Management of Acute Pulmonary Edema in the Emergency Department

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Noninvasive ventilation (NIV) is a safe and effective technique that can prevent side effects and complications related to endotracheal intubation. Acute cardiogenic pulmonary edema is currently the second most common indication for NIV, mainly in emergency departments. In this article we examine recent literature related to the applications of NIV in the acute setting with regard to patients with acute cardiogenic pulmonary edema. In addition, we examine the epidemiology and the pathophysiology of acute heart failure.

Introduction

Acute pulmonary edema (APE) represents one of the most significant clinical problems in patients presenting to an emergency department. Traditional management has focused on the reduction of ventricular filling pressures, principally with nitrates, loop diuretics, and oxygen at high flow rates and more recently with noninvasive mechanical ventilation.

Acute heart failure (AHF) is a syndrome diagnosed by peculiar symptoms along with objective measures of cardiac dysfunction. AHF may be defined as a cardiac dysfunction (of systole and/or diastole) with a relatively rapid onset of signs and symptoms resulting in hospitalization or unplanned office or emergency department visits [1]. One of the most frequent pathophysiologic classes of AHF syndromes is pulmonary edema (verified by a chest radiograph) accompanied by severe respiratory distress, with crackles over the lung and orthopnea, with O_2 saturation usually less than 90% on room air before treatment. The other most frequent pathophysiologic class is acute decompensated heart failure (HF; de novo or as decompensation of chronic HF), which is referred to by signs and symptoms of acute HF that are mild and do not fulfill the criteria for cardiogenic shock, pulmonary edema, or hypertensive crisis.

The underlying mechanisms of AHF may be cardiac or extracardiac; they may be transient and reversible; or they may induce permanent damage leading to chronic HF.

Because AHF is often a life-threatening condition requiring urgent treatment, identifying patients with AHF among the other causes allows the early introduction of the appropriate evidence-based therapy. In this article we review the epidemiology and pathophysiology of AHF and the use of noninvasive ventilation (NIV) in acute cardiogenic pulmonary edema (ACPE).

Definition and Diagnosis

Diagnosing AHF is difficult because many of its features are nonspecific, and there is wide variability in the ability of clinicians to detect these findings [2].

In addition, up to 10% of patients with AHF have multiple causes of pulmonary edema [3–5], and approximately one third of patients with AHF have concomitant chronic pulmonary disease.

Transthoracic echocardiography should be the first approach to assessing left ventricular (LV) and valvular function in patients whose clinical history and physical and laboratory examinations do not establish the cause of AHF [6].

However, it is not always feasible to promptly evaluate every patient with possible AHF by echocardiography. Furthermore, echocardiography is less sensitive in identifying diastolic dysfunction [7].

Thus, a normal echocardiogram by standard methods does not rule out AHF. Consequently, the diagnosis of AHF and the decision to emergently initiate therapy relies on the bedside clinical assessment. This is a challenge for the physician who has to diagnose AHF based solely on clinical history, physical examination, and some rapidly available examinations (eg, chest radiogram, electrocardiogram). Importantly, no individual feature is sufficiently powerful alone to rule HF in [8].

Therefore, diagnosis is based on overall clinical impression derived from all available information. Several sets

of criteria have been extensively used to diagnose chronic HF. These include three clinical scores: the Framingham criteria, National Health and Nutrition Examination Study, and Boston criteria [9].

However, these scores were inaccurate when tested in the emergency diagnosis of AHF. To be useful in this setting, they should have high accuracy and negative predictive value by themselves. Yet, McCullough et al. [10] found that these scores misdiagnose three out of ten cases.

The value of brain natriuretic peptide (BNP) or its amino-terminal (NT-proBNP) levels in narrowing the differential diagnosis in an acute clinical setting is well established [11].

Used in conjunction with standard diagnostic procedures, measurement of BNP can improve the accuracy of AHF diagnosis during the critical window for optimal care; it is especially useful in ruling out AHF. Recently, Baggish et al. [12] reported a simple and accurate scoring system combining NT-proBNP testing and clinical assessment for the evaluation of patients with acute dyspnea in the emergency department, with high sensitivity (96%) and specificity (84%) for the diagnosis of AHF.

Nevertheless, the misdiagnosis rate is 12% (partly because of the multiple comorbidities) in the emergency department, which is where most patients with AHF first present. Overdiagnosis and underdiagnosis occur with equal frequency [13].

Failure to diagnose AHF and/or misclassification increases mortality, prolongs the duration of hospitalization, and increases the cost of treatment [14].

Epidemiology

AHF is among the most common diseases in emergency medicine and the most frequent principal diagnosis among hospitalized adults aged 65 years [15]. Approximately four of five patients who seek care in the emergency department for AHF require hospitalization. In the United States, nearly 1 million hospital admissions per year receive a primary diagnosis of AHF [16].

About 18% to 40% of AHF patients required treatment in the medical intensive care unit or critical care unit in a prospective survey in European centers and the Acute Decompensated Heart Failure National Registry study [17•,18]. In our experience, about 45% of patients admitted to the intensive care unit because of AHF were affected by APE (unpublished data).

Pathophysiology

The classification of AHF [1] may be based on hemodynamic severity and pathophysiologic classes (Table 1). Data from registries [3–5] have shown that most hospitalizations for AHF occur because of congestion (rales, jugular venous distension, edema) rather than a low cardiac output. AHF encompasses essentially two different patient groups: 1) patients with worsening chronic systolic HF (*cardiac failure*), who make up the majority of those with AHF (> 70%) and 2) patients with de novo HF, which may be secondary to a precipitant factor leading to pump failure (ie, nearly 25% of patients with acute coronary syndrome have signs/symptoms of HF) or derived from a sudden increase in blood pressure superimposed on a noncompliant left ventricle and so-called normal contractile function (*vascular failure*) [19,20].

The distinction between vascular failure and cardiac failure is important because the physiology, clinical presentation, and therapeutic management differ (Table 2).

Patients with new-onset AHF and vascular failure are often older, are more frequently women, and have strong sympathetic activation. The impaired cardiac power and extreme vasoconstriction induce a vicious cycle of afterload mismatch resulting in elevated LV end diastolic pressure, which is transferred backwards to the pulmonary capillaries, yielding pulmonary edema [15].

The microvascular permeability can be enhanced, and therefore, the clinical signs are acute and manifest (Table 2). However, the lung clinical examination is relatively inaccurate, because alveolar flooding from any cause will manifest as inspiratory crackles and often rhonchi [6]. Jugular venous pressure may be difficult to assess because of venous vasoconstriction and redistribution of fluids. Auscultation of an S_3 gallop is relatively specific for elevated LV end diastolic pressures and LV dysfunction, but its sensitivity is low [2].

Although the exact triggers of hypertensive crisis are not known, neurohormonal and cytokine activation may contribute to abrupt and excessive peripheral vasoconstriction [21].

By contrast, many compensatory adaptations take place in patients with progressive cardiac failure. They tolerate higher pulmonary vascular pressures. Chronic changes in neurohormonal regulation lead to volume overload. Typically, these patients present with normal blood pressure, gradual worsening of symptoms (over several days), less chest congestion but more weight gain, edema, and a low LV ejection fraction (Table 2).

Increased LV filling pressures initiate further neurohormonal activation, augment LV wall stress, and change the shape of the ventricle (making it more spherical), resulting in repositioning of papillary muscles with functional mitral regurgitation [22].

Myocardial injury is considered a common and important element of the pathophysiology of AHF. Congestion and myocardial injury may progressively exacerbate each other [23].

The "cardiorenal syndrome" has been applied to the presence or development of a renal dysfunction in AHF patients. This combined cardiac and renal insufficiency is observed in 18% to 30% of patients enrolled in the registries [3–5] and carries a poor prognosis [24].

Table 1. Pathophysiologic classes of acute heart failure syndromes based on hemodynamic severity

Acute decompensated HF (de novo or as decompensation of chronic HF)	Signs and symptoms of acute HF are mild and do not fulfill the criteria for cardiogenic shock, pulmonary edema, or hypertensive crisis
Hypertensive acute HF	Signs and symptoms of HF are accompanied by high BP and relatively preserved left ventricular systolic function with a chest radiograph compatible with APE
Pulmonary edema (verified by a chest radiograph)	Accompanied by severe respiratory distress, with crackles over the lung and orthopnea, with O_2 saturation usually < 90% on room air before treatment
Cardiogenic shock	Tissue hypoperfusion induced by HF after correction of preload; usually characterized by reduced BP (SBP < 90 mm Hg or a drop of mean BP > 30 mm Hg) and/or low urine output (< 0.5 mL/kg/h) with a pulse rate > 60 beats/min with or without evidence of organ congestion.
High-output failure	High cardiac output, usually with high heart rate (caused by arrhythmias, thyrotoxicosis, anemia, Paget disease, or iatrogenic or other mechanisms), with warm peripheries, pulmonary congestion, and sometimes low BP, as in septic shock
Right HF	Low-output syndrome with increased jugular venous pressure, increased liver size, and hypotension; there is a continuum from low cardiac output syndrome to cardiogenic shock.

APE—acute pulmonary edema; BP—blood pressure; HF—heart failure; SBP—systolic blood pressure.
Adapted from Nieminen et al. [1].

Table 2. Classification of acute heart failure syndromes based on initial clinical presentation

Signs and symptoms	Vascular failure	Cardiac failure
Blood pressure	High	Normal
Worsening	Rapid	Gradual (days)
Congestion	Pulmonary	Systemic
PCWP	Acutely increased	Chronically high
Rales	Present	May be absent
Radiographic congestion	Severe	May be absent
Weight gain	Minimal	Significant
LVEF	Relatively preserved	Usually low
Response to therapy	Relatively rapid	Gradual

LVEF—left ventricular ejection fraction; PCWP—pulmonary capillary wedge pressure.
Adapted from Gheorghiade et al. [19].

Despite its growing recognition, the underlying pathophysiology remains less understood. Patients with AHF may have renal insufficiency that is permanent and most likely independent of the HF state.

Treatment

A combination of oxygen (10 L/min), furosemide (ranging from 40–80 mg), and nitrates (ranging from 3–9 mg) is the standard treatment for patients with pulmonary congestion, but patients with APE are hypoxemic, often hypercapnic, tachycardic, and hypertensive with increased work of breathing. They present in the emergency department with signs and symptoms of respiratory distress (tachypnea and respiratory muscle fatigue) and arterial oxygen saturation lower than 90% while breathing high oxygen flow. In this condition, despite standard medical therapy, ventilator assistance may be needed.

Noninvasive positive pressure ventilation

Over the past two decades noninvasive positive pressure ventilation (NPPV) delivered by a nasal mask, face mask, or helmet has gained increasingly widespread acceptance for the support of both chronic and acute ventilatory failure. NPPV can be delivered by means of a bilevel positive airway pressure (bilevel PAP) ventilator, pressure support ventilation (PSV), or continuous positive airway pressure (CPAP). Bilevel PAP provides continuous high flow PAP that cycles between a high positive pressure and a low positive pressure. When used in spontaneous breathing mode, bilevel PAP responds to the patient's own flow rates and cycles between higher pressure (inhalation) and lower pressure (exhalation). When inspiration is detected, the higher pressure is delivered until the flow falls below a threshold level. The spontaneous mode of bilevel PAP is similar to PSV. The difference consists in that the expiratory pressure with bilevel PAP is equivalent to the positive end-expiratory pressure (PEEP), and the inspiratory pressure is equivalent to the sum of PEEP and the pressure support level. CPAP should not be considered as a real ventilation modality because it does not actively assist inspiration but only delivers a constant positive pressure during both inspiration and expiration.

The rationale of using PAP in patients with ACPE is reported as follows:

1. Increase in lung compliance
2. Increase in functional residual capacity
3. Improvement in gas exchange by recruitment of collapsed alveoli
4. Reduction of work of breathing
5. Reduction of respiratory muscle fatigue
6. Reduction of preload of left ventricle by reducing venous return
7. Reduction of after-load of left ventricle by reducing transmural pressure
8. Reduction of negative intrathoracic pressure swing

We examined recent literature related to the applications of noninvasive ventilation in the acute setting with regard to patients with ACPE. The results show a decrease of the need for intubation and an improvement of vital signs. Furthermore, there is a trend toward decreased hospital mortality, especially in hypercapnic patients [25••].

CPAP has been used to treat cardiogenic pulmonary edema for many decades [26–30]. In recent years, the question has arisen whether bilevel PAP is not only effective in treating ACPE but also (by virtue of its ability to reduce inspiratory work and augment tidal volume) whether it is more effective than CPAP alone.

An earlier study [31] showed that 14 patients treated with bilevel PAP (inspiratory PAP/expiratory PAP = 15/5) had more rapid reductions in Pa_{CO2} (partial pressure of carbon dioxide in arterial blood) than the CPAP group (13 patients), but the myocardial infarction rate was higher (71% in bilevel PAP group vs 31% in CPAP group, $P = 0.05$). Rates of intubation were similar in both groups (7% in the NPPV group and 8% in the CPAP group) and lower than the 33% intubation rate in an historic control group. More patients in the bilevel PAP group than in the CPAP group had chest pain upon

study entry (10 vs 4, $P = 0.06$), raising questions about adequacy of patient randomization.

Another study did not find any difference in myocardial infarction rates between CPAP and PSV plus PEEP. In this study [32•] we randomized 46 cardiogenic pulmonary edema patients to receive pressure support and PEEP (15 cm H_2O inspiratory and 5 cm H_2O expiratory pressure) or CPAP (10 cm H_2O). The physiologic variables improved at an equally rapid pace in both groups, intubation and mortality rates were similar, and troponin I levels and myocardial infarction rates were not significantly different between the groups. This study demonstrated no clear advantage of PSV plus PEEP over CPAP alone and indicated that PSV plus PEEP does not increase myocardial infarction rates. However, caution is still advised when bilevel PAP or CPAP is applied to pulmonary edema patients with acute coronary syndromes because of the risk of worsening the outcome of this subgroup of patients.

Masip et al. [33] randomized 40 patients to conventional oxygen therapy or noninvasive pressure support ventilation (NIPSV). They found that endotracheal intubation was required in 5% of patients assigned NIPSV and 33% of patients assigned conventional oxygen therapy, but there were no differences in the length of hospital stay or mortality. No difference was seen in the myocardial infarction rate between the two groups. The authors concluded that NIPSV was superior to conventional oxygen therapy.

Nava et al. [34••] performed a multicenter randomized trial in 130 patients with cardiogenic pulmonary edema. Patients were randomized to receive medical therapy plus oxygen or bilevel PAP. Bilevel PAP improved respiratory rate, dyspnea scores, and arterial oxygen tension/fraction of inspired oxygen more rapidly, but there was no difference in the primary endpoint, need for intubation, or other secondary outcomes including the length of hospital stay, myocardial infarction rate, or mortality. In a subgroup analysis, patients with hypercapnia ($Pa_{CO2} > 45$ mm Hg) on admission had a lower intubation rate than normocapnic controls (6% vs 28%, $P = 0.015$). The authors concluded that bilevel PAP, compared with conventional therapy, more rapidly improves physiologic variables in patients with cardiogenic pulmonary edema but does not affect overall clinical outcomes. Bilevel PAP, however, reduced the intubation rate in the subgroup of hypercapnic patients.

Crane et al. [35] randomized 60 patients with cardiogenic pulmonary edema to three different conditions, including conventional therapy, CPAP (10 cm H_2O), or bilevel PAP (15 cm H_2O inspiratory and 5 cm H_2O expiratory pressures). Treatment success, defined as reversal of acidosis and tachypnea at the 2-hour time point, was 15% in the control group, 35% in the CPAP group, and 45% in the bilevel group ($P = 0.116$). The myocardial infarction rate did not differ between the groups. Hospital mortality was 30% in the control group, 0% in the CPAP group, and 25% in the bilevel group ($P = 0.029$). The authors concluded that CPAP use was associated with a lower hospital mortality rate, although the difference in mortality was not statistically significant until after the first week of hospitalization, well after patients had stopped using the devices.

In the study by Park et al. [36••], 80 patients with a clinical diagnosis of ACPE were randomized to one of three groups, including CPAP (11 cm H_20), bilevel PAP (17/11 cm H_20), or oxygen therapy, in addition to standard medical therapy. Treatment with CPAP or bilevel PAP resulted in significant and similar improvements in dyspnea, vital signs, and arterial oxygen tension/fraction of inspired oxygen ratio compared with oxygen therapy. The study was stopped after the second interim analysis because of a significant difference in intubation rates in the groups (42% in the oxygen group and 7% in each noninvasive group, $P = 0.001$). The use of bilevel PAP was not associated with an increase in myocardial infarction rate.

We compared PSV plus PEEP and CPAP in 36 patients with acute hypercapnic ($Pa_{CO2} > 45$ mm Hg) pulmonary edema [37]. There was no difference in resolution time defined as clinical improvement with a respiratory rate of fewer than 30 breaths per minute and pulse oximetry of 96% or more between the CPAP and PSV plus PEEP groups. Arterial carbon dioxide tension decreased after 1 hour from the beginning of CPAP (from 60.5 ± 13.6 mm Hg to 42.8 ± 4.9 mm Hg, $P < 0.001$) and from 65.7 ± 13.6 mm Hg to 44.0 ± 5.5 mm Hg in PSV plus PEEP group ($P < 0.001$). The possible explanation of this result may be related to the fact that alveolar congestion (and consequently a decreased lung compliance) in addition to hyperventilation is the cause of respiratory muscle overload and finally ventilatory pump failure. In this condition, the presence of a PAP by its hemodynamic effects might be the key to success instead of the addition of pressure support to CPAP.

In conclusion, we suggest that in patients with ACPE, CPAP and bilevel PAP are safe, significantly reduce the endotracheal intubation rate compared with standard therapy alone, and are probably equally effective. Bilevel PAP does not induce an increase in myocardial infarction rate and would add no advantage compared with CPAP in hypercapnic patients.

Three questions remain unanswered:

- Which is the best level of bilevel PAP used?
- Which is the best type of ventilator used in the emergency department, and should the choice be adapted to each patient?
- Which are the right criteria for diagnosis of ACPE: hypertensive edema versus nonhypertensive pulmonary edema or diastolic dysfunction, also known as vascular failure versus systolic dysfunction, also known as cardiac failure?

Despite these crucial limitations, noninvasive ventilation has recently been categorized as class IIa, level of evidence A, in the guidelines on the treatment for AHF by the European Society of Cardiology [1].

In addition, a recent meta-analysis showed that bilevel PAP reduces the need for intubation, as previously demonstrated, as well as reducing mortality in patients with ACPE [25••].

Conclusions

We examined recent literature related to the applications of noninvasive ventilation in the acute setting with regard to patients with ACPE. We showed that both modalities, CPAP and bilevel PAP, seem to be equally safe and effective and reduce the need for intubation, but we need more information about the pathophysiology of ACPE in order to select patients who are more suitable for this treatment.

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