Morbidity from chronic obstructive pulmonary disease (COPD) continues to rise, increasing by 58% between 1990 and 2010 (1). The most common causes of death in COPD patients are cardiovascular events, and preliminary data implicate arrhythmias as an important mediator (2,3). This speaks to the need to determine whether COPD is an independent contributor to increased sudden cardiac death (SCD) risk and to delineate the underlying pathophysiologic mechanisms, particularly those that may be amenable to intervention.

In this issue of JACC: Clinical Electrophysiology, Narayanan et al. (4) present compelling epidemiological evidence supporting the notion that COPD is associated with SCD. The authors compared a cohort of 728 SCD cases to a cohort of 548 control subjects with coronary artery disease from the same geographic region. Statistical analyses identified a strong likelihood of SCD patients to have a documented diagnosis of COPD. Despite the limitations inherent to the study design, these findings are consistent with other recently published epidemiological reports (5,6), and invite exploration of the possible causal mechanistic pathways linking COPD to SCD.

The authors are commended on their approach to the difficult task of trying to separate the COPD-SCD association from the effects of coronary artery disease and ischemic cardiomyopathy; prior studies report a positive correlation between the presence and severity of COPD and adverse cardiac events in patients with known coronary disease (6). The possibility of residual confounding from coronary disease and its risk factors was appropriately acknowledged by the authors; for example, although the proportion of smokers was similar in the SCD versus coronary artery disease controls, there may have been differences in the actual cigarette use history (pack-years). Because SCD is relatively uncommon, the possibility of selection bias exists: only SCD patients with an available pre-arrest left ventricular ejection fraction measurement were included in this study. This would imply that previously "healthy" patients with "out of the blue" SCD (no cardiac history, hence no pre-SCD echocardiographic measurements) could not be evaluated in this analysis. Conversely, patients on home oxygen were excluded, suggesting that those patients with the most severe COPD were not taken into account. Thus, the data presented seem not to have included the extremes of the COPD spectrum, namely those well enough to have not merited a cardiac evaluation and those sick enough to need home oxygen.

Narayanan et al. (4) also make the very interesting observation that <4% of SCD patients had a prior implantable cardioverter-defibrillator. One possible implication is that these sudden deaths occurred primarily in patients in whom risk stratification
did not indicate the need for an implantable cardioverter-defibrillator. This invites speculation that inclusion of a COPD-based measure in sudden death risk stratification would increase the accuracy of predicting SCD in patients with other, more traditional risk markers such as reduced left ventricular ejection fraction.

Perhaps the greatest impact of the data presented by these investigators lies in identifying plausible causes underlying the SCD-COPD relationship, particularly the use of medications specific to COPD patients. Their study identified an association between short-acting β-agonists and SCD in those not on β-blocker therapy. In this instance, it would have been particularly helpful to explore whether and how the severity of COPD impacted this result. In other words, were those patients with more severe COPD (who were probably more likely to be using β-agonists and avoiding β-blockers) the ones at greatest risk for SCD? This is relevant, especially in light of recent reports suggesting that β-blocker therapy in COPD patients after myocardial infarction is associated with improved survival (7). Despite these limitations, the investigators pose important questions regarding routine use of β-agonist medications in COPD patients predisposed to SCD, and the results of an ongoing, large, randomized trial are needed to shed further light on the safety profile of these medications in COPD patients with heart disease (8).

Indeed, β-blocker therapy in COPD may be analogous to β-blocker therapy in heart failure, in that both disease conditions have been accompanied by reluctance to use β-antagonist therapy. Randomized, controlled trials resulted in a complete paradigm shift in heart failure. Perhaps we can anticipate a similar future for β-blocker therapy in COPD, so that selective β1-antagonist therapy is prescribed, even, or especially, when β2-agonist therapy is being used.

Even though these data cannot assess the role of ventricular arrhythmias in the etiology of SCD in COPD patients directly, growing evidence speaks to the intrinsic proarrhythmic milieu in the ventricular myocardium in patients affected by COPD (9). This line of thought is not entirely surprising, given the known proarrhythmic associations between COPD and atrial arrhythmias (particularly multifocal atrial tachycardia). Even though the reason for increased arrhythmogenesis in COPD remains open to further investigation (3), the notion that prolonged and inhomogeneous propagation of depolarization could be present in the myocardium of COPD patients has emerged (9). Other hypotheses include sympathetic activation (10), oxidative stress, low oxygenation, pulmonary hypertension, and the use of β-agonist bronchodilators, which have been shown to alter ventricular refractoriness (11). Intriguing results from a randomized pilot study suggested that ventricular ectopy can acutely improve with effective bivelvel positive airway pressure ventilation in COPD patients with respiratory failure, possibly due to improvements in autonomic neural balance (12). Right ventricular strain and hypertrophy are more commonly evident on electrocardiographs of COPD patients, but whether such ECG features translate to arrhythmogenesis in these patients remains unknown (3,13).

REPRINT REQUESTS AND CORRESPONDENCE: Dr. Virend K. Somers, Division of Cardiovascular Diseases, Mayo Clinic, 200 First Street SW, Rochester, Minnesota 55905. E-mail: somers.virend@mayo.edu.

REFERENCES


KEY WORDS arrhythmia, chronic obstructive pulmonary disease, sudden cardiac death.