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# NONCARDIOGENIC PULMONARY EDEMA IN CHILDHOOD*

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**SUMMARY: Karaböcüoğlu M, Sakarcan A. (Department of Pediatrics, University of Texas Southwestern Medical Center, Dallas, Texas, U.S.A.) Noncardiogenic pulmonary edema in childhood. Turk J Pediatr 1994; 36: 309-317.**

**Pulmonary edema is caused by transudation of fluid from pulmonary capillaries into the alveolar spaces and the bronchiolus. It is most frequently secondary to either increased pulmonary capillary hydrostatic pressure (cardiogenic pulmonary edema) or increased pulmonary capillary permeability (noncardiogenic pulmonary edema). Numerous systemic and pulmonary insults are capable of damaging the capillary endothelium and / or alveolar epithelium, resulting in noncardiogenic pulmonary edema. Although clinically similar, the presence of noncardiogenic pulmonary edema requires a different therapeutic approach from that of cardiogenic pulmonary edema.**
*Key words: noncardiogenic pulmonary edema, childhood, etiology, management.*

A commonly encountered problem in the pediatric intensive care unit setting is pulmonary edema (PE) (pulmonary fluid overload)[1, 2]. An understanding of the etiopathogenesis of PE and its treatment requires an appreciation of the physiology of water and protein clearance. Although progressively more complex models are being developed, the traditional principals of Starling are still accepted. The Starling[1] equation states that the flow of fluid across a semipermeable membrane is governed by the driving pressures and barrier conductance.

$$Q = Kf\ [(P_{cap} - P_{int}) - r\ (X_{cap} - X_{int})], \qquad [1]$$

where Q is the net rate of flow across the surface area of the capillary; Kf is the liquid conductance of the microvascular barrier; P is the hydrostatic pressure in the capillary lumen (cap) and in the perimicrovascular interstitial liquids (int); r is the reflection coefficient; and X is the capillary colloid osmotic pressure in the capillary lumen and perimicrovascular liquids.

Although there are many possible causes of PE, a simple analysis of the Starling equation suggests that there are only two major mechanisms of PE, though they may coexist in the same patient[3, 4]. The first mechanism is cardiogenic pulmonary edema (CPE), which develops in patients with heart failure due to

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increased pressure in the pulmonary capillaries. This form of PE is associated with a normal microvascular barrier and preserved selective capillary membrane permeability for proteins[4] (transudative PE). The second mechanism, noncardiogenic pulmonary edema (NCPE), is caused by increased permeability of the pulmonary capillaries with or without loss of integrity of the capillary endothelium and / or alveolar epithelium. In CPE the time course of fluid accumulation is generally slow and is related to the increased hydrostatic pressure in the capillaries. The fluid itself has a low protein concentration. Alternatively, when there is capillary injury resulting in increased permeability, the onset of edema can be very rapid even in the face of normal hydrostatic pressure. The increased capillary permeability allows leakage of large molecular weight compounds; thus the protein concentration is higher in NCPE than in CPE[5].

When NCPE develops, the airspace is flooded due to leaky pulmonary vessels and alveolar membranes, which impedes oxygen transfer from the airspace into the blood[6]. This sequence of events results in hypoxemia, reduced oxygen delivery, hypoxia, and eventually hypercapnia and death if corrective therapy is not applied[7]. Although the resulting clinical syndrome is frequently associated with adult respiratory distress syndrome (ARDS), this syndrome has the following strict criteria[8,9]: 1) a major antecedent precipitating event; 2) the sudden onset of respiratory distress; 3) hypoxemia refractory to a high concentration of inspired oxygen ($PaO_2$ < 50% with $FiO_2$ > 0.60) with increased shunt fraction and dead space ventilation; 4) the presence of diffuse patchy infiltrates on the chest radiographs; 5) a decrease in static lung compliance (overall compliance < 50% normal, usually 20 to 30% normal); and 6) the exclusion of cardiogenic pulmonary edema and chronic pulmonary disease. ARDS is characterized histologically by diffuse alveolar epithelial and endothelial damage and includes characteristics of an acute inflammatory reaction located primarily in the lung[10].

NCPE is a catastrophic and frequently unanticipated complication of an acute illness. A major concomitant of the ARDS, NCPE may affect more than 250.000 patients annually in the United States and is likely associated with greater than a 50 percent mortality rate[11]. The ability to distinguish NCPE from CPE is vitally important, since management, beyond initial stabilization, is radically dissimilar.

In this review, the circumstances under which NCPE most frequently develops will be described, and those methods available to the clinician which may assist in the differentiation of this syndrome from the more common type of edema, CPE, will be reviewed.

## Etiology

Since, in addition to many systemic disease processes, variable factors such

as smoke lead to an excessive amount of water in the lung, there are numerable causes of pulmonary edema[8, 12]. An abbreviated listing is provided in Table I.

Table I: Etiopathogenesis of Noncardiogenic Pulmonary Edema

**Edema Due to an Increased Pressure Gradient Across the Microvasculature**

Hydrostatic interstitial pressure becomes more negative
- Acute atelectasis (drowned lung)
- Rapid re-expansion of hydro- or pneumothorax

Microvascular colloid osmotic pressure decreased
- Hypoalbuminemia due to liver or renal disease
- Starvation

**Edema Secondary to Injured Endothelium or Epithelium**

Infectious agents: Viruses, mycoplasma, other (especially in immunocompromised patients)

Inhaled substances

Gases: oxygen, nitrogen dioxide, sulfur dioxide, smoke and other noxious gases

Liquid aspiration: gastric contents, salt and fresh water drowning

Ingestants

Chemotherapeutic agents: azothioprine, BCNU, bleomycin, busulfan, chlorambucil, cytosine arabinoside, cytoxan, melphalan, methotrexate, mitomycin

Other medications: amphotericin B, colchicine, gold, hydrochlorothiazide, nitrofurantoin, salicylate, penicillamine

Shock, pancreatitis, trauma and sepsis

Radiation

Neurogenic: hypoxic encephalopathy, head trauma, subarachnoid hemorrhage

Unilateral pulmonary edema occasionally may be seen after rapid reexpansion of a previously atelectatic lung or lobe secondary to the rapid removal of air or fluid from the pleural space[4, 13, 14]. This phenomenon is reported most in adult patients whose involved lung has been collapsed for at least three days or at least two liters of pleural fluid has been removed rapidly[4]. Although edema usually presents acutely, its radiologic appearance may be delayed for up to 24 hours[4]. Pulmonary edema may be produced by a decrease in interstitial pressure. Normal values for interstitial pressures have been estimated as between -5 to -10 mmHg, but during certain circumstances they may increase to -80

mmHg[8], such as during increased respiratory effort associated with an obstructed upper airway. Upper airway obstruction leading to PE was recognized predominantly in children as a consequence of acute epiglottitis or foreign body aspiration[15, 16]. Also, this complication may be associated with conditions such as tonsillar or adenoidal hypertrophy and post-extubation laryngospasm[17, 18].

A decrease in the plasma colloid osmotic pressure results in a tendency toward edema formation. Although hypoproteinemia alone seldom leads to pulmonary edema, patients with hypoproteinemia are more likely to present with pleural effusion[19]. This is seen in hypoproteinemic conditions such as nephrotic syndrome, protein-losing enteropathy and malnutrition. Although this condition is a NCPE, it is not due to increased permeability because the microvascular barrier is intact.

A permeability injury to the pulmonary microvasculature may occur from either the epithelial or endothelial side of the barrier membrane. Injury from the epithelial side of the membrane directly disrupts the alveole-capillary barrier, although a subsequent "inflammatory" response may potentiate the increase in permeability. Injury from the endothelial side is due to a cascade of events likely initiated by complement activation and characterized by entrapment of neutrophils within the microvasculature[11].

Injury to the pulmonary vasculature is the presenting feature in a variety of insults. Pulmonary and extrapulmonary infections, severe systemic insults, different toxins and drugs, or a combined cause leading either to direct injury to the lung or to secondary injury to the lung, are associated with NCPE[2, 19, 20]. In terms of the Starling equation, this amounts to an increase in the filtration coefficient and a decrease in the reflection coefficient, which results in relatively protein-rich edematous fluid[8].

Respiratory distress due to pulmonary edema occurring in conjunction with cerebral injury is a well-recognized but poorly understood phenomenon. Neurogenic PE is associated with a major central nervous system insult such as subarachnoid hemorrhage, intracranial bleeding, seizure and head trauma[21, 22]. Hemodynamic monitoring has shown transient increases in systemic and pulmonary blood pressures, considered to be secondary to the increased adrenergic output during central nervous system dysfunction[8, 23].

## Clinical and Laboratory Findings

Although the diagnosis of PE generally is not difficult, differentiation between the cardiogenic and noncardiogenic froms of edema may not be made easily[4].

The initial presentation of both CPE and NCPE is remarkably similar to that of interstitial edema. Findings of pulmonary edema on physical examination vary

according to the severity of respiratory distress and the underlying cause of edema. Some degree of respiratory distress is generally manifested by an increased respiratory rate, labored breathing, intercostal retractions and use of accessory muscles of respiration[8, 24]. Since in NCPE the time course of fluid accumulation is generally faster than in cardiogenic pulmonary edema, the clinical picture develops more acutely. Cyanosis may be noted, and there may be crackles on auscultation. Excessive frothy, pink-tinged sputum is noted in fairly severe pulmonary edema with alveolar flooding. Wheezing has also been noted early in the course of pulmonary edema in children, along with pulmonary hyperexpansion[8].

It is worthwhile to remember that NCPE is invariably associated with an underlying disease which may or may not be readily apparent. Therefore, the diagnosis of NCPE often depends on a high index of suspicion for secondary probabilities; for example, acute respiratory distress and pulmonary edema in a patient with documented peritonitis or pancreatitis must primarily evoke concern for NCPE. Furthermore, NCPE is uncommonly associated with a well-defined cardiac event. Thus, there is no essential prerequisite that NCPE be diagnosed only when there is lack of objective evidence for an acute cardiac event[11]. In contrast to CPE, NCPE is usually a hyperdynamic illness, clinically apparent as a warm, vasodilated periphery. CPE complicating an acute cardiac illness is frequently a low-flow state, with a cool mottled periphery. Auscultation may aid in making a diagnosis. CPE is usually associated with traditional evidence of left ventricular failure, such as an $S_3$ gallop. Unless complicated by concurrent volume overload, patients with NCPE will not manifest such physical signs[11].

In summary, although there will usually be a number of subtle findings which should alert the clinician to the etiology of PE, in any given situation which is potentially of a noncardiac variety[11], the history and physical examination cannot be relied upon to distinguish NCPE from CPE. In the critically ill patient managed in the intensive care unit, right ventricular catheterization with measurement of pulmonary capillary wedge pressure (PCWP) is frequently used to help differentiate CPE from other forms of PE[11, 25]. With CPE, a reduction of PCWP to less than 18 mmHg usually will be accompanied by significant clinical and radiographic improvement within 24 hours[4].

PE fluid suctioned from an intubated patient may be used to help distinguish noncardiogenic PE from CPE. A PE fluid protein to plasma protein ratio of greater than 0.7 is considered diagnostic of increased permeability edema, whereas a ratio less than 0.5 is characteristic for CPE[11, 26, 27].

There is considerable controversy regarding the ability of the plain chest radiograph to differentiate cardiogenic from NCPE[11, 28, 29]. NCPE is usually

characterized by a patchy, frequently peripheral nongravitational distribution of edema with a normal distribution of pulmonary blood flow, normal vascular pedicle width and cardiac size. Septal lines are not seen and peribronchial cuffing and pleural effusions are rare. Although these findings are helpful to distinguish NCPE, they are not specific.

Scintigraphy of the lung following an injection of $I^{131}$ - HSA shows increased extravascular accumulation in NCPE compared to CPE. Extravascular lung water, measured by the thermal-greendye technique, demonstrates a greater quantity of extravascular lung water in NCPE. Due to the investigative nature of the last two techniques, their routine use is prohibited[25].

**Management**

Treatment of NCPE in children is directed toward the initial insult as well as to ongoing support of cardiopulmonary function[8, 30]. Treatment of the participating illness and management of temperature, serum electrolyte balance, glucose levels, acid-base status, hematocrit and nutrional status, along with appropriate monitoring are required[31]. Aggressive chest physiotherapy and pulmonary toilet are also important[25].

The main goals of therapy are two-fold: to maintain systemic arterial oxygenation and to decrease the sum of pressures causing liquid filtration. Patients who require more than 50% $FiO_2$ to maintain arterial oxygen pressures greater than 50 mmHg and those who develop acute hypercapnia ($PaCO_2$ greater than 50 mmHg) benefit from mechanically assisted ventilation. An important adjunct to this form of therapy is positive end-expiratory pressure (PEEP)[30]. PEEP is desired to maintain alveolar patency, thereby minimizing intrapulmonary shunt and hypoxemia as well as poor lung compliance associated with progressive alveolar collapse and atelectasis.

Some studies have found that for patients unresponsive to conventional ventilation, use of pressure control ventilation with inverse inspiratory-to-expiratory ratio (2:1 or longer) results in improved oxygenation. Other patients who have unremitting respiratory failure despite maximal medical management have been managed successfully with high frequency oscillation or with extracorporeal membrane oxygenation[31].

Since $O_2$ transport is governed by arterial $O_2$ content and cardiac output, optimizing these two parameters is crucial[25, 32]. Cardiac output can be increased by increasing preload or contractility and decreasing afterload. To optimize $O_2$ content, hemoglobin should be maintained between 11 and 13 g/dl and hypophosphotemia prevented to reduce its impact on the position of the oxyhemoglobin dissociation curve[25].

Fluid therapy in a patient with NCPE must be monitored closely to avoid compounding pre-existing abnormal pulmonary capillary permeability characteristics. Although in experimental NCPE (caused by oleic acid) furosemide has been reported by some to be beneficial, other studies contradict this finding[33, 34]; thus it is reasonable to decrease lung microvascular pressure. Though no specific recommendations are available regarding the optimum rate of fluid administration, each patient's hemodynamic status must be monitored closely and enough fluids administered to maintain adequate cardiac output[20].

If the adequacy of perfusion or of the volume status of the child is in doubt, central venous pressure (CVP) should be measured[30]. When therapy for poor peripheral perfusion includes pressor agents or vasodilators, a Swan-Ganz thermodilution catheter may help in assessing the effects of those treatments on cardiac output and vascular resistance. Similarly, when more than 10 $cmH_2O$ of PEEP is administered with the ventilator, cardiac output monitoring may allow clinicians to better assess the efficacy of aggressive treatments for NCPE[30].

Prevention, detection, and treatment of complications (such as nosocomial pneumonia, catheter sepsis, stress ulceration, air leak syndromes and multiple organ system failure) are vital in reducing morbidity and mortality. Pulmonary and abdominal sepsis may be particularly insidious, with a high associated mortality rate[31].

Recent studies have shown that high-dose corticosteroids do not enhance recovery from ARDS, and their use is no longer recommended[25, 32]. However, other drugs such as vasodilators, nonsteroidal anti-inflammatory agents, inhaled nitric oxide and prostaglandin E are still undergoing clinical trials in ARDS[25, 32]. Immunotherapy with monoclonal antibodies has been developed against endotoxin and tumor necrosis factor and may prove to be a major form of treatment for ARDS[35]. Replacement therapies with artificial surfactant and liquid ventilation with perfluorocarbon for treatment of ARDS are also being investigated[31, 36].

## Conclusion

Expedient differentiation of NCPE from CPE is important since diagnostic and therapeutic objectives are so radically dissimilar in these two diseases. NCPE is merely a clinical "marker" of an underlying and usually ominous disease. Its successful management can only be anticipated in pediatric intensive care units with the support of cardiopulmonary functions and therapeutic resolution of the underlying disease (e.g., a septic focus).

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