Nipping it in the bud: An inspiring mission for prevention and management of COPD

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An epidemiological survey in China revealed that the prevalence of chronic obstructive pulmonary disease (COPD) was 8.2% among Chinese adults aged 40 years or older (12.4% in men and 5.1% in women) (1). Of the patients surveyed, up to 70.7% suffered from mild (stage I) or moderate (stage II) condition, and were almost free of dyspnea (including exertional dyspnea), or with unspecific symptoms like chronic cough and sputum which were readily neglected. As a result, only 35.1% of these COPD patients had ever been diagnosed, contributing to a rate of detection far below the actual prevalence in the country. Furthermore, of any given COPD stage, less than 25% of the patients ever sought medical attention. These added up to the underdiagnosis and undertreatment of COPD in China and in other parts of the world (2-4). It is not unusual in clinical settings that a COPD patient seeks treatment only when he or she frequently feels dyspneic on exertion or even at rest. In these patients, at least 50% of lung capacity as measured by predicted forced expiatory volume in 1 second (FEV_1) has been destroyed (5), and the best chance for intervention is lost. So why not move upstream the management of COPD as we do for hypertension, coronary heart disease, and diabetes mellitus - starting interventions against elevated blood pressure, dyslipidemia or hyperglycemia despite the clinically silent disease? To date, global control of COPD is lagging far behind what have been done for other chronic diseases, resulting in poor intervention/treatment outcomes and high rates of mortality and morbidity.

Mechanisms underlying the pathogenesis of COPD are yet to be fully elucidated. Due to the following aspects, research on early intervention of this disease remains extremely challenging.

Firstly, we lack sensitive and specific indicators or markers for early diagnosis of COPD. Histological study of surgically resected lung tissue from 159 patients has identified evidences of airway-wall thickening, as reflected by increased volume to surface area (V:SA), even in stage I COPD where the patients' FEV_1 can still be well above 80% of predicted value (6). Exploration of biomarkers for early detection of COPD, such as serum C-reactive protein (CRP), surfactant proteins D and A (SP-D and SP-A), Clara cell proteins (CCPs), tumor necrosis factor-α (TNF-α), interleukins (IL-8, 13 and 32), granzyme B, elastin, chemokine receptor CXCR3, chemokine (C-C motif) ligand 5 (CCL5), brain natriuretic peptide (BNP), vascular endothelial growth factor (VEGF), and chitinase-like protein YKL-40, has been attempted. While these biomarkers may be useful in determining an acute exacerbation, staging and severity assessment of COPD, none

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of them appears competently sensitive for an early diagnosis. In the domain of imaging studies, some authors proposed using airway-wall thickness and severity of emphysema to determine early-stage COPD. In a study by Ley-Zaorozhan *et al*., volumetric CT datasets which allow for 3D-segmentation and skeletonization of the airways were successfully employed to measure the inner and outer diameters of bronchi at any given site (7). Using hyperpolarized ^{3}helium (^{3}He) diffusion MRI, Fain *et al*. (8) detected early signs of disordered diffusing capacities in heavy smokers whose lung function was largely normal. These encouraging attempts shed light on the promising role of radiographic techniques in early identification of airway-wall thickness and emphysema. Lung function test remains so far central to diagnosis of COPD, because of its involvement in the "gold-standard" criteria (post-bronchodilator FEV_1/FVC<0.70) developed by GOLD (Global initiative for chronic Obstructive Lung Disease). As we know that the ratio of FEV_1/FVC in healthy population may decrease with aging (9), the plot then thickens - using this spirometry-based criteria would lead to under-diagnosis of COPD in subjects aged below 50 and misdiagnosis in those aged above 50 years old (10). As an alternative, Enright *et al*. suggested using the lower limit of the normal range (LLN) as defined by the fifth percentile of FEV_1/FVC in a healthy reference population to minimize misdiagnosis of COPD in the elderly (11). Yet this may not mean a perfect solution. The use of LLN worldwide necessitates the availability of population-specific reference equations which are not established in many parts of the world (12). In addition, staging of COPD based on reduction in FEV_1 does not correlate well with quality of life, 6-minute walk distance and frequency of acute exacerbation (13). Nevertheless, using FEV_1/FVC<0.70 can be considerably valuable in diagnosis of asymptomatic COPD. Following this logic, among the 70% of patients who were with symptom-free COPD as we mentioned at the beginning of this paper, measurement of FEV_1 should have identified majority of the subjects at the early stage of this disease. Measurement of expiratory peak flow (PEF) as a simple, effective and affordable diagnostic tool may also provide some help for early diagnosis and management of COPD. Such a strategy was adopted in a recent study where a cohort of community residents was screened for peak expiratory flow (PEF) with portable peak flow meter. Those with PEF below normal expected values were referred to a designated medical center for further evaluation of FEV_1. In this way, detection of COPD yielded a specificity of 77% and a sensitivity of 84% (14). Some authors endeavored to identify early-stage COPD with cardiopulmonary exercise testing (CPET) (15). They found that patients with GOLD stage I COPD had evidence of lowered ventilator reserve and increased dead air-space during incremental cycle exercise, as indicated by significantly higher Borg scale ratings of dyspnea intensity, minute ventilation ($\dot{V}_E$) and ventilatory equivalent for carbon dioxide ($\dot{V}_E/\dot{V}_{CO_2}$) compared with healthy controls. Therefore CPET may be more sensitive than the widespread accepted lung function test in detecting COPD. In addition, Pitta *et al*. (16) noted a dramatic reduction in exercise endurance among patients with mild COPD, suggesting that CPET can also be used in the screening.

Secondly, it has not been widely recognized among clinicians that the annual decline in FEV_1 is more rapid early in COPD. Two clinical trials, "Towards a Revolution in COPD Health" (TORCH) and "Understanding Potential Long-Term Improvements in Function with Tiotropium" (UPLIFT), demonstrated that the rate of annual decline in FEV_1 over a follow-up of 3 to 4 years was –47.0 and –49.0 mL/yr, respectively, in patients with a baseline FEV_1 ≥50% predicted, versus –28.4 and –23.0 mL/yr, respectively, in those with a baseline FEV_1<30%. The findings of these studies also suggested that early intervention may contribute to greater reversibility of the airway. By interpreting the bronchodilator response in COPD patients, Zhang FQ and coworkers (17) showed significantly greater improvement in FEV_1 with salbutamol nebulization in stage I COPD patients [(197±189) mL] compared to those with stage III [(117±103) mL] or stage IV [(168±187) mL] COPD. They speculated that the reduced FEV_1 at early stages of COPD may be largely associated with airway smooth muscle contraction and mucus hyper-secretion, in contrasted to airway remodeling and obvious emphysema at later stages which give rise to poor reversibility of the airway. In collaboration with local health administration, Zhou YM *et al*. (18) implemented a program for COPD prevention and management in a community in Guangzhou, the largest city in southern China. The interventions included educations on tobacco cessation and COPD control, measures to reduce indoor and outdoor air pollutions, and treatment with short-acting beta-agonist (salbutamol) and ipratropium bromide. During the 4-year follow-up, the annual rate of decline in FEV_1 was significantly lower in subjects of the intervention community than those in the control community, particularly for high-risk individuals (occupational exposure and smokers). Implications of this study showed that, as with community-based programs for hypertension or coronary heart disease, simple management can result in encouraging outcomes for early intervention of COPD at the community level.

Thirdly, evidence-based approach to early intervention for COPD is still lacking. While smoking cessation proves indispensable to early intervention, about 40% of COPD patients in China are non-smokers, and less than 20% of smokers will develop COPD later in life. Therefore, studies looking at genetic polymorphisms are urgently needed to identify smokers who are most susceptible to COPD. Undoubtedly, quitting cigarettes continues to be the most crucial intervention for smokers in whom FEV_1 declines faster than as found for healthy subjects each year (19,20). In the case of pharmacotherapy for COPD,

either inhaled glucocorticosteroid (ICS) plus long-acting beta agonists (LABA) in the TORCH study or Tiotropium in the UPLIFT study did not produce a statistical difference in annual rate of FEV_1 decline between patients and controls after a 4-year treatment, though, inspiring clinical efficacy of these medications were implied in a subgroup analysis which showed slower FEV_1 decline in subjects with stage II COPD compared with the controls (21,22). Given this, a question naturally follows whether stage I COPD patients, which accounted for nearly one-fourth of the study population in these two studies, could benefit more from the medications. Today, novel classes of anti-inflammatory drugs, such as PDE4 inhibitors (Roflumilast and Tetomilast) (23,24), have been developed. Notably, animal studies have demonstrated that Tetomilast may suppress the actions of elastase and hence the development and progression of emphysema. Some of PDE4 inhibitors are now commercially available, but they are approved only for moderate and severe COPD patients. The potential benefits of these products in patients with early-stage COPD warrant future studies.

Understandably and conceivably, scientific research should not excessively target the mid- and late-stages of COPD at the expense of early prevention and intervention. Physicians can be prompted for successful examples in coronary heart disease, hypertension and diabetes, where the strategies for management of these diseases are placed with high priorities on early identification, early diagnosis and early intervention. Along with developing practices of evidence-based medicine, it is trustworthily foreseeable that this decade will witness an overwhelming revolution in prevention and management of COPD.

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