Diagnosis and Management of Cardiogenic Pulmonary Edema

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ABSTRACT

Acute cardiogenic pulmonary edema (ACPE) is a common cardiogenic emergency with a quite high in-hospital mortality rate. ACPE is defined as pulmonary edema with increased secondary hydrostatic capillary pressure due to elevated pulmonary venous pressure. Increased hydrostatic pressure may result from various causes including excessive administration of intravascular volume, obstruction of pulmonary venous outflow or secondary left ventricular failure due to left ventricular systolic or diastolic dysfunction.

ACPE must be distinguished from pulmonary edema associated with injury of alveolar capillary membrane caused by various etiologies, i.e. direct pulmonary injury such as pneumonia and indirect pulmonary injury such as sepsis. Numerous clinical manifestations may differentiate ACPE and Non-ACPE.

ACPE usually presents with a history of acute cardiac catastrophe. Physical examination reveals a low-flow state, S3 gallop, jugular venous distention and fine crepitant rales on both lungs. The diagnosis of pulmonary edema is made based on symptoms and clinical signs found through history taking, physical examination, ECG, chest X-ray, echocardiography and laboratory tests including blood gas analysis and specific biomarkers.

INTRODUCTION

Acute cardiogenic pulmonary edema (ACPE) is a common cardiogenic emergency that accounts for 1 million annual hospital admissions in the United States. It is also a leading cause of hospitalization of approximately 6.5 million hospital days each year. The in-hospital mortality rate is quite high, ranges from 10% to 20%, especially when associated with acute myocardial infarct.

Clinical manifestation of ACPE usually includes respiratory distress, tachypnea and orthopnea with fine crepitant rales on both lungs. The diagnosis of pulmonary edema is made based on symptoms and clinical signs found through history taking, physical examination, ECG, chest X-ray, echocardiography and laboratory tests including blood gas analysis and specific biomarkers.

Principles of management in ACPE are improving the hemodynamic symptoms and disorders. Treatment that can be administered includes: vasodilator when there is normal or high BP, diuretics when there is volume overload or fluid retention, and inotropic drugs when there is hypotension or signs of organ hypoperfusion. Intubation and mechanical ventilation may be necessary to achieve adequate oxygenation.

PATHOPHYSIOLOGY OF ACUTE PULMONARY EDEMA

In the normal lung, fluid moves continuously outward from the vascular to the interstitial space according to the net difference between hydrostatic and protein osmotic pressures, as well as to the permeability of the capillary membrane. (Figure 1A) Filtration of fluid across a semipermeable membrane, which determines the amount of fluid leaving the
vascular space is described by the Starling equation, i.e. $Q = K[(P_{mv} - P_{pmv}) - (\pi_{mv} - \pi_{pmv})]$, where $Q$ is the net transvascular flow of fluid, $K$ is the membrane permeability, $P_{mv}$ is the hydrostatic pressure in the microvessels, $P_{pmv}$ is the hydrostatic pressure in the perimicrovascular interstitium, $\pi_{mv}$ is the plasma protein osmotic pressure in the circulation and $\pi_{pmv}$ is the protein osmotic pressure in the perimicrovascular interstitium.

When hydrostatic pressure in microcirculation increases, the rate of transvascular fluid filtration rises (Figure 1B). When the lung interstitial pressure exceeds pleural pressure, fluid moves across the visceral pleura, creating pleural effusions. Since the permeability of capillary endothelium remains normal, the filtrated edema fluid leaving the circulation has low protein content. The movement of edema fluid from the pulmonary air space depends on active transport of sodium and chloride through the alveolar epithelial barrier.

Noncardiogenic pulmonary edema (Figure 1C) occurs when the permeability of microvascular membrane rises due to pulmonary injury either directly or indirectly (including the acute respiratory distress syndrome), resulting in a marked increase in the amount of fluid and protein leaving the vascular space. Noncardiogenic pulmonary edema has high protein content since the microvascular membrane is more permeable. In edema due to acute pulmonary injury, alveolar epithelial injury frequently causes reduced capacity for removal of alveolar fluid, which will delay the resolution of pulmonary edema.

**CLINICAL MANIFESTATION**

The presenting symptoms of acute cardiogenic and noncardiogenic pulmonary edema are similar. Interstitial edema causes dyspnea and tachypnea. Alveolar flooding leads to arterial hypoxemia and it may be associated with cough and expectoration of frothy
edema fluid. The common etiologies of cardiogenic pulmonary edema include ischemia with or without myocardial infarction, exacerbation of chronic systolic or diastolic heart failure, and dysfunction of mitral or aortic valve. Another cause that should also be considered is volume overload. A typical history of paroxysmal nocturnal dyspnea or orthopnea suggests the possibility of cardiogenic pulmonary edema. However, a silent myocardial infarction or occult diastolic dysfunction may also manifest as acute pulmonary edema, with few signs provided by the history.

In contrast, noncardiogenic pulmonary edema is usually associated with other clinical disorders, including pneumonia, sepsis, aspiration of gastric contents and major trauma associated with the administration of multiple blood-product transfusions.

**PHYSICAL EXAMINATION**

A systematic and thorough physical examination focusing on clinical manifestation is very important as well as a focused history taking. Cardiac auscultation should be performed carefully listening to any presence of systolic and diastolic murmur as well as the third and fourth heart sounds (S3, S4). Pulmonary congestion can be detected by chest auscultation which demonstrates rales at both bases with common bronchial constriction of both lungs and it usually suggests elevated left-heart filling pressure. The right heart filling pressure is assessed by evaluating the jugular venous filling. Pleural effusion is also commonly found in acute-decompensate of chronic heart failure.

Patients with ACPE frequently have an abnormal cardiac examination. The presence of S3 gallop on auscultation is relatively specific to elevated left ventricular end-diastolic pressure and left ventricular dysfunction and it may suggest cardiogenic pulmonary edema. The specificity of such finding is high (90 to 97 percent), but its sensitivity is low (9 to 51 percent). The wide range of sensitivity probably reflects the difficulty in clearly identifying an S3 gallop on physical examination, a particularly difficult challenge in a critically ill patient in whom intrathoracic sounds created by mechanical ventilation interferes during auscultation.

**ELECTROCARDIOGRAPHY**

ECG provides important findings on heart rate, rhythm, conduction and often also suggests etiology. ECG may demonstrate altered ischemic ST segment that suggests ST-segment elevation myocardial infarction (STEMI) or non-STEMI. Q-wave indicates the presence of previous transmural infarction. Further evidence should be sought regarding the existing hypertrophy, bundle branch block, electrical dyssynchrony, prolonged QT interval, dysrhythmia, or perimyocarditis.

**LABORATORY TESTS**

Elevated troponin levels may indicate damage to myocytes. Slight elevation of cardiac troponin levels can occur in patient with acute heart failure but without an acute coronary syndrome (ACS). Elevated troponin level which is consistent with ACS is associated with poor prognosis. However, elevated troponin level may occur in patients with severe sepsis in the absence of evidence for ACS.

Plasma levels of brain natriuretic peptide (BNP) are often used in the evaluation of pulmonary edema. BNP is secreted predominantly by the cardiac ventricles in response to cardiac wall stretch or increased intracardiac pressures. Type B natriuretic peptides (BNP and NT-proBNP) found in acute phase have negative prediction value to exclude heart failure, although such evidences are not as vast as in chronic heart failure. There is no consensus on the reference value of BNP or NT-proBNP in acute heart failure. As long as there is ‘flash’ pulmonary edema or acute mitral regurgitation, the natriuretic peptides level may remain normal on hospital admission. Elevated BNP and NT-proBNP level since hospital admission until prior to hospital discharge has important prognostic value.

In patients with congestive heart failure, plasma BNP levels correlate with left ventricular end-diastolic pressure and pulmonary-artery occlusion pressure. According to a consensus panel, a BNP level below 100 pg per ml indicates that heart failure is unlikely (negative predictive value, >90 percent), whereas a BNP level greater than 500 pg per ml indicates that heart failure is likely (positive predictive value, >90 percent). However, BNP levels range between 100 and 500 pg provides no adequate diagnostic discrimination. BNP levels must be interpreted carefully in critically ill patients since the predictive value of BNP levels in this group is uncertain.

**CHEST RADIOGRAPHY**

Chest X-ray must be performed as soon as possible during hospital admission for all patients with
acute pulmonary edema (APE) to assess the severity of pulmonary congestion and to evaluate other pulmonary or cardiac condition (cardiomegaly, effusion, or infiltrate). The margins of radiograph on supination position should be noted in patients with acute illness.

There are several explanations for limited diagnostic accuracy of the chest radiograph. Edema may not be visible until the amount of lung water increases by 30 percent.22

ECHOCARDIOGRAPHY

Doppler echocardiography is an important instrument to evaluate changes of function or structure which is occult or associated with APE. All patients with APE must be evaluated as early as possible. Obtained findings will often suggest management strategies.

Echo/Doppler imaging should be performed to evaluate and monitor the left and right ventricular systolic function globally, as well as the diastolic function, valvular structure and function, pericardial pathology, mechanical complication of acute myocardial infarct and evidences of the presence of dyssynchrony. Semi-quantitative non-invasive assessment on left and right ventricular filling pressure, stroke volume, and pulmonary arterial pressure may affect the management strategies. Repeated studies of echo/Doppler as necessary during hospitalization may deflect the needs of invasive evaluation or monitoring.23

PULMONARY-ARTERY CATHETERIZATION

Insertion of pulmonary-artery catheterization (pulmonary artery catheter, PAC) for diagnosing APE is often unnecessary. PAC may be useful to distinguish cardiogenic and non-cardiogenic mechanism in complex cases in which patients had concomitant heart and lung disease, particularly when the echo/Doppler assessment is difficult. PAC can be useful in patients with unstable hemodynamics who show no response to the expected traditional management.

CORONARY ANGIOGRAPHY

In APE cases with evidences for the presence of ischemia such as unstable angina or ACS, coronary angiography is indicated in patients without strong contraindication. Revascularization options (PCI/CABG) should be considered whenever technically possible in patients who match the acceptable risk-profile. Successful reperfusion therapy has been proven to be effective in improving prognosis.6

DIAGNOSTIC APPROACH

Some treatments such as diuretic therapy for suspected cardiogenic edema, (without any contraindication) may be initiated empirically before testing (e.g. echocardiography) takes place. In addition, 10 percent of patients with acute pulmonary edema may have multiple causes of edema.24,25 On Figure 2, we can see the diagnostic approach for acute pulmonary edema.

MANAGEMENT

The main objectives of management are to alleviate symptoms and stabilize hemodynamic condition as well as to improve outcome. Most patients will need long-term management when the acute episode continues to chronic heart failure (CHF). The management of APE should be followed up with the management program of heart failure as recommended by the existing guidelines. In this article, the management is primarily referred to the ESC guideline, 2008.

Various drugs have been used in ACPE management; however, there are drawbacks on clinical trial and most are empirical. There is also no adequate data regarding long term outcome. In published studies, most drugs improve hemodynamic, but no drugs have been found to reduce the mortality rate.

Oxygen

It is recommended to administer oxygen as early as possible in hypoxaemic patients to achieve 95% arterial oxygen saturation (90% in COPD patients). Caution should be taken in patients with severe airway obstruction to avoid hypercapnia (Class I recommendation, level of evidence C).

Morphine and Its Analogues

Morphine should be considered in the early stage of the treatment of patient admitted with severe acute heart failure, especially if they present with restlessness, dyspnea, anxiety, or chest pain.26-28 Morphine relieves dyspnea and other symptoms in patients with ACPE and it can enhance support for NIV application. Evidences regarding morphine utilization in ACPE are still limited.

Bolus of morphine 2.5 – 5 mg can be administered as soon as the IV line is inserted in patients with ACPE. This dose can be repeated if required. Respiration should be monitored since it may cause respiratory distress. Nausea often occurs and antiemetics therapy may be necessary. Give extra caution
when giving morphine in patients with hypotension, bradycardia, advanced AV block or CO2 retention.

**Loop Diuretics**

Diuretics IV is recommended in patients with ACPE when there is secondary symptom of congestion and volume overload (Recommendation Class I, level of evidence C).

**Points to Ponder**

The clear symptomatic benefit and universal clinical acceptance of acute diuretic treatment have reduced the need of formal evaluation of large-scale randomized clinical trials.\(^{29-32}\) Patients with hypotension (SBP < 90 mmHg), severe hyponatremia, or acidosis rarely responses to diuretic treatment. High dose diuretics may lead to hypovolemia and hyponatremia and increase the possibility of hypotension on ACEI or ARB administration. Alternative treatment such as intravenous vasodilator may reduce the need of high-dose diuretic treatment.

**How to Use Loop Diuretics in The Treatment of Acute Pulmonary Edema**

The recommended initial dose is bolus furosemide 20 – 40 mg i.v. (0.5 – 1 mg bumetanide; 10 -20 mg torasemide) on hospital admission. Patients must be assessed frequently on initial phase to monitor urine output. Bladder catheter is usually suggested to monitor urine output and rapidly evaluate treatment response. In patients with evidence of volume overload, the dose of intravenous furosemide can be increased depending on the renal function and history of chronic oral diuretic treatment. In those patients, continuous infusion may also be considered after the initial dose. Total dose of furosemide must be monitored; 100 mg in the first 6 hours and 240 mg for the first 24 hours.

Thiazides combined with loop diuretics can be useful in cases resistant to diuretics. In cases of ACPE with volume overload, thiazides (hydrochlorothiazide 25 mg p.o.) and aldosterone antagonists (spironolactone, eplerenone 25-50 mg p.o.) can be used in combination with loop diuretics. A combination of drugs in low doses is more effective and has less side effects than the use of higher doses of a single drug.
The Potential Side Effects of Loop Diuretics

Hypokalemia, hyponatremia, hyperuricemia, hypovolemia and dehydration; urine output should be evaluated as frequent as possible. Neurohormonal activation may increase hypotension following administration of ACEI/ARB.

Vasopressin Antagonists

Some types of vasopressin receptors have been identified: V1a receptor which mediates vasoconstriction and V2 receptor in the kidneys which its stimulation may induce water reabsorption. Two most studied vasopressin antagonists are conivaptan (dual V1a/v2 AVP receptor antagonist) in hyponatremia and tolvaptan (selective oral antagonist of V2 receptor) in acute heart failure (AHF). The EVEREST study suggests that tolvaptan relieves symptoms associated with acute heart failure and induces weight loss in acute phase but it does not reduce mortality or morbidity at 1 year.31

Vasodilators

Vasodilators are recommended at initial phase of ACPE without symptomatic hypotension, SBP <90 mmHg or serious obstructive valve disease. (Recommendation Class I, level of evidence B).

Indications

Intravenous nitrate and sodium nitroprusside are recommended in ACPE patients with SBP ≥110 mmHg and it can be used with caution in patients with systolic blood pressure (SBP) between 90 and 110 mmHg. These drugs lower SBP, reduce left and right-heart filling pressure and systemic vascular resistance, as well as relieving dyspnea. Coronary blood flow is usually maintained unless the diastolic pressure is disturbed.32-33

- Vasodilators relieve pulmonary congestion in APE, usually without compromising stroke volume or increasing myocardial oxygen demand, particularly in patients with acute coronary syndrome.
- Calcium antagonists are not recommended in the treatment of APE.
- Any vasodilators must be avoided in APE patients with SBP < 90 mmHg since it may reduce the perfusion of central organs.
- Hypotension must be precluded, particularly in patients with renal dysfunction
- Patients with aortic stenosis may experience overt hypotension following administration of intravenous vasodilator drugs.

How to Use Vasodilators in The Treatment of Acute Pulmonary Edema

Nitrates (nitroglycerin, isosorbide mononitrate, and isosorbide dinitrate), sodium nitroprusside and nesiritide are administered as continuous infusion. Intravenous nitroglycerin is the most widely used drug for APE without predominant venodilator effect. Intravenous nitroprusside is a potential balanced vasodilator with combination of preload and afterload reduction. Intravenous nesiritide, a form of recombinant human B-type natriuretic peptide, is an arterial and venous vasodilator with combination effects of diuretics and moderate natriuretics.

Points to Ponder

- It is recommended to give nitroglycerin at initial phase of APE followed by continuous infusion of nitroglycerin, nitroglycerin spray 400 mg (2 puffs) every 5 -1 0 minutes, buccal nitrate (isosorbide dinitrate 1 mg or 3 mg), or 0.25 – 0.5 mg sublingual nitroglycerin.
- The initial recommended dose of intravenous nitroglycerin is 10 – 20 ug/minute, which can be increased to 5 – 10 ug/minute every 3 – 5 minutes if required.
- Titrating nitroglycerin i.v. gradually and monitoring blood pressure regularly are recommended to prevent drastic SBP decrease. Arterial line is not routinely required, but it will facilitate titration in patients with borderline blood pressure.
- Intravenous nitroprusside must be given with caution. Initial infusion rate is 0.3 ug/kg/minute with titration up to 5 ug/kg/minute.
- Intravenous nesiritide can be given with or without bolus infusion with infusion rate ranging from 0.015 to 0.03 ug/kg/minute. Noninvasive blood pressure monitoring is usually adequate. Combination with other intravenous vasodilators is not recommended.

Side Effects

Headache is often reported in nitrates use. Tachyphylaxis generally occurs after 24-48 hours and increased dose of nitrates is required. Intravenous nitroprusside must be given with caution in patients with ACS since hypotension is not unusual. Hypotension may also occurs with nitroglycerin i.v. or nesiritide infusion.

INOTROPIC AGENTS

Inotropic agents must be considered in patients with low output condition, with signs of hypoperfusion or congestion in spite of vasodilators and/or diuretics given
to relieve symptoms (Class IIa recommendation, level of evidence B).

**Indications for Inotropic Treatment**

Inotropic agents should only be given to patients with low SBP or low cardiac index accompanied with signs of hypoperfusion or congestion. Signs of hypoperfusion include cold and moist skin in patients with vasoconstriction and acidosis, renal and hepatic dysfunction or impaired mentation.

Treatment should be given in patients with hypokinetic and enlarged ventricle. When necessary, inotropic agents must be given immediately and ceased rapidly when the organ perfusion has become adequate and/or the congestion has been diminished. Although inotropic agents may acutely improve hemodynamic and clinical condition of patients with ACPE, they may also cause increase and enhance some pathophysiologic mechanisms, which lead to further myocardial injury and resulting in increased short-term and long-term mortality.

Over infusion of inotropic agents is associated with increased incidence of atrial and ventricular arrhythmia. In patients with atrial fibrillation, dobutamine/dopamine may facilitate conduction through AV node and lead to tachycardia; therefore, continuous clinical monitoring and ECG are necessary.

**Dobutamine**

Dobutamine is a positive inotropic agent acting through stimulation of $\beta_1$-receptors to produce dose-dependent inotropic and chronotropic effects. It is usually given with an infusion rate of 2-3 $\mu$g/kg/min without a loading dose. Afterward, the infusion rate may be modified progressively according to symptoms, diuretic response or clinical status. Its hemodynamic effect has dose-related properties, which can be increased to 15 $\mu$g/kg/min. Blood pressure must always be monitored, either by invasive/non-invasive methods. In patients receiving $\beta$-blocker therapy, dobutamine doses have to be increased to 20 $\mu$g/kg/min to restore its inotropic effect. The elimination of the drug is rapid after cessation of infusion. It is recommended to decrease the dose gradually 2 $\mu$g/kg/min and optimization simultaneously with oral therapy. (Class IIa recommendation, level of evidence B).

**Dopamine**

Dopamine, which also stimulates the beta adrenergic receptor both directly and indirectly through increased myocardial contractility and cardiac output, is an additional inotropic agent. Low dose dopamine infusion (2-3 $\mu$g/kg/min) stimulates dopaminergic receptor but it has limited effect on diuresis. At higher dose, it may be used to maintain the SBP, but there is an increasing risk of tachycardia and arrhythmia and it may stimulate a-adrenergic through vasoconstriction. Dopamine and dobutamine must be used with caution in patients with heart rate of 100 times/min. Alpha stimulation at higher dose may cause vasoconstriction and increased systemic vascular resistance. Low dose dopamine is usually combined with higher dose dobutamine (Class IIb recommendation, level of evidence C).

**VASOPRESSORS**

Vaspressors (i.e. norepinephrine) are not recommended for first-line therapy. They are only indicated in cardiogenic shock when the use of an inotropic agent combined with fluid challenge fail to restore systolic blood pressure (SBP) over 90 mmHg with inadequate organ perfusion, despite an improved cardiac output.

Patients with AHF complicated by sepsis may require a vasopressor. As cardiogenic shock is often associated with high systemic vascular resistance, all vasopressors should be used cautiously and be stopped promptly.

Noradrenaline may be used with any of the aforementioned inotropic agents in cardogenic shock, ideally through a central line perfusion. It is advised to give dopamine, which already has a vasopressor effect, an extra caution. Epinephrine is not a recommended inotrope or vasopressor in cardiogenic shock, and should only be used as a rescue therapy in cardiac arrest. (Class IIb recommendation, level of evidence C).

**Milrinone and Enoximone**

Milrinone and enoximone are the two type III-phosphodiesterase inhibitors (PDEIs) used in clinical practice. These agents may inhibit degradation of cyclic AMP and have inotropic effect as well as peripheral vasodilating effects, with an increase in cardiac output and stroke volume and a concomitant decline in pulmonary artery pressure, pulmonary wedge pressure and systemic and pulmonary vascular resistance. As their site of action is distal to the $\beta$-adrenergic receptors, PDE-Is maintain their effects even during concomitant $\beta$-blocker therapy.
coronary artery disease as it may increase average mortality.37 (Class IIb recommendation, level of evidence B).

Cardiac Glycosides

In APE, cardiac glycosides cause slight increase on cardiac output and decreased filling pressure. These agents may be useful to reduce ventricular rate in APE. (Class IIb recommendation, level of evidence C).

Indication for Non-invasive Ventilation

Non-invasive ventilation (NIV) refers to all modalities that assist ventilation without the use of an endotracheal tube, but using a closed face mask instead. NIV with positive end-expiratory pressure (PEEP) should be considered as early as possible in every patient with acute cardiogenic pulmonary edema and hypertensive AHF as it may improve clinical parameters including respiratory distress. NIV with PEEP improves left ventricle function by reducing left ventricle afterload. However, NIV should be used with caution in cardiogenic shock and right ventricle failure. (Class IIa recommendation, level of evidence B).

CONCLUSION

Diagnostic approach for patients with acute pulmonary edema should be initiated by careful history taking and thorough physical examination. Special caution must be made on signs and symptoms of both acute and chronic heart disease, as well as evidences on the presence of primary pulmonary disease such as pneumonia or non-pulmonary infection causes such as peritonitis.

Electrocardiogram is necessary to exclude ischemic changes; although, merely such changes will not suggest cardiogenic pulmonary edema. Measurement of plasma BNP level is recommended and it is most useful when the value is less than 100 pg per milliliter, suggesting that congestive heart failure occurs almost unlikely.

Chest radiography must be interpreted with caution whenever there is any image suggesting cardiogenic pulmonary edema (e.g. enlarged heart and central distribution of edema), which is contrary to noncardiogenic edema. When the diagnosis cannot be confirmed, transthoracal echocardiography may evaluate left ventricular systolic function as well as aortic and mitral valve function.

By using systematic approach on diagnostic algorithm, most patients with acute pulmonary edema can be diagnosed through non-invasive method and treatment can be provided as long as the diagnostic steps have been conducted. In some patients, particularly who has shock as the main complication of pulmonary edema, insertion of pulmonary artery catheter is required to identify the cause of pulmonary edema as well as the appropriate therapeutical target.

The principles of ACPE treatment are relieving symptoms and improving hemodynamics. Treatment that can be given includes: vasodilators when the BP is normal or high, diuretics if there is excess volume or fluid retention, inotropic agents in patients with hypotenision and signs of organ hypoperfusion. Intubation and mechanical ventilation may be required to achieve adequate oxygenation.

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