Acute heart failure with preserved systolic function

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Many patients with acute heart failure have marked hypertension and preserved left ventricular ejection fraction. In these patients, the heart failure usually does not result from transient systolic dysfunction or valvular abnormalities but rather results from diastolic dysfunction. Treatment of this condition includes control of hypertension, cautious diuresis, and, if necessary, ventilatory support. Further workup after the acute phase should be directed by the overall clinical picture. Other potential contributing factors, such as renal artery stenosis, valvular heart disease, and ischemia, should be strongly considered. Unfortunately, chronic therapy for diastolic heart failure has not yet been standardized due to the paucity of clinical trial data. Strict control of hypertension appears to be of paramount importance. Angiotensin-converting enzyme inhibitors or receptor blockers may be of benefit in preventing repeat hospitalizations. (Crit Care Med 2008; 36[Suppl.]:S52–S56)

KEY WORDS: heart failure; diastolic; systolic; pulmonary edema; hypertension; coronary artery disease; renal artery stenosis; flash; ventilation; valvular disease

A large portion of patients with acute heart failure are subsequently found to have a normal ejection fraction (EF). For example, in a multicenter registry of >52,000 patients hospitalized for acute heart failure, approximately half had an EF that was normal or only mildly reduced (1). In comparison to patients with reduced EF, subjects with acute heart failure and normal EF tend to be older, are more likely to be female, and are less likely to be African American (1, 2). In addition to exhibiting chronic signs and symptoms of congestive heart failure, patients with heart failure and a preserved EF (HFprEF) can also present with acute decompensation with acute pulmonary edema in the setting of elevated systemic blood pressure. Timely diagnosis and aggressive management in the emergency department and intensive care unit setting are imperative and often result in rapid clinical improvement.

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Development of Acute Pulmonary Edema

In chronic congestive heart failure, the left atrial pressure (LAP) can be elevated without evidence of pulmonary edema due to the adaptive response of the pulmonary lymphatic vessels, which help remove fluid from the pulmonary tissue (3). Acute pulmonary edema arises because of a sudden increase in left atrial (and, consequently, pulmonary capillary) pressure to which the lymphatics do not have time to adapt. The cause of this sudden increase in LAP in patients with normal EF has been the focus on numerous investigations.

Role of Hypertension

It is becoming increasingly recognized that systemic hypertension in combination with diastolic dysfunction is a leading cause of acute pulmonary edema. Other potential causes of "flash" pulmonary edema, such as ischemia due to coronary artery disease and transient systolic dysfunction in the setting of systemic hypertension, have also been investigated. In a prospective study, 46 subjects who presented with acute respiratory distress to our institution and who had pulmonary edema on chest radiograph were enrolled on admission and followed for up to 3 yrs (4). On initial presentation, the majority of patients were hypertensive, and the mean systolic blood pressure of all patients was 194 mm Hg. In addition, the majority of patients had an EF >40%. Coronary artery disease, as defined by >50% stenosis in at least one major epicardial artery, was present in 34 patients. Interestingly, recurrence of acute pulmonary edema over the time of follow-up was similar among patients who did not have coronary disease, those who had coronary artery disease and were revascularized, and those who had coronary artery disease and were not revascularized. At the time of recurrence of symptoms, systolic blood pressure was once again elevated (mean at second presentation was 184 mm Hg). Thus, it appears that control of hypertension is important in preventing recurrent pulmonary edema, while coronary revascularization alone may not be effective (4).

Systolic dysfunction brought about by increased afterload has also been proposed as a potential cause of acute pulmonary edema. It has been hypothesized that many patients hospitalized with acute pulmonary edema in association with hypertension have transient left ventricular (LV) systolic dysfunction, which is not present when the LV EF is evaluated after the patient has been treated. To evaluate this hypothesis, we evaluated EF, regional wall motion, and mitral regurgitation in 38 patients both during an acute episode of hypertensive pulmonary edema and 24–72 hrs later, after treatment and resolution of the pulmonary congestion (5). We found that LV EF and regional wall motion were similar during the acute episode of hypertensive pulmonary edema and after resolution of the

congestion and control of the blood pressure. Thus, a normal LV EF after the treatment of a patient with hypertensive pulmonary edema suggests with a high probability that the pulmonary congestion was not due to transient systolic dysfunction but instead was due to diastolic dysfunction in combination with and likely exacerbated by elevated blood pressure.

Patients with acute pulmonary edema and hypertension seem to have more favorable survival than those with low or normal systemic blood pressure. In the OPTIMIZE-HF registry, another large database consisting of nearly 50,000 patients hospitalized for heart failure, approximately 50% had a systolic blood pressure >140 mm Hg. A higher systolic blood pressure was associated with lower in-hospital and 60- to 90-day mortality and a shorter hospital length of stay. Rehospitalization rates, however, were similar regardless of admission systolic blood pressure. In comparison with patients with hypertension, patients who were normotensive or hypotensive were more likely to have systolic dysfunction, myocardial ischemia, and valvular disease. The authors concluded that elevated systolic blood pressure and pulmonary edema represent a distinct pathophysiologic syndrome that may warrant unique management (6).

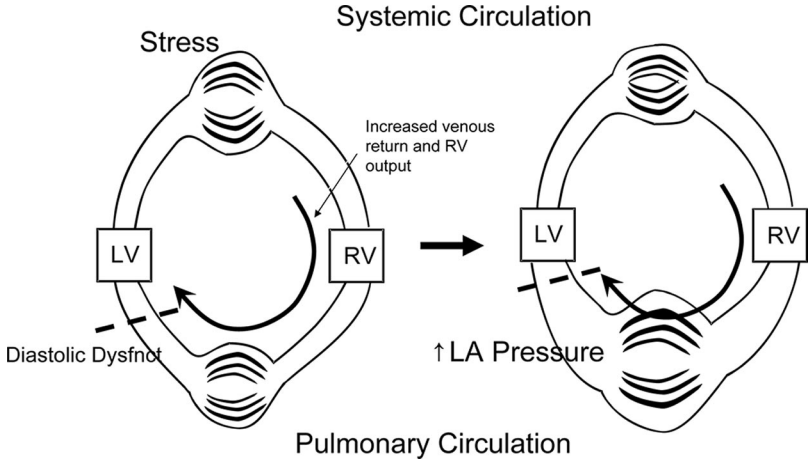

Figure 1. The development of acute pulmonary edema. Stressors, such as exercise, volume loading, or hypertension, acutely increase venous return. This leads to increased right ventricle (*RV*) stroke volume that cannot be accommodated by the left ventricle (*LV*) without an increase in left atrial (*LA*) pressure. Thus, there is a shift of volume from the veins of the systemic circulation into the pulmonary circulation producing pulmonary edema.

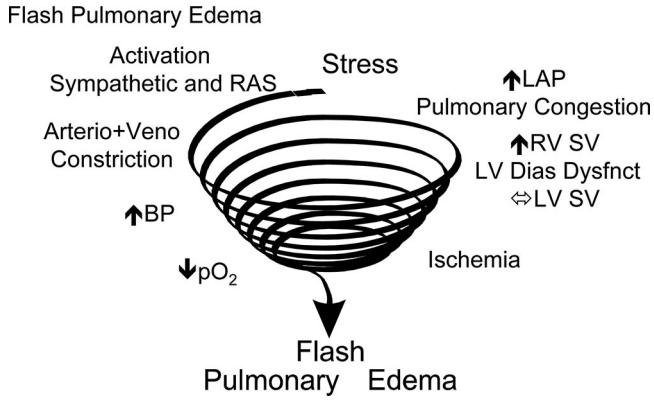

Figure 2. The downward spiral of patients with hypertensive pulmonary edema. Stress induces an increase in left atrial pressure (*LAP*), which causes further distress and neurohormonal activation, leading to worsening clinical status and flash pulmonary edema. *RAS*, renal artery stenosis; *BP*, blood pressure; *RV*, right ventricle; *SV*, stroke volume; *LV*, left ventricle.

Pathophysiology

The physiologic basis of hypertensive pulmonary edema involves the mobilization of volume from the peripheral veins to the pulmonary vasculature. A stress, such as acute volume loading, venoconstriction, or exercise, acutely increases systemic venous return. If the right ventricle (RV) functions normally, this will result in an increased RV stroke volume pumped into the lungs. In the setting of diastolic dysfunction, the LV cannot accommodate this increased blood flow without an increase in LAP (7). Thus, the blood volume in the lungs increases as the RV pumps blood out of the peripheral veins into the lungs. Increasing pulmonary congestion promotes neurohumoral activation with elevated circulating catecholamines and angiotensin II, which increases arterial and venular tone, further elevating venous return and raising systolic arterial blood pressure. The systolic hypertension can further impair LV diastolic function. Eventually, the increasing left atrial and pulmonary artery pressures bring the RV and LV stroke volumes back into balance but at the cost of acute pulmonary edema (Fig. 1).

Other physiologic factors may contribute to this syndrome. A marked increase in LV systolic pressure, especially one that occurs late in systole, leads to a slowing of LV relaxation (8). This is seen even in healthy hearts but is especially pronounced in diseased myocardium. Hypertension may also worsen diastolic function by increasing myocardial turgor, thus causing an increase in LV stiffness (9). Finally, there may also be an ischemic contribution to the increased LAP. Elevated LV diastolic pressure causes extravascular compression of myocardial capillaries and small coronary vessels. This leads to decreased oxygen delivery in the face of increased demand (caused by the hypertension) and can occur even in the absence of epicardial stenoses (10).

Neurohumoral Factors

Congestive heart failure is characterized by up-regulation of the renin-angiotensin system, which leads to hypertension as well as impaired relaxation (11, 12). This up-regulation has made the angiotensin-converting enzyme (ACE) and the angiotensin receptor attractive targets for therapy in heart failure. Both the renin-angiotensin system and sympathetic nervous system play important roles in the initial increase in LAP. The resultant increase in patient distress due to dyspnea and hypoxia causes further activation of these systems. Thus, pulmonary edema and symptoms of heart fail-

ure are propagated by a vicious cycle of neurohumoral activation (Fig. 2).

Other Contributing Factors

Renal artery stenosis (RAS) is frequently referenced as an etiology of acute pulmonary edema. Mechanistically, patients with renovascular disease are at risk for recurrent episodes of acute pulmonary edema brought on by labile elevations in systemic blood pressure (12). These elevations, coupled with underlying diastolic dysfunction (which is usually present given the chronic hypertension that characterizes patients with RAS), are the cause of recurrent acute pulmonary edema in these patients. Therefore, the RAS brings about acute pulmonary edema in concert with diastolic dysfunction. Of note, these patients, especially those who are untreated, are particularly susceptible to symptoms due to the chronic activation of the renin-angiotensin system that typifies RAS.

"Flash" pulmonary edema is more common in bilateral RAS than in unilateral disease (13). Treatment of renovascular hypertension includes medical therapy, such as ACE inhibitors (although caution must be exercised due to the propensity toward decreased glomerular filtration rate and renal failure) as well as revascularization. Revascularization is recommended if there is $\geq$75% stenosis in one or both renal arteries (14). It is associated with a decreased incidence of pulmonary symptoms and a significant reduction in the degree of systemic hypertension (15). The decrease in incidence of acute pulmonary edema with renal revascularization is likely due to the decrease in labile hypertension and, consequently, in exacerbation of diastolic dysfunction.

Other etiologies of acute pulmonary edema, such as acute mitral or aortic regurgitation or atrial fibrillation in the setting of mitral stenosis, must also be considered in the initial evaluation. Although valvular lesions have not been a frequent cause of acute heart failure associated with hypertension in previous studies (5), they are still part of the differential diagnosis, as is myocardial ischemia. The initial physical examination, electrocardiogram, and echocardiography can help determine whether acute pulmonary edema is due to a valvular lesion.

Clinical Presentation

The clinical presentation of acute pulmonary edema can be dramatic. Patients are usually tachypneic, using accessory muscles to breathe, and have difficulty speaking. As such, the initial history should be brief and focused. Symptoms are likely to include progressive dyspnea, cough, and possibly chest discomfort. Patients frequently exhibit hypertension, tachycardia, and hypoxia. Physical examination is often significant for crackles in the chest, consistent with pulmonary edema. There may also be an S3 or summation gallop. Elevated jugular venous pressure may be observed, although this is less common. Chest radiograph findings range from pulmonary vascular congestion to florid alveolar edema, depending on the extent of LAP increase and the chronicity of disease. The electrocardiogram may show signs of chronic diastolic dysfunction, such as left atrial enlargement and LV hypertrophy. One should also carefully assess for ischemic changes and the presence of atrial fibrillation, as patients with diastolic dysfunction may be dependent on atrial contraction to keep LAP low. Laboratory data, such as chemistries and brain natriuretic peptide, may also be helpful.

Aside from acute pulmonary edema, the differential diagnosis of this clinical presentation includes pulmonary embolism, pneumonia, and ischemia. Physical examination, chest radiograph, and electrocardiogram can help in evaluating for these possibilities, and treatment for these may be warranted on initial presentation until a firm diagnosis is reached.

Treatment

Although HFprEF is a common presentation for acute heart failure, there are few data to guide therapy. Initial treatment should be directed toward relieving hypoxia, reversing pulmonary congestion, and, in the hypertensive patient, reducing blood pressure. Supplemental oxygen is often the initial step in improving arterial oxygenation and the patient's dyspnea. Both preload and afterload reduction help in decreasing the LAP and can be attempted with medical therapy. Nitrates are potent venodilators that have a rapid onset of action when administered by the sublingual route and provide a sustained effect when given intravenously. In fact, sublingual nitroglycerin may play an important preventive role in this syndrome. Patients with a history of HFprEF should be instructed to take sublingual nitroglycerin with the onset of dyspnea. This counteracts the venoconstriction that initiates the cascade leading to acute pulmonary edema and may help to prevent further deterioration.

Beta-blockers may also be useful in treating acute pulmonary edema known to be due to HFprEF. Given intravenously, these agents not only help with blood pressure and tachycardia but may also counteract sympathetic nervous tone, reducing patient discomfort. Similarly, morphine may also be used to lessen the patient's sensation of dyspnea and reverse the downward spiral fueled by patient distress. These measures should be taken in concert with the intravenous administration of a loop diuretic, such as furosemide, which has a direct effect on pulmonary vascular congestion. Of note, patients who are diuretic naïve often have a brisk response to furosemide and may not require a large dose. It is important that each patient be treated individually; if contraindications exist to one class of therapy, another therapy should be selected. Other intravenous agents that can be used to promptly reduce blood pres-

Table 1. Agents that can be used in the initial treatment of hypertensive pulmonary edema

Venodilators	Diuretics	Vasodilators
Nitroglycerin	Loop diuretics	Hydralazine
Nitroprusside		Enalaprilat
Nesiritide (also may have diuretic effects)		Nicardipine
Negative chronotropes/ antihypertensive	Centrally acting agents (can cause rebound hypertension)	Other
Metoprolol	α-methyldopa	Morphine
Labetalol	Clonidine	Supplemental oxygen
Diltiazem		Noninvasive ventilation

These agents should be given intravenously (or in the case of nitroglycerin sublingually) to ensure rapid onset of action.

sure include hydralazine, enalaprilat, nitroprusside, or nicardipine (Table 1 provides a list of potential agents that may be useful in treating hypertensive acute pulmonary edema).

Assisted ventilation also plays an important role in the treatment of acute cardiogenic pulmonary edema. There are physiologic benefits of positive pressure ventilation in this syndrome brought about by the increased intrathoracic pressure. Most obvious, venous return is decreased, thereby causing a reduction in LV preload. There is also reduction in afterload due to the elevated pressure gradient between the LV and extrathoracic systemic arteries. In a clinical trial designed to assess the physiologic effects of continuous positive airway pressure on patients with cardiogenic pulmonary edema, it was found that continuous positive airway pressure up to 12.5 cm H_2O was associated with decreased heart rate, decreased systolic blood pressure, and increased LV stroke volume (16). Thus, positive pressure ventilation provides similar benefits as the medications described above.

In general, noninvasive positive pressure ventilation (NPPV) via a nasal or facial mask is preferred over endotracheal intubation owing to the decreased incidence of nosocomial infection (17), barotrauma, and need for sedation. There is some evidence to support early use of NPPV (i.e., on presentation) in patients with acute cardiogenic pulmonary edema. In one clinical trial consisting of 40 subjects, it was found that bilevel NPPV administered on admission in combination with standard medical therapy led to a decreased rate of intubation, a higher oxygen saturation at 15 mins, and a greater reduction in respiratory rate compared with oxygen therapy in combination with medical treatment (18). Favorable effects of NPPV were demonstrated in another clinical trial, which showed that early short-term administration of this therapy was effective in preventing endotracheal intubation (19). Despite these data supporting the use of NPPV, whether continuous positive airway pressure or bilevel NPPV is preferred in acute pulmonary edema remains unclear. Bilevel NPPV provides ventilatory assistance in addition to improved oxygen exchange, thereby reducing patient fatigue, whereas continuous positive airway pressure only improves oxygenation.

Further Diagnostic Measures

Once the acute symptoms have resolved and the patient is stabilized, the question arises as to what further diagnostic measures should be undertaken. A two-dimensional Doppler echocardiogram helps determine whether systolic dysfunction, wall motion abnormalities, or valvular lesions are present and can assess the degree of diastolic dysfunction. Although the diagnostic criteria for HFprEF remain controversial, a normal EF in the context of patient symptoms may suffice. Another controversial subject is the issue of an ischemic workup in patients who present with acute pulmonary edema. One investigation found that revascularization in such patients did not decrease the recurrence of pulmonary edema; however, it also showed a high prevalence of coronary artery disease in this population (4). The decision to proceed with an ischemic evaluation should be based on clinical grounds. Lack of symptoms, such as angina, as well as a lack of electrocardiogram abnormalities in the acute phase of presentation may preclude the need for such an evaluation. The latter finding is especially telling since the tachycardia and hypertension in acute pulmonary edema constitute a significant cardiac stress test.

The control of hypertension is of paramount importance in preventing the recurrence of symptoms. As such, there are situations in which secondary hypertension should be considered. Clinical scenarios, such as the onset of hypertension before the age of 30 yrs, refractory hypertension despite multiple antihypertensive agents, and an acute increase in blood pressure over a previously stable baseline, are situations in which secondary causes of hypertension should be evaluated. Among these are RAS, Cushing's syndrome, Conn's syndrome (hyperaldosteronism), hyperthyroidism, and pheochromocytoma. In cases where secondary hypertension is present, treatment should be tailored accordingly.

Chronic Treatment of HFprEF

Unfortunately, there are scarce clinical trial data regarding treatment of HFprEF. In contrast to systolic heart failure, HFprEF has no standardized treatment regimen. There is some agreement that angiotensin receptor blockade may cause regression of LV hypertrophy (20) and may reduce the rate of hospitalization (21) in HFprEF. The CHARM-Preserved Trial randomized >3,000 patients with HFprEF (EF >40%) to either candesartan or placebo (21). Incidence of cardiovascular death and annual event rates were similar in both groups; however, fewer patients in the candesartan group were readmitted to the hospital for heart failure one or more times. ACE inhibitors may also be of benefit. The PEP-CHF study (22) randomized 850 patients with HFprEF to either placebo or perindopril therapy. At 1 yr, patients in the treatment group exhibited decreased mortality and hospitalization rate and were more likely to have improved New York Heart Association class and a greater 6-min walk distance. Thus, if possible, either ACE inhibitors or angiotensin receptor blockers should be part of the treatment regimen in patients with HFprEF.

In addition, treatment should be targeted toward symptoms and underlying causes. Blood pressure control is, of course, of primary importance and should include the use of a diuretic as in systolic heart failure; in general, a lower dose of diuretic is needed in cases of HFprEF (23). In addition, heart rate control, which increases relaxation time, may be of benefit and, to that end, β-blockers are recommended as part of treatment. Calcium channel blockers may be warranted for the same reason. It is understood that contributing factors, such as coronary artery disease and valvular disease, should be treated in concert.

CONCLUSION

Although HFprEF remains a significant public health concern, there are many uncertainties regarding its etiology, diagnosis, and appropriate treatment. The development of acute pulmonary edema in the setting of preserved EF is often sudden, dramatic, and life threatening. Although insight into the role of diastolic dysfunction in this clinical syndrome is growing, many questions remain unanswered. It is well established, however, that systemic hypertension plays a pivotal role and that treatment of this condition helps to prevent both diastolic dysfunction and the development of acute pulmonary edema. There are also some therapeutic measures, such as NPPV, that have shown some benefit in the acute phase. However, the ultimate goal is to retard the progression to this

acute phase, which can be fatal, and to identify those patients who are at risk and treat them appropriately. For this, more large-scale clinical trials are warranted.

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