Are COPD and cardiovascular disease fundamentally intertwined?

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Elastin loss may be the link between COPD and cardiovascular disease http://ow.ly/YVwFC

Comorbidities and chronic obstructive pulmonary disease (COPD) are ubiquitous, with cardiovascular disease being the most common and significant [1, 2]. Numerous cohort studies have demonstrated an increased risk of cardiovascular-related mortality in patients with COPD [3–6]. Interestingly, this association is often seen in mild and moderate COPD [4]. It is both disappointing and depressing that both the management of cardiovascular disease and the assessment of risk in patients with COPD is repeatedly suboptimal [7]. Defining risk for any individual is likely to lead to an improvement in recognition and, ultimately, risk management and prognosis [8]. In an age where identification of risk is as important as causality, we must challenge the *status quo*. In this issue of the *European Respiratory Journal*, Rabinovich *et al.* [9] report the results of their study of plasma desmosine as a marker of cardiovascular risk in COPD. The amino acids desmosine and isodesmosine are involved in elastin cross-linking, have utility as a measure of elastin breakdown [10], and may have value in determining both risk of cardiovascular disease and a link to a possible causal mechanism.

It should be noted that there are several proposed mechanisms for the association of cardiovascular disease with COPD and it remains possible that these mechanisms may co-exist in any individual. Cigarette smoke, and the repetitive injury associated with this, is recognised to lead to abnormal cell repair [11], increased airway inflammation [12], oxidative stress [13] and extracellular matrix destruction [14]. Another putative mechanism is the effect of increased systemic inflammation, with airflow obstruction as an independent predictor of atherosclerosis [15]; treatment to reduce systemic inflammation in COPD has yet to be successful [16, 17]. There are likely to be direct effects on cardiac function as a consequence of vascular remodelling, originally described in the seminal paper by Dornhorst [18], and that of dynamic hyperinflation [19].

The detection of increased arterial stiffness in patients with COPD furthers our understanding in the possible mechanism for cardiovascular disease in COPD [20, 21]. This change in vascular compliance has been recognised as a prognostic index of cardiovascular disease, independent of hypertension [22], but is a feature of ageing [23]. These physiological changes have been determined to be a consequence of elastin fibre degradation and subsequent deposition of collagen [22]. An increase in elastolysis may be due to either increases in elastolytic enzyme activity or reductions in inhibitors of these enzymes with subsequent replacement of elastin with collagen [24]. The findings of Rabinovich *et al.* [9] help us, as both scientists and clinicians, to understand further the possible mechanism of COPD and cardiovascular disease. They have shown that an increased level of elastolysis, by measuring plasma desmosine as a biomarker of elastin

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breakdown, exists in patients with COPD, in contrast to sex- and age-matched controls. Furthermore, the association of plasma desmosine levels was greatest with ageing, coronary artery calcium burden measured by computed tomography and arterial stiffness, in patients with persistently elevated levels of plasma desmosine. The persistent elevation of plasma desmosine levels associated with worse outcomes suggest that intrinsic or extrinsic modification may be possible or indeed necessary. The lack of any association of plasma desmosine with emphysema or airflow obstruction is in contrast to that found previously [25], but is likely to reflect differences in the population studied, the size of the COPD population studied and possible differences in the definition of emphysema. Most significantly, the authors found an association with all-cause mortality and plasma desmosine levels in the COPD patient population [9]; however, without a control population with only cardiovascular disease it remains unclear if this is a COPD or cardiovascular phenomenon and warrants further investigation.

This work [9] does further the hypothesis that the common factor in any association of COPD and cardiovascular risk is elastin loss. Elastin is highly conserved in our lifetime [26], with a half-life of 74 years [27]; thus, loss by accelerated breakdown, degradation or homeostatic imbalance is irreplaceable [28]. The study by Rabinovich *et al.* [9] finds that age is the factor with the strongest correlation to plasma desmosine levels, and it may prove in time that both COPD and cardiovascular disease represent accelerated ageing [29] with an (early) elastin-deficient process [30, 31]. The authors acknowledge the study has limitations and we have to be cautious with its interpretation. Firstly, we cannot determine which tissue the plasma desmosine measured originates from, with significantly more elastin in the cardiovascular system than the lungs, nor can we assume that degradation occurs equally in lung and endothelial tissue in patients with COPD in comparison to healthy controls with or without cardiovascular disease; measurements of desmosine from the airway and systemic circulation may provide further clues.

Finally, this paper [9] serves to remind us of the importance of comorbidities in COPD. We are reminded of the presence of shared causal factors leading to multiple pathological effects, and of the significance of measuring, monitoring and modifying risk. We are also reminded that elastin loss has been extensively studied and thus far no intervention has been shown to successfully replace it. The long journey to a complete understanding of the pathophysiology of COPD and cardiovascular disease continues, with many challenges on the way.

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