Chronic obstructive pulmonary disease and cardiovascular disease: never the twain shall meet?

Mona Bafadhel, Richard EK Russell
Respiratory Medicine Unit, Nuffield Department of Medicine, University of Oxford

Co-morbidities and chronic obstructive pulmonary disease (COPD) are tightly interwoven. This is most applicable to cardiovascular disease [1, 2]; with numerous studied cohorts demonstrating an increased risk of cardiovascular related mortality in patients with COPD [3-6]; although interestingly this is more often reported as a cause of death in mild and moderate COPD [4]. It is both disappointing and depressing that both management of cardiovascular disease and assessment of risk in patients with COPD is repeatedly sub-optimal [7]. Defining risk for any individual will likely lead to an improvement in its recognition and ultimately its management [8]. In an age where identification of risk is equally as important as causality we can start to challenge the status quo. In this edition of the European Respiratory Journal, *Rabinovich et al*.[9], have studied plasma desmosine as a marker of cardiovascular risk in COPD. The amino acids desmosine and isodesmosine are involved in elastin cross-linking and have utility as a measure in elastin breakdown [10]; and may have value in determining both risk of cardiovascular disease and links to causality.

It should be noted that there are several proposed mechanisms for the association of cardiovascular disease and COPD; 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]; although treatment to reduce systemic inflammation in COPD has yet to be successful [16, 17]. Directly, there are likely to be effects on cardiac function as a consequence of vascular remodeling, originally described in the seminal paper by A.C. Dornhorst [18] and that of dynamic hyperinflation [19].

The detection of increased arterial stiffness in patients with COPD, lends to the further our understanding in the possible mechanism for cardiovascular disease in COPD [20, 21]. It is increasingly recognised as a prognostic index of cardiovascular disease, independent of hypertension [22], but a feature of ageing [23] and

determined to be a consequence of the degradation of elastin fibers and subsequent deposition of collagen [22]. An imbalance of this elastolytic and collagenolytic homeostasis may thus lead to an increase in tissue inhibitors of matrix metalloproteinases, which are important in epithelial wound repair [24] and degradation of the extracellular matrix. In this edition of the European Respiratory Journal, Rabinovich et al. [9] helps us as both scientists and clinicians to understand further into understanding the likely mechanism between COPD and cardiovascular disease. They have showed that an increased level of elastolysis, by measuring plasma desmosine as a biomarker of elastin breakdown, exists in patients with COPD, in contrast to sex and age matched controls. Furthermore, the association between plasma desmosine levels occurred 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 and their worse outcomes, suggests 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 also the 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 cardiovascular disease and plasma desmosine levels it remains difficult to understand if this is a COPD or cardiovascular phenomenon and further studies are warranted.

This work [9] does further cement that an imperative factor in any associations of COPD and cardiovascular risk is elastin loss. Elastin, is highly conserved in our lifetime [26] with a half-life of 74 years [27], loss by accelerated breakdown, degradation or homeostatic imbalance means that this is irreparable [28]. The Rabinovich study finds that age is the factor with the strongest correlation to plasma desmosine levels [9]; and it may prove in time that both COPD and cardiovascular disease is an accelerated ageing [29] and an (early) elastin deficient process [30, 31]. The authors acknowledge there are limitations and we have to be cautious with its interpretation. Firstly, we cannot determine where 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 health controls with or

without cardiovascular disease. Measurements of desmosine from the airway and systemic circulation may provide further clues.

This paper [9] serves to remind us of the importance of co-morbidities in COPD. We are reminded of the presence of shared causal factors leading to multiple pathological effects; and to the significance of measuring, monitoring and modifying risk. Finally we are reminded that elastin loss has been extensively studied and thus far no intervention has been shown to successfully replace it. A long challenge awaits.

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