# Cardiovascular Risk in COPD

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**Editorial**

# Cardiovascular risk in COPD: searching for a culprit

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The notion that chronic obstructive pulmonary disease (COPD) is associated with high prevalence of cardiovascular and metabolic diseases is difficult to refute. Large longitudinal cohort studies have repeatedly reported the common occurrence of concomitant COPD, cardiovascular, and metabolic diseases[1]. This is a deadly association as cardiovascular diseases are top amongst the mortality causes in COPD[2,3]. One of the most challenging question about this issue is whether the concomitant occurrence of COPD and cardiovascular diseases is a mere reflection of common shared risk factors such as tobacco smoking, obesity, or sedentary life style or whether COPD is, by itself, a driving force in the development of cardiovascular diseases.

In this issue of Chest, Soumagne and colleagues assessed (carotid-femoral) aortic pulse wave velocity (aPWV), a surrogate marker of arterial stiffness in patients with COPD[4]. As a whole, they found an elevated aPWV compared to disease-free controls. We are aware of at least 51 studies investigating aPWV in COPD and arterial stiffness is consistently reported to be elevated in patients with COPD compared to disease-free controls or to tobacco-matched patients without COPD. However, the most innovative contribution of Soumagne and colleagues was to study arterial stiffness in smokers vs. non-smokers with COPD. This clever study design provides interesting insights into this important but ambitious question[5]. More specifically, they tried to pinpoint which of COPD or tobacco smoking is the culprit of increased cardiovascular risk. Indeed, their approach was to measure arterial stiffness in 142 patients with mild-to-moderate COPD and in 155 healthy controls being exposed to tobacco smoking, organic dusts or both. They rightfully reasoned that if COPD was the main determinant of increased arterial stiffness, then, increased arterial stiffness should be seen in lifetime non-smokers with COPD compared to non-smokers with normal lung function. What they found was the opposite, increased in arterial stiffness was only seen in tobacco smokers with COPD but not in lifetime non-smokers with COPD.

From this observation, the authors concluded that COPD by itself does not confer an increased risk of cardiovascular diseases. This conclusion was further supported by

regression analysis showing that the magnitude of tobacco smoking was the main determinant of increased arterial stiffness in patients with COPD, even after adjustment for age, mean blood pressure and BMI. These findings are in agreement with a recent report showing that mild COPD is not associated with cardiovascular or metabolic comorbidities[6]. Using a different study design, Van Remoortel and colleagues also found that, in mild disease, tobacco smoking rather than COPD was the main driver of cardiovascular comorbidities[7]. It is likely that the effect of tobacco smoking on arterial stiffness is amplified in individuals developing COPD. For example, a longitudinal cohort examining aPWV in adults whose hypertension begun during childhood, shows a synergistic effect of tobacco smoking and long-term blood pressure measures on arterial stiffening[8]. This observation corroborates the findings of Soumagne et al. and others reporting an increased arterial stiffness in smokers with COPD compared to smokers without COPD.

Collectively, these findings challenge the fact that COPD by itself is a risk factor for cardiovascular morbidity. Nevertheless, it might be premature to conclude that COPD is not a risk factor. First, and as acknowledged by the authors themselves, the measurement of arterial stiffness should not be viewed as a replacement for all other cardiovascular risk factors. Second, Soumagne et al.'s study is cross-sectional and not longitudinal and therefore does not provide data on the long-term risk of developing cardiovascular events in non-smokers with COPD. Perhaps the most compelling argument in favor of a link between COPD and cardiovascular diseases comes from large epidemiological studies convincingly showing that reduced $FEV_1$ is associated with all-cause mortality and cardiovascular disease[9]. This observation is true in lifetime non-smokers irrespective of the cause of reduced $FEV_1$.

Of note, Soumagne et al.'s study was conducted in patients with mild-to-moderate COPD and the results may not be generalized to patients with more severe disease. A certain degree of airflow limitation severity may be required for the relationship

between COPD and cardiovascular disease to emerge. By influencing a number of systemic factors, COPD may, indeed, amplify the risk of developing elevated arterial stiffness[10], and these factors are more predominant with severe form of COPD. For example, COPD induces systemic inflammation, accelerates aging and reduces exercise tolerance, three features to be commonly associated with increased arterial stiffness and cardiovascular risk[4]. More specific to COPD, chronic or intermittent hypoxia may increase arterial stiffness by stimulating pro-inflammatory cytokines and oxidative stress, which, in turn, increase the production of cell adhesion molecules on the vascular endothelium and augment the risk of atherosclerosis[11]. This may explain the positive relationship usually reported between the severity of airflow limitation and aPWV. Moreover, COPD is associated with sympathetic over-activation and decreased baroreflex sensitivity which can both participate in raising blood pressure[11]. Lastly, the severity of emphysema has been found to be associated with arterial stiffness in COPD independently of airflow limitation. This may be due to an increased systemic elastin degradation and to a systemic susceptibility to lung, skin, and arterial connective tissue damage[12].

What can we conclude with these conflicting results? First, and foremost, that the relationship between COPD and cardiovascular diseases is complex and that it is difficult to sort out the mechanisms of their association in human studies where several confounding factors are difficult to control for. Second, for the association between COPD and cardiovascular diseases to emerge, expiratory flow limitation may have to reach a certain degree of severity that was not present in patients studied by Soumagne and colleagues[5]. Irrespective of the mechanisms, Soumagne et al. reinforce the crucial public health message that smoking cessation in patients with COPD reduces all-cause and cardiovascular mortality[2]. Interestingly, exercise training has previously been shown to reduce arterial stiffness in COPD[4] and could be another non-pharmacological tool to reduce cardiovascular risk in patients with COPD. Other large cohort studies are necessary to study the role of tobacco-smoking vs. COPD itself in patients with severe airway obstruction, to better identify patients who are prone to develop concomitant

COPD and cardiovascular diseases and to test the effects of dedicated approaches to reduce cardiovascular risk in these particular *at-risk* populations.

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