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Lessons from the North: CanCOLD, Exercise, and Chronic Obstructive Pulmonary Disease

Canadians have contributed immeasurably to our understanding of chronic obstructive pulmonary disease (COPD). From identifying the importance of small airway disease in COPD (1) and developing the first definition of a COPD exacerbation (2), to the description of eosinophilic bronchitis using induced sputum (3), Canadian researchers have led the way. A further example comes from the pioneering work of the Kingston, Ontario, group on exercise physiology in COPD. They were the first to recognize the importance of dynamic hyperinflation of the lungs in moderate to severe COPD with its consequences for neural drive and dyspnea and subsequently showed how inhaled bronchodilators modulated this problem (4). However, changes in end-expiratory lung volume during exercise are less dramatic in those with more preserved lung mechanics. In the last decade, attention has focused on the effects of increased physiological dead space as a source of ventilatory inefficiency and increased ventilatory demand during exercise. The Kingston group showed that the dead space–to-V_T ratio is closely related to the $\dot{V}_E$ per liter of $\dot{V}_{CO_2}$ calculated during an incremental workload exercise test (5), and this relates to the intensity of reported breathlessness. By contrast, this mechanism does not seem to explain the breathlessness reported by some smokers without evidence of airflow obstruction, where subtle mechanical abnormalities within the lungs may be more important (6). These conclusions derive from careful physiological studies of relatively few individuals, and how generalizable these findings are remains uncertain.

Fortunately, another Canadian innovation, CanCOLD (the Canadian study of Chronic Obstructive Lung Disease), can help answer this question. CanCOLD is a large, representative population sample of Canadians more than 40 years old who completed an extensive battery of tests, including Medical Research Council Breathlessness and COPD Assessment Test scoring, measurements of resting and exercise physiology, and quantitative computed tomography (CT) scanning (7). It has already contributed important insights into the loss of small airways early in the natural history of COPD (8) and the role of elevated blood eosinophil counts in accelerating disease progression (9). In this issue of the *Journal*, Phillips and colleagues (pp. 1391–1402) report, in considerable detail, the results from 1,250 individuals drawn from nine contributing centers and separated into four discrete groups: 445 never-smokers (mean FEV_1 97% predicted), 381 ever-smokers (mean FEV_1 100% predicted, 21% still smoking), 284 Global Initiative for Chronic Obstructive Pulmonary Disease (GOLD) grade 1 (mean FEV_1 95% predicted, 19% still smoking), and 200 GOLD 2–4 (mean FEV_1 65% predicted, 32% still smoking, and mostly GOLD grade 2 COPD) (10). The authors wished to determine whether a high nadir $\dot{V}_E/\dot{V}_{CO_2}$ was associated with greater breathlessness and worse exercise tolerance in a general population, which lung function and imaging variables were most closely related to the nadir $\dot{V}_E/\dot{V}_{CO_2}$, and whether smokers without airflow obstruction differed in their nadir $\dot{V}_E/\dot{V}_{CO_2}$ from never-smokers without obstruction. The nadir $\dot{V}_E/\dot{V}_{CO_2}$ was categorized as abnormal if it fell outside the values identified in a healthy population of older people (11).

The groups were well matched for age and body mass index, although the ever-smokers contained proportionately more women, and the FEV_1/FVC in the never-smokers clearly included some patients with airflow obstruction despite a normal FEV_1, which may explain some of the subsequent findings. There was a clear gradient in tobacco exposure across the groups, with ever-smokers reporting fewer pack-years than subjects with obstruction. As anticipated from the resting lung function, the people with GOLD-defined airflow obstruction and a smoking history achieved significantly lower peak work rate than the "healthy" never- and ever-smokers. The nadir $\dot{V}_E/\dot{V}_{CO_2}$ was highest in GOLD 2–4 subjects but did not differ in the other three groups. However, 12%, 13%, 23%, and 26% of never- and ever-smokers, GOLD 1, or GOLD 2–4 subjects had nadir $\dot{V}_E/\dot{V}_{CO_2}$ values above the upper limit of normal. These individuals consistently had more breathlessness and lower peak oxygen consumption than those with more efficient ventilation, irrespective of the group. High nadir values were associated most strongly with the K_{CO}, whereas other statistically significant associations with mid-expiratory flows and CT-based variables were much weaker. Occult pulmonary vascular pathology might explain the impaired exercise performance of some GOLD grade 1 subjects in whom the K_{CO} was reduced. However, other pathologies might be present, not least occult cardiovascular disease and abnormal gas mixing with relatively preserved lung mechanics.

Inevitably, there are limitations to consider, even in a comprehensive report such as this one. Crucially, much of the evidence for the importance of the nadir $\dot{V}_E/\dot{V}_{CO_2}$ is dependent on the stability of the classification of normality. It would be reassuring to see that individuals who were abnormal remained so at subsequent visits. Likewise, it would help to know that those in the GOLD 1 group remained in that group over time. This is a concern, as CanCOLD has already highlighted the risk of diagnostic reclassification over time (12). Thankfully, CanCOLD participants return for retesting, and it should be possible to address both these issues. Why people without obstruction exhibit inefficient ventilation is unclear, raising issues about the utility of the normative data. Whether this ventilatory inefficiency is because of subject selection or perhaps different degrees of dysanapsis within the airways, itself a risk factor for future COPD, merits further study (13). The lack of CT correlation is surprising, as

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the total airway count is related to disease progression in COPD (8), and further work to explain this is needed. Possibly, the inclusion of oscillometric variables, which seem to identify impaired exercise performance in smokers, would be useful here (6).

Whatever its limitations, the CanCOLD exercise data set is a remarkable achievement that takes our understanding of exercise limitation in COPD to a new level. Clearly, mechanical constraints associated with dynamic increase in end-expiratory lung volume during exercise restrict performance in patients with well-established COPD. However, there is now evidence that ventilatory inefficiency plays a role in those with relatively preserved lung function and even in those for whom airflow obstruction has yet to develop. This study broadens our understanding of impaired exercise performance, suggests new approaches to its understanding, and will no doubt be succeeded by more exciting data. It is a fine addition to the long and honorable history of Canadian research into the pathophysiology of COPD. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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Down to a T: The Functional Importance of Lymphopenia in Severe COVID-19

The emergence of the novel coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in late 2019 has led to a pandemic that has had widespread detrimental effects on populations globally. Ample evidence now supports that immunopathology associated with severe coronavirus disease (COVID-19) relates to a key role for inflammatory mediators such as TNF-α (tumor necrosis factor α) and IL-6 that are augmented systemically as part of a "cytokine storm" (1, 2) and can be targeted by immunomodulatory therapies, including dexamethasone and JAK (Janus kinase)-inhibitors.

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