Is It the Heart or the Lung? Sometimes It Is Both

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Chronic obstructive pulmonary disease (COPD) exacerbations have been recently redefined as "an event characterized by dyspnea and/or cough and sputum that worsen over ≤14 days, which may be accompanied by tachypnea and/or tachycardia and is often associated with increased local and systemic inflammation caused by airway infection, pollution, or other insult to the airways." Though much has been understood about the pathogenesis and impact of exacerbations, our definition of an exacerbation remains subjective and reliant on patient-reported symptoms. Our attempts to find objective, readily measurable markers to diagnose an exacerbation, "a lung troponin," have been unsuccessful to date.

In this issue of the Journal of the American Heart Association (JAHA), Dransfield and colleagues have extended previous observations of increased cardiovascular events following a COPD exacerbation by looking at the adverse events reported in the course of a large clinical trial of prevention of exacerbations of COPD with different combinations of inhaled long-acting bronchodilators and corticosteroids. The increased odds of having a cardiovascular event are remarkable, especially for hospitalized (severe) episodes. However, the numbers for the cardiovascular events that occur during the exacerbation have to be carefully interpreted. The dyspnea of an exacerbation often turns out to be related to congestive heart failure, a cardiac arrhythmia, or cardiac ischemia. Absence of objective markers of an exacerbation contributes to this diagnostic confusion. The frequent occurrence of these events during the exacerbation, especially cardiac arrhythmias, is not surprising, given the arrhythmogenic nature of the pathophysiological changes accompanying an exacerbation, including hypoxemia, hypercapnia, acidosis, and pulmonary hypertension. Treatments routinely used for an exacerbation do not help given the well-recognized potential adverse effects of β-agonists and anticholinergics, a necessary risk that we have to take to treat the patient. Whether comorbid cardiac disease is a contributor or complication, this study emphasizes that it should be carefully evaluated in every patient with a COPD exacerbation, especially if they are hospitalized.

Dransfield et al. found a substantial increase in cardiovascular events that persists after the exacerbation, as has been shown in other studies. Understanding the mechanisms underlying these observations would be critical to prevent them. The putative mechanism is the proinflammatory state and oxidative stress that accompany an exacerbation, which are not confined to the lungs. This notion is supported by observations in patients hospitalized with community-acquired pneumonia, where a similar increase in cardiovascular events is seen after the acute episode. Inflammatory profiles at exacerbation vary with cause, and whether that relates to the frequency and nature of cardiovascular consequences is unknown. Even though we

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may stop the treatment of an exacerbation after a few days and assume it has ended, it has been shown that the inflammatory state takes longer to resolve, especially in individuals whose symptoms have not returned to baseline.7

How do we prevent these adverse cardiovascular consequences of exacerbations? Reducing exacerbation events is clearly the most desirable approach. Substantial progress in that regard has been made in the management of COPD, with excellent evidence that long-acting bronchodilators, inhaled corticosteroids, phosphodiesterase inhibitors, and chronic antibiotics, when used in the appropriate patients, reduce exacerbations with a favorable risk–benefit ratio. It is disappointing when real world data show that there are substantial underrecognition and undertreatment of COPD, such that many avoidable exacerbations are occurring with their attendant consequences, including cardiovascular ones.8 This study adds weight to the argument that appropriate diagnosis and treatment of COPD can have far-reaching benefits to the patient, beyond the lung.

Addressing risk factors for COPD and cardiovascular disease can also reduce the cardiovascular consequences of COPD exacerbations. In this regard, the importance of smoking cessation cannot be emphasized enough. Obesity, diabetes, and metabolic syndrome have become common in COPD and addressing them could be another effective intervention.9 Clearly, lifestyle modification, though not easy, could provide us the “biggest bang for the buck” and is a discussion that I have repeatedly with my patients with COPD.

Could certain medications reduce the risk of cardiovascular events following a COPD exacerbation? Intuitively, if inflammation drives these events, anti-inflammatory therapy at exacerbation or before the exacerbation could be beneficial. A burst of systemic corticosteroids reduces treatment failure and hastens resolution of exacerbations and is the standard of care in hospitalized patients with COPD exacerbation. However, there is no indication of a reduction in mortality or cardiovascular outcomes in placebo-controlled trials.10 In this study, there was no difference in cardiac events following exacerbation among patients in the 3 treatment groups, suggesting that inhaled steroids did not prevent these events. Only subgroups of the randomized patients, who experienced an exacerbation, were included in this analysis, which may be a confounding factor. However, this observation is consistent with results of the SUMMIT (Study to Understand Mortality and Morbidity in COPD) trial, where inhaled corticosteroids alone or combined with a long-acting beta agonist, were not able to reduce mortality or cardiovascular events in patients with moderate COPD who were at high risk for cardiovascular disease.11 Statins have well-recognized anti-inflammatory activity and in retrospective studies reduce exacerbations and mortality among patients with COPD. STATCOPE (Simvastatin Therapy for Moderate and Severe COPD), a well-done prospective trial to determine if a reduction of exacerbations could be seen with simvastatin, failed to confirm retrospective observations.12 A reduction in cardiovascular events or mortality was not seen, though this study was not powered for these endpoints. Current data do not support initiation of pharmacological treatment to reduce cardiovascular events in stable COPD or following an exacerbation, unless there are other indications to use a statin or inhaled corticosteroids.

Should we be screening for cardiac disease in our patients with COPD, and could diagnosing and managing asymptomatic cardiovascular disease prevent what was observed by Dransfield et al.? Screening is likely to be of high yield, as suggested in a study where 20% of elderly patients with COPD were found to have previously undiagnosed congestive heart failure.13 Though screening for cardiovascular disease has been advocated, what is lacking is evidence that such an approach is cost effective and improves outcomes, both in stable COPD and following an exacerbation.14 A common clinical scenario is a patient with COPD whose activity is limited by dyspnea because of his lung condition. Would short-term and long-term outcomes be different if we were to find asymptomatic ischemic heart disease in such a patient?

Despite the uncertainties, heightened awareness about cardiovascular comorbidity in patients with COPD, both in stable disease and especially at and following an exacerbation, is warranted. Conversely, COPD and the presence of low lung function have been associated with worse outcomes in cardiovascular diseases such as congestive heart failure, myocardial infarction, and atrial fibrillation.15 As specialists, we tend to focus on our body system of expertise, but the extent of comorbidity between COPD and cardiovascular disease does raise the question if that is the best approach.

ARTICLE INFORMATION

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