

develop early intervention strategies that can be implemented to prevent rather than treat lung disease in patients with CF.

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Idiopathic Pulmonary Fibrosis A Shot through the Heart?

Atherosclerosis is the result of an exuberant fibroproliferative response of the endothelium and smooth muscle of the arterial wall to injury. Recruitment of leukocytes, accumulation of cholesterol-laden macrophages, smooth muscle cell proliferation, deposition of extracellular matrix, and angiogenesis lead to progression of systemic arterial lesions. Idiopathic pulmonary fibrosis (IPF), too, is often characterized by leukocyte infiltration (of alveolar walls), endothelial and smooth muscle hypertrophy of the pulmonary vasculature, stimulation of myofibroblasts, and aberrant vascular proliferation in response to an (as yet unidentified) insult. Despite the shared profile of maladaptive “wound healing,” the clinical association of these cardiopulmonary syndromes is not well defined.

In this issue of *AJRCCM* (pp. 1257–1261), Hubbard and colleagues (1) provide data that seemingly strengthen the ties between these disease states. Two separate analyses were performed. The first was a population-based case-control study which showed that angina, acute coronary syndrome, and deep vein thrombosis were associated with an increased probability of an eventual clinical diagnosis of IPF, as recorded in a general medical care database. The second was a retrospective cohort study of patients without a preexisting cardiovascular diagnosis which showed that IPF was also a risk factor for developing an acute coronary syndrome or deep vein thrombosis. Strengths of the study include the novel questions asked, the use of a population-based cohort, a large sample size, a long follow-up period, and the execution of two distinct analyses. Weaknesses include lack of information on covariates and detailed multivariate analyses, a clinical diagnosis of IPF that does not necessarily conform to accepted diagnostic criteria, and possible “protopathic bias,” which could affect the conclusions regarding the association of medication use and IPF (2).

In light of these strengths and weaknesses, what are the possible explanations for the associations between cardiovascular disease, cardiac medications, and IPF? The skeptic could conclude that the findings from both case-control and cohort analyses could be entirely attributable to residual or unmeasured confounding. Smoking status is a traditional risk factor for both cardiovascular disease and IPF, although there was no association with the latter in this study. Because the intensity and duration of smoking were not considered (and there were some missing data for smoking status), residual confounding by smoking could account for the apparent association between coronary artery disease (CAD) and IPF. More pack-years of smoking in an individual could result in both a higher probability of cardiovascular events and a greater risk of IPF compared with the probability of these diseases in individuals with a lesser smoking history, creating the appearance of a causal relationship between these two syndromes. Similarly, if the cases with missing data for smoking history actually were more often smokers than the control subjects with missing data, smoking could again account for the findings.

Other important risk factors for cardiovascular disease, such as race/ethnicity, obesity, diabetes mellitus, systemic hypertension, family history of premature atherosclerosis, and lipid levels were similarly not included in the analyses. While these are not definitively associated with IPF, one study has suggested that diabetes mellitus might indeed be a risk factor (3). Infection, environmental exposures, or a shared genetic predisposition could account for the association between CAD and IPF (4–6). Confirmatory studies need to include such data in multivariate analyses to eliminate potential confounding by these factors.

It is possible that IPF increases the risk of CAD, as implied by the findings from the cohort analysis. To explain the findings of the case-control study under this paradigm, subclinical pulmonary fibrosis would have had to precede both the onset of cardiovascular disease and the actual diagnosis of IPF. Previous human and animal investigations of lung injury and fibrosis demonstrate up-regulation of protease inhibitors (7), leading to hypercoagulability, suppression of fibrinolysis, and, possibly, thrombotic events. IL-4, tumor necrosis factor (TNF)- α , and IL-13 are elevated in pulmonary fibrosis and are atherogenic. IL-4 and TNF- α up-regulate cell adhesion molecules and facilitate recruitment of leukocytes to the vascular intima (8). In addition, IL-4 and IL-13 stimulate lipoxygenases that augment proatherogenic, oxidized low-density lipoprotein (LDL) (9) and reduce hyaluronectin, promoting angiogenesis and atherosclerosis (10). Furthermore, immune activation as seen in patients with IPF could predispose to atherosclerosis by converting normally antiinflammatory high-density lipoprotein (HDL) into proinflammatory HDL, supporting LDL oxidation and atherogenesis (11).

A causal relationship between CAD and IPF could explain Hubbard and colleagues' findings. Angiogenesis is an essential process and supports fibroplasia, deposition of extracellular matrix, and chronic inflammation in atherogenesis (12). Similarly, an abundance of angiogenic chemokines, as compared with angiostatic chemokines, has been demonstrated in both animal models and tissue specimens from patients with IPF (13). Conceivably, a circulating angiogenic factor could originate from the systemic vascular endothelium and affect the lungs. For instance, IL-8 is associated with the angiogenesis underlying atherosclerotic plaque growth (12) as well as the vascular remodeling seen in IPF (13). Hubbard and coworkers also showed associations between certain medications prescribed for cardiovascular indications and an increased risk of IPF. The possible role of subclinical manifestations of IPF in contributing to the indication for prescribing these medications makes these results important to confirm before drawing conclusions.

Future investigations are required to better understand the relationship between IPF and systemic vascular disease as well as the mechanisms shared by the two syndromes. Whether IPF is to blame for cardiovascular disease (or vice versa) is interesting but as yet unproven. Future investigations of the common pathways shared by these conditions could provide insights into the natural history of both. Furthermore, if a causal association were confirmed (with a clear direction), the presence of IPF itself could constitute a sufficiently potent risk factor for CAD such that more aggressive goals in risk factor modification would be warranted. Until then, we do not know if we need to take a diagnosis of IPF to heart and intervene before the damage is done.

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