

The major limitation to exercise performance in COPD is inadequate energy supply to the respiratory and locomotor muscles vs. lower limb muscle dysfunction vs. dynamic hyperinflation. Missing pieces.

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Commentaries on Point:Counterpoint: The major limitation to exercise performance in COPD is inadequate energy supply to the respiratory and locomotor muscles vs. lower limb muscle dysfunction vs. dynamic hyperinflation

COMMENT ON POINT:COUNTERPOINT

TO THE EDITOR: Two comments.

1) It is extremely unlikely that all patients with COPD have the same major limitation (1, 2, 4).

2) As regards the three choices, I would choose none of the above. I do not understand the term dynamic hyperinflation. Hyperinflation refers to a large lung volume that is a static not dynamic measurement. A major limitation to exercise performance in COPD is the inability of the patient to increase his ventilation. The basic mechanism for this is dynamic compression of the airways. This may lead to hyperinflation but the fundamental problem is that any increase in expiratory flow rate is impossible because the flow is independent of effort (3). Incidentally this year is the 50th anniversary of this landmark paper.

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THE REAL CAUSE OF EXERCISE LIMITATION IN COPD

TO THE EDITOR: The *ménage à trois* on exercise limitation in COPD (1, 3, 4) misses the point: limitation is not ascribable to any single structural or functional abnormality, in health or in disease. Exercise depends on an in-series system wherein ventilation, gas exchange, blood flow, hemoglobin, muscle O₂/CO₂ transport and O₂ utilization/CO₂ production all contribute (6). Thus, having three articles each claiming that their mechanism rules unfortunately deemphasizes this fundamental concept. However, certain steps in O₂/CO₂ transport may differently influence exercise in COPD versus health.

Debigaré and Maltais claim muscle dysfunction, but when one COPD leg is exercised alone, peak muscle $\dot{V}O_2$ is normal, whereas in the same patient, it is reduced during cycling (5). This does not necessarily mean muscles function normally, nor that muscle training is pointless (2). But it does show that the muscles contribute little to limit whole body exercise in COPD.

Aren't the major contributors to exercise limitation in COPD mechanical derangements reducing maximal ventilation? Emphysema reduces airway radial traction and increases compliance, increasing dynamic compression. Chronic bronchitis ag-

gravates this, increasing airway resistance by secretions, bronchomotor tone, and thickened airway walls. Tidal volume and thus ventilation are limited, hyperinflation and early dyspnea ensue, and exercise therefore stops early—well before the heart (absent overt heart failure) and muscles have reached functional limits.

O'Donnell and Webb come closest, but dynamic hyperinflation seems not to be the root cause. It is a consequence of the root cause: structural abnormalities causing mechanical derangements (that limit maximal ventilation).

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INTERPRETATION OF EXERCISE INTOLERANCE IN COPD REQUIRES AN INTEGRATED, MULTISYSTEMIC APPROACH

TO THE EDITOR: The notion that exercise intolerance in COPD is a multifactorial construct can be appreciated from a circum-spect analysis of the points raised by the authors (1, 4, 5). Unfortunately, the issue is further complicated by the intervening effects of comorbidities on individual patients, which can differently impact on physical impairment in specific disease phenotypes. Much of the ongoing controversy may also stem from inadequate patient comparisons as any of the discussed pathophysiological mechanisms can dominate the scene on a given moment in the natural history of COPD. Moreover, different conclusions can be drawn from distinct testing paradigms and modalities (e.g., maximum incremental vs. high-intensity constant work rate or cycling vs. walking).

The highest sustainable exercise work rate (“critical power”), for instance, has been associated with the rate of development of ventilatory limitation (6) and dynamic hyperinflation (7). However, the argument in favor of inadequate

energy (O₂) supply is also compelling and there is new evidence coming out suggesting that this is indeed a relevant limiting mechanism in patients with more advanced disease (2, 3).

In this context, a less biased interpretation of the available evidence indicates that the fundamental pulmonary-mechanical derangements associated with COPD are likely to produce perceptual (dyspnea) and physiological (DH, increased WOB) consequences that can modulate energy supply to the peripheral muscles. Resolution or amelioration of exercise intolerance in these patients, therefore, may also require a multifaceted approach aiming to increase energy supply (e.g., reducing DH and WOB, supplementing O₂) and optimize energy utilization (e.g., training, improving mechanical efficiency).

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COMMENT ON POINT: COUNTERPOINT

TO THE EDITOR: Skeletal muscle dysfunction, dynamic hyperinflation, and excessive expiratory muscle activity may play independent roles in limiting exercise in COPD. However, the following consideration should be made. 1) Evidence has been provided of skeletal muscle metabolic reserve in COPD similar to that seen in fit healthy subjects (5). Moreover, the contractile properties of vastus lateralis are preserved, and muscle strength per unit cross sectional area is not impaired in COPD patients (2). 2) The increase in expiratory muscle pressure is twice the increase in inspiratory muscles pressure, suggesting the major role played by the expiratory muscles in increasing dyspnea sensation in exercising flow-limited healthy humans (4). An expiratory muscle fatigue-induced metaboreflex results in sympathetic vasoconstrictor outflow, reduced blood flow and locomotor muscle fatigue (3). We might also expect the work of expiratory muscles to the point of fatigue in exercising COPD patients. However, might an imbalance between energy supplies and demands, or a plateau in the limb blood flow curtail incremental exercise in Gold stage I COPD patients as in those

with severe airflow narrowing and more intense dyspnea at a lower work rate (6)? On the other hand, does activation of limb muscle metaboreflex influence blood flow to the respiratory muscles? 3) Changes in intrathoracic and intra-abdominal pressures influence venous return, ventricular preload and after load, and stroke volume. However, how does this respiratory pressure influence cardiac output in exercising humans? A peripheral imbalance between energy supply and demand might be demonstrated if specific measure were employed (2).

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MEASUREMENTS, ESTIMATES, INTERPRETATIONS, MYTHS

TO THE EDITOR: The three papers each present a different view of the main factors limiting exercise in COPD- expiratory muscle work with excess respiratory $\dot{V}O_2$ (1), leg muscle dysfunction (2), and inspiratory muscle effort due to hyperinflation (5). All three accept that there are many factors that contribute to limitation, which probably accounts for them all remaining standing at the end of round 2. Spectators look on, matching their own biases with those of the protagonists. From my perspective, the calculations presented by Aliverti and Macklem (1) are unconvincing, in according a primary role to respiratory muscle oxygen consumption.

No one doubts that some patients do (but most don't) develop high intrathoracic expiratory pressures (6, 7) in excess of the pressure needed to achieve maximum expired flow/volume. We do not know the validity of respiratory muscle work estimated from pressure/volume measurements, nor the calculations of respiratory muscle $\dot{V}O_2$. The stealing of 55% of oxygen uptake by the respiratory muscles seems an overestimate.

In contrast to the respiratory muscles, the increase in oxygen uptake by skeletal muscles during cycling may be accurately estimated from power output (W). In a large study of COPD patients (4), the $\dot{V}O_2/W$ relationship was parallel to that of healthy subjects but higher by 150 ml/min, similar to the excess $\dot{V}O_2$ that accompanies maximum respiratory loading during exercise (7), but less than their estimates.

Many factors, acting in a combination that is unique to the individual, contribute to symptom intensity, which is what stops all of us exercising.

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EXERCISE INTOLERANCE IN COPD: PUTTING THE PIECES OF THE PUZZLE TOGETHER

TO THE EDITOR: The Point:Counterpoint articles (1–3) highlight the complex mechanisms underlying exercise intolerance in COPD. Recent studies (4, 5) suggest that the major limitation to exercise is largely dependent on lung disease severity classified by GOLD. Accordingly, although patients of all GOLD stages exhibited pulmonary mechanical derangements and dynamic hyperinflation (DH) at the limit of exercise tolerance and this DH increased with increasing lung disease severity (4, 5), the predominant limiting symptom in stages I and II was leg fatigue (4, 5), whereas in stages III and IV it was dyspnea (5). Naturally, exercise capacity was higher in stages I and III compared with stages II and IV, respectively (4, 5). However, in stages II and III exercise capacity was similar (5). Since most of stage II patients did not exhibit expiratory flow limitation (EFL) during exercise, substantial expiratory muscle activity resulted in higher expiratory flow rates compared with stage III, thereby attenuating DH and the intensity of dyspnea (5); however, high expiratory pressures possibly caused adverse circulatory events, thus limiting energy supply to locomotor muscles and inducing leg fatigue (1, 5). This mechanism might also be involved in stage I. In stage III, EFL was more severe, expiratory abdominal muscle activity was minimal, and DH was greater, thus restricting tidal volume expansion that intensified dyspnea (5). Although stages III and IV exhibited similar DH, exercise capacity in the latter was more impaired than in the former owing to the fact that DH in stage IV occurred in lower minute ventilation (5).

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COPD POINT: COUNTERPOINT COMMENTARY

TO THE EDITOR: “You jest about what you suppose to be a triviality, in asking whether the hen came first from an egg or the egg from a hen, but the point should be regarded as one of importance, one worthy of discussion, and careful discussion at that” (Macrobius, 400 AD). This debate illustrates the difficulties in determining the primary physiological abnormality that limits exercise performance in COPD. It is apparent from the arguments put forth that there is compelling evidence to support the presence of dynamic hyperinflation (DH) resulting from expiratory flow limitation (1) and intrinsic peripheral muscle dysfunction in patients with COPD (2). While the hypothesis put forth by Drs. Aliverti and Macklem (5) of inadequate energy supplies and learned response to exercise is interesting, there is little evidence that DH is caused by a derecruitment of expiratory muscles. In fact, it has been observed even in mild COPD (6). Furthermore, dyspnea does not correlate with expiratory effort (4). As pointed out by Drs. Debigaré and Maltais (2), it is also unlikely that low oxygen availability to the lower limb in COPD is a main factor for most patients (3, 7) in that both structural and functional muscle abnormalities persist despite lung transplantation and optimal bronchodilation. Most importantly, however, a key concept that must be recognized in this debate is the heterogeneity of the COPD population and the likelihood that, for the individual, one or more of these pathophysiological mechanisms may be major contributors to exercise limitation, and therefore be the appropriate target(s) for intervention.

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MULTIPLE MECHANISMS LIMIT EXERCISE IN COPD

TO THE EDITOR: This stimulating Point:Counterpoint has marshaled persuasive arguments in support of dynamic hyperinflation (5), inadequate energy supply to exercising muscle (both respiratory and locomotor) (1) and lower limb muscle dysfunction (4) as the principal cause of exercise limitation in COPD. Most data are derived from patients with severe or very severe disease and in this setting multiple mechanisms are likely to operate. Thus reducing operating lung volume can be associated with a reduced peak work rate if the chest wall volume change is inappropriate (2) while Pepin et al. have shown that COPD patients developing quadriceps fatigue on exercise do not increase their exercise performance after a bronchodilator (6). Thus different mechanisms limit performance in advanced disease in different patients. O'Donnell and Aliverti appear to be referring to different phenomena when considering dynamic hyperinflation, with the former focusing on changes in lung volume and the latter on chest wall volume. Thus "passive" increases in EELV can occur in the face of active chest wall volume reduction that can produce substantial gas compression and blood shifts. Changes in cardiac output secondary to this process are compatible with data describing a relative slowing of central oxygen uptake kinetics compared with peripheral muscle oxygen extraction during heavy exercise in severe COPD (3). More data about the time course of an individual's change in EELV would be welcome as would studies in milder COPD testing each mechanism in the same person to establish when in the natural history of COPD exercise limitation begins and why.

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MISSING PIECES

TO THE EDITOR: In a nutshell, the question addressed here is whether lower limb muscle, either through muscle dysfunction (3) or reduced energy supply to that muscle (1) or dynamic hyperinflation (5) causes exercise intolerance in COPD. However, we must realize that there is a huge gap in our understanding regarding the origin and progression of limb muscle impairment in COPD simply due to the fact that the majority of studies focused on patients with severe COPD. The result of this being that hardly any literature is available on patients with mild to moderate COPD (GOLD stages I and II) (6) let alone in subjects at risk (i.e., smokers). We clearly demonstrated the lack of such data in early COPD for lower limb muscle abnormalities (4). To really understand whether limb muscle dysfunction is the cause or consequence (or neither) of reduced exercise capacity in COPD, future studies should incorporate the earlier stages of COPD as well as the effects of smoking. A longitudinal study design would be ideal for this. Another approach would be to evaluate exercise capacity after interventions targeted at the suspected mechanisms, for example, after lung volume reduction surgery or lung transplantation (target: hyperinflation). Likewise, Calvert et al. (2) recently showed that exercise performance improved in COPD after a pharmacological intervention known to activate muscle pyruvate dehydrogenase complex in rest, thereby improving energy supply to muscle mitochondria (target: muscle energy supply). These are the kind of studies that we need to solve this puzzle.

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“IN MEDIO STAT VIRTUS”

TO THE EDITOR: The points raised by the authors (1, 2, 4) certainly support the hypothesis that the origin of exercise intolerance in COPD is multifactorial, reflecting a combination of “peripheral” and “central” factors.

When examining the causes of reduced exercise tolerance in COPD, however, it is important first to clarify whether one is referring to exercise performance on a classical rapid-incremental exercise test or on a high-intensity constant work-rate test (Tlim) for which the characteristics of the power-duration relationship (i.e., critical power and W') are important (7). Exercise modality should also be considered, significant differences having been reported in the ventilatory and gas exchange responses to cycle ergometry and free walking in COPD patients, for example (5).

Furthermore, making judgments about the normalcy or otherwise of the ventilatory response to an exercise challenge requires an appropriate frame of reference (e.g., as is provided by factors such as the pulmonary CO₂ output (\dot{V}_{CO_2}), the set-point level at which arterial PCO₂ is regulated and level of gas exchange inefficiency [i.e., the physiological dead space fraction of the breath (V_D/VT)]. This, however, is a shortcoming of several of the studies cited by the authors (1, 4).

Regardless, there would seem to be little question that exercise tolerance in COPD, particularly in patients with emphysema, is compromised because of severe dyspnea and ventilatory limitation: the improvements in Tlim engendered by supplemental oxygen (3) and heliox administration (6) clearly support this hypothesis.

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THERE IS NO MAGIC BULLET IN COPD

TO THE EDITOR: Aliverti and Macklem (1), Debigaré and Maltais (2), and O'Donnell and Webb (3) passionately speak to the question “what is the major limitation to exercise performance in COPD?” In presenting their opinions, there is a fundamental assumption that a single mechanism prevails to primarily limit exercise. While each author's evidence is compelling and provides a rationale that, at least in some patients, increases in exercise performance are limited by one of the three proposed mechanisms, it is obvious that a single mechanism does not dominate in every patient.

Delaying dynamic hyperinflation with bronchodilators (5, 6), hyperoxia (5), or heliox (4) increases exercise tolerance in only some patients. In these patients, the limitation is presumably ventilatory, and increases in exercise tolerance are associated with increased leg muscle limitation. In others, this intervention has minimal effect on exercise ability, which suggests a greater peripheral muscle limitation (6). Although the debate regarding exercise limitation in COPD is an important one physiologically, it is also a rather arcane one. Practically speaking, the more important question is “how do we best improve exercise tolerance and functional ability in patients with COPD?” Answers to this question will most certainly be reflected in the responses to this Point:Counterpoint debate; however, the fundamental problem has yet to be resolved.

The mechanisms of exercise limitation and their consequences are intertwined and vary from patient to patient. It seems more cogent that COPD patients stand facing a firing squad of physiological derangements culminating in exercise limitation. There is no magic bullet in COPD.

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