

Pulmonary edema: new insight on pathogenesis and treatment

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Pulmonary edema is one of the most serious and life-threatening situations in emergency medicine. Lately it has become apparent that in most cases pulmonary edema is not caused by fluid accumulation but rather fluid redistribution that is directed into the lungs because of heart failure. Based on a series of recently published studies, we propose that often the pathogenesis of pulmonary edema is related to a combination of marked increase in systemic vascular resistance superimposed on insufficient systolic and diastolic myocardial functional reserve. This resistance results in increased left ventricular diastolic pressure causing increased pulmonary venous pressure, which yields a fluid shift from the intravascular compartment into the pulmonary interstitium and alveoli, inducing the syndrome of pulmonary edema. Therefore, the emphasis in treating pulmonary edema has shifted from diuretics (*ie*, furosemide) to vasodilators (*ie*, high-dose nitrates) combined with noninvasive positive airway pressure ventilation and rarely inotropes. New classes of drugs that are currently being investigated for treating decompensated heart failure such as natriuretic peptides, calcium promoters, and endothelin antagonist are also being assessed for treating pulmonary edema. This review will explore this new hypothesis put forward to explain the pathogenesis of pulmonary edema and the evolving management strategies. *Curr Opin Cardiol* 2001, 16:159–163 © 2001 Lippincott Williams & Wilkins, Inc.

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Abbreviations

BiPAP bi-level positive pressure ventilation
CHF congestive heart failure
CPAP continuous positive airway pressure
ICAM intracellular adhesion molecule
ISDN isosorbide-dinitrate

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Pathogenesis of pulmonary edema

Until recently, the pathogenesis (and hence treatment) of pulmonary edema was based on the pathological finding of congested lungs leading to the concept that pulmonary edema is caused by fluid accumulation that because of severe heart failure is directed backward into the lungs. Therefore, the preferred treatment for this condition has been massive diuresis. The main problem with this theory is that pulmonary edema is an acute process, usually developing over a few hours and sometimes even minutes, often during the early morning hours when usually no fluid intake occurs. Therefore, fluid accumulation *per se* cannot be accepted as the main mechanism of pulmonary edema. Instead, it is now widely accepted that a process of fluid redistribution takes place by which a portion of the intravascular volume is redistributed to the lungs. This theory explains both the increased fluid content of the lungs during the acute event as well as the prerenal azotemia, which is frequently observed concomitantly with pulmonary edema.

The main question that remains unanswered is why does this sudden shift in fluid occur? In a landmark article published under the category of “Viewpoint” in the *Lancet* in 1996 [1], David Northridge, MD, hypothetically compared furosemide with nitrates for the treatment of acute heart failure. In this article he states: “acute heart failure is characterized by sudden reduction in stroke volume which increases sympathetic nervous system activity in an attempt to maintain systemic arterial pressure. Tachycardia and peripheral vasoconstriction shift blood into the thorax and, if there is impaired ventricular pumping capacity, may result in pulmonary edema... (therefore) acute heart failure is not associated with fluid retention...”.

Pursuing this viewpoint we have recently concluded a study [2] in which hemodynamic variables were assessed in 100 patients with CHF and systolic dysfunction, pulmonary edema, and cardiogenic shock, comparing them with 20 normal volunteers.

We measured over the study period of 1 year the exact hemodynamics of 11 patients who developed pulmonary edema while under invasive monitoring with Swan–Gantz catheters. Our findings are that during pulmonary edema cardiac index is extremely low ($1.4 \pm$

0.3 L/min/M²), and wedge pressure is high (33 ± 9 mmHg), whereas systemic vascular resistance (4144 ± 800 dyn) was extremely high.

However, cardiac index is completely identical in patients with cardiogenic shock and pulmonary edema as opposed to systemic vascular resistance, which is 70% higher in pulmonary edema ($P = 0.0001$). Our conclusion is that pulmonary edema is caused by a combination of events in which inappropriate increase in vascular resistance is met with insufficient systolic and diastolic myocardial functional reserve, leading to acute afterload mismatch. A vicious cycle is established by which impaired function is met with inappropriately high resistance, causing additional impairment in contractility. This increased vascular resistance leads to increased left ventricular diastolic pressures, which is transferred backwards to the pulmonary veins leading to pulmonary edema. Furthermore, as pulmonary edema worsens and oxygen saturation drops, a second vicious cycle is initiated by which the reduced systemic oxygen saturation leads to further impairment of cardiac contractility enhancing the process of pulmonary edema. A third vicious cycle is that of the right heart. The combination of increased pulmonary venous pressure, decreased oxygen saturation, and sympathetic activity induces an increase in pulmonary vascular resistance. This right ventricular afterload mismatch causes an increase in right ventricular end diastolic pressure and this increases left ventricular failure through the diastolic ventricular interaction [3].

The possible interaction between vascular resistance and myocardial systolic and diastolic reserve as a possible mechanism of pulmonary edema is exemplified by an article of Gandhi *et al.* [4], which was recently published in the *New England Journal of Medicine*.

In this study, Gandhi *et al.* examine the cardiac contractility of patients with pulmonary edema presenting to the emergency room with high blood pressure. They found that echocardiographic ejection fraction was almost within normal range (EF = 0.5 ± 0.15). The most significant finding during acute pulmonary edema, which subsided in later echocardiographic examinations, was diastolic dysfunction.

Translating these findings into simple hemodynamics, it is obvious that if a patient has very high blood pressure (mean 140 ± 25 mmHg) while cardiac contractility is almost normal (by echocardiography), vascular resistance must be high (vascular resistance = [mean arterial blood pressure - right atrial pressure]/cardiac output; therefore if mean arterial blood pressure is high and cardiac output is normal to low, systemic vascular resistance must be extremely high). Therefore, again, the assumption that pulmonary edema is caused by an excessive increase in systemic vascular

resistance leading to an acute afterload mismatch accompanied by significant diastolic dysfunction is substantiated.

We do not yet know what is the exact mechanism by which vascular resistance increases exceedingly in patients with pulmonary edema. In a recent unpublished preliminary study we observed that in patients with pulmonary edema both inflammatory mediators (TNF α) and markers of endothelial activation (Selectins and ICAM) are very significantly increased. Moreover, in some recently published studies [5] it has been suggested that pulmonary vascular permeability is increased in patients with pulmonary edema. Therefore, it is possible that our observation of inappropriately increased vascular resistance in patients with pulmonary edema could be explained by endothelial activation (which might be induced by inflammatory mediators), leading to both inappropriate vasoconstriction as well as increased vascular permeability.

Medical treatment of pulmonary edema

Furosemide

Despite being used as front-line therapy in patients with pulmonary edema for many decades, only a few studies examined the role and effect of furosemide in its treatment. However, from a few small, uncontrolled observational studies, it appears that intravenous furosemide causes a significant decrease in pulmonary capillary wedge pressure and right atrial pressure while concomitantly decreasing stroke volume and increasing vascular resistance. Furthermore, it seems that this effect takes place early (usually within 15 minutes), in many cases before diuresis starts. Therefore, furosemide causes a decrease in preload, which is partially related to venodilatation and partially because of diuresis [6].

We have recently published a prospective randomized study [6,7] in which the effect of two treatment strategies were compared in patients with pulmonary edema. In group A patients were given a small dose of morphine (3 mg) and furosemide (56 ± 28 mg), while treatment with IV isosorbide-dinitrate (ISDN) was given at high doses (repeated boluses of IV 3 mg; total dose 11.4 ± 6.8 mg during the first hour). In group B patients were given a small dose of morphine (3 mg) and low-dose IV ISDN drip (1–2 mg/h; total dose 1.4 ± 0.6 mg during the first hour), while IV furosemide was given as repeated boluses of 80 mg as required (total dose 200 ± 65 mg). The results of the study (Tables 1,2) indicate that in all primary and secondary endpoint measures patients treated by high-dose furosemide (as had been the practice in our center before this study) fared significantly worse than patients treated with lower doses of furosemide and high-dose nitrates. Therefore, based on the results of this study (as well as the theoretical considerations) we recommend that IV furosemide should be used with caution for treating pulmonary

Table 1. Results of treatment of patients with pulmonary edema by predominant intravenous isosorbide-dinitrate (Group A) compared with predominant furosemide (Group B)

Primary end-point	Group A (n = 52)	Group B (n = 52)	P
Death	1 (2%)	3 (6%)	0.61
Required mechanical ventilation	7 (13%)	21 (40%)	0.0041
Myocardial infarction	9 (17%)	19 (37%)	0.047
Any adverse event	13 (25%)	24 (46%)	0.041

edema. The doses to be used in most cases should not exceed 80 mg during the initial treatment.

Morphine

Morphine has been a major drug for treating acute heart failure, myocardial infarction, and unstable angina for over seven decades. However, the extended clinical experience is not supported by any quality studies with this drug.

The current recommended dose is 2 to 5 mg IV every 5 to 30 minutes. (There are however no "optimal dose" finding studies to support this practice). Morphine exerts a few favorable effects on patients with acute heart failure and ischemia: It reduces preload and to a lesser extent afterload (systemic vascular resistance) and heart rate. Morphine reduces sympathetic nervous system activity, and alleviates anxiety. These yield a significant reduction of myocardial oxygen demand and work and may reduce ischemia and heart failure.

However, morphine may result in central nervous system suppression and ventilatory failure. It may also aggravate bradycardia and hypotension (especially in the volume-depleted patient or in patients with right heart failure and pulmonary diseases). These unfavorable effects of morphine can be reversed by naloxone.

In a recent retrospective analysis [8] the use of morphine sulfate in the emergency department for pulmonary edema was associated with increased need for ICU admission, and mechanical ventilation. Therefore, the pivotal role of morphine sulfate in treating pulmonary edema is currently being challenged.

Nitrates

In accordance with the assumption made by Northridge [1] and after a previous elegant comparison of the effects of furosemide and ISDN in post myocardial infarction pulmonary edema by Nelson *et al.* [9], we evaluated the effect of high-dose IV ISDN boluses in the treatment of pulmonary edema, as compared with high-dose furosemide [7]. In this study, IV ISDN was administered as repeated (every 4 minutes) 3 mg boluses, which were given until oxygen saturation increased to greater than 96% or systolic blood pressure decreased significantly. Thereafter, IV ISDN was continued as IV drip starting with a dose compatible with the amount of ISDN required to relieve edema.

This specific regiment was chosen because of some theoretical consideration. Firstly, as noted by Northridge [1] nitrates seem to be suited for treating pulmonary edema because they reduce both preload and afterload, they may reduce myocardial ischemia, and they do not increase myocardial oxygen demand. Secondly, we have previously used IV boluses of ISDN for treating acute ischemia [10] and found it to be an effective and easily controlled way of nitrate administration.

Thirdly, the high-dose of nitrates was chosen because it is our experience that during pulmonary edema (as in chronic congestive heart failure [11]) patients are relatively resistant to the effect of nitrates and higher doses are required to achieve vasodilatation. Finally, we have chosen ISDN as the nitrate preparation to be used in the study because it has been our experience that high-dose IV nitroglycerin is sometimes associated with pain during fast IV administration. Our results (Tables 1,2) strongly support the beneficial effect of this treatment regiment. Furthermore, in a recently published study [12] we have shown this treatment to be superior to combination of conventional therapy and noninvasive positive airway pressure ventilation in patients with pulmonary edema. Accordingly, we recommend the use of high-dose nitrates, preferably administered as repeated boluses, as the first line of treatment of pulmonary edema. It is possible that if an IV line cannot be established repeated administration of sublingual nitrates could be used as an emergency initial measure. Although no controlled trial has been performed in this

Table 2. Results of treatment of patients with pulmonary edema by predominant intravenous isosorbide-dinitrate (Group A) compared with predominant furosemide with (Group B): secondary outcome measures

Variable	Group A			Group B			P
	Before Rx	After Rx	Change	Before Rx	After Rx	Change	
Pulse, <i>beats/min</i>	117 ± 18	102 ± 15	-15 ± 22	113 ± 22	104 ± 19	-9 ± 14	0.024
Respiratory rates, <i>breaths/min</i>	42 ± 17	31 ± 14	-11 ± 7	35 ± 8	30 ± 8	-5 ± 6	<0.0001
Oxygen saturation, %	78 ± 8	96 ± 7	18 ± 9	79 ± 7	92 ± 10	13 ± 9	0.0063

regard, we currently recommend the use of repeated SL nitrate spray to patients who suffer repeat episodes of fulminant pulmonary edema as an emergency self-treatment while awaiting the arrival of the EMS team.

Intravenous positive inotropic drugs

Although positive inotropic drugs (dopamine, dobutamine, phosphodiesterase inhibitors) are routinely used for treating decompensated heart failure, no quality studies have been done to assess their efficacy in the treatment of pulmonary edema. Because these drugs increase oxygen demand and are potentially arrhythmogenic, they raise significant safety concerns. Therefore, for the time being their use cannot be recommended as routine first choice in treating pulmonary edema, and should be spared for patients not responding to more conventional therapy.

New drugs for treating heart failure

Endothelin antagonists

Endothelin is the strongest vasoconstrictor known. Therefore, in recent years several antagonists of its action have been developed, specifically designated for treating chronic as well as acute decompensated heart failure. In a few studies, the hemodynamic effect of these drugs was examined. It seems that endothelin antagonists reduce systemic as well as pulmonary vascular resistance, increase cardiac output, and decrease pulmonary capillary wedge pressure [13–15]. Therefore, theoretically, these drugs seem suitable for treating pulmonary edema.

Natriuretic peptides

These drugs, which combine a natriuretic and significant vasodilatory effect are developed for treating heart failure. The clinical and hemodynamic effects of Neiseritide (which was the first to be examined in a double-blind, placebo-controlled study) were recently reported [16]. Compared with placebo, this drug induces significant beneficial hemodynamic effects including a decrease in capillary wedge pressure and vascular resistance as well as an increase in cardiac index. These hemodynamic effects are translated into a decrease in subjective dyspnea and improved patient status. Accordingly this drug may become an important tool in treating pulmonary edema. However, prospective controlled studies are required to examine its effectiveness.

Calcium promoters

This new class of drugs was designed for treating heart failure. Their main effect is to enhance myocardial Troponin calcium binding and hence, improve contractility. Recently, the hemodynamic effect of Levosimendan was reported [17]. Compared with placebo, Levosimendan induces a significant increase in cardiac index while reducing wedge pressure and vascular resistance. Again this is translated into improved subjective dyspnea. As with previous drugs, further studies are required to examine its efficacy and safety in the treatment of pulmonary edema, in particular their long-term survival effect.

Noninvasive ventilation

The use of noninvasive positive airway pressure ventilation either as continuous or as bi-level positive pressure ventilation (CPAP, BiPAP) has been reported to be effective in treating pulmonary edema in a few uncontrolled studies [8]. Recently two prospective randomized studies were performed examining the effect of BiPAP ventilation in pulmonary edema. Unfortunately, the results of these studies were contradictory. We have performed a study [11] in which high-dose IV ISDN boluses were compared with conventional treatment combined with BiPAP ventilation. Our study was terminated prematurely after recruitment of 40 patients because of a decision of the safety committee, which observed significantly worse outcome in the BiPAP arm. On the other hand, Masip *et al.* [18] randomized 38 patients with pulmonary edema to conventional treatment with and without BiPAP ventilation.

The results of this study indicate that BiPAP was effective in treating pulmonary edema by improving oxygen saturation and reducing the need for mechanical ventilation. It is difficult to reconcile the different results of these two studies (Table 3). On one hand, patients in the control group were treated differently (by conventional treatment in the study by Masip *et al.* versus high-dose nitrates in our study).

This may explain the different results in the control group of the two studies. However, this cannot explain the difference in outcome between the two BiPAP arms, in which both medical therapy and BiPAP ventilation were remarkably similar. The only possible explanation

Table 3. Results of bi-level positive pressure ventilation for pulmonary edema: comparison

	Sharon <i>et al.</i> [12]		Massip <i>et al.</i> [18]	
	Control	BiPAP	Control	BiPAP
Death	0 (0%)	2 (10%)	2 (11%)	0 (0%)
Mechanical ventilation	4 (20%)	16 (80%)	6 (33%)	1 (5%)
Myocardial infarction	2 (10%)	11 (55%)	6 (33%)	5 (26%)
O ₂ saturation increase	+17%	+9%	+9%	+19%

BiPAP, bi-level positive pressure ventilation.

could be the significant differences in baseline characteristics among the two treatment groups.

Therefore, until larger controlled randomized studies are performed, noninvasive ventilation should be regarded only as an alternative treatment to be used in patients who failed other treatment modalities.

Conclusions

In recent years we have learned that vascular control mechanisms have an important role in the pathophysiology and hence treatment of acute heart failure and pulmonary edema. Previous reliance on furosemide and morphine as the main treatment modalities has shifted to a more balanced view in which vasodilators have become the primary treatment. Accordingly, we recommend that patients with pulmonary edema should be treated with oxygen, low doses of intravenous morphine, and furosemide (or other loop diuretics) and high doses of nitrates, preferably given as repeated boluses until the patient has stabilized and then continued as an intravenous drip. Until further evidence is available, noninvasive ventilation and positive inotropic drugs should be used only when the above-mentioned treatment fails, before performing intubation and mechanical ventilation. New drugs that are currently being developed and assessed (endothelin antagonists, natriuretic peptides, and calcium promoters) are promising exciting new modalities and may replace high-dose nitrates in the future.

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