Does Chronic Obstructive Pulmonary Disease Cause Cardiovascular Disease?

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In this issue of *Hypertension*, Fisk et al[1] attempt to dissect the intrinsic contribution of chronic obstructive pulmonary disease (COPD) to augmented risk of cardiovascular disease. Presence of common risk factors, notably smoking, and other confounders makes this an ambitious exercise. Data from 2 observational cohorts were studied in a case–control design in subjects who had undergone investigations of key surrogate markers of cardiovascular risk, namely, subclinical atherosclerosis (carotid intima–media thickness) and arteriosclerosis (arterial stiffness measures based on aortic pulse wave velocity and augmentation index).

Patients with COPD and confirmatory spirometry were aged ≥40 years, with ≥10 pack-years of smoking and free of exacerbations in the preceding 4 weeks before study entry. Control patients were matched on the basis of age, sex, and body mass index. As expected in such studies, there were multiple demographic factors that were significantly different between the 2 groups: angina, myocardial infarction, stroke, and peripheral vascular disease and diabetes mellitus were all more common in the COPD cohort, as was therapy for hypercholesterolemia. The latter may explain the slightly lower mean low-density lipoprotein cholesterol in the COPD group compared with control subjects, but the mean value in the patients with COPD was still high (3.00 mmol/L), suggesting undertreatment. These findings were concordant with the higher carotid intima–media thickness values in patients with COPD. Similarly, although there was no difference in antihypertensive therapy, systolic blood pressure (mean, 145 mm Hg) and pulse pressure (mean, 64 mm Hg) were higher in patients with COPD, and all measures of arterial stiffness, after appropriate corrections, were also significantly worse. When patients with COPD were compared with current/ex-smokers without COPD, the same general differences were seen (ie, higher systolic and pulse pressure, increased arterial stiffness indexes, and increased subclinical atherosclerosis in patients with COPD). To account for these differences, regression analyses were used and confirmed that COPD was an independent predictor of arterial stiffness and subclinical atherosclerosis.

There are inevitably some limitations in this type of study design, including the observational nature of the study and the inability to measure all putative mediators of vascular risk. The number of patients with COPD was relatively small, and the control group also included only a minority with carotid intima–media thickness measurements. The hs-CRP (high-sensitivity C-reactive protein) was higher, as expected, in the COPD group. Because inflammation has often been cited as a potential mechanism linking COPD to vascular disease, lack of inclusion in the regression analyses is another limitation. The only drug classes analyzed were antihypertensive and hypercholesterolemia medications, but drugs that may cause vascular harm (eg, some antihyperglycemic agents, β-agonists, and inhaled and oral corticosteroids) were not analyzed. Even so, the strength of this analysis is the attempt to provide multiple adjustments for known risk factors common to both cardiovascular and COPD and for many other confounders. The sample size ratio of 3:1 of controls:COPD cases is relatively large, and the surrogate markers of cardiovascular risk are well accepted. The comparison of patients with COPD with those who are current/former smokers without COPD is also a strength. Furthermore, the conclusions are concordant with other observations linking vascular abnormalities to COPD and to airflow obstruction.[2–4]

Accordingly, this article helps to further bolster the link between COPD and cardiovascular risk with COPD per se as a major multiplier of this risk. Cardiovascular risk in patients with COPD has been estimated to be 2.5-fold, and such patients also have an approximately one-third higher risk of the traditional risk factors of hypertension and diabetes mellitus.[5] Systematic reviews of other studies, which have also attempted to control for confounders, have documented important and significant associations between COPD and carotid intima–media thickness, prevalence of carotid plaque, endothelial dysfunction, increased coronary artery calcium, and abnormal ankle–brachial index measurements.[3,4] The mechanisms underlying these findings remain conjectural and complex[6]: humoral and cellular mediators of inflammation, hypercoagulability, augmented platelet activation, enhancement of pathways leading to oxidative stress, accelerated senescence of epithelial and endothelial cells, hypoxemia-mediated mechanisms, including activation of the sympathetic nervous system, and abnormalities of extracellular matrix or protease/antiprotease imbalances that increase elastin degradation. All are implicated in the pathogenesis of both COPD and atherosclerotic vascular disease, including the surrogates studied by Fisk et al.[1]

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The authors conclude appropriately that trials of novel therapies targeted toward these surrogate markers of cardiovascular risk are required. But the article implies more. It is sobering to consider that in spite of advances in COPD therapy, temporal trends indicate worsening age-adjusted mortality[7] with 50% of that still accounted for by cardiovascular causes. There are currently no COPD-specific medications that have curtailed cardiovascular comorbidity. The prominence of cardiovascular morbidity and mortality is seen in other diseases, for example, diabetes mellitus, which imparts its own unique set of mediators of direct vascular injury that also interact with and augment the effects of traditional mediators of cardiovascular morbidity and mortality. Only recently have some drugs with hypoglycemic effects been shown to clearly have beneficial effects on cardiovascular outcomes, even though the latter is not through lowering glucose. However, comprehensive vascular protection has been a long-standing, major tenet of chronic diabetes mellitus management, and the approach has been shown to reduce mortality.[8]

Lee et al[9] have shown that both cardiovascular and total mortality prediction can be significantly improved when COPD severity and global cardiovascular risk, as determined by traditional risk factors, are considered together. This approach would identify patients with COPD with sufficient risk to warrant comprehensive modification of risk factors including lipids, blood pressure, and diabetes mellitus, all shown in the study of Fisk et al[1] to be more common in patients with COPD and perhaps not adequately treated. Thus, although more research is required to unravel the mechanisms and relationship to surrogate markers, this study should also bring to mind that the contribution of COPD per se to cardiovascular morbidity and mortality might be curtailed substantially by traditional cardiovascular risk reduction. Among the interventions most directly related to amelioration of the surrogates evaluated in this study and also associated with cardiovascular risk reduction are statins, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers. Given the common comorbidity of diabetes mellitus, certain diabetes mellitus agents, such as sodium glucose transport-2 inhibitors or glucagon-like peptide-1 receptor agonists, may also be relevant. Although a trial of statins in subjects not meeting indications for statin use and, therefore, at low risk of cardiovascular disease did not show any impact through pleiotropic effects on COPD end points, the study was underpowered to demonstrate potential value for reducing cardiovascular comorbidity in these low-risk patients and does not preclude a benefit in higher-risk patients.[10] The important article of Fisk et al[1] suggests that more assiduous, traditional cardiovascular risk assessment and therapy may have a palpable impact on cardiovascular comorbidity of COPD. It is time to routinely assess cardiovascular risk factors in patients with COPD and initiate cardiovascular risk reduction treatment in a similar fashion to the current practice in patients with diabetes mellitus.

Disclosures

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