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A murine model of elastase- and cigarette smoke-induced emphysema: is it an opportunity to understand CT emphysema in humans?

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COPD is an important public health care problem, being the third leading cause of death in the United States. In addition, researchers say that the prevalence of COPD will rise over the next decades. This fact is explained by the increase in smoking in developing countries and by worldwide aging, considering that COPD is up to three times more prevalent in elderly people (> 60 years of age) than in younger people. Consequently, COPD has been related to accelerated lung aging, including cell senescence and antiaging molecules. Therefore, knowing COPD-related changes that come with aging might help to discover novel therapies against this important disease.[1]

Classically, COPD is defined by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) as a disease that causes respiratory symptoms and persistent airflow limitation. This airflow limitation is shown by spirometry with reduced FEV_1/FVC ratio (post-bronchodilator FEV_1/FVC < 0.70).[2] However, it has been recently demonstrated that smokers with preserved FEV_1/FVC ratio may already present with respiratory symptoms, respiratory exacerbations, limitation of activities, emphysema, and airway wall thickening on chest CT.[3-5]

In special, people with emphysema on chest CT and preserved FEV_1/FVC ratio present with lower DLCO, altered quality of life, more frequent respiratory exacerbations, and even increased mortality.[3,6] Therefore, we have to pay attention to patients with CT emphysema (CTE) before they present with an altered FEV_1/FVC ratio. However, how can we prevent the progression of CTE to GOLD-defined COPD?

One possibility is to use angiotensin II receptor blockers (A2RB) or angiotensin converting enzyme inhibitors (ACEI). A recent study evaluated 4,472 participants and showed that A2RB and ACEI were associated with a slow progression of CTE.[6] However, this finding merits to be confirmed in randomized clinical trials including patients with CTE and normal FEV_1/FVC ratio, especially considering that, to date, there is no treatment recommended for these people.[2]

Another possibility is to use experimental models in order to study how to prevent the progression of emphysema from an initial to an advanced phase (i.e., from normal respiratory mechanics parameters to altered parameters). At this point, the model proposed by Rodrigues et al. is interesting.[7] It induces initial emphysema with a short course of cigarette smoke exposure due to the potentializing effect of elastase, which facilitates the use of this model by other researchers (because of the short amount of time needed to induce emphysema). However, it is important to use this experimental model in future studies in order to show whether or not emphysema progresses after cigarette smoke exposure cessation. The confirmation of this progression will allow researchers to test interventions to inhibit the worsening of emphysema using this murine model. Possible therapies that are interesting to study are physical activity, use of anti-inflammatory drugs, and use of N-acetylcysteine.

Physical activity was evaluated in a population-based study involving 6,790 participants.[8] The authors found that active smokers who had regular, moderate-to-high-intensity physical activity presented with a slower development of COPD when compared with those who had low-intensity physical activity. However, additional studies in humans as well as in animals are necessary to improve the understanding about these effects and to confirm the possible benefits of physical activity in decreasing the incidence of COPD and preventing COPD progression.

Another point to investigate is the potential role of exercising in asthma-COPD overlap. Recently, studies in humans and in animals have shown beneficial effects of exercise on asthma. Freitas et al.[9] performed a randomized controlled trial involving 52 obese patients with asthma, one group being submitted to a weight loss (WL) program plus exercise and one group submitted to a WL program plus sham (breathing and stretching training). The WL plus exercise group showed improvements in clinical control and pulmonary function, as well as reduced airway and systemic inflammation when compared with the sham group. Additionally, in an animal model of asthma, exercise has also reduced airway inflammation and even airway remodeling.[10]

In summary, this experimental model[7] is easier to use in research and may open new windows for the understanding of the disease and for testing inhibitors of emphysema progression.

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