EDITORIAL

Computed tomography scan for atherosclerosis and emphysema: A great hope or a great hype?

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Chronic obstructive pulmonary disease (COPD) affects more than 700,000 Canadians over 40 years of age and accounts for 120,000 deaths every year in Canada, making COPD the fourth leading cause of mortality (1). By the year 2020, COPD is expected to become the third leading cause of mortality worldwide, surpassing infectious diseases and cancer (2). This COPD epidemic is being driven by an aging population, the increase in smoking prevalence in developing countries and the current absence of disease-modifying treatments.

Although the traditional belief was that most patients with COPD died from respiratory failure, recent epidemiological data indicate that patients with COPD are at increased risk of lung cancer and cardiovascular diseases (3). Indeed, in mild to moderate COPD, lung cancer is the leading cause of mortality and ischemic heart disease is the second, accounting for nearly 25% and 20% of all deaths, respectively (3). In advanced cases of COPD, cardiovascular disorders are the primary causes of mortality in nearly 25% of patients. Cardiovascular diseases are the leading cause of hospitalization in COPD patients, accounting for nearly 50% of hospital admissions. Independent of age, smoking (current status and past history of smoking), lipid levels, comorbidities and other salient cardiovascular risk factors, COPD patients have two to three times the risk of ischemic heart disease compared with individuals without COPD (4). At a population level, COPD may be responsible for 20% to 25% of all deaths related to ischemic heart disease, independent of the effects of cigarette smoking (5). Indeed, in one study (5), the risk of death from ischemic heart disease imposed by COPD was as great as that imposed by hypercholesterolemia or hypertension. Not surprisingly, given these observations, therapies that reduce the burden of ischemic heart disease, such as statins, beta-blockers and angiotensin-converting enzyme inhibitors, are associated with improved health outcomes in patients with COPD (6,7).

Although at the population-level the relationship between COPD and heart disease is relatively straightforward, the relationship between COPD phenotypes and heart disease remains poorly defined. There are two major phenotypes in COPD: emphysema and airway disease (8). Emphysema is characterized by destruction of distal airspaces, leading to poor gas exchange, while airway disease is characterized by airway remodelling. Both phenotypes produce airflow limitation that is detectable using spirometry and is poorly reversible or nonreversible using bronchodilator therapy (9). Thus, these phenotypes cannot be differentiated using spirometry alone. The 'gold standard' for COPD phenotyping is quantitative morphometry, performed on resected lung tissue in pathology laboratories. Although this approach is highly accurate, this method is clearly inappropriate for disease surveillance or therapeutic follow-up studies requiring (multiple) serial measurements.

Non-contrast-enhanced computed tomography (CT) is a noninvasive imaging tool that has the potential to accurately phenotype COPD and detect disease progression. Over the past 10 years, there has been an explosion of studies that have used CT scanning to phenotype and monitor COPD patients. CT scan attenuation data can be analyzed semiquantitatively using trained observers or quantitatively using computerized measurement of lung tissue x-ray attenuation values. Both techniques correlate reasonably well with patient lung function, as assessed by forced expiratory volume in 1 s or by single-breath carbon monoxide diffusing capacity (10). Owing to its noninvasive nature and widespread availability, CT scanning is now routinely used to quantify the severity and distribution of emphysema during preoperative workup for lung volume reduction surgery and in large-scale clinical and epidemiological studies of COPD patients to track disease progression and responses to novel therapies (11).

Besides phenotyping and quantifying COPD, noncontrast thoracic CT scans can provide additional clinically useful information, including improved detection of small lung nodules offering increased potential for curative lung cancer resection. Noncontrast CT scans are also being performed to detect calcium deposits in coronary vessels for detection of subclinical coronary atherosclerosis. Given the unique motion issues of cardiac imaging, a specialized electron beam computed tomography (EBCT) scanner was developed in the 1980s to visualize rapidly moving cardiac structures. This scanner proved to be useful, allowing accurate detection of calcified plaques in coronary vessels. Extensive research in the 1990s using EBCT facilitated the development of automated software that calculated the coronary artery calcium (CAC) score. This score is a measure of the underlying coronary atherosclerotic burden and is predictive of the risk of future coronary events (12-14). A CAC score of 100 or higher, for instance, is associated with approximately a sevenfold increase in the risk for nonfatal or fatal coronary artery disease, compared with a CAC score of zero (12), independent of other risk factors for coronary artery disease such as age, sex, smoking status, lipid levels, history of coronary events or diabetes (15).

The recent development of multidetector row CT scanners has allowed the implementation of cardiac gated coronary scans on conventional (non-EBCT) scanners. Recently, investigations have shown that CAC scoring performed on multidetector scanners is comparable with those scores obtained using EBCT scanners (16). Therefore, the extensive body of CAC research performed on EBCT scanners can be applied to cardiac gated multidetector CT scans, which are commonly obtained in community and academic hospitals worldwide. While EBCT provides more rapid image acquisition (50 ms to 100 ms) than multidetector conventional CT (83 ms to 165 ms), contrast and spatial resolution is inferior using EBCT. Therefore, emphysema detection is likely less sensitive using semi-quantitative analysis of EBCT images compared with those obtained using multidetector scanners.

On pages 369-372 of this issue of *The Canadian Journal of Cardiology*, Alhaj et al report findings from a large epidemiological study of patients who received thoracic EBCT scans at their centre in New York (n=1720). They found that 5% of the cohort had "typical bilateral bullous changes" involving apical areas, indicating emphysema, and 45% had a CAC score higher than zero on EBCT scans. As may be expected, smokers were 3.5 times more likely to have the typical emphysematous changes on EBCT scans compared with nonsmokers. Of note, subjects with emphysema were approximately 63% more likely to have a CAC score of 100 or higher than subjects without emphysema (P=0.013). Advanced age, male sex, a history of hypertension and current smoking status were all independently associated with increased CAC scores in this study.

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These findings are consistent with other epidemiological studies that have shown a link between reduced lung function (as measured by spirometry) and coronary events (4). However, none of the previous epidemiological studies used CT scans to assess emphysema; rather, they relied almost exclusively on spirometry. Because both airway disease and emphysema contribute to reduced lung function, these studies could not determine the relationship between the 'emphysema' phenotype of COPD and coronary artery disease. The study by Alhaj et al demonstrated that the emphysema phenotype is an independent risk factor for coronary artery disease.

The major strengths of the study by Alhaj et al include the large sample size and the unbiased nature of the assessment of lung and coronary artery disease. There were also some limitations. The cross-sectional nature of the study design precludes any inference regarding the directionality of the relationship. While we believe that emphysema contributes to the development of atherosclerosis, reverse causation cannot be fully discounted. However, we are not aware of any experimental model wherein atherosclerosis leads to emphysema. We also cannot dismiss the possibility that the findings of this study were by chance or due to shared risk factors. Cigarette smoking and air pollution are both risk factors for atherosclerosis and emphysema, which were suboptimally adjusted for in this analysis. The study investigators also did not conduct lung function measurements and did not perform any quantitative assessments for emphysema or airway disease. Our personal experience with CT scanning is that qualitative assessment by an experienced radiologist (as was the case in this study) tends to underestimate the extent and severity of emphysema, whereas quantitative assessment using an automated computerized algorithm tends to overestimate it. Combined with the inferior spatial and contrast resolution of the EBCT scanner, the 5% emphysema prevalence in this study is likely a very conservative estimate of the 'true' prevalence of emphysema in this cohort.

Notwithstanding these limitations, the study by Alhaj et al has added to a growing body of literature that indicates that COPD (and, more specifically, emphysema) is a risk factor for atherosclerosis. More importantly, the study provides empirical evidence that EBCT and other methods of CT scanning can be used to noninvasively assess emphysema and coronary artery disease simultaneously, providing great hope that this technology can be used in the future to gain a greater understanding of the heart-lung interactions in COPD and to evaluate new therapies that can impact both lung and heart disease.

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