The Pulmonary Manifestations of Left Heart Failure*

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Determining whether a patient's symptoms are the result of heart or lung disease requires an understanding of the influence of pulmonary venous hypertension on lung function. Herein, we describe the effects of acute and chronic elevations of pulmonary venous pressure on the mechanical and gas-exchanging properties of the lung. The mechanisms responsible for various symptoms of congestive heart failure are described, and the significance of sleep-disordered breathing in patients with heart disease is considered. While the initial clinical evaluation of patients with dyspnea is imprecise, measurement of B-type natriuretic peptide levels may prove useful in this setting.   (CHEST 2004; 125:669–682)

Key words: Cheyne-Stokes respiration; congestive heart failure; differential diagnosis; dyspnea; pulmonary edema; respiratory function tests; sleep apnea syndromes

Abbreviations: CHF = congestive heart failure; CSR-CSA = Cheyne-Stokes respiration with central sleep apnea; CPAP = continuous positive airway pressure; D_{LCO} = diffusing capacity of the lung for carbon monoxide; DM = membrane conductance; FRC = functional residual capacity; OSA = obstructive sleep apnea; TLC = total lung capacity; VC = capillary volume; $\dot{V}_E/\dot{V}_{CO_2}$ = ventilatory equivalent for carbon dioxide

Nearly 5 million Americans have congestive heart failure (CHF), with 400,000 new cases diagnosed each year.[1] Unfortunately, despite the considerable progress that has been made in understanding the pathophysiology of pulmonary edema, the pulmonary complications of this condition continue to challenge the bedside clinician. This review presents a physiologic basis for understanding the pulmonary manifestations of left heart failure (*eg*, left ventricular failure and/or mitral valve disease). Particular emphasis is placed on the effects on the lung of both acute and chronic pulmonary venous hypertension, while congenital heart disease is not considered. We reviewed the MEDLINE database for articles relevant to the pathophysiology and clinical consequences of pulmonary venous hypertension and pulmonary edema. Additional sources were culled from the references in these articles. For simplicity in this article, we have used the convention of referring to left-sided CHF (*eg*, left ventricular failure and/or mitral valve disease) as CHF.

For a detailed review of the pathophysiology of high-pressure pulmonary edema, the reader is referred to several excellent recent reviews.[2–4]

The Pathophysiology of Pulmonary Congestion

Clinicians who are experienced in the care of patients with chronic CHF are familiar with the body's remarkable ability to adapt to a chronically elevated pulmonary capillary wedge pressure. How is it that a previously healthy individual develops pulmonary edema when the pulmonary capillary wedge pressure reaches 25 mm Hg, whereas a patient with longstanding CHF is ambulatory at a filling pressure of 40 mm Hg (Fig 1)? The answer lies in a variety of adaptations that occur in an individual who has been exposed to chronically elevated filling pressures.

Under normal conditions, there is a linear increase in pulmonary blood flow from the apex to the base of the lung. Elevated left atrial pressure results in pulmonary venous hypertension and a more uniform distribution of blood flow.[5] This redistribution is accomplished through capillary distension and recruitment.[6] Modest elevations in pulmonary capillary wedge pressure are accommodated in this manner, without the development of pulmonary edema.

At higher filling pressures, fluid may begin to cross the microvascular barrier. Ernest Starling first de-
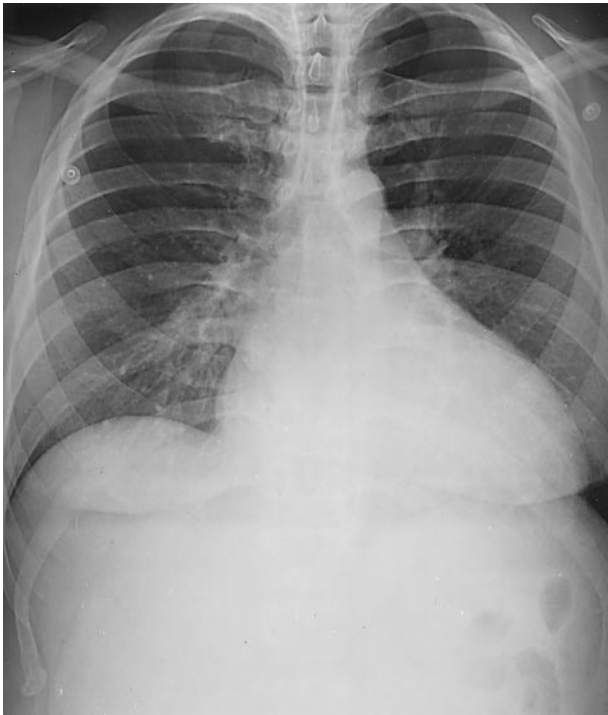
FIGURE 1. Chest radiograph of a 28-year-old man in whom an idiopathic dilated cardiomyopathy was diagnosed after presenting with weight gain and breathlessness. This chest radiograph was obtained when the patient's pulmonary capillary wedge pressure was 40 mm Hg, and prior to a 40-lb diuresis. Pulmonary edema is notably absent, although cardiomegaly and distension of the left upper lobe vein suggest the presence of heart disease.

Table 1—*Safety Factors Protecting the Lungs Against Alveolar Edema Accumulation**

Factors	Description
Alveolar barrier properties opposing edema	Extremely low alveolar epithelial barrier permeability
	Low alveolar surface tension (surfactant)
	Active transport by alveolar epithelial cells
Microvascular barrier properties opposing increased pressure filtration	Low permeability to protein
	Washdown of perimicrovascular protein osmotic pressure
	Plasma protein concentration
	Interstitial exclusion volume
Alveolohilar interstitial pressure gradient	
Perimicrovascular interstitial compliance	
Coagulation of edema fluid	
Liquid clearance pathways	Lung lymphatic system
	Loose peribronchovascular connective tissue sumps
	Resorption into blood vessels
	Mediastinal drainage
	Pleural space
	Expectoration

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scribed the basic forces regulating fluid flux across this barrier in 1895, stating that fluid exchange in the lung represents a balance between capillary hydrostatic forces favoring pulmonary edema and interstitial oncotic pressures opposing it. Although it was originally thought that the lung was "dry" in health, it is now recognized that Starling forces favor the transudation of fluid under normal conditions.[7] Fortunately, there are a number of mechanisms that prevent pulmonary edema from occurring. Table 1 provides a comprehensive list of these protective mechanisms, or "safety factors," several of which are described in more detail below.[2] The first of these safety factors is the dual nature of the alveolar-capillary unit, which is composed of a thin side and a thick side (Fig 2). The thin side consists of a capillary closely apposed to the alveolar airspace. Here, the capillary endothelium and alveolar epithelium are attenuated, the basement membranes are fused, and complex epithelial junctions exist. The low permeability of this region, coupled with the short distance necessary for diffusion, make the thin side well-suited for gas exchange. The thick portion of the alveolar-capillary unit contains an interstitium with a gel-like protein component. A rise in capillary hydrostatic pressure favors the formation of edema first in this interstitial compartment, removed from the critical gas-exchanging regions. As fluid accumulates
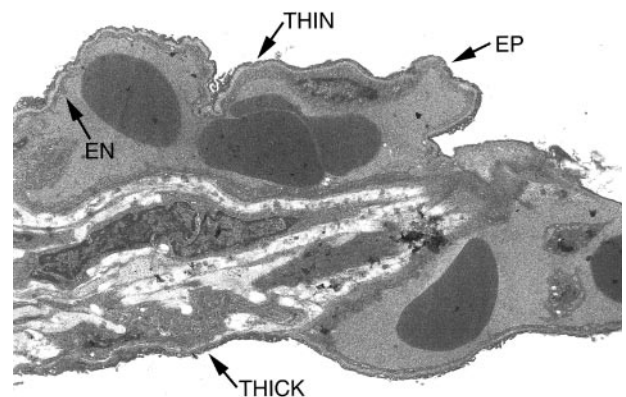

FIGURE 2. Electron micrograph of a normal alveolar-capillary unit. On the thin side of the alveolar-capillary unit (THIN), the basal laminae of the alveolar epithelium and capillary endothelium are fused. The thick side of the barrier (THICK) contains an interstitial matrix that separates the alveolar epithelium from the capillary endothelium. (Human lung surgical specimen, transmission electron microscopy.) EP = alveolar epithelium; EN = capillary endothelium.

in the interstitial compartment, there is a rise in its hydrostatic pressure and a lowering of its oncotic pressure, both of which serve to oppose further fluid flux.

Once fluid forms in the interstitium, it is transported along a negative pressure gradient to the interlobular septae, then to the peribronchovascular space, and finally to the hila.[8–11] Edema fluid also collects in the pleural space, which accommodates up to one quarter of all excess lung water in animal models of pulmonary edema.[12] Lymphatic vessels that are responsible for fluid clearance are contained within the connective tissue of the interlobular septa, the peribronchovascular sheath, and the pleura. The lymphatic system is highly recruitable, able to increase the clearance of lung water by more than 10-fold over time.[13]

Together, the interstitial and pleural spaces act as a sump for excess lung water.[3] Following the accumulation of sufficient interstitial fluid, the alveoli begin to flood. Once this occurs, the alveolar epithelium and distal airways actively transport water back out of the gas-exchanging units of the lung.[14]

West and coworkers[15,16] have described disruption of some or all layers of the alveolar-capillary unit by elevated capillary hydrostatic pressures, a phenomenon they termed *pulmonary capillary stress failure*. This phenomenon is visible in electron micrographs of lung specimens taken from animal models of acute pulmonary venous hypertension. These micrographs demonstrate breaks in the capillary endothelial layer, the alveolar epithelial layer, and, less commonly, the comparatively strong type IV collagen-containing basement membranes. When all of these layers are disrupted, RBCs may be seen traversing the alveolar-capillary membrane. Pulmonary capillary stress failure represents a process that blurs the distinction between high-pressure and low-pressure pulmonary edema, as the disruption of the alveolar-capillary membrane by high hydrostatic pressures may render it more permeable to fluid and proteins. The resulting edema fluid has a higher concentration of protein than would be expected in conventional high-pressure pulmonary edema.[17] These observations may explain such seemingly diverse disorders as high-altitude pulmonary edema, neurogenic pulmonary edema, and hemoptysis in mitral stenosis.

How is it, then, that a patient with long-standing CHF can have a pulmonary capillary wedge pressure of 40 mm Hg and not experience pulmonary edema? Apart from the defenses to pulmonary edema described above, significant pulmonary vascular changes have been described in pathologic studies[18–23] of lung specimens that were obtained either from autopsies or from surgical biopsies at the time of mitral valve replacement. At a micro-scopic level, many such specimens demonstrate alveolar fibrosis, while electron micrographs show thickening of the capillary endothelial and alveolar epithelial cell basement membranes. These changes are thought to reduce the permeability of the alveolar-capillary membrane to water, and thus prevent the formation of pulmonary edema. Pulmonary arteries exhibit intimal fibrosis and medial hypertrophy, with extension of the muscular layer into small arterioles (*ie*, muscularization). Pulmonary veins are abnormally thick-walled, and lymphatic vessels are dilated and occasionally muscularized. Finally, hemosiderosis is present in a substantial number of cases, likely from erythrocyte egress across the alveolar-capillary membrane as a consequence of microvascular trauma.

The natural history of severe mitral stenosis provides an excellent example of how pulmonary vascular remodeling can cause variability in the clinical presentation of pulmonary venous hypertension. While the early course of this disease is marked by recurrent episodes of pulmonary edema, over many years the frequency and severity of episodes of pulmonary edema decreases. Consequently, patients present later in the course of mitral stenosis not with pulmonary edema but, rather, with pulmonary hypertension and right ventricular failure.

Similar to longstanding mitral stenosis, chronic left ventricular failure may result in pulmonary hypertension. Either condition may be associated with an elevated transpulmonary gradient (*ie*, mean pulmonary artery pressure minus mean pulmonary capillary wedge pressure) and increased pulmonary vascular resistance. Interestingly, while some individuals develop poorly reversible pulmonary hypertension, others do not. Elevations in pulmonary vascular resistance reflect the varying contributions of abnormal pulmonary vascular tone and structural remodeling, the former of which is typically reversible, while the latter is not.[24] Which factors lead to increased vascular reactivity, and why some patients develop poorly reversible pulmonary hypertension, is poorly understood. In fact, patients with chronic CHF who have a pulmonary vascular resistance exceeding 480 to 640 dyne cm^{-5} have an increased risk of postoperative right ventricular failure following heart transplantation.[25] When the pulmonary vascular resistance can be lowered pharmacologically (*eg*, with IV nitroprusside) this risk is generally thought to be reduced.[26] Such reversibility probably indicates that significant vascular remodeling has not occurred. Because CHF confers an increased risk of venous thromboembolism,[27] the

exclusion of this condition may be appropriate in selected patients with poorly reversible pulmonary hypertension.

Clearly, the lung exhibits a variety of complex adaptations to an elevation in capillary pressures. Following this brief review of the acute and chronic effects of pulmonary venous hypertension, it is now possible to consider the impact of these processes on the mechanical and gas-exchange properties of the lung.

Pulmonary Function in Heart Disease

Diuresis of healthy subjects results in increased lung volumes and flows, suggesting that, even in health, pulmonary function is influenced by the water content of the lung.[28] Abnormalities in the mechanical and gas-exchanging properties of the lung have been described in patients with both acute pulmonary edema and chronic CHF, although the findings differ somewhat (Table 2 includes these abnormalities).

Ventilatory Abnormalities

Relatively few studies have investigated the effects of acute pulmonary congestion on lung mechanics. Muir and colleagues[29] found that rapid saline solution infusion in healthy subjects caused an asymptomatic decrease in both total lung capacity (TLC) and FVC, although lung compliance was unchanged. Volume loading provoked airflow obstruction and a decrease in alveolar-capillary membrane conductance (see below) in a study of 10 nonsmoking patients with asymptomatic left ventricular dysfunction.[30] A similar obstructive ventilatory defect has been described in patients with decompensated CHF.[31–33] The plethysmo-graphic determination of lung volumes rarely has been attempted in the setting of pulmonary edema, but at least one study found mild restriction.[34] In that study, recovery from pulmonary edema was associated with improvements in TLC, FVC, and FEV_1, with an additional improvement in the FEV_1/FVC ratio occurring in nonsmokers. Lung compliance may be reduced, but the extent to which this occurs, beyond that caused by a decrease in the area of the lung being aerated, is controversial.[35–39]

Numerous studies have described pulmonary function abnormalities in patients with mitral stenosis. Rhodes and coworkers[40] have reported that stable patients with mitral valve disease (predominantly mitral stenosis) have an increase in residual volume, and a decrease in FVC, FEV_1, and diffusing capacity of the lung for carbon monoxide (DLCO) that are correlated with the severity of the valve disease. Although wheezing[40] and an increase in airways resistance[41,42] are common, significant airflow obstruction is infrequent.[40] TLC is generally preserved until late in the course of the disease.[43] Pressure-volume curves of the lung reveal increased recoil (lower compliance) at large lung volumes, but decreased recoil at low volumes.[41] Mitral valve replacement has a normalizing effect on pulmonary function and compliance.[42,44]

Patients with chronic, predominantly nonvalvular CHF frequently exhibit a restrictive ventilatory defect, while obstruction is uncommon (Fig 3 and Table 3).[45–53] The reduction in TLC is proportional to the severity of heart disease as assessed by cardiopulmonary exercise testing.[53] As in mitral stenosis, these abnormalities can be improved by the correction of the cardiac abnormalities, either through medical treatment or heart transplantation. Ultrafiltration causes an improvement in FVC, FEV_1, and exercise performance in stable patients with chronic

Table 2—*Possible Pulmonary Complications of Pulmonary Venous Hypertension*

| Complications	Description
Pulmonary function abnormalities	Decreased lung volume
	Airflow obstruction, especially in acute pulmonary edema
	Air-trapping
	Decreased lung compliance
	Arterial hypoxemia
	Decreased diffusing capacity (may be irreversible in long-standing CHF)
Sleep-disordered breathing	CSR-CSA
	OSA
Myopathy of peripheral and respiratory muscles	
Unusual manifestations	Hemoptysis, pulmonary hemorrhage
	Hemosiderosis
	Ossific nodules
	Mediastinal lymphadenopathy[135]
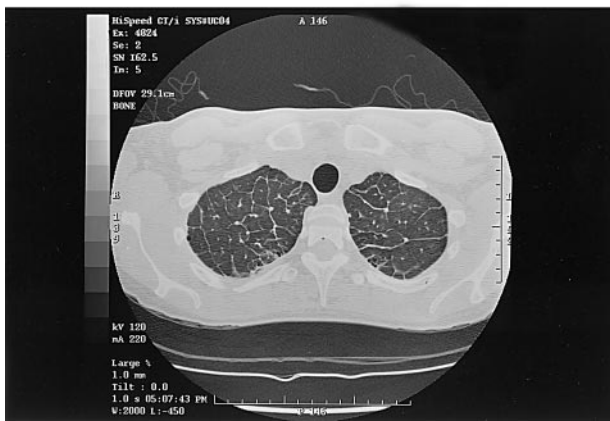
FIGURE 3. A chest radiograph of a 50-year-old woman with chronic cough. The chest radiograph (*top*) showed a fine basilar interstitial abnormality and a normal cardiothoracic ratio. There are a few Kerley B lines in the left lower lobe, and the distension of the right upper lobe and the right lower lobe veins suggests a diagnosis of CHF. A high-resolution CT scan (*bottom*) revealed pulmonary edema (thickened interlobular septae are shown) and mediastinal lymphadenopathy. Pulmonary function tests (Table 3) demonstrated a restrictive defect. The chronic cough, interstitial abnormality, mediastinal lymphadenopathy, and restrictive ventilatory defect all resolved with treatment of the patient's CHF.

heart failure.[54] Heart transplantation results in an improvement in pulmonary function by 3 months following surgery,[51] and normal lung volumes and flows (but not DLCO; see below) are achieved by 1 year posttransplant.[50–52] Interestingly, up to 70% of the improvement in FVC can be accounted for by the reduction in cardiac volume, as assessed by chest

Table 3—Pulmonary Function Test Results*

Parameter	Baseline, L	After Treatment, L
TLC	3.78 (65)	5.37 (90)
FVC	2.25 (60)	3.48 (90)
FEV$_1$	1.82 (63)	2.67 (91)
DLCO	Normal	Normal

*Values given as No. (%).

radiography.[55] This finding suggests that the simple displacement of the lung by the enlarged heart accounts for a substantial portion of the restrictive abnormalities in CHF, while the balance of the ventilatory deficit may result from interstitial edema, pleural effusions, vascular engorgement, and respiratory muscle weakness.

DLCO

The overall resistance of the lung to gas transfer is the inverse of the DLCO and is described as follows: $1/D_{LCO} = 1/DM + 1/\theta VC$, where DM is membrane conductance and θVC is a term describing the rate of reaction of the gas with hemoglobin and the volume of the capillary blood (VC). Therefore, reductions in DLCO may arise from a decrease in capillary blood volume or hemoglobin, or from an increase in the resistance of the alveolar-capillary membrane to diffusion. CHF might be expected to increase DLCO through an increase in capillary blood volume and thus θVC. In fact, although positively correlated with pulmonary capillary wedge pressure in patients with chronic severe CHF, the DLCO is commonly reduced.[56] This reduction must result, therefore, from a decreased DM. Studies have shown that DM is reduced in chronic CHF even after correction for lung volume in proportion to the duration of heart failure and inversely correlated with pulmonary vascular resistance.[47,57] Decreased membrane conductance may represent thickening of the alveolar-capillary barrier from the accumulation of fluid or fibrosis. Remodeling of this barrier is indirectly supported by data suggesting that patients with chronic CHF have reduced pulmonary microvascular permeability.[58] This process may be a defense against pulmonary edema in patients with chronic pulmonary venous hypertension. Pulmonary function data from patients before and after heart transplantation have suggested that the reduction in membrane conductance may not be fully reversible.[47,50–52] Following heart transplantation, there is an initial decline in the DLCO. By the end of 1 year posttransplant, the DLCO (corrected for lung volume) has returned to the pretransplant value. This unchanged DLCO reflects a decrease in pulmonary capillary blood volume (*ie*, VC) that is not adequately compensated for by the increase in DM.[47] Chronic CHF likely leads to irreversible changes in the alveolar-capillary membrane, possibly as a consequence of pulmonary capillary stress failure and subsequent remodeling. While this process may represent a defense against pulmonary edema, it also may contribute to exercise intolerance, as will be discussed below.

Sleep Disorders in CHF

Evidence is accumulating of an important association between sleep-disordered breathing and CHF. Either obstructive sleep apnea (OSA) or, more commonly, Cheyne-Stokes respiration with central sleep apnea (CSR-CSA) has been detected in as many as 50% of patients with chronic CHF.[59-62] Each disorder is considered separately below.

The risk factors for OSA in a population of 450 men and women with CHF who had been referred to a sleep laboratory for evaluation differed according to gender. Body mass index was associated with OSA in men, while increasing age conferred increased risk for OSA in women.[63] Observational studies[64] have suggested that OSA may itself be an independent risk factor for CHF. There are several mechanisms whereby OSA may stress the cardiovascular system. First, the significantly negative intrathoracic pressure generated in response to each episode of upper airway obstruction increases left ventricular afterload[65] and reduces left ventricular preload.[66] OSA also results in intermittent hypoxia, elevated sympathetic nervous system activity,[67] nocturnal increases in systemic BP, and, probably, hypertension.[68-70] Treatment with continuous positive airway pressure not only reduces obstructive respiratory events but also left ventricular afterload.[65,71]

CSR-CSA is characterized by repetitive cycles of central apnea followed by crescendo/decrescendo ventilation. This disorder represents respiratory control instability that is caused by oscillations of the arterial P_{CO_2} around the level that causes apnea.[72] When hyperventilation lowers the arterial P_{CO_2} below the apnea threshold, the drive to breathe is diminished. In the absence of the wakefulness drive to breathe, apnea may occur. If an arousal results, the newly elevated arterial P_{CO_2} is recognized as inappropriately high for wakefulness. This results in hyperventilation. It is thought that the background hyperventilation commonly found in patients with CHF may be caused by the stimulation of pulmonary J receptors from an increase in interstitial pressure. This theory is supported by the finding of larger left ventricular volumes in heart failure patients with CSR-CSA than in those without it,[73] as well as by a correlation between pulmonary capillary wedge pressure, and both the degree of hypocapnia and the frequency and severity of central apneas.[74] While this background hyperventilation is permissive for the development of CSR-CSA, elevated fast-acting peripheral ventilatory responsiveness determines the periodicity of breathing.[75]

The presence of CSR-CSA in a patient with CHF confers a worse prognosis.[76,77] Conceivably, therapy with continuous positive airway pressure (CPAP) could ameliorate CSR-CSA and improve overall outcomes for patients with CHF by improving cardiac function. Indeed, CPAP has been found to decrease left ventricular afterload when applied to awake patients with chronic CHF.[71] Unfortunately, there are few data on the advisability of treating CSR-CSA in patients with CHF. In small studies, CPAP has been shown to decrease apneas and hypopneas,[78] reduce sympathoneural activity,[79] increase ejection fraction,[80] improve circulation time and New York Heart Association class,[81] and improve cardiovascular outcomes,[82] although some other investigators have not found a benefit.[83,84] Larger studies of the long-term efficacy of CPAP in patients with CHF are underway. The subject of sleep disorders and cardiovascular disease has been the subject of a recent comprehensive review.[66]

Pulmonary Symptoms of Heart Disease

Wheezing

Although airflow obstruction in the setting of pulmonary edema has long been familiar to clinicians,[85] the mechanisms responsible for this observation remain obscure. The elevation of pulmonary or bronchial vascular pressure likely results in reflex bronchoconstriction.[86] Other potential causes of airway narrowing include a geometric decrease in airway size from reduced lung volume, obstruction from intraluminal edema fluid, and bronchial mucosal swelling.[86] Some investigators,[87,88] but not all,[89] have found an increase in bronchial responsiveness to methacholine in patients with left ventricular dysfunction or mitral valve disease. The significance of this finding is not clear. Contrary to earlier reasoning, there is no evidence that engorged bronchovascular bundles directly compress small airways.[90] There are very few data concerning the effects of bronchodilating drugs on pulmonary function in patients with pulmonary edema, although one small study[91] of patients with acute exacerbations of chronic CHF found that ipratropium bromide administration produced bronchodilation.

Orthopnea

The assumption of the supine position in an individual with CHF causes an increase in airway resistance within 5 min, imposing a resistive load to breathing.[92] Furthermore, while healthy individuals experience a 500-mL decrease in functional residual

capacity (FRC) on lying supine, the FRC does not fall in patients with CHF. Since the FRC in upright patients with heart failure is usually normal, and because such patients may have an additional 500 mL or so of blood contained within the heart and blood vessels, the assumption of the supine position may result in a chest wall that is displaced outward by a liter compared with its normal position.[3] Although difficult to separate from other contributors to dyspnea, this chest wall displacement conceivably could produce dyspnea.

Dyspnea in Acute Pulmonary Edema

It is unclear which of the many aberrations provoked by pulmonary edema result, singly or in combination, in dyspnea. Again, vascular engorgement and cardiac enlargement may cause an extra 500 mL of blood to be contained within the thorax, expanding the chest wall past its usual position.[3] This may cause dyspnea through the activation of chest wall position sensors, as well as through an increase in the elastic work of breathing. Reduced pulmonary compliance similarly imposes an elastic load, just as an increase in airway resistance imparts a resistive load.[35,86] Discrepancies between the neural output of the brain and the resulting work performed by the mechanically disadvantaged respiratory muscles may result in dyspnea.[93] At the same time that the respiratory muscles are working harder, they may experience impaired oxygen delivery as a consequence of reduced cardiac output and arterial hypoxemia. Finally, vascular distension and interstitial edema may directly stimulate nerve endings and result in dyspnea,[86] although this hypothesis has been challenged.[94]

Exercise Intolerance

Fatigue and dyspnea on exertion are common complaints even for well-compensated patients with CHF. Although the mechanisms responsible for exercise intolerance in these patients are incompletely understood, cardiopulmonary exercise testing has allowed investigators to describe a number of characteristic abnormalities.

A reduction in exercise capacity may occur in patients with heart disease of any cause and is expressed as a reduced peak oxygen uptake. This abnormality is not specific to cardiovascular disease, but the magnitude of the abnormality is of considerable prognostic importance, serving as a means of selecting appropriate candidates for heart transplantation in most centers. Chronic heart failure is also associated with an abnormally elevated ratio of ventilation to carbon dioxide production, a relationship described as the ventilatory equivalent for carbon dioxide ($\dot{V}E/\dot{V}CO_2$).[95] There are likely several contributions to this abnormally increased $\dot{V}E/\dot{V}CO_2$ ratio, including the earlier onset of metabolic acidosis during exercise, a lowering of the CO_2 set point for ventilation, and a disproportionately high dead space (ie, wasted ventilation) from poor pulmonary perfusion.[96]

Other abnormalities contribute to the exercise intolerance of CHF patients. Pulmonary congestion reduces the compliance of the lung, increasing the work of breathing.[35,97] Gas exchange abnormalities were previously thought to be of limited clinical significance, since significant exertional arterial desaturation is uncommon in patients with CHF. However, DM is correlated with maximum oxygen uptake and is inversely related to pulmonary vascular resistance.[98] Interestingly, angiotensin-converting enzyme inhibitors improve resting DLCO, and reduce the exercise dead space fraction and $\dot{V}E/\dot{V}CO_2$, possibly through an improvement in pulmonary capillary diffusion and ventilation-perfusion relationships.[99] The coadministration of aspirin eliminates this effect, suggesting an influential role for prostaglandins in regulating pulmonary blood flow.[99]

A variety of functional, metabolic, and histologic abnormalities have been described[100–104] in the peripheral and respiratory muscles of patients with CHF, which may contribute to exercise intolerance. Deconditioning likely contributes to these abnormalities; however, additional mechanisms are required to explain these findings adequately. Current theories include influences as diverse as cytokine activation from chronic CHF to underperfusion.[100] Currently, the respiratory and peripheral muscle abnormalities associated with CHF are poorly understood.

Unusual Pulmonary Manifestations of Heart Disease

Underdeveloped regions of the world have produced large numbers of patients with rheumatic heart disease. Much of the literature describing unusual pulmonary manifestations of heart disease consists of descriptive studies of such patients, particularly those with mitral stenosis. Hemosiderosis from microvascular hemorrhage may be visible radiographically as small nodules, 1 to 5 mm in size, that generally, but not exclusively, are in the lower lobes.[105,106] Ossific nodules consist of lamellated bone that forms within the alveoli.[107] The irregular size and shapes of ossific nodules may be helpful in distinguishing these nodules from healed histoplasmosis and tuberculosis.[105] Increased interstitial

markings may indicate pulmonary fibrosis from chronic venous hypertension and hemosiderosis.

Such findings are now unusual in the developed world. Still, hemoptysis and/or pulmonary hemorrhage occasionally may be seen, usually in patients with mitral valve disease (Fig. 4, 5).[18,108] The bleeding may arise either from the pulmonary microcirculation or from engorged submucosal bronchial veins.[15,108,109] The bleeding typically resolves on effective treatment, whether medical or surgical, of the pulmonary venous hypertension.

DIAGNOSTIC DIFFICULTIES IN LEFT HEART FAILURE

A comprehensive discussion of all of the diagnostic tools used to evaluate cardiopulmonary disease is beyond the scope of this review. Herein we highlight selected difficulties encountered in the routine evaluation of patients with pulmonary edema.

Clinicians often are required to differentiate heart disease from lung disease in a patient with breathlessness. Unfortunately, the initial clinical
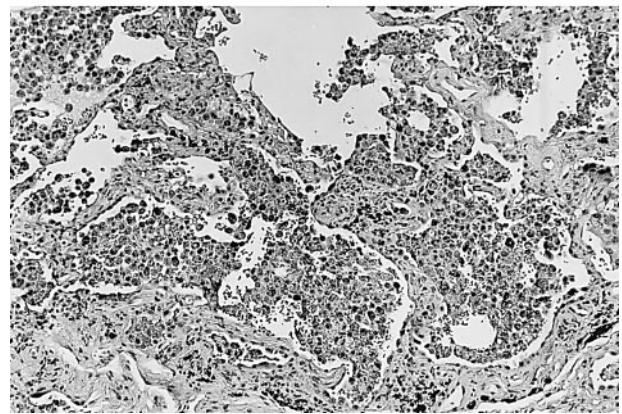
FIGURE 5. A 74-year-old woman receiving therapy with warfarin for atrial fibrillation presented with a 5-year history of brown sputum production, and recent dyspnea and hemoptysis. A high-resolution CT scan (*top*) revealed diffuse septal lines and lobular wall thickening that were consistent with a deposition disorder such as hemosiderosis or amyloidosis. Echocardiography showed a stenotic and rheumatically deformed mitral valve, while surgical lung biopsy (*bottom*) demonstrated chronic alveolar hemorrhage and pulmonary hypertension without evidence of vasculitis. The numerous darkly pigmented intra-alveolar cells are hemosiderin-laden macrophages (hematoxylin-eosin, original ×40).

FIGURE 4. A chest radiograph of a 48-year-old woman with hemoptysis. The chest radiograph demonstrates cardiomegaly and mild pulmonary edema. The left atrium is enlarged, and there are Kerley B lines in the right costophrenic angle. Symptoms resolved on medical management of her mitral regurgitation and CHF.

evaluation of dyspnea is imprecise, with one review suggesting an overall accuracy of approximately 70%.[110] Studies examining the accuracy of many of the classic signs of CHF yield a wide range of results, perhaps indicating differences in the populations studied or the abilities of the observers.[111] The physical examination may be particularly insensitive in patients with chronic CHF, in whom crackles and edema are frequently absent even when the pulmonary capillary wedge pressure is elevated.[112] Furthermore, determining the cause of dyspnea in the patient with both heart and lung disease presents special challenges. For example, the crackles of pulmonary edema may be inaudible in the patient with emphysema.

Chest radiography also possesses limitations in

the diagnosis of pulmonary edema (Fig 1, 6 and Table 4). Coexisting lung disease may cast extra shadows, which may falsely suggest or else obscure pulmonary edema. The radiographic appearance of pulmonary edema may be atypical in patients with emphysema, probably because of the destruction of the vascular bed associated with this disease.[113–115] Pulmonary edema also presents variably on chest radiographs, depending on the tempo of the illness.[116] A previously healthy patient with acute pulmonary edema from massive volume overload or myocardial infarction is likely to exhibit dense alveolar infiltrates in a medullary distribution, while the stigmata of subacute or chronic venous hypertension, such as pleural effusions, may be absent. On the other hand, patients
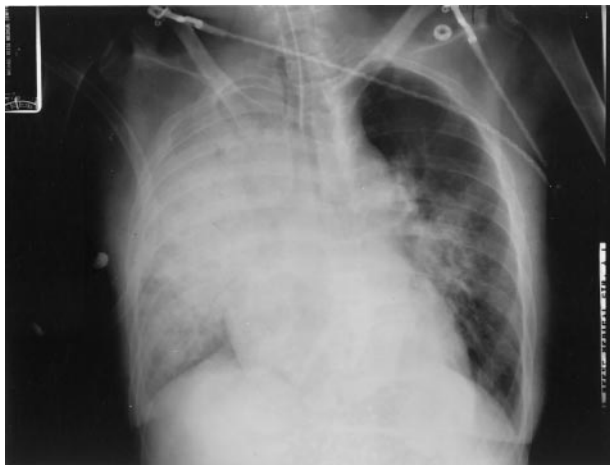

FIGURE 6. Atypical pulmonary edema. *Top*: asymmetric pulmonary edema is shown in a 59-year-old woman with hypertension and mitral regurgitation who presented with respiratory failure from acute pulmonary edema. She recovered completely with diuresis. *Bottom*: patchy pulmonary edema is shown in a 60-year-old man with coronary artery disease and progressive dyspnea. The chest radiograph demonstrates predominantly alveolar pulmonary edema in a medullary distribution, with sparing of the periphery, particularly on the right. Echocardiography showed severely diminished left ventricular function, and diuresis resulted in the resolution of the parenchymal infiltrates.

with longstanding elevations in pulmonary capillary wedge pressure may show surprisingly little evidence of pulmonary edema.[117] As mentioned above, the blood vessels and alveolar-capillary membranes undergo significant remodeling when exposed to chronically elevated pressures.[18–23] These changes protect the lung from pulmonary edema and cause the chest radiograph to be unreliable as a measure of either central hemodynamics or cardiac function. In selected cases, for example, when the differential diagnosis includes parenchymal lung disease, a high-resolution CT scan of the chest may be useful in supporting a diagnosis of CHF. Characteristic findings include septal thickening, ground-glass opacities, peribronchovascular interstitial thickening, pleural effusions, and cardiomegaly.[118] A comparison of supine and prone views also may be helpful. In contrast to interstitial lung disease, the basilar infiltrates associated with pulmonary edema may improve in the prone position.

Echocardiography also possesses limitations in the diagnosis of CHF. Despite prevalence studies suggesting that nearly half of all patients with CHF have diastolic heart failure,[119] there exists no consistent standard for the diagnosis of this condition.[119–121] Pulmonary artery catheterization frequently reveals information that differs from the clinical evaluation,[122] but controversy surrounds its use.[123]

Finally, the evaluation of pleural effusions in the patient with known or suspected CHF can be problematic. While it is appropriate in most circumstances not to perform thoracentesis in the patient with established CHF, certain circumstances (*eg*, fever, a unilateral effusion, or significant discrepancy in size between the two sides) mandate the performance of thoracentesis. Unfortunately, up to 20% of patients with CHF will have exudative effusions by the criteria of Light et al,[124] with most of these patients receiving diuretic therapy.[125] In such cases, the measurement of a pleural fluid/serum albumin gradient of > 1.2 g/dL indicates that the effusion is likely from CHF. The conversion of a pleural effusion from a transudate to an exudate with diuretic therapy has been documented.[126]

The measurement of B-type natriuretic peptide, which is produced in response to ventricular strain or stretch, has shown promise in the diagnosis of CHF. The results of initial studies[127–130] have suggested a diagnostic accuracy of 80 to 90% in patients presenting to an emergency department or urgent care settings with acute dyspnea. Moreover, the negative predictive value for a diagnosis of CHF may be as high as 96% for a B-type natriuretic peptide level < 50 pg/mL.[130] Importantly, B-type natriuretic peptide levels are ele-

Table 4—Common Limitations in the Radiographic Diagnosis of Left Heart Failure

Limitations	Description
Difficulties caused by coexisting lung disease	Extra shadows from lung disease may mimic or obscure pulmonary edema
	Vascular redistribution may be from lung rather than heart disease
	Pulmonary edema patterns may be atypical because of underlying lung disease (no vasculature = no edema)
Acute vs chronic pulmonary venous hypertension	Acute: pleural effusions may be absent, interstitial edema may be less prominent
	Subacute to chronic: typical signs of pulmonary edema more likely
	Chronic, with vascular remodeling: fewer signs of pulmonary edema

vated not only in patients with systolic dysfunction but also in individuals with diastolic abnormalities seen on echocardiography, suggesting a role for this assay in helping to secure a diagnosis of diastolic heart failure in patients with normal systolic function.[131] Elevated B-type natriuretic peptide levels are also predictive of adverse outcomes in patients with chronic left heart failure[132] and in those with acute coronary syndromes.[133] Still, these data suggest that the chief value of this assay may be in rapidly excluding CHF in the urgent care setting. Further studies should validate the utility of this assay in other populations, such as ICU patients.

Given the significant limitations of all approaches to diagnosing CHF and the frequency with which this condition is encountered, a high index of suspicion is merited, particularly in the case of a patient with diastolic heart failure.

SUMMARY

The pulmonary manifestations of heart disease are diverse (Table 2). Pulmonary function is frequently abnormal, with a fall in vital capacity shown to precede the clinical recognition of CHF.[134] While a restrictive defect may be seen in patients with both chronic CHF and acute pulmonary edema, significant airflow obstruction is more likely to occur in the latter. The DLCO is often mildly reduced and does not normalize following heart transplantation. Reduced lung compliance, increased dead space ventilation, and muscle weakness contribute to the preceding abnormalities in producing exercise limitation. Sleep apnea, particularly of the central variety, is associated with chronic CHF and confers a worse prognosis. Limitations of the clinical evaluation may lead to errors in the diagnosis of heart failure, particularly when the presentation is atypical or when lung disease coexists. While the measurement of B-type natriuretic peptide levels represent a promising point-of-care test for the diagnosis of CHF, further studies

are required to define its limitations. Only through an appreciation of the complex interactions between the heart and the lung can errors in diagnosis be minimized.

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