that patients affected by morbid obesity and OSA had reduced aerobic capacity, exercise tolerance and ventilatory response with an associated higher P_{ETCO_2} at peak exercise compared with controls affected by obesity without OSA. Moreover, patients with OSA did not sufficiently increase their ventilation beyond the respiratory compensation point, leading to a flattened decrease of P_{ETCO_2}. Interestingly, these distinctive ventilatory response and efficiency patterns were positively affected by nasal continuous positive airway pressure (CPAP) treatment during sleeping hours in patients with OSA [9, 11]. It can be hypothesised that an adaptation of central chemoreception and metabolic setpoints that affect ventilatory drive and response during exercise may be caused by chronic carbon dioxide retention and/or intermittent hypoxia in patients with OSA.

Finally, it can be stated that the mechanisms underlying the inadequate ventilatory response in patients with morbid obesity are not fully understood. In addition to the mechanical ventilatory constraints, chronic carbon dioxide retention due to sleep apnoea may also contribute to metabolic set point adaptation, affecting ventilatory drive, particularly at elevated exercise intensities [12].

We agree with the proposal by Collins *et al.* [1] to implement V'_E/V'_{CO_2} at peak exercise as a useful clinical marker when evaluating these patients. Nonetheless, the behaviour of the P_{ETCO_2} at intensities beyond the respiratory compensation point should also be considered in the interpretation of this metric. Indeed, ΔP_{ETCO_2} max−peak, the difference between the maximum P_{ETCO_2} value reached during testing and P_{ETCO_2} at peak exercise, has been suggested as an objective and reproducible predictor of OSA in patients with morbid obesity. This metric could be helpful for clinically evaluating ventilatory and functional limitations to exercise [9]. Indeed, we proposed that ΔP_{ETCO_2} max−peak might be of interest for clinical decision making. A cut-off value of <2 mmHg may be helpful for physicians to screen patients for OSA and check treatment efficacy after CPAP application.

In conclusion, different ventilatory phenotypes may exist among patients with obesity, as suggested by the current evidence. Such different phenotypes would be predominately determined by an interaction of expiratory flow limitation, mechanical ventilatory constraints, adaptations of chemoreception and metabolic setpoints, leading to different ventilatory responses to exercise. In future trials, this issue should be addressed explicitly in different standardised subpopulations of obese individuals, considering comorbidities and investigating the ventilatory drive and associated pathophysiological adaptations at peak exercise intensity.

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