Dynamic hyperinflation and pulmonary inflammation: a potentially relevant relationship?

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ABSTRACT: **In patients with moderate-to-severe chronic obstructive pulmonary disease (COPD), end-expiratory lung volume increases under conditions of greater minute ventilation (*e.g.* exercise). This abnormal response is termed dynamic hyperinflation (DH) and has now been recognised as a key determinant of symptomatology and exercise intolerance in COPD. Reduced elastic recoil, loss of alveolar attachments and increased airway resistance are the mechanical factors traditionally invoked to explain the occurrence of DH in COPD. An abnormal inflammatory response to, most frequently, tobacco smoking is a key pathophysiological component of COPD, but its potential relationship with DH has not been directly investigated and is poorly understood. The present article discusses, first, the mechanisms by which DH can enhance inflammation in COPD (including cellular stretching, tissue damage and danger signals, hyperventilation and hypoxia). It then reviews how the abnormal inflammatory response that characterises the disease can augment DH (oedema and increased airway resistance, increased mucus production and alveolar destruction). Finally, it speculates that if these relationships eventually prove to be real, then the use of long-acting bronchodilators may help reduce the inflammatory load of these patients and, conversely, the use of anti-inflammatory therapy can contribute to the reduction of DH.**

KEYWORDS: Bronchodilators, chronic bronchitis, dyspnoea, emphysema, exercise, steroids

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The term dynamic hyperinflation (DH) refers to the increase in end-expiratory lung volume (EELV) that may occur in patients with airflow limitation when minute ventilation increases (*e.g.* during exercise, hypoxia, anxiety *etc.*) [1, 2]. DH often occurs in patients with moderate-to-severe chronic obstructive pulmonary disease (COPD) and it has now been recognised as a key determinant of symptoms and exercise intolerance in these patients [3].

DH in COPD is traditionally explained on the basis of the abnormal lung mechanics that characterise this disease [1, 2]. Factors such as reduced elastic recoil, loss of alveolar attachments and increased airway resistance are normally quoted to explain the occurrence of DH in patients with COPD [1, 2]. The role and interaction among these different mechanical factors has been reviewed elsewhere [1, 2] and will not be discussed here any further. In contrast, the potential relationships between DH and inflammation, a key pathophysiological component of COPD [4, 5], have been much less investigated and are far less well understood. Given the key role of both DH and inflammation in COPD, a

better understanding of these previously unexplored relationships may have potentially relevant clinical implications.

This manuscript discusses: first, the different mechanisms by which DH can contribute to inflammation in COPD; and secondly, how, conversely, inflammation can contribute to the pathogenesis of DH in COPD. Finally, although many of these potential relationships between DH and inflammation are, admittedly, speculative, their potential clinical implications are also highlighted and discussed. The final goal of the present article is to stimulate research into an area that is largely unexplored but potentially relevant to a better understanding of COPD pathophysiology and to eventually improve patient management and outcomes.

PRO-INFLAMMATORY EFFECTS OF DH
DH can exert pro-inflammatory effects through a number of potential mechanisms (fig. 1); perhaps the most obvious is cellular stretch. Several studies have now shown that cellular stretch is a potent pro-inflammatory stimulus. For instance, VLAHAKIS *et al.* [6] showed that alveolar epithelial
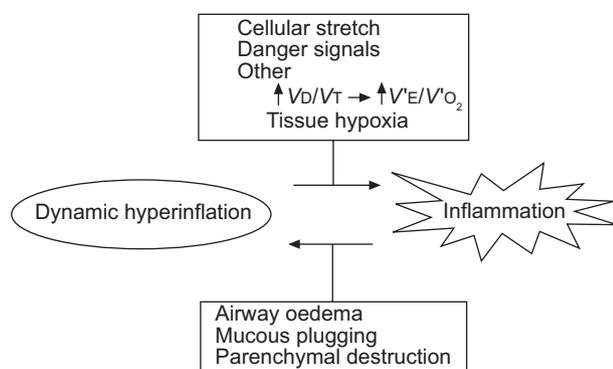
FIGURE 1. Potential mechanisms relating dynamic hyperinflation and inflammation in patients with chronic obstructive pulmonary disease. V_D: dead space volume; V_T: tidal volume; V'_E: minute ventilation; V'_{O_2}: oxygen uptake.

cells cultured on a deformable silico-elastic membrane and stretched by 30% for up to 48 h, released ~50% more interleukin (IL)-8 than static controls (p<0.001). Furthermore, it is well known that by overdistending alveolar regions, mechanical ventilation can induce a cytokine response characterised by increased concentrations of IL-1β, IL-6 and IL-1 receptor agonist, tumour necrosis factor (TNF)-α and TNF-α receptors in bronchoalveolar lavage and plasma, and that this inflammatory response may be attenuated by a strategy to minimise overdistention of the lung [7].

The so-called ''danger signals'' are key controllers of the inflammatory response [8]. A principal endogenous danger signal released by injured mammalian cells is uric acid [8]. Uric acid stimulates dendritic cell maturation and, when co-injected with antigen *in vivo*, significantly enhances the generation of responses from CD8+ T-cells [8]. Several articles have shown that mechanical forces during breathing are capable of causing failure of the remodelled extracellular matrix at loci of stress concentrations and therefore contribute to the progression of emphysema [9–12]. Thus, by causing cell stretch DH has the potential to contribute to cell injury. If so, through the release of danger signals, DH can also contribute to the enhancement of the inflammatory response and/or jeopardise tissue repair.

Finally, there are other potential mechanisms that, although speculative, less apparent and acting indirectly, may also contribute to the enhancement of the pro-inflammatory effects of DH. For instance, the mechanical factors that cause DH (reduced elastic recoil, loss of alveolar attachments and increased airway resistance) also cause ventilation/perfusion inequalities and, in patients with COPD in particular, increased wasted ventilation [13]. This implies that for any given exercise load, minute ventilation should be higher than normal in order to provide enough oxygen to sustain the metabolic demand [14]. Several studies have shown that hyperventilation can be pro-inflammatory in itself. For instance, DAVIS and FREED [15] showed that exercise-induced hyperpnoea increased the concentration of neutrophils, eosinophils and leukotrienes in the bronchoalveolar lavage fluid of experimental animals. Likewise, the structural abnormalities of the lung parenchyma that characterise COPD (bronchitis, bronchiolitis and alveolar emphysema) can jeopardise pulmonary gas

exchange and cause tissue hypoxia. The links between the latter and inflammation are also well recognised [16].

INFLAMMATION CAN CONTRIBUTE TO DH
There are several mechanisms by which inflammation can contribute to the pathogenesis of DH and most of them are quite apparent (fig. 1). Oedema is one of the key components of inflammation. Airway oedema increases airway resistance and has, therefore, the potential to produce DH.

Neutrophils are important effector cells in the abnormal inflammatory response that characterises COPD [17]. Neutrophil elastase is a very potent secretagogue [18] and excess mucus production is one of the cardinal clinical features of COPD [4]. Increased mucus production can lead to mucous plugging, which has the potential to limit airflow and, therefore, contribute to the pathogenesis of DH.

Alveolar destruction (emphysema) is another key component of COPD [4]. Chronic inflammation is thought to play a key role in the pathogenesis of emphysema [4]. One of the main consequences of emphysema is loss of elastic recoil, which is also a key determinant of DH [2]. Thus, the relationship between chronic inflammation, emphysema and DH seems straightforward.

POTENTIAL IMPLICATIONS
The relationships previously outlined between DH and inflammation are speculative and by no means comprehensive. However, a better understanding of these relationships is of great potential clinical relevance because both DH and chronic inflammation are key pathogenic components of COPD and can both be potentially modified by current therapies (long-acting bronchodilators and inhaled steroids). Thus, by reducing one of them, it is theoretically possible to influence the other one.

DH is one of the main factors limiting exercise capacity (and, consequently, health status) in these patients. Current bronchodilator therapy is effective in reducing DH, in alleviating symptoms and in improving exercise capacity in patients with COPD [4]. Actually, bronchodilator therapy currently forms the cornerstone of the management strategy in these patients [4]. What is less often realised is that, if the links discussed previously between DH and inflammation are true (fig. 1), then bronchodilator therapy in COPD may not only decrease DH (and hence improve symptoms and exercise capacity) but may also contribute by itself to the reduction of the inflammatory load that occurs in these patients, both within and outside the lungs [4]. If this is the case, this might have an impact upon other important outcomes, such as acute exacerbations, cancer, cardiovascular disease and death [19].

Conversely, if chronic inflammation has the potential to contribute to DH (fig. 1), then anti-inflammatory therapy would also be expected to contribute to its reduction. Surprisingly, and to the best of the present authors' knowledge, no published study has explored this possibility directly so far. However, some indirect evidence may support it. First, a *post hoc* analysis of a study investigating the effects of the antioxidant molecule *N*-acetylcysteine on lung function decline found that, in a subgroup of patients, the chronic use of this molecule (to some extent, an anti-inflammatory molecule) had

an effect on hyperinflation [20]. Secondly, several studies have clearly shown positive clinical effects resulting from the combination of bronchodilator therapy and inhaled steroids upon several relevant clinical outcomes in COPD [21–23]. Finally, there are a number of population-based studies that link COPD severity to inflammatory markers, mainly in the Third National Health and Nutrition Examination Survey (NHANES-III) [24, 25]. To date, no DH population data are available, simply because EELV and other parameters were not measured. Ongoing natural history studies might collect EELV or other DH data. An epidemiological association would add weight to the potential causality of the relationship between DH, inflammation and COPD [26].

CONCLUSIONS

The relationship between dynamic hyperinflation and inflammation in patients with chronic obstructive pulmonary disease is poorly understood but is of great potential relevance. There are a number of mechanisms *via* which dynamic hyperinflation can have pro-inflammatory effects and several pathways *via* which chronic inflammation can contribute to dynamic hyperinflation. In fact, it is possible that by treating dynamic hyperinflation with bronchodilator therapy, inflammation is actually being influenced and, *vice versa*, by using anti-inflammatory drugs, dynamic hyperinflation and its consequences may actually be decreased, mainly the symptoms and exercise intolerance. Although these possibilities will have to be tested directly in future studies, the consideration of potential relationships between dynamic hyperinflation and inflammation may open up new avenues in the understanding and treatment of chronic obstructive pulmonary disease.

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