Association between Impaired Lung Function and Cardiovascular Disease. Cause, Effect, or Force of Circumstance?

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Large, population-based cohort studies have consistently shown that lung function, and particularly FEV1, predicts cardiovascular mortality. For example, in 2005, Sin and colleagues undertook a major systematic review comprising a total of 83,880 participants in 12 studies and reported that pulmonary function predicted cardiovascular mortality (1). The pooled relative risk for the lowest compared with the highest lung function group was 1.99 (95% confidence interval, 1.71-2.29) (1). However, despite the considerable interest surrounding cardiovascular comorbidity in chronic obstructive pulmonary disease (COPD) (2), the mechanisms underlying this doubling in cardiovascular mortality remain uncertain.

For many observers, there are three potential hypotheses linking COPD with cardiovascular morbidity and mortality. First, reduced lung function may cause cardiovascular disease through increased systemic inflammation, promoting atheromatous disease and a prothrombotic state (3). Second, shared avoidable risk factors, such as smoking habit and other environmental factors, may simultaneously and independently cause endothelial dysfunction in both the pulmonary and systemic vasculature, with resultant disease in both organ systems (4). Finally, lung function may, similar to height, reflect a range of adverse fetal and early life factors, predisposing individuals to increased cardiovascular risk as well as a range of other adverse outcomes (5).

Determining the causal mechanism underlying this well-established association between pulmonary function and cardiovascular disease is the subject of the article published in this issue of the Journal by Chandra and colleagues (6). It focuses on the first of these possibilities, hypothesizing that reduced pulmonary function causes endothelial dysfunction, and subsequently atheroma formation. In a cross-sectional design incorporating two cohorts of 231 and 328 participants selected from larger population-based cohorts (the former selected to have a smoking history of >10 pack-years), the authors found that reduced FEV1 was moderately associated with markers of atheromatous disease, as identified on B-mode carotid ultrasound and non-ECG gated computed tomography coronary artery calcification (odds ratios per 25% decrement in FEV1 ranged from 1.28 to 1.76 across different measures). They also demonstrated that markers of endothelial dysfunction, measured via ultrasound-assessed flow-mediated dilatation and the reactive hyperemia index, were moderately associated with atheroma (odds ratios per 1 SD increment ranged from 1.30 to 1.36 across different measures). However, importantly, the association between FEV1 and atheroma was not attenuated by adjusting for endothelial dysfunction, as might have been expected if endothelial dysfunction had been a mediator.

Previous observational studies examining atheroma burden in relation to lung function and emphysema have yielded variable results (7-12). In the Multi-Ethnic Study of Atherosclerosis study, coronary artery calcification was not associated with FEV1 after adjusting for age, sex, and demographic features (12). However, in the largest study, conducted in the Atherosclerosis Risk in Communities study, FEV1 was associated with the ankle brachial index (an indirect measure of atheroma), even among never- smokers (9). The current study adds weight to the suggestion that atheroma in the coronary arteries may be associated with FEV1.

In the present analysis, flow-mediated dilatation was performed in fasted patients having withheld caffeine, alcohol, and inhalers, thereby reducing variability. Moreover, sonographers were blinded to each participant's lung function status, making measurement bias less likely. The study participants were drawn from population-based cohort studies, making it unlikely that the observed associations were caused by

selection bias. These methodological strengths increased the reliability and validity of the findings. However, although the combined sample size across the two cohorts was likely sufficient to examine the exposure-outcome association (between FEV1 and atheroma), surprisingly large sample sizes may be needed to estimate mediation effects, particularly where the exposure-outcome association is weak or moderate (13). As a consequence, the finding that endothelial dysfunction was not a mediator may be a result of random error, especially as only noninvasive markers of endothelial function were employed. Nonetheless, as discussed by the authors, one potential explanation of these findings is that FEV1 causes atheroma through mechanisms independent of endothelial function, such as via increased arterial stiffness or elastocalcinosis (14-18). However, another possibility is that FEV1 and cardiovascular disease are not causally related, but are simply confounded because of the presence of shared environmental and lifestyle factors (hypothesis 2).

As well as cardiovascular disease, reduced pulmonary function predicts a broad range of adverse health outcomes, including cancer from all causes, non-respiratory cancer, rupture of aortic aneurysm, and even psychiatric illness (5, 19, 20). Moreover, FEV1 is associated with ischemic heart disease mortality in a broadly linear fashion, with no evidence of a plateau beyond normal levels of lung function (5). These observations are consistent with the view that FEV1 may be a broad marker of cardiovascular risk (and health more generally), rather than a specific cause of cardiovascular disease (hypothesis 3). If this is true, we can expect more null findings in studies examining causal links among pulmonary function, endothelial dysfunction, and cardiovascular disease, such as in the article by Chandra and colleagues (6).

Life-course epidemiology may help determine the nature of the relationship between FEV1 and cardiovascular disease. Both pulmonary function (2l) and cardiovascular risk (22) are known to have early life determinants. However, just as clinical trials of effective cholesterol-lowering therapies unequivocally demonstrated that serum cholesterol plays a causal role in coronary heart disease, it is likely that clinical trials will be needed to resolve the causal question of how pulmonary function relates to cardiovascular risk in COPD. The recent Study to Understand Mortality and Morbidity trial examining the use of pulmonary therapies in COPD, for example, has included cardiovascular events as a secondary outcome (23). Findings from this and other studies intervening on lung function are needed to identify whether reduced pulmonary function causes cardiovascular disease in adult life. The debate continues.

Conflicts of Interest

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