References

Mild Chronic Obstructive Pulmonary Disease Does Exist—and Affects Gas Exchange during Exercise

The last few years have seen an intense debate about the definition of chronic obstructive pulmonary disease (COPD) and how it should be assessed physiologically. The Global Initiative for Chronic Obstructive Lung Disease group initially defined COPD in terms of persistent airflow limitation objectively confirmed by an FEV1/FVC ratio of 0.7 or less (1). Others highlighted the age-related decline in this ratio (2) and suggested that to avoid overdiagnosing the condition, it should only be diagnosed when the ratio was below the lower limit of normal derived from appropriate predictive equations for the population under study (3). This debate continues, and when agreement finally breaks out, hopefully we will have found some robust and practical ways of identifying patients with COPD. However, this focus on which absolute criterion to use for the diagnosis of a condition rather ignores the fact that COPD is progressive over time (4) and that lung damage is commonly present if you look carefully long before the patient presents clinically. The early loss of small airways and the related development of centriacinar emphysema has been observed in lung resection specimens (5), and we have known for many years that small airways function can be abnormal in subjects with relatively preserved spirometry, something that is easier to evaluate with modern methods for measuring forced oscillatory respiratory mechanics and gas washout techniques (6). However, understanding how these subtle changes might affect a patient has remained difficult.

One way to do this is to stress the respiratory system by observing how well gas exchange is maintained during exercise. In patients with established disease and resting hyperinflation of the lungs, exercise is commonly restricted by the inability of the lungs to achieve their true relaxation volume at the end of expiration, and the resulting dynamic hyperinflation means the patient reaches a critical inspiratory reserve volume, recently termed the O’Donnell threshold (7), more rapidly than usual. The resultant severe dyspnea leads them to stop prematurely, although an effect on blood supply to exercising muscle secondary to hyperinflation and changes in chest wall volume (8) plays a role in some patients. Abnormalities in gas exchange including significant oxygen desaturation appear to be secondary to the deranged lung mechanics in established disease. In contrast, in mild COPD, there is a widened alveolar–arterial gradient and a preponderance of low VA/Q lung units. We have fewer data about what happens during exercise, although one important study suggested that the alveolar–arterial gradient widened further during exercise, but oxygenation improved as ventilation was more evenly distributed within the lungs (9). However, until now we have not had any data in which measurements of gas exchange and lung mechanics have been combined in exercising patients with very mild COPD. Even more important, we lack data compared with that available in in age-matched control subjects.

This gap has been addressed in this issue of the Journal by Elbeihary and colleagues (pp. 1384–1394), who report a very carefully conducted and remarkably comprehensive assessment of lung mechanics and gas exchange at rest and during exercise in two carefully selected subject groups (10). They recruited 11 patients with very mild COPD (mean FEV1, 90% predicted; FEV1/FVC, 61%; and no evidence of hyperinflation) who were symptomatic with a raised total St. George’s Respiratory Questionnaire score and a reduction in daily activity. The researchers compared these patients with another 11 individuals matched for age and body mass index who were not smokers and who did not report exertional breathlessness. All participants underwent a comprehensive physiological evaluation that showed that the patients had abnormal oscillatory mechanics and a higher closing volume, both of which are pointers to small airways dysfunction. After appropriate acclimatization, all subjects had an incremental cycle exercise test with 20-W increases in load every 3 minutes until symptom-limited. The mechanical behavior of the COPD was similar to the healthy subjects until late in exercise, when they began to hyperinflate. However, their exercise was mechanically limited earlier because they had a higher ventilatory demand at any workload. As anticipated from the earlier studies, arterial oxygen tension increased, whereas the widened alveolar–arterial gradient noted at rest was unaffected by exercise. All the changes in ventilation were driven by the need to ventilate the higher physiological dead space, and the VE/VCO2 relationship was closely related to this variable.

Inevitably, it is possible to find fault, and one wonders what might happen if a more sedentary group of control subjects had been selected. However, it is hard to conceive that abnormalities so closely related to increased dead space would limit exercise in deconditioned subjects in whom a higher VCO2 might be expected. Similarly, the interpretation of the expiratory flow volume
measures of flow limitation the authors cite as evidence for coexisting mechanical exercise limitation is open to criticism. Other methods of testing for flow limitation during tidal breathing might have given a more definitive answer on this point (11). However, these are minor issues, and the authors are to be congratulated on finding such well-matched subjects.

So what does this tell us about “mild” COPD? Clearly, patients can develop modest degrees of exercise limitation and symptoms when their spirometric abnormalities are relatively trivial. Neither resting nor dynamic hyperinflation were needed for this to be present. However, this does not necessarily translate into a need for more bronchodilator therapy, as a recent study of tiotropium illustrated (12). The physiological responses to exercise including the tidal volume and inspiratory capacity changes were normal in the patients with the extra ventilatory demand, suggesting that an increase in the physiological dead space was the earliest physiological change in these subjects. This could be identified by the raised VE/VCO2 slope, but how this variable relates to other indices of small airway dysfunction will have to wait for larger studies to resolve. All of this emphasizes that important functional, and hence structural, changes that occur in COPD happen well before we become aware of them as clinicians. Future studies should use these insights from physiology to plan mechanistic intervention studies to determine whether we can do more to prevent progression in COPD apart from just encouraging smoking cessation.

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References

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Plasma Transfusion in Critically Ill Children
A Magical Mystery Tour?

The Joint Commission and the American Medical Association-Convened Physician Consortium held a National Summit on Overuse on September 24, 2012, in Chicago, Illinois. It identified five overused treatments that can harm patient safety, among which blood transfusion was ranked second, after antibiotic use for common cold (1). Blood transfusion occurs in 1 in 10 hospital stays with a procedure (2). About 4 million plasma units are transfused each year in the United States (3). In England, 12.7% of critically ill adults received at least one plasma transfusion while occupying the intensive care unit (4); almost the same proportion (12.2%) is reported for critically ill children (5). In addition, about 3% of all children in U.S. hospitals received at least one plasma transfusion (6).

Plasma is frozen for storage to preserve the level of coagulation factors. It is named “fresh-frozen plasma” if refrigerated within 8 hours of collection, and “frozen plasma” if within 24 hours. Frozen plasma units are collected from a single donor, whereas units of solvent detergent plasma are constituted from a pool of frozen plasma collected from approximately 700 donors; the solvent detergent process inactivates lipid-enveloped viruses. On average, plasma units contain 1 unit/ml of all coagulation factors, but there is significant variability among individual units, which is attributable to biological variation in factor levels among individual donors. The content in factor VIII of frozen plasma is slightly lower than in fresh frozen plasma units, but the difference is so small that both types of plasma are essentially interchangeable.

In this issue of the Journal, Karam and colleagues (pp. 1395–1402) completed a large prospective multicenter international point-prevalence study to collect data on the epidemiology