Clinical Approach to Patients with Chronic Obstructive Pulmonary Disease and Cardiovascular Disease

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It has long been recognized that reduced lung function is a major risk factor for cardiac death. It has also become clear that cardiac events are the major cause of death for patients with chronic obstructive pulmonary disease (COPD) with all stages of disease. These associations could be from shared risk factors, most notably cigarette smoking. However, there are mechanistic and physiologic relationships that could account for these associations. This raises the possibility that treatment of COPD could benefit cardiac risks. Despite this, the monitoring of lung function in cardiac patients is not routine. Neither is optimization of lung function, although it may greatly benefit exercise training designed to minimize cardiac risks and symptoms. Conversely, many patients with COPD are at greater risk for cardiac disease than may be recognized, because their COPD is often undiagnosed. Recognition of increased risk could impact the aggressiveness with which other risk factors, hypertension, and hypercholesterolemia are managed. Finally, the interactions between cardiac and pulmonary disease have important implications for the development of novel therapies. It is plausible that treatment of pulmonary inflammation characteristic of COPD will alter cardiac risk. Such an approach would offer a novel approach for the development of treatments for these common conditions.

Keywords: cardiovascular disease; chronic obstructive pulmonary disease; comorbidity; diagnosis; therapy

THE CLINICAL INFORMATION-BASE PROBLEM

Clinical understanding of the patient with chronic obstructive pulmonary disease (COPD) derives from many sources. Observations made by the astute clinician caring for individual patients are often regarded with the lowest level of authority, sometimes being called expert opinion (1, 2) and sometimes disparaged as anecdotal. Despite the increasing recognition that the grading systems used have limitations (1), the highest level of regard, particularly for therapeutic recommendations, comes from well-controlled, randomized clinical trials (2). Most often, these are conducted for the purpose of evaluating specific treatments. The rigors of such studies often require well-defined patient populations. To avoid confusion, patients with severe or unstable comorbidities are routinely excluded. The consequence of this is that the most highly regarded clinical information often pertains only to a small subset of the patient population. In the EUROSCOP trial (European Respiratory Society Study on Chronic Obstructive Pulmonary Disease) evaluating inhaled corticosteroids in COPD, for example, more than 25 subjects were screened for each that completed the trial (3, 4). This situation is not rare. It is common for large clinical trials to screen many patients of whom only a fraction are included. Many of these may subsequently drop out, further limiting the population base on which important clinical recommendations are commonly made.

COMORBIDITIES

Among patients with COPD, comorbidities are extremely common for a number of reasons. First, COPD is a disease that increases in importance with age (5, 6). Because most chronic disorders of adults also increase with age, statistically, comorbidities will be relatively common among patients with severe COPD. In addition, the major risk factor for the development of COPD is cigarette smoking (5, 6). Smoking is also a major risk factor for a large number of other illnesses, including cardiovascular disease (Table 1) (7). As a result of sharing common risk factors, patients with COPD are at further increased risk to suffer these comorbidities.

There may be additional mechanisms in operation. Epidemiologic studies evaluating the risk of heart disease have consistently shown an increased risk among patients with COPD (8, 9). This is true even when the data are "corrected" for smoking. There are several mechanisms that may account for this association (Figure 1). First, the lung disease may serve as a "marker" for the cardiac disease. That is, individuals who smoke and are susceptible to the injury caused by smoking may suffer both lung disease and heart disease. Alternatively, it is possible that the lung disease could contribute to the development of cardiac disease, or vice versa. Several lines of evidence suggest that inflammation can contribute to the development of atherosclerosis (10). Increases in C-reactive protein, for example, represent a major risk factor for cardiovascular disease (11, 12). In this context, COPD is also an inflammatory disease (13) and increases in C-reactive protein are present in patients with COPD (14, 15).

Acute inflammation in the lung, moreover, may put the heart at risk. In this context, periods of increased particulate air pollution are associated with increased mortality, much of which is from cardiac mortality (16, 17). Although a number of mechanisms could explain how particulate air pollution could lead to heart disease, induction of inflammation in the lung could do so by at least two mechanisms: first, inflammation in the lung could lead to autonomic instability and predispose to arrhythmias (18); and second, the production of inflammatory cytokines in the lung—for example, interleukin 6—could lead to the hypercoagulable state predisposing to thrombosis (19, 20). Finally, inflammation in the lungs, through the release of circulating cytokines such as granulocyte-macrophage colony–stimulating factor, could lead to increased circulating leukocyte numbers and/or activation, which could predispose to an inflammatory rupture of atheromatous plaques (21–23). Although considerable research will be required to determine the mechanisms that account for the association between COPD and heart disease, it seems likely that many patients will suffer from both conditions as a result of shared pathophysiologic mechanisms.

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TABLE 1. DISEASES ASSOCIATED WITH CIGARETTE SMOKING

- Cardiovascular
  - **Atherosclerotic vascular disease**
    - **Coronary artery disease**
    - **Carotid vascular disease**
    - **Abdominal aortic aneurysm**
    - Mesenteric, renal, iliac
  - Peripheral vascular disease
    - Thromboangiitis obliterans (Berger's)
    - Deep venous thrombosis
    - Pulmonary embolus
  - Cardiac disease
    - Angina pectoris
    - Coronary artery spasm
    - Arrythmia
- Malignancy
  - Respiratory tract
    - **Lung cancer**
      - Squamous cell
      - Adenocarcinoma
      - Large cell
      - Small cell
    - **Laryngeal cancer**
    - **Oral cavity and pharyngeal cancer**
  - Other tissues
    - **Esophagus**
    - **Pancreas**
    - **Bladder**
    - **Uterine cervix**
    - **Endometrial**
    - Breast
    - Kidney
    - Anus
    - Penis
    - **Stomach**
    - Colorectal
    - Liver
    - **Leukemia (acute myeloid leukaemia)**
- Lung disease
  - **Chronic obstructive pulmonary disease**
    - **Emphysema**
    - **Chronic bronchitis**
  - **Asthma**
  - Other lung diseases
    - Idiopathic pulmonary fibrosis
    - Histiocytosis X
    - Respiratory bronchiolitis
    - Goodpasture's syndrome
    - Sleep apnea
    - Pneumothorax
    - **Pneumonia**
- Gastrointestinal disease
  - Peptic ulcer disease
    - **Associated with *Helicobacter pylori***
  - Gastroesophageal reflux
  - Chronic pancreatitis
  - Crohn's disease
  - Colonic adenomas
- Dermatologic disease
  - Skin wrinkling
  - Psoriasis
- Reproductive disease
  - Ovarian failure
  - **Reduced fertility (women)**
  - Pregnancy-related
    - **Preeclampsia (reduced risk)**
    - **Prematurity**
    - **Premature rupture of membranes**
    - **Placenta previa**
    - **Placental abruption**
    - Spontaneous abortion
  - **Decreased sperm quality**
  - Fetal effects
    - **Low birth weight**
    - **Impaired lung growth**
    - **Sudden infant death syndrome**
    - Febrile seizures
    - Reduced intelligence
    - Behavioral disorders
    - Atopic disease/asthma
- Effects on children of parental smoking
  - Asthma
  - Rhinitis
  - Otitis
  - Pneumonia
  - Increased risk to smoke
- Rheumatologic and bone disease
  - Osteoporosis
- **Post menopausal**
  - **Hip fractures**
  - Rheumatoid arthritis
- Psychiatric
  - Depression
  - Schizophrenia
- Oral disease
  - **Periodontal disease**
  - Caries
  - Loss of taste
- Loss of olfaction
- Infectious disease
  - Tuberculosis
  - Pneumococcal infection
  - Meningococcal infection
- Endocrine disease
  - Altered hormonal secretion
  - Grave's disease
  - Antidiuresis
  - Goiter
- Renal disease
  - Glomerulonephritis
- Benign prostatic hypertrophy
- Eye disease
  - **Nuclear cataract**
  - Nuclear opacity
  - Macular degeneration
  - Grave's disease ophthalmopathy
- Erectile dysfunction

Modified from Reference 79. Items listed have been suggested to be associated with smoking. Those for which the Surgeon General's report found sufficient evidence to suggest a causal relationship are indicated in bold type (7).

FUNCTIONAL INTERDEPENDENCE

The heart and lungs are, obviously, integrated physiologically. Patients with COPD likely stress their hearts in a number of important ways both at rest and with exercise (Figure 2). First, the work of breathing is increased in patients with COPD. This is true at rest and becomes increasingly so as the respiratory rate increases. Total oxygen uptake can more than double when a patient with COPD voluntarily hyperventilates and increases ventilation only twofold. In contrast, a normal individual can voluntarily increase ventilation eight- to tenfold with only a 25% increase in total oxygen consumption (24). This increased work of breathing, particularly with the hyperventilation of exercise, where work of breathing may represent 50% of total oxygen consumption (25), may constitute a very real problem for an individual with compromised cardiac function.

To make matters worse, cardiac function can be compromised by the presence of COPD. Pulmonary hypertension can develop

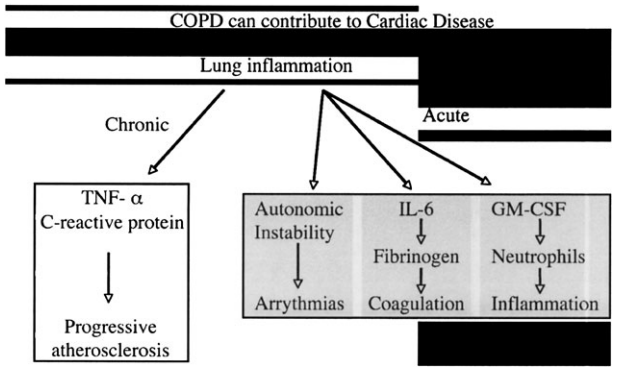

Figure 1. Chronic obstructive pulmonary disease (COPD) can contribute to cardiac disease by a variety of mechanisms. Chronic inflammation in the lung may lead to circulating cytokines and mediators (e.g. tumor necrosis factor α [TNF-α] or C-reactive protein), which may accelerate the development of atherosclerosis. Acute inflammation may predispose to the development of acute cardiac events by a number of mechanisms (*see* text for details). IL-6 = interleukin 6; GM-CSF = granulocyte-macrophage colony–stimulating factor.

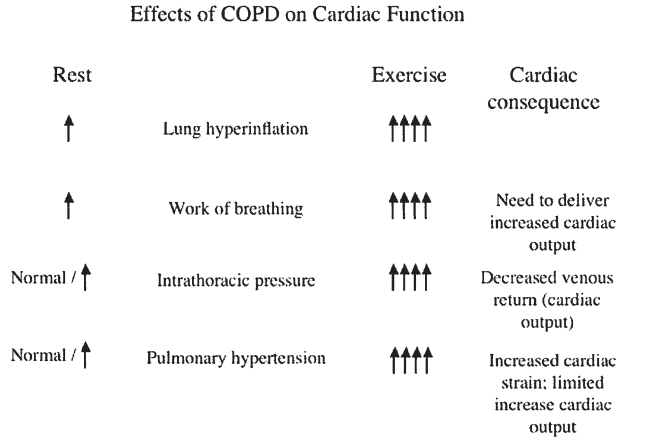

Figure 2. The abnormally functioning lung in COPD can compromise cardiac function in several ways. At rest, COPD has relatively mild effects, although work of breathing, hyperinflation, intrathoracic pressure, and pulmonary vascular pressures may be elevated. These are markedly worsened by exercise. These dysfunctions increase the demands on the heart to deliver oxygen to tissues (the muscles of respiration) while limiting the ability to increase cardiac output. Interventions could improve lung function in several ways: for example, reduction in dynamic hyperinflation, reduction in intrathoracic pressure, reduction in pulmonary vascular pressure, and reduction, which, by affecting the lung, could secondarily improve cardiac performance. In addition, reducing the work required for breathing could result in reduced demand on the heart and an apparent improvement in cardiac performance (*see* text for details).

in patients with COPD either as a result of loss of alveolar capillary bed or as a consequence of chronic alveolar hypoxia with secondary vasoconstriction. *Cor pulmonale*, which is characterized by hypertrophy, dilatation, and finally failure of the right ventricle, classically develops as a result of chronic pulmonary hypertension (26). The routine use of long-term oxygen therapy for patients with hypoxic COPD improves survival (27, 28) and likely has markedly reduced the prevalence of *cor pulmonale*, probably by prevention because reversal of pulmonary hypertension, when present, is only modest (29, 30). Fluid and electrolyte balance is abnormal in patients with COPD with *cor pulmonale* caused by abnormal production of naturietic hormones from both hypoxia and distension of pulmonary vessels and the right side of the heart (26). Even in the absence of pulmonary hypertension, however, fluid balance in COPD may still be abnormal. The factors that contribute to abnormal fluid and electrolyte balance in COPD are not completely defined, but systemic abnormalities likely play a role (31).

Because the lung normally accommodates increasing cardiac output by recruiting additional vessels, exercise, with the associated increased cardiac output, may further exacerbate pulmonary hypertension in patients with COPD where the pulmonary capillary bed is compromised (32). In addition, with exercise, respiratory rate increases. As a result, there is insufficient time for the lung to fully empty, and the lung becomes progressively and dynamically hyperinflated (33). This is a major cause of dyspnea after exercise and will further increase work of breathing. In addition, attendant with this hyperinflation is an increase in intrathoracic pressure that can restrict venous return and compromise cardiac output (25). Clinically, it is often difficult to distinguish between cardiac and pulmonary disease as a cause for dyspnea. Often, detailed functional exercise testing is required to help determine a physiologic basis for symptoms (34). Acute exacerbations of COPD and chronic heart failure can also be difficult to distinguish clinically. The assessment of brain naturietic peptide (BNP) may prove useful in this regard (35).

CLINICAL GUIDELINES

Recognizing that heart disease and lung disease are frequently concurrent and may be interconnected pathophysiologically, what recommendations have been made to guide the clinician? There is, unfortunately, a striking lack of specific recommendations for the management of patients with concurrent COPD and cardiac disease. This is not because of a failure to recognize the association. Rather, it reflects the lack of evidence on the specific management of patients with the simultaneous presence of both problems. The most recent guidelines for the management of the patients with COPD are those provided by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) (13), which have been recently expanded by the American Thoracic Society/European Respiratory Society (13). Although these two sets of guidelines recognize that cardiac disease is often present as a comorbidity, no specific recommendations for dealing with the practical issues that a clinician is likely to encounter are given. This results directly from the tension to keep the guidelines "evidence-based" and that the majority of clinical "evidence" comes from clinical trials that selectively exclude patients with significant comorbidities.

The American College of Cardiology/American Heart Association guidelines for the evaluation of management of chronic heart failure in the adult (36) also make note of the common association of heart failure and pulmonary disease. Exercise testing with blood gas measurements, possibly with right heart catheterization, is suggested as a means to help determine which conditions are most important. Therapeutically, specific recommendations are given regarding angiotensin-converting enzyme inhibitors and β-blockers. Because both metoprolol and bisoprolol lose β-1 selectivity when used in doses sufficient to improve survival in patients with heart failure, these agents are not indicated for patients with asthma. On the other hand, they can be used effectively in patients with COPD who do not have acute bronchospasm (37, 38), and this is included in the guidelines.

Heart failure is only one form of heart disease, and guidelines have also been prepared for conditions associated with increased

risk of cardiovascular disease, including the following: National Institutes of Health Guidelines on Evaluation and Treatment of Overweight and Obesity in Adults (39); Treatment of High Blood Cholesterol in Adults (40) and on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (41); the U.S. Public Health Service Clinical Practice Guideline: Treating Tobacco Use and Dependency (42); and the American Heart Association Guidelines for Primary Prevention of Cardiovascular Disease and Stroke (43). COPD is not addressed in the obesity or hypertension guidelines and is not included in the list of cardiac risk factors in the cardiovascular disease guidelines. There is, therefore, a paucity of recommendations to guide clinicians in the specific care of patients with COPD who suffer from obesity, hypercholesterolemia, hypertension, or other risk factors. The best advice would be to treat patients with COPD in the same way they would other patients with these disorders. However, this may not always be correct.

OBESITY

Although obesity is clearly a risk factor for mortality from cardiac disease, the relationship between weight and COPD risk may be more complex. For patients with COPD, mortality is increased as weight decreases. Two studies demonstrated this across all weight groups and mortality was lowest for patients who were obese (44, 45). These results differ slightly from the follow-up of the first National Health and Nutrition Examination Survey (NHANES). Although in NHANES, mortality was highest among those who were underweight, mortality also began to rise again among individuals who were obese (46). Starvation, moreover, is associated with the development of emphysema, both in animal models (47, 48) and in humans (49). Thus, whether the recommendation to lose weight should be given to overweight and obese patients with COPD as it would to such patients without COPD is unclear. It is reasonable to assume that obesity can compromise the mechanical efficiency of the chest and can increase the work required for daily activities. Additional data on the effects of weight loss in obese patients with COPD, therefore, are needed.

The mechanisms that account for the association between loss of weight and increased mortality among patients with COPD have been the subject of much study. Weight loss in patients with COPD has been attributed to the effect of circulating cytokines. In particular, the cytokine tumor necrosis factor-α (TNF-α), which has been related to cachexia in a number of conditions, has been suggested to play a role. TNF-α is produced in the lung in COPD (50), and increased amounts are reported in bronchoalveolar lavage fluid (51) and induced sputum (52). Although controversial (53, 54), several studies have demonstrated increased levels of TNF-α in the circulation in patients with COPD who have lost weight (55–59). In addition, underweight patients with COPD have peripheral blood monocytes that appear to produce increased amounts of TNF in response to a standard stimulus (60). Finally, polymorphisms in the TNF-α gene that may account for increased TNF-α production have been described in a population in Taiwan (61), although this has not been repeated in other studies (62–64). TNF-α is a potent inducer of apoptosis in many cell types. Whether it contributes to the skeletal muscle abnormalities present in COPD (65) is unclear, but a relationship between loss of muscle mass and circulating TNF-α has been reported (57). Whether cytokines other than TNF-α play a similar role is largely unexplored.

Patients with COPD likely lose weight for a variety of reasons (66, 67). In addition to the effects of circulating cytokines, caloric needs may be increased because of the increased work of breathing and inefficient exercise performance. Depression or other factors that compromise nutrition could also play a role. How these factors may interact with cardiac disease and whether they are relevant to the patient with COPD who is overweight remains to be determined. However, even overweight patients with COPD may have a decrease in fat-free mass (66). This may account for decreased exercise performance. Because decreased muscle mass is a major driver of decreased performance in patients with COPD (68), simple recommendations to lose weight may not be correct for overweight patients with COPD.

REHABILITATION AND EXERCISE

Both patients with COPD and patients with cardiac disease can benefit from exercise training. Rehabilitation programs can substantially reduce cardiac risk and should, therefore, be part of the management program of all patients who are at hazard (69). Rehabilitation can, moreover, dramatically improve quality of life among patients with COPD (70, 71).

How best to implement the rehabilitation program among patients with concurrent cardiac and heart disease is not fully determined. In this regard, the intensity of the exercise training is a key factor in determining the training benefit (72). Even modest degrees of COPD, however, can compromise training. In this regard, increasing respiratory rate is associated with dynamic hyperinflation (33). This likely leads to dyspnea and may, as noted previously, compromise cardiac output (25). As a result, the benefits of exercise training may be difficult to achieve in the presence of even mild COPD. Additional studies of exercise training and rehabilitation among patients with concurrent cardiac disease and COPD are needed to determine whether interventions for COPD that may be otherwise asymptomatic may improve training benefits and result in cardiac benefits.

BRONCHODILATORS

Bronchodilators can result in a reduction in dynamic hyperinflation (73, 74). This benefit may accrue even when there are modest effects on airflow measured at rest (75). Whether bronchodilators should be used routinely during exercise training, particularly among patients with mild COPD, remains undetermined. Such an intervention, however, by permitting more effective training may have a dramatic impact on the ability of exercise training to reduce cardiac risk.

OXYGEN

A similar potential benefit has been demonstrated by Casaburi for oxygen (73). Oxygen administration reduces respiratory rate even among individuals who are normoxic both at rest and with exercise (76). The reduction in respiratory rate may be caused by an effect on the carotid body and may be independent of improved oxygen delivery. By whatever mechanism, patients with COPD who are normoxic can exercise to higher levels of intensity with supplemental oxygen, presumably because of reduced dynamic hyperinflation. The improved exercise training may be of benefit, particularly for those patients with concurrent heart disease. Such an intervention, however, has not been tested with sufficient rigor to warrant inclusion in any practice guideline.

SMOKING CESSATION

Smoking cessation is the most important health intervention for all smokers (77). Cessation early in the course of the disease can slow the progression of COPD (78). Cessation is associated with a rapid reduction in risk of acute cardiac events and, over longer time frames, with improvement in atherosclerotic vascular disease (77). Smoking cessation, in addition, has numerous other

TABLE 2. CARDIAC RISK FACTORS TO CONSIDER IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Hypertension
Diabetes
Cholesterol
Renal compromise (glomerular filtration rate $<$ 60 ml/minute)
Microalbuminemia
Obesity
Physical inactivity
Family history
Suggested lung assessment in patients at risk for cardiac disease
FEV_1
FVC or FEV_6
If any abnormalities present, consider
Post-bronchodilator FEV_1
Lung volumes
DL_{CO}
Exercise challenge (with and without bronchodilator*)

Definition of abbreviation: DL_{CO} = carbon monoxide diffusion coefficient.
* It is possible that reduced tachypnea will lead to increased exercise tolerance. The clinical implications of this are uncertain. *See* text for details.

health benefits (77). Currently recommended smoking cessation treatments have been evaluated in patients with both cardiac disease (79) and COPD, and the available data support their efficacy in these populations (42).

NOVEL APPROACHES TO THERAPY

There are several reasons to consider novel approaches to the development of cardiac and pulmonary diseases by evaluating them together. The physiologic interdependence of the organ systems makes it possible that treatment of otherwise mild cardiac disease may benefit respiratory function in patients with COPD and vice versa. This may result in novel endpoints in clinical trials. It is also possible that cardiac and respiratory disease can share mechanisms. For example, antiinflammatory therapy treatment of COPD may benefit cardiovascular disease, and statin therapy for heart disease could have antiinflammatory effects on lung disease. Specific information on the management of patients with concurrent cardiac and pulmonary disease would, at a minimum, be helpful to the clinician.

THE CLINICIAN'S ISSUES

What is clear is that the clinician faced with a patient who has either cardiovascular disease or COPD is facing a patient who is at risk for both conditions. All patients with COPD, therefore, should be carefully evaluated for cardiac risk factors (Table 2). Those risk factors should be treated appropriately according to current guidelines. Similarly, patients with cardiovascular disease should be routinely assessed for the presence of COPD. The current GOLD guidelines suggest that any airflow limitation below 80% predicted is an indication for consideration of bronchodilators (13), particularly with exercise. Because routine exercise training is indicated even for the "asymptomatic" patient with cardiac and lung disease, it is reasonable to consider bronchodilator therapy, and perhaps oxygen, as needed to facilitate performance.

What is also clear is that a large number of crucially important questions remain unanswered. To what degree shared pathophysiologic mechanisms can be addressed remains unanswered. Would treatment of lung inflammation, for example, decrease risk of acute cardiac events? Would treatment of lung inflammation decrease risk for progression of atherosclerosis? Would treatment of lung inflammation decrease risk for thrombotic events? Finally, it is unclear whether treatment of heart disease can affect the progression of lung disease. Recent studies by Kasahara and colleagues (75) have clearly demonstrated that abnormalities in the pulmonary vasculature consequent to impaired signaling through vascular endothelial growth factor can lead to the development of emphysema (74). Similar abnormalities seem to be present in patients with COPD (75). Whether treatment of cardiac disease designed to correct vascular physiology will benefit lung disease is unclear. Finally, although the lung may be a source of inflammatory cytokines, it may also be a target. Systemic administration of TNF-α, for example, has been reported to lead to the development of emphysema in animal models (76). Statin drugs are routinely used to lower cholesterol, but these agents may have clinically relevant antiinflammatory effects (77, 78). The recognition that atherosclerosis is an inflammatory disease will likely lead to treatment of heart disease with these or other antiinflammatory modalities. The implications of such therapy for COPD are unknown, but such intervention could potentially affect the progression of lung disease. The resolution of these questions holds great promise to improve the care of the large group of patients who suffer from both heart and lung disease.

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