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Systemic effects and mortality in chronic obstructive pulmonary disease

Along with impaired lung function, COPD can cause weight loss, skeletal muscle dysfunction, and cardiovascular disease.

ABSTRACT: Chronic obstructive pulmonary disease (COPD) is associated with several systemic consequences, including weight loss, muscle dysfunction, cardiovascular disease, and lung cancer. Because these consequences can seriously affect quality of life and worsen prognosis in patients with COPD, preventing and treating systemic effects is important in COPD management. Mechanisms proposed for these effects include persistent local and systemic inflammation and oxidative stress. For patients with advanced COPD, respiratory failure is the leading cause of mortality; for patients with mild or moderate COPD, cardiovascular disease and lung cancer are the predominant causes of death. Prognostic indicators can help predict mortality in COPD and direct management. Values that predict mortality include forced expiratory volume in 1 second, scores from the BODE index, St. George's Respiratory Questionnaire, Charlson index, and C-reactive protein levels. Since COPD is more likely to be listed as a contributing cause of death, COPD mortality data probably underestimate true COPD mortality. In future, a better understanding of the underlying mechanisms of systemic effects should help reduce morbidity and mortality for patients with COPD.

Chronic obstructive pulmonary disease (COPD) is characterized by progressive and irreversible airflow obstruction associated with a chronic inflammatory process in the lungs in response to the inhalation of particles and toxic fumes such as tobacco smoke and air pollution. In addition to causing pulmonary abnormalities COPD is associated with systemic consequences outside the lungs, such as weight loss, skeletal muscle dysfunction, systemic inflammation, and cardiovascular disease (**Figure 1**).[1] The evidence for these effects comes from strong epidemiological observations. Proposed mechanisms for these changes include persistent inflammation and oxidative stress.[2,3]

Together, impaired lung function and systemic effects can seriously affect quality of life and worsen clinical prognosis in COPD patients. Accurately classifying the severity of disease and predicting mortality for patients with COPD can help with clinical management.

Systemic effects

While the mechanisms for systemic effects are not yet understood, the effects themselves are common and well documented.

Weight loss

Unexplained weight loss in patients with COPD, particularly in those with severe COPD,[4] is mainly due to a loss of skeletal muscle and wasting of limb muscles. These patients may also have osteopenia.[5] Most patients with COPD have an increased metabolic demand and unbalanced protein synthesis and protein breakdown, particularly in the "pink puffers." The increased metabolic demand may be caused by the increased work of breathing combined with medications, systemic inflammation,[1] tissue hypoxia, or a combination of these. Low body weight, which is a strong predictor of mortality in COPD,[6] can be reversed in part by nutritional supplementation.

Skeletal muscle dysfunction

Skeletal muscle dysfunction is common in patients with COPD. It is characterized by the reduction in muscle strength and endurance as well as by the increase in muscle fatigability. Lower limb muscles are more likely to be affected than are upper limb muscles.[7] Muscle atrophy is largely

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responsible for the reduction in muscle strength, whereas changes in fibre type (a reduced proportion of type I fibres and an increase in type II fibres) are related to the reduction in muscle endurance.[7] The mechanisms of skeletal muscle dysfunction are unclear, but systemic inflammation and a high tumor necrosis factor-α level may play an important role.[1]

Several studies have reported that comprehensive exercise training significantly improved muscle fatigue resistance, exercise tolerance and endurance, respiratory symptoms, and quality of life in patients with COPD.[8] Some studies have reported that exercise at high intensity produced more benefits than exercise at lower levels of intensity.[9]

Cardiovascular disease

Compelling epidemiological evidence has demonstrated that impaired lung function is an independent predictor of all-cause and cardiac-specific mortality.[10] Even modest reductions in expiratory flow volumes increase the risk of cardiovascular mortality by twofold or threefold,[10] independent of age, gender, and smoking history. In age- and sex-matched studies, patients with COPD were more likely to have cardiovascular diseases, including coronary artery disease, myocardial infarction, arrhythmia, angina, and congestive heart disease.[11]

The mechanisms underlying this relationship between COPD and cardiovascular disease are unclear. Obviously, tobacco smoking and older age are shared risk factors for both COPD and cardiovascular disease. In addition, the persistent, low-grade, systemic inflammation caused by COPD may contribute materially to the pathobiology of cardiovascular diseases.[12] Oxidative stress can also contribute to the development of atherosclerosis.

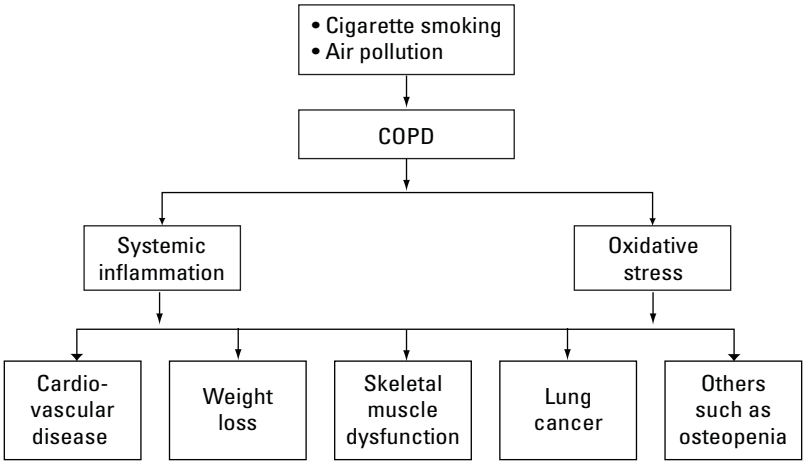

Figure 1. Systemic effects of chronic obstructive pulmonary disease.

Lung cancer

Strictly speaking, lung cancer is not a condition that is outside the respiratory system, but it is still considered a systemic effect. It is important to note, however, that COPD is an independent risk factor for lung cancer. Several studies have revealed that emphysema or chronic bronchitis increased the risk of lung cancer from twofold to fivefold, independent of smoking status and duration and intensity of smoking.[13] The relationship between impaired lung function and the risk of lung cancer is dose-dependent; a decrease of FEV_1 (forced expiratory volume in 1 second) is associated with an increased risk of lung cancer.[10] This relationship is particularly significant in women.

Chronic inflammation in the airways and parenchyma in COPD may play a role in the pathogenesis of lung cancer.[14] Moreover, reduced mucociliary clearance of inhaled carcinogens from the lungs may also contribute to the increased risk of lung cancer in COPD patients.

Possible mechanisms

Two main mechanisms have been proposed in the pathogenesis of the systemic changes in COPD: persistent local and systemic inflammation and oxidative stress.[2,3] Although the hypotheses related to these possible mechanisms are interesting, there has been no long-term study to show that a reduction in oxidative stress or in local and systemic inflammation will result in a reduction in the systemic manifestations in COPD.

Mortality in COPD

Patients with COPD often have multiple comorbid conditions, and it is difficult to identify the precise cause of death. COPD is more likely to be listed as a contributing cause than a primary cause of death, or may not be cited at all. Among patients with at least one known hospitalization due to COPD, the diagnosis of COPD was mentioned in fewer than 50% of the death certificates. Therefore, COPD data probably underestimate true COPD mortality. In several studies where some vigorous attempts were made to identify the cause of death in patients with COPD, it has been shown that deaths may vary according to the underlying severity of airflow obstruction (**Figure 2**).[11] In patients with advanced COPD, respiratory

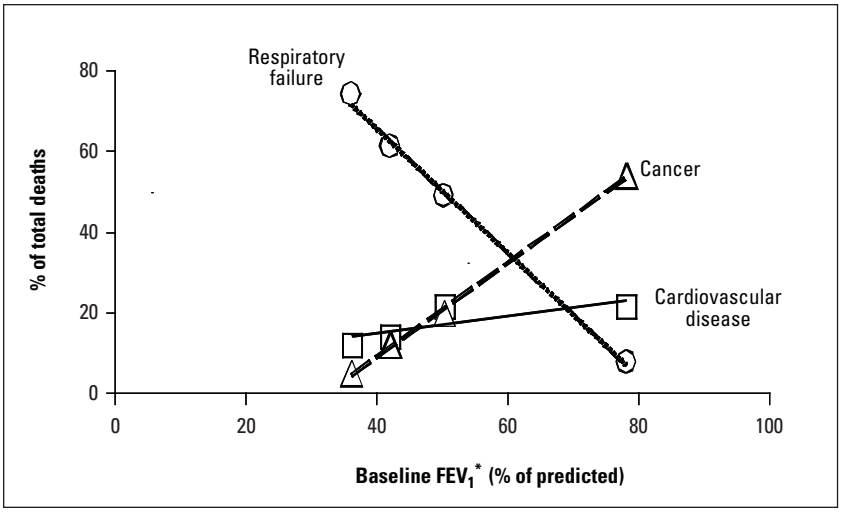

Figure 2. The relationship between baseline lung function and percentage of total deaths from cardiovascular disease, cancer, and respiratory failure in large cohort studies of patients with COPD.

*FEV_1: forced expiratory volume in 1 second
Source: Adapted from Mortality in COPD: Role of Comorbidities[11]

failure, primary or secondary to an infection, is listed as the leading cause of death. However, for patients with mild or moderate COPD, cardiovascular disease and lung cancer are listed as the predominant causes of death.[11]

Prognostic indicators

Using validated indices to accurately classify the severity of disease and predict mortality for patients with COPD is an important part of clinical management. FEV_1 is the most widely used prognostic indicator. Reduced FEV_1 is associated with increased risk of all-cause mortality as well as mortality resulting from cardiovascular disease and lung cancer.[6] Other sources of prognostic indicators are as follows:

- BODE index
- St. George's Respiratory Questionnaire
- Charlson index
- C-reactive protein

BODE index

Celli and colleagues constructed the BODE index (**B**ody mass index, degree of airflow **O**bstruction, **D**yspnea, and **E**xercise capacity), a multidimensional 10-point grading system that integrates four values: FEV_1 (% of predicted), 6-minute walk distance, modified Medical Research Council dyspnea score, and body mass index measure (**Table**).[6] They reported that a 1-point increase in the BODE score was associated with a 34% increase in all-cause mortality and a 62% increase in respiratory mortality for COPD patients.[6]

St. George's Respiratory Questionnaire

The St. George's Respiratory Questionnaire (SGRQ) is used to measure the impact of COPD on overall health, daily life, and perceived well-being. The SGRQ has 76 items that are divided into three sections including symptoms (frequency and severity), activity (activities limited by breathlessness), and impacts (social functioning, psychological disturbances). Scores for each section and a total score range from 0 to 100, with higher scores indicating poor health.[15] Several studies have shown that poor health status at baseline is associated with increased risk of all-cause and respiratory mortality.[16] Domingo-Salvany and colleagues reported that every 4-point increase in the SGRQ total score (a change that has been suggested as clinically relevant) is associated with a 5.1% increase in all-cause mortality.[15,16]

Charlson index

The Charlson index is designed to quantify the number and the seriousness of comorbid diseases that might significantly increase the risk of mortality.[17] Not unexpectedly, patients who had a Charlson index score of 3 or more (representing two chronic diseases or one severe disease in addition to COPD) were 2.2 times more likely to die compared with those with a lower burden of comorbidities.

C-reactive protein

C-reactive protein (CRP) is a stable nonspecific biomarker of systemic inflammation. The Copenhagen City Heart Study reported that patients with a baseline CRP level greater than 3 mg/L were 2.2 times more likely to die from COPD during the period of 8-year follow-up when compared with those with a baseline CRP level equal to or less than 3 mg/L. The Lung Health Study compared COPD patients in the highest quintile for CRP levels (mean, 7.1 mg/L) at baseline with those in the lowest quintile (mean, 0.2 mg/L) and found that the risk of all-cause mortality increased by 79% for the highest quintile group during the period of 7.5-year follow-up.[18]

Conclusions

COPD is no longer regarded as a disease defined only by its local inflammation and structural remodeling in the lungs. It is a condition often asso-

ciated with systemic effects such as weight loss, skeletal muscle dysfunction, and cardiovascular disease. COPD is also associated with an increased risk of lung cancer. When the mechanisms underlying these systemic effects are better understood, future therapeutic targets can take this new understanding into account and clinicians can manage these effects to improve quality of life and reduce morbidity and mortality for patients with COPD.

Table. Variables and cutoff values for points 0 to 3 in the BODE index computation.

	Point on BODE index*			
	0	1	2	3
FEV_1 (% of predicted)	≥65	50–64	36–49	≤35
Distance walked in 6 minutes (m)	≥350	250–349	150–249	≤149
Dyspnea scale score	0–1	2	3	4
Body mass index measure	>21	≤21	—	—

*Values range from 0 (best) to 10 (worst)
Source: Adapted from the Body-mass Index, Airflow Obstruction, Dyspnea, and Exercise Capacity Index in Chronic Obstructive Pulmonary Disease[6]

Competing interests
None declared.

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