

Chronic Obstructive Pulmonary Disease and Work: Is It Time to Stop?

The burden of chronic obstructive pulmonary disease (COPD) and its effect on quality of life is well known, but the effect COPD has on work is less widely recognized. Although COPD is often thought of as a disease of the elderly, approximately two-thirds of people with COPD in the United States are younger than 65 years (1). Nearly 20 years ago, in a survey of 3,265 patients from nine countries in North America and Europe, 35.7% said their condition kept them from working, limited their ability to work, or had caused them to have time off work in the last year (2). One third of the 447 patients from the United States in the study reported that they were prevented from working because of their COPD, and a further 18% were limited in their ability to work. In a more recent survey of nearly 2,500 patients in Brazil, China, Germany, Turkey, the United States, and the United Kingdom aged 45–67 years, nearly 40% had retired prematurely because of COPD at an average age of 54 years (3), and numerous subsequent studies have confirmed that people with COPD are more likely to be not working (4). Some studies have suggested that working rates fall as the severity of airflow obstruction increases, but the relationship is inconsistent (4), possibly because many patients also have comorbidities that may be the reason for not working, rather than COPD. In some cases, not working may reflect the fact that occupational exposures worsen symptoms, and exposures can, of course, also contribute to the development of COPD (Figure 1) (5). Workers with COPD reported that issues leading them to stop working included work worsening their COPD, problems getting to work, and superiors making negative comments about their disease and not taking it into consideration enough (6).

As well as leading to stopping working, COPD leads to increased absenteeism (4). People with COPD are approximately twice as likely to have a short-term disability and more than four times as likely to have long-term disability (7), although comorbidities may also influence this. Symptoms may also limit the productivity of patients who remain at work. A number of large cross-sectional studies in the United States and other countries found that people with COPD were significantly more likely to report presenteeism (4), and results from studies using self-report data indicate that approximately 13–18% are limited in what they can do (8).

The interpretation of many of the previous studies is limited by the fact they have mostly depended on self-reported diagnoses, have been cross-sectional, and have generally not taken comorbidities into account. These limitations have been overcome in the survey reported in this issue of the *Journal* by Schofield and colleagues

(pp. 1228–1233), which examined the loss of employment over an 18-month-long period in patients with spirometrically confirmed airflow limitation (9). They found that the adjusted risk for loss of employment was tripled for those with moderate or severe chronic obstructive pulmonary disease (relative risk, 2.89; 95% confidence interval, 1.80–4.65), with no difference between men and women. The risks were higher in those with worse airflow obstruction or breathlessness, but were not related to comorbidities. Patients were more likely to remain working if they had financial dependents.

The strengths of this study are its prospective nature; the clinical characterization of the patients at baseline, including postbronchodilator spirometry and assessment of comorbidities; and the excellent response rate to the follow-up questionnaire (93.3%). Limitations include the fact that only 33% of the eligible population responded to the initial questionnaire, and that the survey was performed in a single county in the United Kingdom, perhaps affecting its generalizability. Nevertheless, the study provides important insights into the problems faced by people with COPD in relation to continuing working.

Working generally has a positive effect on health and functioning. Becoming unemployed is associated with significantly higher levels of depression and anxiety, together with lower self-esteem and confidence (10); however, in the short term, it may lead to improved physical health, particularly when symptoms have been exacerbated by working conditions. The effect of COPD-related loss of work on individuals is likely to be greatest in countries that do not have welfare systems to support the unemployed or in which healthcare has to be paid for. Globally, it is estimated that 384 million people had COPD in 2010 (11), with the main burden falling in Latin America, sub-Saharan Africa, India, China, and Southeast Asia. In many of these countries, the cost of medication is very high in comparison to average earnings, and its availability through government health systems is poor (12). Without an income, these costs exacerbate the financial vulnerability of households in low- and middle-income countries and may force patients to finance care by household borrowing and selling assets (13).

Even in affluent countries such as Australia, not being in paid employment is associated with significant economic hardship related to the affordability of medical treatments, particularly if patients are receiving multiple medications (14). Hardship was still present even when patients were eligible for welfare, as this was insufficient to meet their healthcare costs in addition to daily living expenses. Similarly, in a study of low-income seniors in the United States, one in five did not fill all their prescriptions because of cost, and they missed doses to make their prescriptions last longer (15).

Unemployment, absenteeism, and presenteeism also have significant implications for national economies, both because of lost productivity and because of the costs of benefits paid to patients. Estimates of the total indirect costs attributable to COPD vary from

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Originally Published in Press as DOI: 10.1164/rccm.201908-1627ED on September 12, 2019

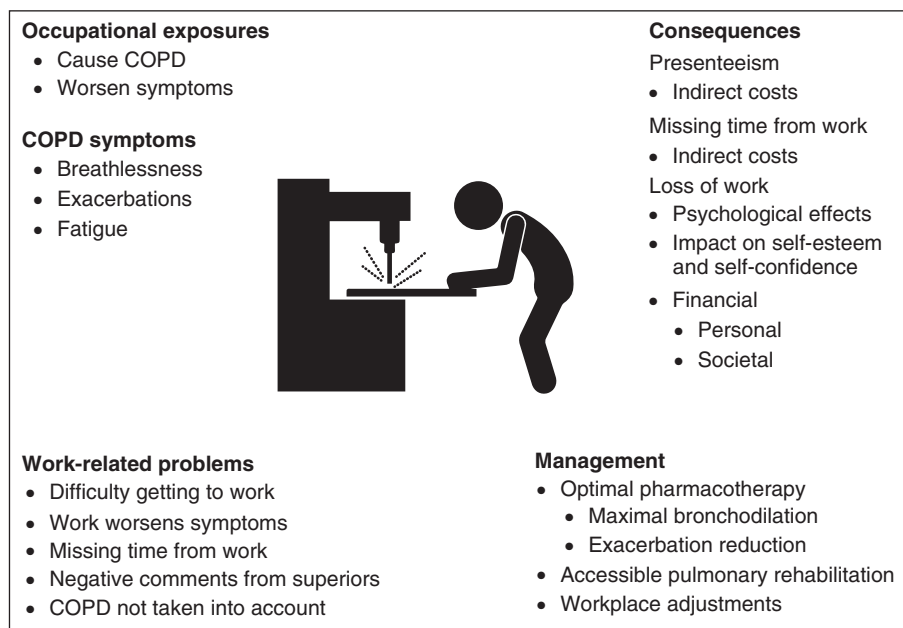


Figure 1. Chronic obstructive pulmonary disease (COPD) and work.

\$1,521 to \$3,348 for every person with COPD (8), and Sin and colleagues estimated that among the total COPD population in the United States there was a productivity loss of \$9.9 billion per year (16).

What can be done to maintain patients' ability to work and be productive for as long as possible? Maximally reducing breathlessness and maintaining exercise capacity with dual bronchodilator therapy in patients who are of working age may help, as may strategies to reduce exacerbation rates. Pulmonary rehabilitation has much to offer, but it is essential that programs are organized in ways that are accessible to patients who work. This might mean running sessions in the evenings or at weekends. Workplace adjustments, such as reducing or adjusting workload or hours and reducing exposures to dust or irritants, may also be necessary. Such measures can help keep patients working (6), and patients should be encouraged to discuss them with their employers. Maintenance of ability to work should be seen as an important objective of COPD management. ■

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

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Ⓢ Sugarcoating Lung Injury: A Novel Role for High-Molecular-Weight Hyaluronan in Pneumonia

Despite many decades of active research and several clinical treatment trials, acute lung injury (ALI)/acute respiratory distress syndrome remains a severe complication of pneumonia and severe sepsis, and pharmacological treatment is still lacking (1). The traditional treatment of pneumonia (and infections in general) has been to focus on the microbial component and treat patients with antibiotics. In recent years, increased attention has been given to the host response and ways to ameliorate the dysregulated inflammatory response and tissue injury occurring after infection.

In this issue of the *Journal*, Liu and colleagues (pp. 1234–1245) provide an important contribution to the literature (2) by using translationally relevant human ALI and pneumonia models to demonstrate the utility of high-molecular-weight hyaluronan (HMWHA) in ALI in infection. There is increased awareness that extracellular vesicles (EVs) play an important role in the initiation and propagation of acute lung injury (3). The authors demonstrate that EVs are released after the administration of *Escherichia coli* in *ex vivo* perfused human lungs, predominantly by endothelial cells and circulating platelets. These EVs then promote an inflammatory response, leading to lung injury. Addition of HMWHA in the perfusate after EV administration improved alveolar fluid clearance, which would decrease alveolar edema, and decreased TNF α (tumor necrosis factor α) and IL-6 levels in the lung lavage fluid. Interestingly, a decrease in cytokine levels was noted after HMWHA treatment, even though total white blood cell and neutrophil counts did not significantly change, suggesting that HMWHA reduced inflammatory cell activation. Interestingly, in spite of its very large size (molecular weight > 1,000 kD), HMWHA added in the perfusate was detected in the alveolar after *E. coli* instillation. *Ex vivo*, HMWHA improved bacterial clearance by phagocytes, and this was mirrored by decreased colony-forming units in the pneumonia model. Furthermore, HMWHA decreased EV uptake by monocytes in

a (at least partially) CD44 (cluster of differentiation 44)-dependent manner and reduced inflammatory cytokine release after EV exposure. In aggregate, these findings support that HMWHA may be of therapeutic utility in ALI and pneumonia.

What is the relevance of these exciting findings? Hyaluronic acid (HA) is a deceptively simple molecule present in all extracellular matrices, consisting of repeating disaccharides made of N-acetylglucosamine and glucuronic acid, and does not undergo further modification after its expression by HA synthases. Reactive oxygen species (e.g., HOCl) released by activated inflammatory cells, as well as exposures such as ozone and halogens, degrade HMWHA to low-molecular-weight fragments (LMWHA) of 0.1–500 kD (4, 5). Although HMWHA and LMWHA bind to the same receptors, they exert opposite effects (4). LMWHA activates innate and adaptive immunity and increases permeability and airway resistance by activating RhoA (ras homolog gene family, member A) and ROCK2 (rho-associated coiled-coil containing protein kinase 2), whereas HMWHA has strong antiinflammatory and prohomeostasis functions (4). The reason for this difference may be differences in receptor engagement or cell uptake depending on size, but ultimately remains elusive. Recent work suggests that HMWHA may create a transmembrane “picket fence” barrier, tethered on CD44 and the cellular cytoskeleton, that prevents ligands from reaching and activating their respective receptors, an effect that is abolished after HA degradation (6). HMWHA also binds several extracellular proteins with strong antiinflammatory potential, such as inter- α -inhibitor, which is associated with decreased endothelial injury (7) and organ dysfunction (8, 9) in sepsis, and pentraxin-3, which contributes to host defense, including prevention against aspergillosis in stem cell transplant recipients (10). Furthermore, HMWHA is a recently recognized crucial constituent of the endothelial glycocalyx, and HA homeostasis is central to the maintenance of a healthy endothelial barrier and the avoidance of tissue injury (11). Finally, HA has well-described antimicrobial properties, inhibiting bacterial adhesion and promoting phagocytosis (4). Thus, HMWHA acts along with its binding partners in the cell, the circulation, and the interstitium and on pathogens to reduce inflammation and promote antibacterial properties of the host.

A major theoretical concern, whenever antiinflammatory applications of HMWHA are being discussed, is its potential degradation into smaller, proinflammatory fragments. It is interesting to note, however, that in this study, HMWHA retained its large molecular weight despite being several hours in a

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This work was funded, in part, by the Division of Intramural Research, National Institute of Environmental Health Sciences (S.G.), and by 5 U01ES026458 from the National Institute of Environmental Health Sciences (S.M.).

Originally Published in Press as DOI: 10.1164/rccm.201908-1554ED on August 28, 2019