The restrictive–obstructive continuum and the failing heart

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The close interrelationship between the heart and lungs was early recognised by medical scientists. In a paper from 1895, Alfred Lee Loomis stated that dyspnoea could be divided into four categories on an aetiological basis: laryngeal dyspnoea, bronchial dyspnoea, pulmonic dyspnoea and cardiac dyspnoea. The term cardiac dyspnoea was used if dyspnoea arose 'from arrest in the passage of blood through the heart to the lungs'.[1] Early studies using spirometry observed that patients with heart disease had lower vital capacity than 'normal individuals'.[2] Many years later, prospective analyses of population-based cohorts showed that reduced lung function also could predict the onset of cardiac diseases.[3 4] Many studies since have shown that reduced vital capacity or FEV_1 is associated with increased incidence of cardiovascular diseases among individuals from the general population.[5 6] The relationships have been quite strong and comparable with the effects of traditional cardiovascular risk factors, such as obesity or hyperlipidaemia. The increased risk is not limited to those with the smallest lung volumes; in many studies there is a dose–response relationship over the whole distribution of FEV_1 or FVC.

However, even though much research has been performed over the past decades, the underlying causal reasons for the increased cardiovascular risk remain elusive. Cardiovascular and pulmonary diseases certainly share some important risk factors, such as smoking, inflammation and physical inactivity, but the increased risk in individuals with low lung function has usually persisted after extensive adjustments for other risk factors, and significant relationships have been shown in studies of never-smokers.[6] It has been reported that cardiovascular disease and reduced lung function share common genetic determinants, but this probably cannot explain more than a small fraction of the excess risk.[7]

The fact that cardiovascular disease is a very heterogeneous concept further increases the complexity of the interactions with lung function. Reduced FEV_1 or FVC has been linked to quite different cardiovascular complications, such as myocardial infarction and stroke,[5 6] ventricular arrhythmia,[8] incidence of atrial fibrillation,[9] diabetes mellitus[10] and blood pressure variability.[11]

Similarly, 'reduced lung function' includes many different phenotypes and more research is needed to clarify which aspects of lung function impairment are most important. Even though there are several exceptions in the literature, it is noteworthy that many population-based studies have reported increased risk for individuals with low FEV_1 or FVC, well within the normal range, but no clear relationship with low FEV_1/FVC.[10 12] Since COPD is characterised by low FEV_1/FVC ratio, this is in contrast with the findings in many clinical settings, which often have reported high prevalence of cardiovascular disease co-morbidity in patients with COPD.[13] Indeed, there is reason to believe that the risk of cardiovascular diseases is associated with more than one type of lung function impairment. A recent study reported that the natural history of airway obstruction leading to COPD could be quite different; some individuals had a rapid FEV_1 decline while others had low FEV_1 already in early adulthood.[14] The natural history leading to cardiovascular disease could similarly involve different pathways and much more research is needed to fully characterise the phenotypes with high risk. Prospective studies of cohorts with detailed information about respiratory function have the potential to add new and important insights into the natural history of both cardiovascular and respiratory diseases.

The comorbidity between COPD and heart failure has received much attention in the past few years. However, few studies have explored whether reduced lung function predicts future onset of heart failure. In the current issue of *Thorax*, Wannamethee *et al*[15] assessed the relationships between lung function, circulating cardiac markers and incidence of heart failure, in 3242 older men. The research was performed in the British Regional Heart study, a well-known population-based cohort, which was established with the purpose of studying cardiovascular disease and its risk factors. The authors show that N-terminal pro-brain natriuretic peptide (NT-proBNP) and troponin T, markers of myocardial wall stress and myocardial injury, are inversely associated with FEV_1 and FVC. Both cardiac markers were increased in men with restrictive pattern on spirometry as well as for those with moderate or severe obstruction. Incidence of heart failure was increased in men with moderate or severe obstruction, while the increased incidence in men with pulmonary restriction was attenuated and non-significant after adjustments for risk factors. The same pattern was seen when the analyses were restricted to never smokers and long-term ex-smokers. NT-proBNP and troponin T are sensitive measures of preclinical cardiac injury and adjustments for these markers should substantially reduce the risk of reverse confounding in this study, that is, that preclinical heart failure caused the abnormal findings on spirometry. The increased levels of cardiac markers both in the restrictive and obstructive ends of the continuum illustrate that the cardiovascular risk could have at least two distributions. Since low FVC is associated with increased risk of diabetes,[10] it could be speculated that the restrictive pattern represents a 'metabolic' risk group, which also may be linked to early life exposures,[16] while the obstructive pattern could be acquired later in life and represent other pathways to cardiovascular disease.

The men were 60–79 years old at baseline and were followed up over a mean time of 13 years. One question, acknowledged by the authors, is whether the results can be generalised to younger age groups. The fixed ratio between FEV_1 and FVC was used both for the definition of obstruction according to Global Initiative for Chronic Obstructive Lung Disease (FEV_1/FVC<0.70) and to define restrictive airway pattern (FEV_1/FVC≥0.70 and FVC% predicted <80%). Since FEV_1/FVC declines with increasing age, it is likely that the proportions of and characteristics of men fulfilling the obstructive and restrictive definitions depend on the age group of the study. Hence, further studies of women and younger populations are of interest.

The causal relationships between lung function and incidence of cardiovascular disease are complex and elusive and much research is still needed to clarify the nature of the associations. The study by Wannamethee *et al* has taken us one step further by their report of cardiac markers

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and incidence of heart failure along the restrictive–obstructive continuum of pulmonary function.

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