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EDITORIAL

Premature vascular ageing in cystic fibrosis

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It is increasingly recognised that chronic inflammatory disorders of the lungs, such as chronic obstructive pulmonary disease (COPD), and other organs, such as rheumatoid arthritis, are associated with systemic effects that result in comorbidities [1, 2]. Cystic fibrosis (CF) has also been shown to have systemic effects, for example loss of muscle mass and decreased bone density associated with a systemic inflammatory response [3]. A further systemic effect of chronic inflammatory conditions, such as COPD and rheumatoid arthritis, is the development of systemic vascular abnormalities with resultant cardiovascular comorbidity [4, 5], which has important adverse effects on morbidity and mortality in these conditions. Many of these comorbid conditions are a feature of ageing, and it has been suggested that the presence of these comorbidities reflects an accelerated ageing process in conditions such as COPD [6].

Increased central arterial stiffening is a hallmark of the ageing process even in healthy individuals without any cardiovascular disease [7], and is a consequence in many disease states, such as diabetes, arteriosclerosis, chronic renal impairment [8] and COPD [9]. Arterial stiffening is also a marker of increased cardiovascular risk, including myocardial infarction, heart failure and total mortality [10]. There is very little clinical or epidemiological data linking increased cardiovascular risk in CF patients, perhaps due to the shortened lifespan in these patients or to protection against the development of cardiovascular disease due to a favourable lipid and blood pressure profile in these patients [11]. In this issue of the *European Respiratory Journal*, HULL *et al.* [12] suggest that the presence of systemic inflammation in CF patients may lead to vascular changes, specifically an increase in vascular stiffness, which may predict future increased cardiovascular risk that might become apparent with the increase in longevity in these patients.

In a cross-sectional study, 50 adult patients with CF and a mean±SD age of 28.0±8.2 yrs had their arterial stiffness measured by aortic (carotid-femoral) and brachial (carotid-radial) pulse wave velocity (PWV) [12]. In addition, the central arterial wave form was analysed to calculate the augmentation index (AIx), which is another measure of arterial stiffness [13]. Measurements in CF patients were compared with 26 healthy, age-matched controls. The study showed that the AIx was significantly greater in CF patients than in controls, after adjustment for most of the known potential confounders, such as age, sex, height and peripheral mean arterial pressure [12]. AIx was related to age in both control subjects and patients, and was greater in patients than controls in each age range. In addition, AIx was greater in patients with CF-related diabetes compared to patients with non-CF-related diabetes. However, PWV was not different between controls and patients, although aortic PWV was greater in the subgroup of CF-related diabetic patients, than in either the non-CF diabetic patients or controls. HULL *et al.* [12] suggest that these changes in aortic AIx reflect increased arterial stiffness and represent accelerated arterial ageing in CF patients.

Arterial stiffness can be assessed using a variety of different techniques [13]. However, PWV is currently considered the ''gold standard'' measurement of arterial stiffness. It measures the speed at which the pressure wave form propagates along the segment of the arterial tree; the stiffer the vessel, the faster the wave travels. There is a curve-linear relationship between age and the aortic PWV; thus, age-related changes in aortic PWV are less marked in younger subjects and become increasingly prominent after 50 yrs of age [14]. The AIx provides a composite measure of wave reflection and systemic arterial stiffness. There is a gradual rise in AIx with age, but again the relationship to the age is non-linear, in that greater changes are seen with age in younger individuals than after 55 yrs of age where the AIx changes very little [15]. Thus, the dissociation of effects of CF on AIx and PWV reported in the study by HULL *et al.* [12] may be expected, since AIx is considered more sensitive to change at a young age than PWV. However, the measurement of AIx is not without difficulties. AIx not only reflects arterial stiffness but is also influenced by a number of factors, including left ventricular ejection fraction, PWV, timing of reflection, arterial tone, structure at peripheral reflecting sites, blood pressure, age and heart rate. There is also concern over the accuracy and validity of central AIx derived from the analysis of a peripheral pulse wave form [13]. There is a significant linear relationship between AIx and heart rate [16] and the CF patients had higher heart rates than controls. However, in the study by HULL *et al.* [12], aortic index was corrected for heart rate and adjusted for age and blood pressure but not for some other confounders.

The changes in aortic stiffness in the CF patients in the study by HULL *et al.* [12] were also not explained by traditional cardiovascular risk factors, such as plasma lipids, increased blood pressure, physical activity or smoking history. A significant relationship was, however, found between log C-reactive protein (CRP) and AIx, and in a multiple regression analysis, age, height and log CRP were predictive of AIx and accounted for 50% total variance in AIx. HULL *et al.* [12] suggest that systemic inflammation, which is associated with increased cardiovascular risk in various populations [17], has an effect on both endothelial function and arterial stiffness. Aortic PWV

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has been shown to be related to the level of systemic inflammation even in healthy individuals [18]. However, the mechanism relating arterial stiffness in CF may be more complicated. Vascular stiffening develops from a complex interaction between stable and dynamic changes involving structural and cellular elements in the vessel wall [8]. Structural components of the arterial wall, mainly collagen/elastin, together with the transmural pressure are considered to be major determinants of vessel stiffness. These structural components in the arterial wall undergo changes with ageing, such as alteration of the ratio of elastin/collagen and other matrix proteins [19]. Endogenous circulating enzymes, such as elastase and matrix metalloproteases (MMP), can break down elastin and collagen, and it is interesting that circulating MMP-9 levels correlate with PWV in hypertensive subjects [20]. Increased circulating MMP-9 levels have also been related to osteoporosis in patients with COPD [21] and there is a relationship between arterial stiffness and osteoporosis in COPD [22]. Thus, increased systemic proteolytic activity could also be a mechanism for the increased arterial stiffness in CF. Systemic inflammation may also affect endothelial function, which also influences arterial stiffness [8, 23]. Vascular smooth muscle also regulates vessel stiffness and there are a number of locally derived and circulating factors, including nitric oxide, endothelin-1 and the natriuretic peptides, which contribute to regulation of large arterial stiffness. Changes in the balance between these factors and in particular a reduction in nitric oxide production may result in arterial stiffening [8]. Thus, there are several mechanisms by which arterial stiffness could develop in chronic inflammatory conditions such as CF.

The implication of the finding of increased arterial stiffness in CF patients and the impact of increased arterial stiffness in a young population on future outcomes is not known. Longitudinal studies are required to determine the relevance of the findings of increased arterial stiffness on future cardiovascular outcome in these patients. However, the study by HULL *et al.* [12] does suggest the potential for increased cardiovascular risk in these patients, which may become more apparent as the lifespan of CF patients is prolonged. Measurements of arterial stiffness are increasingly used as a marker of assessing vascular function. Further elucidation of the mechanisms that result in systemic vascular stiffness in chronic inflammatory diseases, such as CF, will aid more specifically targeted therapeutic interventions for this aspect of the disease.

STATEMENT OF INTEREST

A statement of interest for W. MacNee can be found at www.erj.ersjournals.com/misc/statements.dtl

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