

Modern Management of Cardiogenic Pulmonary Edema

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Cardiogenic pulmonary edema (CPE) is a common and potentially deadly condition frequently encountered in emergency medicine. Many conditions exist that directly or indirectly lead to the development of pulmonary edema. Regardless of the underlying cause of CPE, all patients who develop CPE must be diagnosed and managed expeditiously. Patients who have developed CPE can quickly develop respiratory failure if delays occur in recognition or management of the condition. Patients who develop CPE, in fact, have an in-hospital mortality of 15% to 20%, and mortality may be even higher when the condition is associated with acute myocardial infarction (AMI) or acute valvular dysfunction [1–3]. Acute care providers should maintain a high level of vigilance for this condition and initiate management strategies promptly.

Pulmonary edema can be defined as an increase in lung fluid caused by extravasation of fluid from the pulmonary vasculature into the interstitium and alveoli of the lungs [1,2]. The buildup of fluid leads to progressive deterioration of alveolar gas exchange and resulting hypoxia. Pulmonary edema is generally classified as noncardiogenic and cardiogenic. The causes and treatment of non-CPE are beyond the scope of this article. CPE is more common and is discussed in this article. The pathophysiology, etiologies, and emergency department (ED) evaluation is discussed briefly. Modern management strategies are the main focus.

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Pathophysiology

CPE results from leakage of fluid from the pulmonary capillaries and venules into the alveolar space as a result of increased hydrostatic pressure. When the pulmonary capillary hydrostatic pressure exceeds pulmonary interstitial pressure, fluid transudates into the pulmonary alveoli and interstitium [2]. Hydrostatic pressure rises when the left ventricle (LV) is unable to effectively handle its pulmonary venous return [4]. Once fluid begins to build up in the pulmonary interstitium, a vicious self-perpetuating cycle of events follows: alveolar edema leads to impaired gas exchange and hypoxia, leading to increased catecholamine production, leading to increased systemic vascular resistance and blood pressure, leading to increased myocardial wall tension and oxygen demand, leading to myocardial ischemia, leading to LV systolic and diastolic dysfunction, leading to decreased cardiac output and increased end-diastolic pressure, leading to increased pulmonary fluid buildup. During this cycle, activation of the renin-angiotensin-aldosterone system occurs as a result of elevations of end-diastolic pressure and results in increased sympathetic tone. Hypoxia and increased work of breathing result in patient anxiety, which also causes increased catecholamine production and sympathetic tone; therefore, at its most basic level, the end result of this cycle is to have an LV trying in vain to pump against a markedly elevated systemic vascular resistance (increased afterload), resulting in poor cardiac output. Meanwhile, the right-sided filling continues unabated (elevated preload) resulting in even greater pulmonary interstitial fluid. This cycle eventually results in florid pulmonary edema, hypoxia, and respiratory failure unless the cycle is terminated [2].

The goals of management of CPE should focus on breaking this cycle of events by (1) decreasing preload and (2) decreasing afterload. In most cases, accomplishment of these two goals alone results in marked improvement of LV function and significantly increases cardiac output, resolving the pulmonary edema. In some cases, however, further strategies may be needed to (3) improve LV function (inotropic support). In the “Management” section of this article, we discuss optimal strategies to accomplish all three goals.

Etiologies

There are five major causes of CPE in clinical practice (Box 1). The most common cause is an acute exacerbation of chronic LV failure. Chronic LV failure usually is the result of congestive heart failure (CHF) or a cardiomyopathy. An acute exacerbation of chronic LV failure can occur because of medication or dietary noncompliance (eg, discontinuation of diuretic medications, excessive salt intake, and so forth) or from acute cardiac ischemia.

Patients without a prior history of chronic LV failure can develop acute LV dysfunction also. AMI can induce significant deterioration of

Box 1. Major etiologies of cardiogenic pulmonary edema

- Exacerbation of chronic left ventricular failure
- Acute myocardial ischemia/infarction
- Severe systemic hypertension
- Left-sided valvular disorders
- Acute tachydysrhythmias and bradydysrhythmias

myocardial performance and pulmonary edema when infarction occurs in at least 25% of the LV myocardial mass. Acute severe hypertension can also result in LV dysfunction. In this scenario, the heart initially develops impaired ventricular compliance, or relaxation (diastolic dysfunction), which leads to poor ventricular filling and decreased cardiac output. The decrease in cardiac output sets in motion the cascade of events noted in the section “Pathophysiology,” eventually resulting in a combination of diastolic and systolic dysfunction leading to pulmonary edema. Additionally, the impaired ventricular compliance produces severely elevated LV pressures, which are then transmitted backward to the pulmonary capillaries, raising hydrostatic pressures and causing fluid transudation.

Patients who experience left-sided valvular (aortic, mitral) disorders can also develop CPE. Patients who experience aortic or mitral regurgitation develop elevated left-sided pressures, similar to patients who develop severe systemic hypertension; this pressure can easily be transmitted backward to the pulmonary circulation and produce interstitial edema. Acute aortic regurgitation, which most often occurs from aortic dissection, infective endocarditis, or blunt trauma; and acute mitral regurgitation, which usually occurs from rupture of the chordae tendinae or papillary muscle dysfunction in association with myocardial infarction (MI), or from infective endocarditis, can easily result in CPE as a result of an abrupt increase in LV pressures. Patients who develop chronic aortic stenosis are also predisposed to the development of CPE. The patients develop noncompliant hypertrophied LVs, which are dependent on high filling pressures to maintain adequate cardiac output [2]. Even slight increases in left-sided pressures in these patients are transmitted backward to the pulmonary capillaries and result in pulmonary edema.

Acute dysrhythmias can also produce CPE. Severe bradydysrhythmias in the face of normal or elevated right-heart filling can induce elevations in pulmonary capillary hydrostatic pressures, leading to CPE. Tachydysrhythmias often lead to CPE caused by poor diastolic filling, which also leads to elevations in pulmonary capillary hydrostatic pressures. Treatment of CPE in either case is simply based on correction of the underlying dysrhythmia using standard Advanced Cardiac Life Support protocols.

Several other conditions can also result in CPE by exacerbating LV function, including sepsis, severe anemia, thyrotoxicosis, myocarditis, and myocardial toxins [1,2]. Additionally, fluid overload in the presence of end-stage renal disease can result in CPE. The general management strategies discussed in “Emergency Department Evaluation” are usually effective for the major etiologies of CPE, although the management should also focus on reversing any of these underlying conditions whenever possible.

Emergency department evaluation

Traditionally, the diagnosis of CPE in the ED has been based on history, physical examination, and chest radiography. Most patients presenting with CPE have a prior history of CHF. Most report the onset of dyspnea on exertion progressing to dyspnea at rest, orthopnea, peripheral edema, and paroxysmal nocturnal dyspnea. The progression of symptoms before ED presentation may take hours to days; however, an episode of acute ischemia or acute valvular dysfunction may cause symptoms to progress much faster. Physical examination findings usually include tachycardia and hypertension from increased catecholamine production, tachypnea, hypoxia, and diaphoresis. Auscultation of the lungs reveals rales or wheezes, and cardiac auscultation may be notable for an S3 heart sound. The remainder of the examination may be notable for jugular venous distension, hepatojugular reflux, and peripheral edema. When CPE is associated with cardiogenic shock, evidence of poor tissue perfusion including skin mottling or pallor may be found. Unfortunately, none of these vital signs or physical examination findings have greater than 70% sensitivity [5]. As many as one third of these patients have chronic obstructive pulmonary disease (COPD) and many also have risk factors for pulmonary embolism and AMI [4,5], any of which can mimic CPE, which further complicates the ability to make an accurate clinical diagnosis.

Chest radiography complements the history and physical examination in the initial evaluation of patients who experience CPE. The classic radiographic findings of CPE include cardiomegaly (in patients who experience underlying CHF), pulmonary vascular redistribution, thickening of interlobular septa (Kerley B lines), alveolar edema, pleural effusions, and bilateral infiltrates in a “bat wing” pattern [3,6]; however, these classic radiographic findings are not always found at the time of initial presentation. As much as a 12-hour delay may occur between the onset of symptoms and the development of significant radiographic abnormalities when the onset of CPE is abrupt [7,8]. Even the presence of cardiomegaly, which is often considered one of the most reliable radiographic abnormalities associated with systolic dysfunction, often is absent in patients who have developed CPE [9]. Other limitations of chest radiography also exist. Patients who develop chronic lung abnormalities may have scarring that

impairs image quality or may mimic vascular redistribution. Image quality is also often impaired in obese patients and patients who develop COPD [10].

The clinical diagnosis of acute heart failure is estimated to be incorrect in more than 50% of cases, with frequent overdiagnosis and underdiagnosis [11–13]. Because of the limitations of clinical assessment and chest radiography in distinguishing acute heart failure and CPE from other causes of acute dyspnea, B-type natriuretic peptide (BNP) testing has emerged as a valuable diagnostic tool in ED practice. BNP is an endogenous cardiac neurohormone that is secreted from the ventricles in response to increased wall tension. BNP counteracts the effects of the renin-angiotensin-aldosterone system by promoting natriuresis, diuresis, and vasodilation. In the setting of acute heart failure and CPE, plasma BNP levels increase. These measurable levels of BNP have been demonstrated to correlate with the severity of LV filling pressures, clinical status, short-term and long-term mortality, and response to in-hospital therapy [10,14–18]. Measurement of BNP levels in patients presenting to the ED with acute dyspnea can be helpful in distinguishing acute heart failure and CPE from other acute or chronic lung diseases [11,19]. A BNP level less than 100 pg/mL makes acute heart failure unlikely and is associated with a negative predictive value of 90%. Conversely, a BNP level greater than 500 pg/mL makes acute heart failure likely and is associated with a positive predictive value of 90%. A BNP level in the range of 100 to 500 pg/mL can be caused by acute heart failure but can also be caused by other conditions that induce elevated ventricular wall tension, including cor pulmonale and acute pulmonary embolism. Falsely-low BNP levels can occur during the first 1 to 2 hours after symptom-onset in cases of flash pulmonary edema [20].

Emergency department management

Initial management of patients who experience CPE should focus on the “ABCs” of resuscitation. Large bore intravenous (IV) lines should be in place to administer needed medications. Patients should be placed in an upright sitting position attached to a cardiac monitor and pulse oximetry. Supplemental oxygen should be provided by way of a facemask with fraction of inspired oxygen of 1.0. If the patient remains persistently hypoxic despite the supplemental oxygen, or if the patient develops respiratory fatigue or a depressed level of consciousness, mechanical ventilation should be instituted (see section “Ventilatory Support”). An ECG should be obtained quickly to assess for bradydysrhythmias or tachydysrhythmias that may have precipitated the CPE. If a dysrhythmia has occurred, standard Advanced Cardiac Life Support measures should be performed. The ECG should also be assessed for evidence of acute myocardial ischemia or AMI, in which case appropriate anti-ischemia and reperfusion therapies should be used. A discussion of the acute management of acute coronary syndrome and MI is discussed elsewhere in this issue.

Most patients who experience CPE, however, do *not* have ECG evidence of an acute dysrhythmia or AMI. Treatment should therefore be aimed at redistributing the excessive pulmonary interstitial fluid into the systemic circulation, which improves alveolar oxygen-carbon dioxide exchange and hypoxia; therefore, pharmacologic agents that provide preload reduction and afterload reduction should be administered. In some cases, inotropic support is required also.

Pharmacologic therapy

Preload reduction

The first goal in pharmacologic treatment of CPE is preload reduction. Preload reduction reduces right heart and pulmonary venous return and, therefore, right-heart filling pressures and pulmonary capillary hydrostatic pressures, resulting in early symptomatic improvements in dyspnea. The typical medications used for preload reduction are nitroglycerin, morphine sulfate, and loop diuretics. More recently, a recombinant form of beta-natriuretic peptide known as nesiritide has been used for preload reduction also.

Nitroglycerin

The most effective and rapidly-acting preload-reducing medication is nitroglycerin (NTG) [21–25]. Multiple studies have demonstrated the superiority of NTG over furosemide [21,24,26–28] and morphine sulfate [28–30] for preload reduction, symptomatic improvement, and safety. NTG can be administered in sublingual, IV, or transdermal form, although the transdermal absorption can be erratic in the patient in extremis. NTG also has the benefit of a short half-life; therefore, if the patient develops a precipitous fall in blood pressure (generally uncommon in CPE patients), the blood pressure should return to previous values within 5 to 10 minutes of discontinuation of administration. Preload reduction and noticeable symptomatic improvements can be accomplished within 5 minutes of sublingual administration of NTG [31,32], and the dose can be repeated every 5 minutes during the first 10 to 15 minutes of presentation. If IV NTG is preferred, an initial dose of 10 to 20 $\mu\text{g}/\text{min}$ should be titrated upwards rapidly until a dose of at least 100 $\mu\text{g}/\text{min}$ is achieved. This type of aggressive administration of NTG also confers the benefit of afterload reduction [33,34], and therefore, NTG can function as an effective single agent therapy for patients who develop CPE. Unfortunately, many physicians are uncomfortable with administering these higher dosages of NTG for CPE and tend to use suboptimal dosages of the IV NTG infusion. Some investigators, therefore, recommend using *bolus* administration of IV NTG to insure adequate dosing [26,33]. In one study [26], 3 mg IV boluses of NTG were administered every 5 minutes to patients who had developed

CPE, a dose equivalent to a 600 µg/min infusion. This protocol was found to be safe, well-tolerated, and effective for these patients and associated with reduced need for mechanical ventilation and more rapid resolution of symptoms. Standard anti-anginal dosages of sublingual NTG with which most physicians are comfortable (ie, 400 µg every 5 minutes), has the bioequivalence of an IV NTG infusion of 60 to 80 µg/min. Physicians should, therefore, be comfortable with the safety of even higher dosages of NTG for patients who experience CPE and usually present in a hyperadrenergic state with moderately-to-severely elevated blood pressures.

Tolerance may develop to IV infusions of NTG but rarely within the first 12 hours. Nitrates should be avoided if the patient is already hypotensive or becomes hypotensive. Nitrates should be avoided also in patients taking sildenafil or other related medications for erectile dysfunction because of reports of precipitous drops in blood pressure. Also, nitrates should be used with extreme caution, if at all, in patients who have developed aortic stenosis and pulmonary hypertension because of their dependence on preload to maintain adequate blood pressure.

Morphine sulfate

Morphine sulfate (MS) has been used as a standard preload-reducing medication for many years; however, despite decades of use in patients who have developed CPE, MS has not been studied in a randomized fashion to confirm hemodynamic benefits. MS probably exerts mild indirect hemodynamic benefits through anxiolysis, which results in a decrease in catecholamine production, indirectly resulting in vasodilation. Early studies demonstrated some evidence of vasodilation and venous pooling in the peripheral circulation (ie, in forearm and hand veins) after the administration of MS [35,36]; however, a consistent *central* preload-reducing effect (ie, reduction in pulmonary capillary wedge pressures [PCWP]) has not been found. In contrast, MS may be associated with adverse hemodynamic effects, including *increases* in left and right heart filling pressures [37] and reductions in cardiac index [29,37] caused by a direct myocardial depressant effect on the already-reduced contractile state of the ischemic heart [38]. The adverse hemodynamic effects are also apparent clinically. In one prehospital study [28] evaluating the use of various medications in patients who develop presumed CPE, 38% of patients who received MS had subjective deterioration (eg, increased dyspnea) in clinical status and 46% had objective deterioration (eg, increased respiratory rate). In another study of ED treatment of CPE [39], the use of MS was associated with a 5:1 odds ratio for need for intubation or ICU admission.

MS is sometimes administered to patients who present with CPE for its anxiolytic effect; however, MS has an undesirable side-effect profile, including nausea and vomiting, pruritis, rash, and urticaria. Any of these side effects can produce an increase in catecholamine output, which can exacerbate afterload. The authors prefer the use of low-dose benzodiazepines

when patients require anxiolysis. Low-dose benzodiazepines have a more preferable side-effect profile and are not associated with myocardial or respiratory depression. Given the superiority of NTG for preload reduction and benzodiazepines for anxiolysis, little justification exists for the modern-day use of MS in patients who present with CPE.

Loop diuretics

IV loop diuretics, especially furosemide, have been used for many years as the cornerstone of treatment in patients who present with CPE. These medications produce a decrease in preload by inhibiting sodium chloride reabsorption in the ascending loop of Henle, which promotes increases in urine volume and excretion [2,40]; however, because patients who develop CPE have elevated systemic vascular resistance (afterload), renal perfusion is markedly diminished [41]. As a result, diuretics have a significantly delayed effect, often taking 45 to 120 minutes to produce effective diuresis [25,42–45]. Further complicating the use of diuretics in these patients is evidence that as many as 40% of patients who present with CPE have intravascular euolemia or hypovolemia [41,46,47]. The use of diuretics in these patients may be associated with adverse effects, including electrolyte abnormalities and hypotension [28] caused by overdiuresis.

Also, diuretics are presumed to decrease preload through direct vascular effects. Early studies indicated that the use of furosemide produces rapid reductions in left and right heart filling pressures [25,48–52] in patients who are experiencing end-stage renal failure [50,53,54]. The evidence supporting this concept is far from convincing, however. Many other investigators have found that the acute use of furosemide in patients who have developed CPE is associated with initial adverse hemodynamic effects—including elevations of mean arterial pressure, heart rate, PCWPs, and left and right heart filling pressures (preload), and systemic vascular resistance (afterload)—and reductions in stroke volume and cardiac output [27,42,43,55–59]. The adverse effects seem to be related to an initial activation of the renin-angiotensin-aldosterone system and increased sympathetic activation [27,43,57] that occurs immediately after administration of furosemide. These adverse effects generally resolve once diuresis occurs, but often diuresis is significantly delayed because of depressed renal perfusion. The adverse hemodynamic changes may be blunted by administration of preload-reducing (eg, NTG) and afterload-reducing (eg, angiotensin-converting enzyme inhibitors) medications *before* furosemide [27].

Nesiritide

In recent years, a recombinant form of BNP has been suggested as an alternative to NTG for patients who develop acute left heart failure and CPE. Natriuretic peptides are hormonelike substances produced by the myocardium that modulate diuresis, natriuresis, venodilation, and vasodi-

lation; however, when patients who develop chronic CHF develop acutely decompensated CHF and CPE, the ventricle's production of this substance is often inadequate; therefore, a recombinant form of BNP, "nesiritide," was manufactured for IV administration in patients who experience acutely decompensated CHF. Early manufacturer-supported human studies [60,61] demonstrated IV infusions of nesiritide-produced dose-related reductions in PCWP and increases in stroke volume and cardiac index. Symptomatic improvements were noted also, without an increase in heart rate or dysrhythmias. Beneficial effects were maintained throughout a 24-hour infusion (no evidence of tolerance). Occasional patients developed hypotension lasting up to 3 hours, but it was otherwise well-tolerated.

A more recent trial (the VMAC Study) compared the use of IV nesiritide with IV NTG [62]. In this manufacturer-supported study, patients receiving "standard treatment" were randomized to receive nesiritide (dose by protocol) or NTG (dose at the discretion of the treating physician). The patients receiving nesiritide were reported to have a greater decrease in PCWP compared with patients receiving NTG at 3 hours (decrease in PCWP by 5.8 mm Hg for nesiritide versus 3.8 mm Hg for NTG) and also at 24 hours (8.2 mm Hg for nesiritide versus 6.3 mm Hg for NTG). Patients receiving nesiritide were also reported to have greater improvement in "global clinical status" at 24 hours.

Many limitations in the VMAC study prevent simple extrapolation of the results to everyday ED practice [63]. Patients in the study received "standard treatment" before receiving the study drug. "Standard treatment" generally consists of MS and furosemide, neither one of which would be considered "optimal treatment" in the modern management of CPE. Some of the patients also received dopamine or dobutamine at the discretion of the treating physicians. Neither of these medications has been demonstrated to improve patient survival. Patients did not receive aggressive dosing of NTG (average doses of NTG were 30–40 µg/min), and investigators admitted knowledge that physicians generally tend to be reluctant to use high-dose NTG or to up-titrate NTG doses [64].

No indication existed that patients routinely received angiotensin-converting enzyme inhibitors or other vasodilators, and no indication that patients routinely received noninvasive positive pressure ventilation (NPPV), all of which have been shown to hasten resolution of CPE (see later discussion). The comparative improvements in PCWPs noted in the study between nesiritide and NTG were minimal (2.0 mm Hg difference at 3 hours; 1.9 mm Hg difference at 24 hours) and were not associated with any subjective improvement in dyspnea [62]. The "global clinical status" scale used in the study was undescribed and admitted to be a nonvalidated scoring system. No improvement in mortality occurred with nesiritide, and a trend occurred toward higher mortality at 90 days (19% for nesiritide, 13% for NTG, $P = .08$) [63]. A more recent pooled analysis of three randomized trials involving 485 patients receiving nesiritide versus 377

patients not receiving nesiritide also demonstrated an increased 30-day mortality associated with use of this medication (7.2% mortality in patients treated with nesiritide, 4.0% in patients not receiving nesiritide) [65]. Another recent concern is that the use of nesiritide seems to be associated with worsening renal function. An evaluation of five randomized studies involving 1269 patients demonstrated the following: (1) patients who experience acutely decompensated heart failure and were treated with nesiritide were more likely to have significant elevations in serum creatinine; in addition, they more often required medical intervention for worsening renal function than non-nesiritide-treated patients (11.1% versus 4.2%), although there was no increase in the need for hemodialysis [66]. Finally, questions exist regarding the cost-effectiveness of nesiritide because the cost is approximately 40 times that of NTG and patients in the study that received nesiritide had a 2-day longer duration of hospital stay [62].

Nesiritide may be useful for patients in whom NTG is contraindicated (eg, patients taking sildenafil) or in cases for which a prolonged infusion of NTG is needed because tolerance in these patients limits the efficacy of NTG; however, until future studies demonstrate (1) the safety of nesiritide in renal function and mortality and (2) the efficacy of nesiritide in patients who have received “*optimal* treatment” for decompensated CHF and CPE (ie, high-dose NTG, afterload-reducing medications, and NPPV) we cannot recommend routine ED administration of nesiritide for the early treatment of CPE.

Afterload reduction

Most patients who present with CPE have elevated catecholamine levels, which produce a marked increase in systemic vascular resistance—afterload. The already-compromised heart has difficulty producing an effective cardiac output against this increased resistance. Afterload reduction with vasodilator medications produces an increase in cardiac output and reduction in pulmonary interstitial edema. Another benefit is improved renal perfusion, which can lead to substantial improvements in diuresis even before administration of diuretics [67]. Afterload reduction can be accomplished using any one of several available medications. High-dose IV NTG effectively reduces afterload, but prolonged infusion can induce tolerance and limit its efficacy. Nitroprusside is a potent afterload-reducing medication, but it can induce labile fluctuations in blood pressure and requires intra-arterial hemodynamic monitoring. Reflex tachycardia can also occur when nitroprusside is used. Hydralazine is also an effective afterload-reducing agent; however, reflex tachycardia often occurs with hydralazine also.

Angiotensin converting enzyme inhibitors (ACEIs) are effective afterload-reducing agents have other acute hemodynamic benefits in patients who develop CPE. The administration of sublingual (captopril) or IV

(captopril, enalapril) forms of ACEIs to patients who develop CPE is associated with reductions in systemic vascular resistance (afterload) and improvements in PCWP (preload), stroke volume, cardiac output, and mitral regurgitation without causing adverse changes in heart rate or mean arterial pressure [67–74]. These hemodynamic improvements and subjective improvements in dyspnea are noted within 6 to 12 minutes. Subjective and objective improvements are also noted when ACEIs are administered to patients who have already received other “standard” therapies, including MS, furosemide, and NTG [75], and in patients who have hemodialysis-dependent renal failure [76]. The use of ACEIs in patients who present with CPE has been shown to decrease rates of endotracheal intubation, intensive care unit (ICU) admission rates, and ICU length of stay [40,72], factors that are associated with reduced hospital costs. In the authors’ experiences, regardless of whether a sublingual or IV form of ACEI is used, the single dose rarely needs to be repeated during the ED stay. ACEIs can be used safely in conjunction with NTG to provide combination preload and afterload reduction. Furthermore, because ACEIs seem to produce improvements in preload on their own, they can be used as an effective single agent in patients who cannot tolerate NTG (eg, if the patient has recently taken sildenafil).

Afterload-reducing agents should be avoided in patients who are hypotensive; however, these agents can be administered cautiously in conjunction with vasopressors in hypotensive patients. Preload- and afterload-reducing agents should be used with caution in patients who also have severe aortic stenosis. ACEIs specifically should be avoided in patients who have a previous history of ACEI-related angioedema.

Inotropic support

Although inotropic agents should improve outcomes in patients who present with CPE and depressed MI, routine use of inotropes is not recommended. Inotropic agents can cause tachycardia, dysrhythmias, increased myocardial oxygen demand, myocardial ischemia, and sometimes increased mortality [77,78]. Consequently, these medications should be reserved for patients who have hypotension and, therefore, are unable to tolerate the use of preload- and afterload-reducing medications noted earlier. When inotropic agents are used and have produced sufficient improvements in blood pressure, IV NTG or nitroprusside can then be added to provide the desired preload and afterload reduction to relieve pulmonary congestion [79,80]. These patients are best managed with pulmonary artery catheterization and invasive monitoring to closely track their hemodynamic status and allow precise titration of the medications [2,4,81]. Traditional agents used for inotropic support fall into two main classifications, catecholamines and phosphodiesterase inhibitors.

The catecholamine inotropes include dobutamine, dopamine, and norepinephrine. No studies to date have demonstrated a mortality benefit of these over the others in the ED setting. Dobutamine provides the advantage of inducing mild reductions in preload and afterload in addition to inotropic support; however, dobutamine occasionally causes a reduction in blood pressure also, precluding its continued use [82]. In this case, dobutamine should be discontinued and dopamine or norepinephrine can be used to support the patient's blood pressure. Dopamine and norepinephrine improve blood pressure by increasing systemic vascular resistance, which in turn can worsen cardiac output; therefore, when these agents are used, preload- and afterload-reducing medications should be added as soon as possible to improve LV performance and relieve pulmonary congestion.

One of the limitations of catecholamine inotropes is that their activity depends on adrenoceptor sensitivity. Unfortunately, patients who develop CHF have chronically elevated levels of circulating catecholamines that produce adrenoceptor tolerance. As a result, when catecholamine inotropes are administered, higher dosages than normal are required. High dosages of these medications are associated with increased adverse effects. Patients who experience CHF also develop tolerance to these medications more rapidly. Additionally, many patients who experience CHF are now treated chronically with beta-adrenergic receptor antagonists ("beta-blockers"). These medications antagonize the effects of catecholamine inotropes, causing a need for higher dosages of the inotropes.

Phosphodiesterase inhibitors (PDEIs) have the advantage over catecholamine inotropes of working independent of adrenoceptor activity, so they are unaffected by circulating catecholamine levels or beta-blocker medications [83]. PDEIs work by increasing intracellular cyclic adenosine monophosphate levels, which produces a positive inotropic effect on the heart, induces peripheral vasodilation, and reduces pulmonary vascular resistance. As a result, PDEIs induce improvements in preload, afterload, and cardiac output [84]. Several studies have directly compared the use of milrinone, the most well-studied PDEI, with dobutamine in patients who experience severe acutely decompensated CHF and CPE [85–91]. Milrinone was consistently noted to produce similar or greater improvements in stroke volume, cardiac output, PCWP, and systemic vascular resistance. Milrinone was also associated with less tachycardia than dobutamine, is well-tolerated, and is not associated with sustained tachydysrhythmias [92,93]. Despite the apparent hemodynamic benefits, however, milrinone has not been demonstrated to improve hospital length of stay or mortality [90,91].

Levosimendan is a new IV medication classified as a "calcium sensitizer" that has recently been suggested as another alternative to dobutamine for patients who present with acutely decompensated heart failure [94,95]. A recent randomized double-blind trial compared 24-hour infusions of this agent with dobutamine in patients who presented with severe low-output heart failure [96]. Levosimendan produced more significant improvements in

cardiac output and PCWP. Patients who received levosimendan also had a lower 180-day mortality rate (26% versus 38%) compared with patients who received dobutamine. Although the study demonstrated in-hospital and long-term benefits, further trials are needed to clarify whether levosimendan has a role in the acute ED management of patients who have developed CPE.

Ventilatory support

Noninvasive positive pressure ventilation

NPPV has been used successfully in patients who present with CPE and has gained popularity amongst acute care physicians. There are two types of NPPV, continuous positive airway pressure (CPAP) and bilevel positive airway pressure (BiPAP). In CPAP, the patient breaths against a continuous flow of positive airway pressure. In BiPAP, the patient receives additional positive pressure during inspiration. As a result, higher pressures can be applied during inspiration and lower pressures during expiration, allowing for greater patient comfort. Either form of NPPV assists patients who develop CPE by maintaining the patency of stiff fluid-filled alveoli and preventing them from becoming atelectatic during expiration. The work of breathing decreases because less energy is spent trying to reopen collapsed alveoli. The improved alveolar patency also results in improved oxygen and carbon dioxide exchange in the lung [2,97]. NPPV produces an increase in intrathoracic pressure, which leads to improvements in preload, afterload, and cardiac output [97–100].

CPAP and BiPAP use in patients who present with CPE are associated with a reduced need for endotracheal intubation (ETI) [97,101–106] and reduced ICU length of stay [76,107] and resulting reductions in hospital costs. Only one study has directly compared CPAP with BiPAP in patients who present with CPE [108]. The study was terminated prematurely because of safety concerns when it became apparent that more patients in the BiPAP group had MIs; however, the results of the study have been questioned because more patients in the BiPAP group had chest pain from the start. Subsequent studies comparing BiPAP with mask ventilation in patients who present with CPE [109] and BiPAP versus CPAP in acute respiratory failure of heterogeneous causes [110] failed to demonstrate an increase in MI or mortality in patients receiving BiPAP. In the latter study, a subgroup analysis focusing on the patients who presented with CPE also failed to demonstrate an increase in MI or mortality. Regardless of which form of NPPV is chosen, it must be administered early in the patient's course (ie, on arrival to the ED).

Mechanical ventilation

ETI and mechanical ventilation provides definitive airway support and allows for maximal oxygenation and ventilation. The decision to perform

ETI should be made on clinical grounds and should not wait for arterial blood gas testing. General indications for ETI in the patient who has developed CPE includes hypoxia despite maximal supplemental oxygenation, failed attempts at NPPV, decreased level of consciousness, worsening subjective or objective clinical appearance (eg, increasing fatigue, diaphoresis, anxiety, and so forth), and cardiogenic shock (CS) [2]. Once ETI is accomplished, positive end expiratory pressure (PEEP) should be added to the ventilator settings. The addition of PEEP produces the same hemodynamic benefits as NPPV, including improvements in preload, afterload, and cardiac output, and decreases the duration of mechanical ventilation [111].

Assisted circulation

Placement of an intra-aortic balloon pump (IABP) can be a life-saving intervention in patients who experience CS. Shock in these patients is usually the result of a large AMI or acute valvular disorder. The IABP serves as a temporizing measure while preparations for more definitive therapies are made. IABP counterpulsation provides blood pressure support while also providing improvements in coronary diastolic perfusion, afterload, and cardiac output. Definitive therapy for the patient who experiences CS caused MI involves angioplasty or cardiac bypass surgery. Definitive therapy for the patient with CS caused by acute valvular disorders involves emergent valvuloplasty or valve replacement. Placement of an IABP is usually performed by a cardiologist or cardiac surgeon.

Disposition

Although patients who experience mild CHF decompensations that are attributable to dietary indiscretions (excessive salt intake) or medication noncompliance can receive diuretics in the ED for symptomatic improvement and be discharged, patients who present with pulmonary edema should be admitted to a cardiac-monitored bed. Patients who require mechanical ventilation, experience acute valvular dysfunction, require inotropic support, and present with evidence of acute cardiac ischemia/infarction (based on ECG changes or elevated cardiac biomarkers) should be admitted to an ICU setting [112,113]. Other correlates of in-hospital mortality include advanced age, renal dysfunction, hypotension, digoxin use, chest pain, and anemia (Box 2) [114–118]. A recent analysis of a large registry (the Acute Decompensated Heart Failure National Registry, ADHERE) of patients hospitalized with decompensated heart failure identified (1) high admission levels of blood urea nitrogen (≥ 43 mg/dL) followed by (2) low admission systolic blood pressure (<115 mm Hg)

Box 2. Predictors of in-hospital mortality in patients who experience cardiogenic pulmonary edema

- Need for mechanical ventilation
- Acute valvular dysfunction
- Need for inotropic support
- Elevated cardiac biomarkers
- ECG evidence of ischemia or dysrhythmias
- Advanced age
- Renal dysfunction (serum elevations of blood urea nitrogen or creatinine)
- Hypotension
- Digoxin use
- Chest pain
- Anemia

followed by (3) high levels of serum creatinine (≥ 2.75 mg/dL) as the best predictors for in-hospital mortality [117].

Emergent consultation of a cardiologist should be obtained if the cause of the acute CHF exacerbation is AMI or acute valvular dysfunction; or if the patient requires inotropic support. Consultation of a cardiac surgeon should also be considered if severe valvular dysfunction is present. The goal of admission should include symptomatic treatment of hypoxia and pulmonary edema and should also focus on discovering and treating the underlying cause.

Summary

CPE is a life-threatening condition associated with an in-hospital mortality rate of 15% to 20%. To minimize morbidity and mortality, physicians must be able to promptly diagnose and treat these patients. The use of BNP testing is associated with improvements in diagnostic ability beyond physical assessment and chest radiography. Treatment should focus on fluid redistribution through preload and afterload reduction rather than simply diuresis. The most effective and safest preload-reducing medication is NTG. Nesiritide shows promise as an effective preload-reducing medication for patients who present with CPE also, though recommendations for its routine use in the ED should await further studies.

Effective afterload reduction can be accomplished with high-dose NTG or ACEIs, either of which provides preload and afterload reduction, though the combination of medications is more effective than either one alone. ACEIs exert beneficial symptomatic and hemodynamic effects within

minutes, and they have been demonstrated to reduce ICU use, intubation rates, and hospital costs.

Inotropes should not be used routinely in patients who present with CPE; however, in patients who develop CS or in patients who cannot tolerate preload- and afterload-reducing medications because of borderline blood pressure, the use of inotropes is often necessary. Milrinone provides greater hemodynamic benefits than traditional catecholamine inotropes, but a mortality difference is not apparent. Levosimendan is a new inotrope, still in investigation, which seems to provide greater hemodynamic benefits and mortality benefits compared with dobutamine. Ongoing studies should clarify its role in patients who have developed CPE.

Ventilatory support is critical in patients who present with CPE. NPPV should be used routinely in these patients. NPPV has been shown to produce improvements in oxygenation, preload, afterload, and cardiac output, and decreased ICU use, intubation rates, and hospital costs. Patients who fail NPPV or demonstrate evidence of respiratory fatigue and decreased level of consciousness require ETI and mechanical ventilation.

Patients who present with CPE should be admitted to a cardiac-monitored bed. Several factors have been found to be associated with increased in-hospital mortality. Emergency physicians should become familiar with these factors and admit these patients to an ICU.

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