Should 'C' in COPD Stand for 'Cognition'?

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Chronic obstructive pulmonary disease (COPD) affects 13 million adults in the USA [1], an underestimate by most accounts. It is the third leading cause of death in the USA, claiming 125,000 lives in 2007 alone [2]. Initially thought to be primarily a disorder of the lungs, COPD has now been increasingly characterized as a multi-component syndrome with psychological, physical and social implications. Based on the study by Li et al. [3] published in this issue of *Respiration* and on others [4–7], cognitive dysfunction could now be added to the list of impairments attributed to COPD.

The cross-sectional analysis by Li et al. [3] demonstrates a moderate relationship between severe COPD and cognition, after adjusting for relevant variables. The authors classified COPD based on the severity, as assessed by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines. Their elegant study further adds to the growing literature highlighting the presence of cognitive impairment in COPD patients. However, a notable and innovative addition to the literature was the measurement of serum clusterin levels. Clusterin is a biomarker of chronic neuroinflammation, and is intimately associated with cognition. Measurements of its levels may provide useful pathophysiological insights into the link between COPD and cognitive dysfunction. Keeping in mind the limitations of the Mini Mental Status Examination (MMSE) for assessing cognitive function [6], and the nonlongitudinal design of the study as

acknowledged by the authors, a moderate correlation between MMSE and FEV₁ in patients with severe COPD can still be appreciated.

Several important aspects concerning cognitive impairment and COPD are worthy of consideration. The evidence linking COPD and cognitive impairment comes mainly from cross-sectional and case-control studies with few longitudinal cohorts, and a number of these studies used MMSE to evaluate cognition. As MMSE does not identify subtle cognitive deficits, an argument can be made for the use of sophisticated and comprehensive neuropsychological batteries. The other concern is the absence of an optimal and standardized definition of cognitive impairment in this particular group. At present, we are extrapolating from studies conducted in the general population. As increasing evidence connects anticholinergic exposure to cognitive impairment [8, 9], the contributory role of commonly used anticholinergic agents (ipratropium and tiotropium) to cognitive dysfunction in the COPD population needs to be further defined. Another important and unexplored area thus far is the impact of cognitive impairment on the activities of daily living, health-related quality of life, medication adherence, acute care utilization and mortality of COPD patients. Finally, the big question is whether or not any interventions targeting cognition will revert or attenuate its downward trajectory with concomitant improvement in other outcomes.

So, where does the current state of literature on cognitive impairment in COPD patients lead us? Two scenarios seem to emerge as future directions. A purist would recommend further exploration of the mechanisms behind increased cognitive dysfunction in COPD patients, arguing that effective interventions will originate from a better understanding of this relationship. A pragmatist would counter that with the current epidemic of an aging population with a high prevalence of both COPD and cognitive impairment, we do not have the luxury of waiting. Instead of just spending time pursuing mechanistic studies, it is high time to test a well-designed, comprehensive program that simultaneously targets the multiple facets of COPD. This could be achieved through a system-based intervention designed on the principles of complexity science [10], collectively involving pulmonary and cognitive rehabilitation, oxygen therapy, smoking cessation and optimal treatment of chronic comorbidities.

This may hold the potential for achieving improved cognitive and pulmonary aging in this vulnerable group. Investigators exploring a relationship between cognitive dysfunction and COPD should be commended for their efforts, but their work represents only half of the achievement in this area. The other half has yet to begin.

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