The untreated treatable trait: Cardiovascular disease in COPD exacerbations

Key words: COPD, cardiovascular, imaging.

Cardiovascular disease, the ‘silent killer’ in chronic obstructive pulmonary disease (COPD), seldom presents a more vexed clinical challenge than during acute exacerbation of COPD (AECOPD). In this demanding situation, treatments have changed little in decades and new approaches are needed to improve outcomes. The conundrum is to achieve diagnostic certainty and assure therapeutic benefit in this extraordinarily complex situation.

Both COPD and cardiovascular disease are characterized by exceptional heterogeneity, displaying myriad diverse pathologies and clinical manifestations. Pathology in both disease categories can range in severity from subclinical to severe and can be modified by wide-ranging medical comorbidities as well as social factors. Furthermore, during AECOPD, a slew of intercurrent, superimposed factors may influence COPD and cardiovascular disease—these include viral and bacterial infections, inflammation, hyperinflation and pharmaco-therapeutic effects. Consequently, cardiovascular disease and COPD may be present independently, coexist or masquerade as the other during AECOPD. Deciphering this complicated disease network during a time of acute illness can be difficult.

Clinicians are usually adept at recognizing severe but previously undiagnosed lung or cardiac pathology, however, this phenomenon only represents the tip of the ‘diagnostic iceberg’. Populations with COPD are known to be enriched in cardiovascular risk factors such as smoking, age, physical inactivity and airflow limitation, and during AECOPD, signs of cardiovascular dysfunction including cardiac biomarker elevation are common and of prognostic importance.

Thus, the challenge is to identify which cardiovascular pathology (or pathologies) are present in each individual. Until recently, this has been difficult to achieve. For example, apparent, fundamental data on the prevalence of heart failure and coronary atherosclerosis in individuals presenting to hospital with AECOPD had not been reported. To examine this question, we recently employed a novel dynamic (i.e. video) cardiac computed tomography (CT) protocol, examining the prevalence of severe heart failure with reduced ejection fraction and severe calcific coronary atherosclerosis in hospitalized AECOPD. Briefly, dynamic CT can assess multiple important parameters which were previously difficult to assess including coronary atherosclerosis, atrial, ventricular, pulmonary and systemic vascular function in addition to pulmonary pathologies.

In this population with severe airway limitation, during acute hospitalized COPD exacerbation, severe coronary disease was present in approximately one-third of patients, and heart failure with reduced ejection fraction was present in about 10% of patients. Both were clinically covert in up to two-thirds of these patients, that is, standard tools (clinical examination, cardiac enzymes, chest X-ray and electrocardiogram) did not detect these pathologies. Put another way, the diagnosis of key treatable traits during these acute COPD hospitalizations could only be achieved through advanced imaging technology—with noteworthy implications.

First, the impact of cardiovascular disease is likely to have been underestimated in studies that did not directly assess cardiovascular-related mortality. For example, the UPLIFT study is frequently cited in support of the contention that in mild and moderate COPD cardiovascular deaths predominate and that in severe COPD respiratory deaths predominate. This study used central mortality adjudication to determine causality and there was disagreement between site investigators and the adjudication committee in cardiovascular death attribution. Moreover, of deaths attributed by the adjudication committee to COPD exacerbation, data were incomplete in a majority. Taken together, these findings imply that cardiovascular deaths could have been unrecognized and may have been causal or at least a contributor to patient mortality.

Second, the viewpoint of cardiovascular disease during AECOPD as an ‘alternate’ or ‘differential diagnosis’ may need to be reconsidered as this is likely to lead to underdiagnosis. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) and COPD-X suggest a clinically directed approach to detection of cardiovascular disease during AECOPD, using descriptors such as ‘alternative’, ‘complications’ (COPD-X) and ‘differential’ (GOLD) to frame cardiovascular disease. Such terminology would imply that AECOPD and cardiovascular disease are mutually exclusive; however, it is clear that both diseases can be simultaneously present. An additional conundrum for the clinician is that these influential documents acknowledge that the conventional clinical cardiovascular diagnostic armamentarium is blunted in COPD, but still suggest a clinically directed approach. Overall, current clinical approaches and cognitive frameworks to detecting cardiovascular disease during AECOPD are likely to result in underdiagnosis.

Third, treatment opportunities are likely to be greater than previously anticipated. For coronary
atherosclerosis, recent Dutch data systematically examining patients with COPD in community care indicate that over 90% of patients can be categorized as high or very high coronary risk.17 Our data complement this notion: 55% of individuals with hospitalized AECOPD had sufficiently severe coronary atherosclerosis to warrant aspirin and lipid-lowering therapy but most were not treated.18 Thus, it would be common for patients with AECOPD to have some degree of coronary atherosclerosis that is undertreated.11 In addition, emerging data suggest that therapeutic responses may vary according to cardiac imaging phenotype.19 Overall, as underdetection of impactful ‘traits’ such as severe coronary atherosclerosis is common, it would be reasonable to expect that addressing diagnosis and treatment during AECOPD would improve outcomes. Further work is required to ascertain whether imaging assessment, followed by cardiovascular phenotype-directed intervention, could improve outcomes in AECOPD and beyond. The role of advanced CT imaging in advancing approaches to cardiovascular disease in COPD is promising but nascent. Cardiac CT can help disentangle the protean (and frequently subclinical) manifestations of cardiovascular disease. Cardiovascular traits may have differential impacts on outcomes. Our data show that aortic stiffness has an important effect during AECOPD,20 and unpublished data indicate that ventricular parameters powerfully influence outcomes including mortality (Fig. 1).

In conclusion, there is compelling evidence that a key treatable trait, cardiovascular disease in COPD, is underdiagnosed and undertreated. AECOPD are an opportune time to assess this pathology using innovations in cardiac imaging that overcome limitations of conventional diagnostic modalities. As clinicians grapple with the challenge of implementing precision medicine in AECOPD to improve outcomes, recognition and treatment of specific and impactful cardiovascular disease traits is an attractive target.

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