Review Article

Sympathetic crashing acute pulmonary edema

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Abstract

Sympathetic crashing acute pulmonary edema (SCAPE) is the extreme end of the spectrum of acute pulmonary edema. It is important to understand this disease as it is relatively common in the emergency department (ED) and has better outcomes when managed appropriately. The patients have an abrupt redistribution of fluid in the lungs, and when treated promptly and effectively, these patients will rapidly recover. Noninvasive ventilation and intravenous nitrates are the mainstay of treatment which should be started within minutes of the patient's arrival to the ED. Use of morphine and intravenous loop diuretics, although popular, has poor scientific evidence.

Keywords: Diuretics, emergency department, high-dose nitroglycerin, noninvasive ventilation, pulmonary edema, sympathetic crashing acute pulmonary edema

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Introduction

Acute heart failure syndrome (AHFS) is a common underlying cause for dyspnea in patients presenting to emergency departments (EDs) throughout the globe.[1,2] The clinical syndrome is characterized by elevated cardiac filling pressures, causing rapid accumulation of fluid in pulmonary interstitial and alveolar spaces.

The spectrum of patients presenting with AHFS is wide, ranging from mild pulmonary edema to cardiogenic shock. This particular subset of patients with sympathetic crashing acute pulmonary edema (SCAPE)[3] have severe AHFS and present with dramatic onset and rapid progression of symptoms (flash pulmonary edema), giving the emergency physicians a narrow time window to intervene and improve patient outcome.

Flash pulmonary edema is the most severe clinical scenario of all the AHFS.[4] It is known by various names: Crashing pulmonary edema, severe acute pulmonary edema, acute decompensated heart failure, and so on. Due to the central role of increased sympathetic activity in the pathophysiology of this subset of patients, SCAPE is a better terminology for understanding the syndrome of rapid onset, life-threatening pulmonary edema.

We hereby present the review of various underlying pathophysiologic mechanisms as well as approach to emergent treatment of patients with SCAPE.

Methods

The literature search was done using PubMed and Google Scholar. The search was done using the following terms flash pulmonary edema, acute pulmonary edema, AHFS, high-dose nitroglycerin (NTG), and noninvasive ventilation (NIV). Abstract was read for each of the searched articles. The appropriately considered articles were downloaded using our institute portal. Different sections of 36 articles were read, and a review was written.

Pathophysiology

Pulmonary fluid homeostasis is equilibrium between forces that drive fluid into the alveolar spaces and the

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mechanisms responsible for its clearance. AHFS is associated with increased cardiac filling pressures, which are transmitted to pulmonary capillaries and eventually drive intravascular fluid into pulmonary interstitium and alveoli.[5,6] There are three stages of progression of AHFS:

- Stage 1: Distension of small pulmonary capillaries due to increased left atrial pressure
- Stage 2: Interstitial edema
- Stage 3: Flooding of alveolar space causing hypoxia.

Underlying pathophysiologic mechanisms are similar for AHFS and SCAPE. However, there are notable differences between the two. SCAPE develops over minutes-to-hours into a life-threatening condition. Important distinguishing features are the pathophysiologic changes resulting in stress failure and increased permeability of the pulmonary capillaries causing abrupt onset and rapid progression.[7]

Sympathetic system is an important factor in cardiovascular physiology. Left ventricular dysfunction predisposes to abrupt increase in sympathetic tone and release of catecholamines that can precipitate flash pulmonary edema.[8-10] Increased catecholamines cause increased heart rate and decreased diastolic time. It causes activation of renin–angiotensin–aldosterone system (RAAS), which further worsens diastolic stiffening and increased diastolic pressures causing pulmonary fluid overload. Increased sympathetic tone adversely affects the pulmonary circulation by increasing permeability and/or provoking stress failure of the pulmonary capillaries.[10-12] Other factors contributing to flash pulmonary edema include decreased nitric oxide and increased endothelin activity.[5,10]

Clinical Features and Diagnosis

Diagnosis of SCAPE is purely clinical. Patients with SCAPE present with a relatively abrupt onset of shortness of breath which progresses over minutes-to-hours into life-threatening pulmonary edema. Patients present with extremely severe respiratory distress. They are restless, diaphoretic, and hypoxic on arrival to the ED. There are tachycardia and marked hypertension, suggesting elevated sympathetic activity *in vivo*.[13,14] SCAPE is a subset of hypertensive heart failure, and hence almost always presents with high systolic blood pressure. Extensive bilateral crepitations are present of chest auscultation.

These patients are too unstable and orthopneic to lie down for performing a 12-lead ECG at the time of arrival. Cardiac sensitive troponin is elevated in significant proportion of patients with heart failure and is associated with increased mortality.[15,16] Bedside, screening echocardiography during the acute presentation would reveal preserved (ejection fraction >0.5), suggesting that underlying mechanism is worsening of diastolic dysfunction.[14,17,18]

Management Principles

SCAPE is not a diagnostic dilemma. Early recognition and prompt initiation of treatment is the key to preventing morbidity and mortality. Immediate ED management of severe pulmonary edema has its impact on subsequent clinical course, rates of invasive mechanical ventilation, and rates of Intensive Care Unit (ICU) admissions.[19] Various options for initial treatment include NTG, NIV, diuretics, and morphine.

Invasive ventilation

Intubation and use of invasive mechanical ventilation can be averted if high-dose NTG and NIV are rapidly initiated in the emergency room. When a patient presents late with impending respiratory fatigue or without spontaneous breathing efforts, then the attending physician should proceed with intubation. Intubation may be difficult in view of extreme agitation of these patients. Patients are agitated and orthopneic on arrival making it difficult to preoxygenate and position the patient for tube placement, thereby decreasing the first pass success. Preexisting hypoxia and inadequate preoxygenation may lead to increased risk of peri-intubation cardiac arrest.[20,21]

Noninvasive ventilation

Two commonly used forms of NIV are bi-level positive airway pressure (BiPAP) and continuous positive airway pressure (CPAP). NIV provides oxygenation, stents open the flooded alveoli and decreases dead space ventilation. It decreases preload and afterload, thereby decreasing cardiac oxygen demand workload.[22-24] In addition, BiPAP also decreases the work of breathing during inspiration in severely orthopneic patients with SCAPE. NIV is associated with decreased rates of invasive mechanical ventilation and decreased mortality in patients with cardiogenic pulmonary edema, thereby decreasing the rates of associated complications.[24-27]

The application of NIV is an art in itself. All physicians should personally apply NIV mask to the patient. An important aspect of NIV treatment in SCAPE is its early application. Rapidly screen for contraindications for the use of NIV, in the absence of which, NIV mask should be applied as soon as the patient is diagnosed of having SCAPE. The mask should be held and not strapped to the patient's face. When the two modes

of NIV (CPAP and BiPAP) are compared, there is no major difference in efficacy or safety, for the treatment of cardiogenic pulmonary edema in patients presenting to the ED.[25,28] One effective way of using NIV pressures in treatment of SCAPE is to begin with expiratory pressures (CPAP/expiratory positive airway pressure) of 6 cmH_2O which is rapidly increased to 12–14 cmH_2O. Once there is a clinical improvement, pressures are then sharply decreased to 6–8 cmH_2O and then titrated to patient's requirements. NIV interfaces include nasal and oronasal masks. Both are associated with similar improvements in gas exchange and avoidance of intubation.[29]

Nitrates

Nitrates have a beneficial effect in AHFS by causing preload reduction, thereby decreasing the cardiac workload. They can be used sublingual until an intravenous access is gained. Initial intravenous dose of NTG in patients with cardiogenic pulmonary edema is 10–20 μg/min infusion with gradual up-titration. Nitrates cause only venodilatation in these dose ranges, with higher doses required to cause arteriodilatation.[30] Nitrates can cause hypotension, especially in volume-depleted patients and should be avoided in hypotensive patients.

However, the use of nitrates in SCAPE differs from that of other varieties of AHFS. Intense sympathetic activity causes both venous and arterial tone to increase significantly causing diastolic failure. Hence, the aim is to decrease the afterload at the earliest to cut the vicious cycle caused by sympathetic upsurge. Thus, initiating the treatment with low-dose nitrates (venodilatory doses) with gradual titration does little to target the underlying pathophysiology. Furthermore, it takes more time to reach effective doses, thereby missing important window for treatment of these patients.

Preferred treatment of SCAPE patients would target increased afterload using high doses of nitrates on arrival. In a feasibility study, Levy *et al*. used 2 mg boluses of NTG every 3 min (666 μg/min) for first 30 min in patients presenting to the ED with severe decompensated heart failure and hypertension. These were compared to the patients receiving NTG infusion beginning at 30 μg/min with up-titration. There were decreased rates of endotracheal intubation and ICU admissions in high-dose NTG group. Only one patient developed hypotension in high-dose NTG group, which was managed with a crystalloid bolus with no further adverse events.[31] Although the study was nonrandomized and was open label, it gives valuable information about the efficacy and safety of high-dose nitrates in SCAPE. Various other studies have demonstrated the efficacy and safety of high-dose nitrates for the treatment of severe cardiogenic pulmonary edema.[30,32,33] Thus, precipitous hypotension is unusual with high-dose NTG and even if it occurs, stopping the infusion transiently, with a crystalloid bolus is all that would be required for treatment.

A feasible method of use of high-dose nitrates is thus followed in patients with SCAPE. An initial "bolus" dose of 500–1000 μg given over 2 min can be safely used.[30-32] This is followed by high-dose infusion at 100 μg/min with rapid up-titration till there is a clinical improvement, the usual target systolic BP being 140 mmHg. Then, the infusion rate is sharply reduced and slowly discontinued as patient's condition allows [Figure 1].

Morphine

Morphine has long been used as an initial agent for the treatment of cardiogenic pulmonary edema. It causes venodilatation, thereby decreasing preload;[34] it decreases anxiety and pain, thereby decreasing the myocardial oxygen demand and hence has potential benefit during AHFS. However, morphine can cause respiratory depression,[35] which may lead to worsened hypoxia and respiratory arrest.

In some reports, morphine use has been associated with bad patient outcome in the form of increased rates of mechanical ventilation and ICU use.[19,36] Thus, role of morphine in severe acute pulmonary edema is largely nonevidence based and controversial. However, it can be useful in conditions where analgesia is desired, such as myocardial ischemia causing AHFS.

Diuretics

Loop diuretics such as furosemide have been primarily used in the management of acute pulmonary edema. The diuretic effect of furosemide starts in 30 min and peaks in 1.5 h. However, despite its popularity, there is only poor

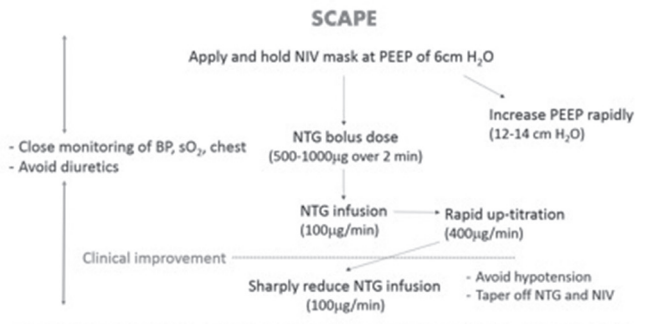

Figure 1: Suggested algorithm for sympathetic crashing acute pulmonary edema treatment

evidence supporting its current use in SCAPE patients.[37] In fact, it may be detrimental to this subset of patients due to its stimulation of RAAS and sympathetic nervous system.[37] Furthermore, patients with SCAPE may be systemically hypovolemic or euvolemic due to long-term use of diuretics and high-dose intravenous diuretics may cause further deterioration in clinical condition.[4]

Current evidence does not support nor does it completely abolish the use of diuretics in SCAPE patients and carefully designed studies may be required to that purpose. Currently, it is recommended as an additional regimen to vasodilator therapy using NTG which remains the mainstay of treatment for SCAPE.

Conclusion

The need to understand this pathology and its very prompt management in the ED cannot be emphasized more. SCAPE is the extreme end of the spectrum of acute pulmonary edema. It is one of those high-yield emergencies presenting to the ED which when treated quickly and effectively will not only save a life but also obviate the need for intubation and ICU care. In this subset of patients, there is redistribution of fluid in the body mainly in the lung while patient may still be hypovolemic or euvolemic.[4] The patients present to the emergency with extreme respiratory distress associated with restlessness, diaphoresis, and high blood pressure (usually systolic above 180 mmHg). The mainstay of management is NIV and high-dose nitrate infusions within minutes of the patient's arrival to the ED. Use of intravenous diuretics and morphine, although popular, is not supported by good scientific evidence.

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Conflicts of interest

There are no conflicts of interest.

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