Rethinking Chronic Obstructive Pulmonary Disease

Chronic Pulmonary Insufficiency and Combined Cardiopulmonary Insufficiency

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Abstract

Almost 70 years ago, Drs. Baldwin, Cournand, and Richards defined chronic pulmonary insufficiency by the presence of respiratory symptoms, radiologic evidence of pulmonary emphysema on chest radiography, and physiologic gas trapping. A decade later, airflow obstruction on spirometry was added to the definition and insufficiency became a disease. Contemporary studies are reviving the diagnostic approach described by these early luminaries, with researchers finding that symptomatic smokers with preserved spirometry have increased exacerbations and that smokers and non-smokers with normal spirometry but emphysema on chest computed tomography have increased mortality. Hence, the Baldwin-Cournand-Richards concept of disease defined by respiratory symptoms, radiologic findings, and physiology—regardless of spirometric criteria—is being rediscovered. Baldwin, Cournand, and Richards also stated that “functionally, it is obvious that the pulmonary and circulatory apparatus are one unit,” and they defined

combined cardiopulmonary insufficiency as chronic pulmonary insufficiency with (left or right) cardiac and pulmonary artery enlargement. They appreciated the complexity of these interactions, which include the potential role of gas trapping in heart failure with reduced ejection fraction; the impact of emphysema on blood flow in heart failure with preserved ejection fraction; multiple contributions to cor pulmonale with increased pulmonary artery pressure; and cor pulmonale parvus in emphysema; all of which may be amenable to specific therapeutic interventions. Given the complexity of heart–lung interactions originally identified by Baldwin, Cournand, and Richards and the potentially large therapeutic opportunities, large-scale studies are still warranted to find specific therapies for subphenotypes of combined cardiopulmonary insufficiency.

Keywords: chronic obstructive pulmonary disease; cardiopulmonary; heart failure; cor pulmonale; heart failure with preserved ejection fraction

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Rethinking Chronic Obstructive Pulmonary Disease: Chronic Pulmonary Insufficiency

Several years before their landmark report of the first right heart catheterizations in patients, André Cournand and Dickinson Richards, Jr. examined “chronic pulmonary insufficiency” (1) and, in evolving papers over a decade, defined it by clinical, radiologic, and physiologic criteria (1–3). With Eleanor deForest Baldwin, the director of the cardio-respiratory laboratory at Columbia-Presbyterian Medical Center (4),

they defined chronic pulmonary insufficiency on the basis of chronic respiratory symptoms, the presence of pulmonary emphysema on chest radiography (Figure 1A), and hyperinflation (residual air volume greater than predicted and residual air volume/total lung capacity >0.36) (3). Further, Baldwin, Cournand, and Richards subcategorized chronic pulmonary insufficiency into three “uncomplicated” groups according to arterial oxygen desaturation on exercise with or without carbon dioxide retention and a fourth group that was “complicated” by combined

cardiopulmonary insufficiency, defined by the presence of cardiac and pulmonary artery enlargement (Table 1) (3). Hence, there was a requirement for clinical symptoms, radiologic emphysema, and physiologic gas trapping but not airflow obstruction in the Baldwin-Cournand-Richards criteria for chronic pulmonary insufficiency.

The Baldwin-Cournand-Richards definition held sway for more than a decade until the Ciba Symposium introduced airflow obstruction in the place of gas trapping and Renzetti demonstrated the greater prognostic significance of the forced

Figure 1. Chest radiographs of patients with Baldwin-Cournand-Richards–defined (A) chronic pulmonary insufficiency and (B) combined cardiopulmonary insufficiency. Reprinted by permission from Reference 3.

expiratory volume in 1 second compared with the Baldwin-Cournand-Richards criteria; thereafter, “obstructive” was inserted into “chronic pulmonary” and insufficiency became a disease (5, 6).

Almost 70 years after Baldwin, Cournand, and Richards’s work, the pulmonary community is rediscovering chronic pulmonary insufficiency outside spirometrically defined chronic obstructive pulmonary disease (COPD), be it called (collectively) chronic lower respiratory disease (7), chronic lung diseases (8), or (syndromic) COPD. Tan and colleagues found that respiratory exacerbations occur not infrequently in the general population without COPD or asthma (9), and Regan and colleagues found that many older smokers with normal spirometry have respiratory symptoms and radiographic abnormalities on computed tomography (CT) (10). More specifically, Woodruff and Han found that many smokers with preserved pulmonary function have symptoms and exacerbations, and that this phenotype is characterized by airway wall

thickness on CT and, as Kesimer and Boucher demonstrated, altered sputum biology (11, 12). In the Multi-Ethnic Study of Atherosclerosis Lung Study, my colleagues and I observed that pulmonary emphysema on CT occurs in approximately 1 in 10 older adults in the general population, mostly with preserved spirometry, and is associated, even with preserved spirometry, with dyspnea, reduced activity levels, desaturation with exercise, and increased mortality without modification by smoking status (13–16).

Thus, the Baldwin-Cournand-Richards concept of chronic pulmonary insufficiency as an insufficiency or disease defined symptomatically, radiologically, and physiologically, and including patients with normal spirometry who do not meet current guidelines (17), is being rediscovered. The contemporary observational data are increasingly unequivocal in showing that many, possibly most, patients with symptoms of and poor prognosis resulting from chronic pulmonary insufficiency have normal spirometry when stable. The current

randomized evidence base for treatment, however, is limited to spirometrically defined COPD. Randomized clinical trials for smokers with chronic respiratory symptoms and normal spirometry, such as the RETHINC (Redefining Therapy in Early COPD for the Pulmonary Trials Cooperative) study (<https://clinicaltrials.gov/ct2/show/NCT02867761>), are just beginning to be performed.

Rethinking Chronic Obstructive Pulmonary Disease: Combined Cardiopulmonary Insufficiency

Baldwin, Cournand, and Richards stated that “functionally, it is obvious that the pulmonary and circulatory apparatus are one unit” (2), and performed cardiac catheterization to measure pulmonary blood flow and cardiac output, for which Cournand and Richards were awarded the Nobel Prize. Baldwin, Cournand, and Richards defined combined cardiopulmonary insufficiency as chronic pulmonary insufficiency with cardiac and pulmonary artery enlargement (Figure 1B) (3). In their view, combined cardiopulmonary insufficiency included left heart failure or right heart failure, which fits with the anatomic, physiologic, and cellular interactions of the heart and lungs. These interactions are complicated and may vary in opposing ways among contemporary subphenotypes of chronic lung disease. A brief and somewhat simplistic overview of potential mechanisms of combined cardiopulmonary insufficiency follows.

Left Heart Failure with Reduced Ejection Fraction

Left heart failure with reduced ejection fraction (HFrEF) occurs in patients with COPD (18, 19), and low lung function is an independent risk factor for incident HFrEF and cardiac events in prospective cohort studies (20, 21) and hospital-based studies (22). The major reason for the increased prevalence of HFrEF in COPD is increased atherosclerotic heart disease due to the high prevalence of smoking in patients with COPD; whether this risk is independent of standard cardiac risk factors is arguable (20, 23–25).

In addition, ventilation at the operating lung volumes observed in obstructive lung disease requires more negative intrathoracic pressures that may cause not only pulmonary edema as a result of increased hydrostatic pressure gradients (26) but also increased left ventricular (LV) afterload as a

Table 1. Baldwin-Cournand-Richards criteria for chronic pulmonary insufficiency and combined pulmonary insufficiency

Criteria for the Diagnosis of Chronic Pulmonary Insufficiency

- Chronic respiratory symptoms
- Emphysema on chest radiograph
- Residual “air” greater than predicted and residual “air”/total lung capacity >0.36

(Sub)Groups of Chronic Pulmonary Insufficiency

Uncomplicated:

1. Postexercise oxygen saturation $\geq 92\%$
2. Postexercise oxygen saturation $< 92\%$, partial pressure of carbon dioxide ≤ 48 mm Hg
3. Postexercise oxygen saturation $< 92\%$, partial pressure of carbon dioxide > 48 mm Hg

Combined cardiopulmonary insufficiency:

4. Cardiac and pulmonary artery enlargement

This table is a summary of findings from Reference 3.

result of lower juxtacardiac pleural pressure. Consistent with this physiology, gas trapping (increased residual “air” volume) is associated with LV hypertrophy, a known risk factor for HFrEF (27), even in predominantly mild to moderate COPD (28).

There are multiple proven therapies for HFrEF, and though none has been tested specifically in COPD, it is likely that most are beneficial in HFrEF with COPD, with a caveat about judicious use of β -blockers in COPD (29). Whether pulmonary interventions to reduce gas trapping cause regression of LV hypertrophy or affect heart failure endpoints remains to be proved.

Left Heart Failure with Preserved Ejection Fraction

Patients with low lung function are also at increased risk for incident left heart failure with preserved ejection fraction (HFpEF) (20). There are a large number of reports describing echocardiographic signs of LV diastolic dysfunction in COPD (30–36). LV diastolic dysfunction is characterized by increased stiffness of the left ventricle, leading to increased LV end-diastolic pressure, left atrial enlargement, and pulmonary edema. Recent work using four-dimensional flow magnetic resonance imaging additionally suggests that abnormal vorticity of blood flow in the left ventricle may contribute to LV diastolic dysfunction in COPD (37).

There are no proven therapies for HFpEF besides symptomatic treatment in the absence or presence of COPD (29). However, distinguishing “pseudo-HFpEF” from true HFpEF, as described below, may suggest specific therapies for the former group of patients.

Pseudo-Heart Failure with Preserved Ejection Fraction

Echocardiographic signs of LV diastolic dysfunction based on mitral inflow indices yield false-positive results in the setting of reduced LV end-diastolic pressure, such as that resulting from upstream resistance due to elevated pulmonary vascular resistance or pulmonary hyperinflation (38). My colleagues and I have previously shown that, other than age, percent emphysema based on CT is the major correlate of LV filling in the general population and in COPD (15, 39). Contemporary studies measuring LV end-diastolic pressure in COPD and emphysema are lacking; however, my colleagues and I found that pulmonary microvascular blood

flow and pulmonary vein sizes visualized by magnetic resonance imaging were markedly reduced in COPD (15, 40), and Watz and colleagues found that hyperinflation was related to LV filling (41).

Furthermore, reduced pulmonary vascular volume on CT was associated with reduced left atrial size, reduced LV volumes, and dyspnea in smokers in the general population (42). These findings suggest, consistent with smaller studies (37), that some and possibly most LV “diastolic dysfunction” on echocardiography in COPD may be due to low LV filling pressures unrelated to the LV—in other words, pseudo-HFpEF. Further studies are needed to fully elucidate these relationships and how they correspond to contemporary COPD subphenotypes. Distinguishing true HFpEF from pseudo-HFpEF is important because pseudo-HFpEF may be amenable to therapies targeting the pulmonary vasculature in mild COPD and other pulmonary, rather than cardiac, intermediaries as described below.

Cor Pulmonale

The definition of cor pulmonale is right ventricular (RV) hypertrophy that can progress to RV failure (43). Cor pulmonale classically occurs in a subset of patients with COPD (43, 44) and is common in other forms of pulmonary hypertension (45). As noted by Burrows and Diener, cor pulmonale was common in type B (“British”) COPD, characterized by pulmonary hyperinflation, gas trapping, carbon dioxide retention, and preserved cardiac output, but it was rare in type A (“American”) COPD, in which emphysema was prominent and cardiac output was reduced (46–49). Although contemporary measures of subclinical pulmonary hypertension are associated with exacerbations in COPD (50), clinically significant cor pulmonale in COPD is now rare in both the United States and Britain, although precise data are lacking (45). Trials of pulmonary vasodilators developed for pulmonary arterial hypertension have generally not gone well in severe COPD, owing to worsened ventilation–perfusion mismatch.

Cor Pulmonale Parvus

One would expect that the right ventricle would respond to pulmonary vascular damage in emphysema by hypertrophying, as occurs in pulmonary arterial hypertension (43, 44, 51). Instead, my

Figure 2. Cardiopulmonary imaging combining state-of-the-art measures of lung structure visualized by computed tomography with cardiopulmonary and four-dimensional flow magnetic resonance imaging. The image is of a participant in the Multi-Ethnic Study of Atherosclerosis Chronic Obstructive Pulmonary Disease Study who had chronic obstructive pulmonary disease, severe centrilobular emphysema shown as loss of lung tissue in both upper lobes, and impaired cardiac function related to impaired right heart filling and function. Blue and red lines show the blood entering the right heart from the superior and inferior vena cava, respectively, and its ejection into the main pulmonary artery visualized by four-dimensional flow magnetic resonance imaging.

colleagues and I found that RV volumes were markedly reduced in COPD and that there was no evidence for increased RV mass in contemporary mild to moderate COPD (52). Furthermore, smaller RV volumes were specifically related to the extent of emphysema on CT. The same contrarian observations were made in the general population (53) and older autopsy and radiologic studies (e.g., “tear-drop” heart on chest radiography; see Figure 1A) (54). Collectively, the observation that COPD and emphysema are associated predominantly with smaller RV volumes may be best described by the term cor pulmonale parvus (52).

The reasons for cor pulmonale parvus may include impaired venous return to the right heart due to gas trapping, diaphragmatic impingement on the inferior vena cava due to pulmonary hyperexpansion, right heart stiffness and distortion, RV diastolic dysfunction, and reduced blood volume (52). All of these will reduce LV filling, potentially with a low LV end-diastolic pressure and potentially

yielding false-positive echocardiographic findings of HFpEF—or pseudo-HFpEF.

A recent short-term randomized clinical trial showed that in severe COPD with hyperinflation, short-term long-acting β -agonist/inhaled corticosteroid inhalation therapy increased RV and LV end-diastolic volumes and stroke volume (55). The mechanistic interpretation of this trial, however, is complex. It does not clarify the relative contributions of the following:

1. Reduced gas trapping leading to improved venous return to the right heart, reduced compression of the pulmonary vasculature and heart, and reduced LV afterload with improved LV output;
2. Reduced hyperexpansion resulting in less compression of the inferior vena cava;
3. Vasodilation of the pulmonary vasculature with lowered pulmonary vascular resistance; and
4. Potential antiinflammatory effects.

Hence, combined cardiopulmonary insufficiency identified by Baldwin,

Cournand, and Richards is complex and involves different physiologic mechanisms that vary with specific subphenotypes of chronic lung disease. Population-based estimates are lacking; however, it would appear that these subphenotypes often occur separately, although they can co-occur in the same patients and are potentially identifiable with advanced imaging (Figure 2), and physiologic and molecular approaches—rather than invasive ones used earlier—to facilitate specific therapies targeted at subsets of patients with heart-lung failure. Large-scale studies of cardiopulmonary interactions in chronic lung disease are warranted to determine the overlap, examine if there are distinct risk factors, and identify patients for targeted therapies.

Conclusions

Baldwin, Cournand, and Richards laid down a three-pronged approach to the diagnosis of chronic pulmonary

insufficiency based on respiratory symptoms, imaging-defined alterations in lung structure, and pulmonary function. Seventy years after their observations, contemporary large-scale studies are defining subphenotypes of chronic pulmonary insufficiency based on these axes to provide insights into the distinct pathogenesis of, individual risk for, and personalized paths to treatment for chronic respiratory insufficiency. Baldwin, Cournand, and Richards also recognized the tight but complex anatomic, physiologic, and pathologic linkage of the heart and lungs. Large-scale studies are still warranted to examine heart-lung interactions to better understand their pathophysiology and find specific therapies for subphenotypes of combined cardiopulmonary insufficiency. ■

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