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New concepts in management of pulmonary edema

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INTRODUCTION

Pulmonary edema is the pathologic condition in which the water content of the lung interstitium is greater than normal[1]. Our understanding of the factors which affect movement of fluid out of the pulmonary microcirculation and into the interstitium has increased dramatically and the fundamental principles are presented below. New areas of research focus on biochemical mediators of increased permeability of the microvascular exchange barrier, mechanisms for removal of excess interstitial fluid (edema resolution)[2], lymphatic function, and mechanical stress related factors (overinflation, very high pulmonary vascular pressures)[3]. Recent clinical evidence suggests improved outcome in critically ill patients in whom lung water accumulation is minimized[4)~6]. This has led to renewed interest in improved techniques for bedside determination of extravascular lung water[7].

CLINICAL MANIFESTATION

Although small amounts of excess pulmonary interstitial fluid are probably well tolerated, sufficient increases impair lung function in several ways. An early effect of excess interstitial lung water is a decrease in pulmonary compliance : that is, the lung becomes stiffer[8]. This produces a restrictive type defect with pulmonary function testing. An early sign of increased lung water is tachypnea which is typical of patients with decreased pulmonary compliance. However, there may be volume or stretch receptors in the lungs which induce tachypnea in the presence of edema even in the absence of decreased compliance. The presence and function of these "J-receptors" in humans is still considered speculative.

A second problem arises when edema fluid leaks into the alveoli (alveolar flooding). A fluid filled alveoli cannot participate in gas exchange, resulting in an lung region in which the ratio of ventilation/perfusion (V/Q ratio) is decreased. In the left atrium, blood which perfuses unventilated alveoli (shunt) mixes with blood which is fully saturated and lowers the overall arterial partial pressure of oxygen. When the fraction of desaturated blood rises high enough, hypoxemia develops. Studies of ventilation/perfusion ratio distribution in ARDS demonstrate an "all or none" phenomenon. That is, perfused lungs units either have appropriate ventilation or no ventilation[9].

The pattern of where edema fluid collects in the lung may also cause problems. Edema fluid initially collects in the area around the alveoli and then travels along both the pulmonary vein sheath and the pulmonary arterial/airway sheath. Fluid may accumulate in sufficient quantities in the bronchioles to result in airway narrowing and manifest as rales. Expiratory rales (cardiac asthma) are sometimes present in patients with pulmonary edema secondary to congestive heart failure. Surprisingly, the associated bronchospasm can be reduced with bronchodilators[10].

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There are apparently other mechanisms contributing to the airway narrowing besides the presence of edema fluid.

RADIOLOGIC MANIFESTATIONS

As water has a higher radiodensity than air, pulmonary edema presents as increased densities in roentgenographic studies and may be detected on chest X-ray before it is clinically apparent.

Familiarity with the various changes associated with increased lung water, which are listed in **Table 1**, can help to differentiate the process from atelectasis, pneumonia and chronic lung disease. Theradiographic appearance of pulmonary edema is frequently dependent not only on the etiology (ARDS vs fluid overload) but also on underlying pulmonary disease. For example, patients with lung regions which are minimally perfused (emphysema, infarction) show very little change radiographically with fulminant pulmonary edema. However in most critically ill patients chest X-ray is a sensitive indicator of pulmonary edema. Some investigators believe that carefully obtained chest X-rays may the best indicator of the amount of lung water[11].

Table 1　Radiographic signs of pulmonary edema

Increased vascular markings
Blurred vessels edges
Increased cardiac silhouette
Kerley A lines (long, mid lung field)
Kerley B lines (short, periphery)
Peribronchial cuffing
'Bat wing' or butterfly appearance
Pleural effusions
Unilateral is unusual
Acinar shadows (patchy areas of consolidation which coalesce over time)

PATHOPHYSIOLOGY

Any understanding of the formation of pulmonary edema requires a familiarity with the principles governing lung fluid balance. The equation most commonly used to describe fluid flux out of the capillaries is called the Starling equation. A review of the history of this equation makes understanding much easier. Starling's (1866-1927) major contribution was the realization that the osmotic pressure exerted by the plasma proteins prevented the formation of edema by counterbalancing the hydrostatic pressure in the vessels. He observed that a decrease in the plasma protein concentration led to the development of edema. Thus, Starling's concept was：

$$Jv = Pc - \pi c \qquad (1)$$

where Jv is the rate of fluid flux out of the capillary, Pc is the capillary hydrostatic pressure and πc is the colloid osmotic pressure. Subsequent investigators realized that the interstitial space outside the capillary had its own hydrostatic and colloid osmotic pressures as well. Thus, the driving pressures were a result of the differences between the capillary and interstitial pressures as shown in Equation 2.

$$Jv = (Pc - Pt) - (\pi c - \pi t) \qquad (2)$$

where Pt and πt represent the interstitial (tissue) hydrostatic and colloid osmotic pressures, respectively. Next, the permeability of the capillary membrane to the plasma proteins was recognized as an important factor in fluid exchange. If the membrane became more permeable, then the plasma proteins would exert less of an effect on fluid filtration as concentration differences would tend to dissipate. The reflection coefficient (σ), which ranges from 0 to 1, represents the fraction of plasma proteins that is "reflected" by the capillary membrane. To determine water permeability, the filtration coefficient (Kf) has been added. Thus the current equation is：

$$Jv = Kf[(Pc - Pt) - \sigma(\pi c - \pi t)] \qquad (3)$$

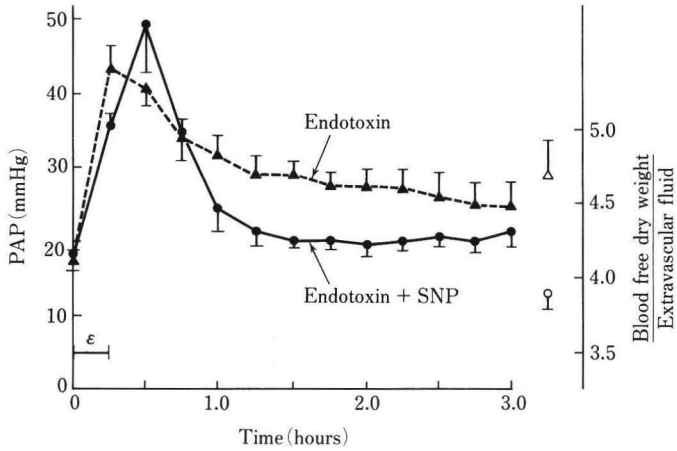

Figure 1 Compared to control (triangles) edema was reduced by treating pulmonary hypertension with SNP (circles) in ARDS model. LAP was not different. *$p<0.05$[13].

Components of Starling Equation

Pulmonary capillary hydrostatic pressure (Pc) represents the major force driving fluid out of the capillary and into the interstitium. The pulmonary capillary wedge pressure (PCWP) is sometimes confused with Pc. PCWP is used as an estimate of left atrial pressure (LAP) and reflects the pressure downstream from the pulmonary capillaries. In order for fluid to flow from the right side of the heart through the lungs and into the left atrium, LAP must be lower than the upstream Pc. Under normal conditions, the gradient between the two is small, i. e. within 1-2 mmHg of each other. The degree to which PCWP approximates Pc is dependent on how much of the total pulmonary vascular resistance resides in the postcapillary sphincter (pulmonary venous resistance).

In congestive heart failure, the pressure rises in the left atrium due to decreased contractility and fluid retention. This increased pressure is transmitted upstream in the pulmonary circulation resulting in an increase in Pc. If the increase is sufficient, fluid enters into the interstitium fast enough to cause pulmonary edema. This mechanism of pulmonary edema is commonly referred to as "cardiogenic." The implication of this term is that increases in Pc are due to, and reflected by, the PCWP (LAP). However, in pulmonary hypertension, the difference between Pc and PCWP may widen considerably. Sepsis related pulmonary hypertension results in a dramatic increase in pulmonary venous resistance and Pc may rise while PCWP falls[12]. Thus, in some instances, hydrostatic edema may be accompanied by a normal or low PCWP. This has been demonstrated experimentally by an animal model of endotoxin induced ARDS. This model produces significant pulmonary edema in a few hours. However, when we infused sodium nitroprusside (SNP) to reduce pulmonary hypertension, no edema occurred, even while LAP was unchanged (**Figure 1**)[13].

Pulmonary hypertension in some disease states such as sepsis and ARDS may contribute to pulmonary edema formation even in the presence of a normal or low PCWP. In a patient study, Gattinoni et al found that the amount of pulmonary edema directly correlated with the pulmonary artery pressure, but not with

PCWP[14]. Some of the increased pressure in the pulmonary arteries is transmitted to the level of the capillaries but not to the left atrium.

A major problem with lung fluid balance studies is the difficulty in measuring PC. Based on data taken from isolated lung preparation, it has been estimated in intact animals. However, the isolated preparation does not accurately reflect the in vivo situation. Analysis of the pulmonary artery waveform tracing as the balloon is inflated holds the most promise for a reasonable bedside technique but debate continues on the appropriate mathematical model to be used. Computer analysis of digitized waveform may be necessary to optimize the reproducibility of this method. Normal Pc is probably around 8 mmHg.

Capillary colloid osmotic pressure (πc) represents the osmotic force generated by the plasma proteins that do not easily pass through the capillary membrane. πc is the major force that opposes Pc. Thus, simply a decrease in πc results in an increase in fluid flux out of the capillary (Jv) and may enhance the formation of edema. Direct measurement of πc involves the use of an artificial membrane of arbitrary pore sizes while the capillary membrane consists of pores of various sizes. As the artificial membrane does not exactly reproduce the capillary membrane, many investigators measure the protein concentration and calculate the πc from derived equations. Normal πc is 24 mmHg.

Reflection coefficient (σ) is the fraction of protein that is reflected by the capillary membrane. This is a measure of the relative permeability of the membrane and determines how much an effect the osmotic gradient will exhibit on fluid filtration. Some tissues such as the brain are essentially impermeable to proteins and have a σ of 1.0. At the other extreme, liver σ is near 0 ; that is, the hepatic capillary is completely permeable to plasma proteins and the amount of fluid leaking off the surface of the liver is related almost solely to the hydrostatic pressure. The lung σ lies between these extremes at 0.7. The pulmonary capillary membrane serves to sieve plasma proteins from the fluid leaving the capillary and may allow a third of the plasma proteins to leak into the interstitium. Thus, filtration fluid has a lower protein concentration than plasma. Certain compounds and disease states are associated with a decrease in the pulmonary capillary σ (increase permeability)[15].

Filtration coefficient (Kf) represents the physical characteristics of the membrane such as the permeability to water and the total surface area. Similar to Pc, Kf can be measured in isolated lungs but is difficult to estimate *in vivo*. Increases in the surface area of the microvascular exchange region or increases in water permeability will result in more fluid entering the interstitium even if the other factors do not change.

Impact of Increased Permeability

Figure 2 demonstrates the effect of permeability changes on lung water accumulation. The solid line indicates with normal permeability, that capillary pressure needs to be increased 15 mmHg to produce significant amounts of lung water. However, when permeability is increased, capillary pressure still has to be increased to produce edema but not as much (dotted line). It has been difficult to document any disease process which disrupts permeability such that pulmonary edema occurs with normal pulmonary vascular pressures.

Anti-Edema Safety Factors

Inspection of Equation 3 reveals that increases in Pc or decreases in πc or σ will result in an increase in fluid egress out of the capillary (Jv) and into the interstitium. However, a modest increase in Jv does not necessar-

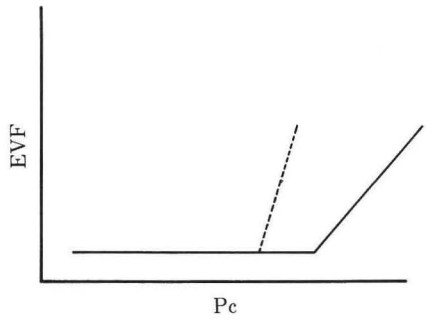

Figure 2 Effect of normal (solid) and increased (dotted) permeability (P) on lung water. With increased P (open circles), edema begins at lower Pc, but still not at normal values[1].

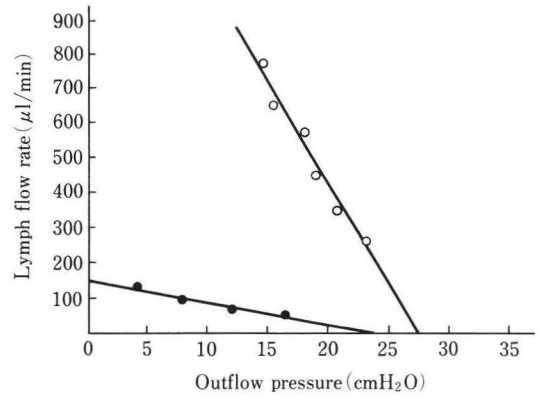

Figure 3 Lymph flow rate vs. outflow pressure at baseline (solid circle) and edema, x-intercept is driving pressure and slope is resistance which increases with edema[1].

ily lead to edema formation because of the presence of anti edema safety factors. **Figure 2** represents the amount of rise in Pc that an awake sheep will tolerate before developing significant increases in edema (extravascular fluid [EVF]). Normal, nonedematous EVF is 2.9+0.1 which occurs when normal Pc is present. These data show that Pc may be increased 10～15 mmHg above baseline values before significant increases in lung water develop[1]. The anti edema factor of most clinical interest is increased rate of lymph flow.

Increased rate of lymph flow. Fluid that enters the interstitium is removed by the lymphatic system. Increases in the rate of fluid entering the interstitium are matched by increases in the rate of lymph flow. This increase in lymph flow rate is produced in the lung by a small increase in tissue driving pressure and a large decrease in lymphatic resistance. However, there is a limit to the increase in lymph flow rate. Thus, once fluid enters the interstitium faster than it can be removed, edema develops.

Effect of CVP

In the previous section we presented the importance of the increase in lymph flow rate in the prevention of edema. Any factor that results in a decrease in the rate of lymph flow may enhance the development of edema. Lung lymphatic vessels drain into veins in the neck that empty into the superior vena cava. Thus, central venous pressure (CVP) is the outflow pressure against which lymphatic vessels must pump lymph. At one time, the lymphatics were believed to be capable of generating pressures great enough to overcome any clinically obtainable CVP. However, as shown in **Figure 3**, lymph flow rate under normal conditions is linearly dependent on outflow pressure (solid circles). Edema results in a shift of this relationship such that for any given outflow pressure, lymph flow rate is higher (open circles). This increase in lymph flow rate is produced in the lung by a small increase in tissue driving pressure (represented by the x-intercepts) and a large decrease in lymphatic resistance (represented by the slopes). Thus, increases in CVP may impair lymph flow rate sufficiently to reduce removal of interstitial fluid and enhance the development of edema. This is demonstrated in **Figure 4.** The dotted line represents sheep in whom CVP (actually, only SVCP to prevent

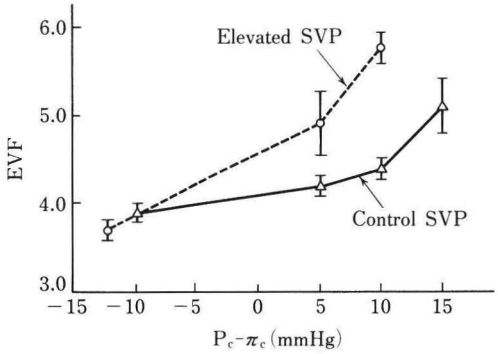

Figure 4 By opposing lymph drainage, increased venous pressure exacerbates edema (y axis). (o) represent sheep in which venous pressure was increased. *p<0.05[16].

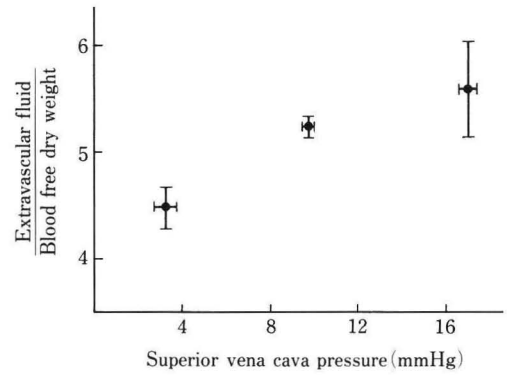

Figure 5 Effect of venous pressure (SVCP) increase on pulmonary edema caused by endotoxemia. Increases to 10 and 17 mmHg significantly increased the amount of edema. *p<0.05[17].

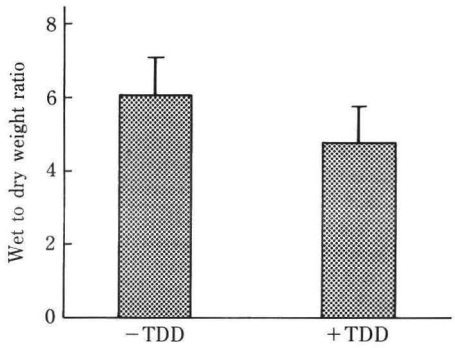

Figure 6 Effect of thoracic duct drainage on pulmonary edema. Pulmonary edema is (p<0.05) less with thoracic duct drainage[18].

decreases in cardiac output) was raised to 20 mmHg. At control Pc, no increase in lung water was detected in the presence of elevated SVCP. However, at each subsequent Pc increase, significant increases in lung water were found[16]. Thus, elevations in CVP may enhance the formation of pulmonary edema by impairing the removal of excess fluid by the lymphatics. This finding has substantial clinical implications as many therapeutic interventions in critically ill patients, such as positive pressure ventilation, fluid infusions and vasoactive drugs, result in increases of CVP. Routine therapy may be contributing to edema accumulation or at least slowing its resolution.

We found a similar response when SVCP was elevated even 7 mmHg in an endotoxin model (**Figure 5**)[17]. These data suggest endotoxin may impair lymphatic function and that even small increases in CVP may significantly enhance pulmonary edema accumulation in septic patients.

Although increased CVP enhances the formation of pulmonary edema caused by either increased LAP or increased permeability, lowering CVP is not always feasible without producing hemodynamic compromise in critically ill patients. An alternative is to divert the lymphatics so that they can flow against a lower outflow pressure. We studied the effect of thoracic duct drainage in an model of pulmonary edema due to increased LAP. Thoracic duct drainage resulted in significantly less edema (**Figure 6**) as well as smaller pleural effusions[18].

Nonlymphatic edema clearance pathways

Although the lymphatic system is the most important pathway for edema clearance, other routes may also play a role[19]. Reabsorption is

one route but can only occur if the Starling forces that led to edema accumulation have returned to normal. Interstitial protein is probably not removed to any degree by this route. Excess pulmonary interstitial fluid may also be removed by leaking across the pleura. We and others have shown that as excess interstitial fluid forms, pleural effusions of similar protein concentrations also begin to appear[20) 21)]. Severe pulmonary edema is also associated with alveolar fluid. Some of this fluid is cleared via the trachea either by coughing or suctioning but some is reabsorbed back into the interstitium by means of an active Na pump in the type II alveolar epithelial cells. The relative importance of these other pathways is under investigation.

CLINICAL IMPLICATIONS

The development of pulmonary edema may result in a spectrum of clinical findings. Patients with small amounts of pulmonary edema due to fluid overload or congestive heart failure may only exhibit tachypnea. On the other hand, those with fulminant ARDS may develop massive pulmonary edema leading to ventilatory failure and hypoxemia necessitating prolonged intubation and mechanical ventilation. The main threat pulmonary edema poses to patients is life threatening impairment of gas exchange. However even if hypoxemia is avoided, there is growing evidence that decreasing pulmonary edema in critically ill patients may contribute to improved survival[4)~6)].

Besides the acute physiologic derangements of pulmonary edema there appears to be alterations of the interstitium. Evidence suggests that remodeling of the pulmonary interstitium begins to occur within a short time if edema does not resolve quickly. This remodeling is associated with increased amount of collagen and fibrosis. Preliminary results suggest that excess interstitial fluid is incorporated into the interstitium leading to increased wet-to-dry weight values even after the forces that caused the edema have resolved. In addition, there is clinical evidence that this remodeling also leads to a decrease in pulmonary permeability[22)].

Congestive Heart Failure. Pulmonary edema develops when elevations in LAP cause Pc to rise sufficiently to overwhelm the anti-edema safety factors. Treatment of pulmonary edema in this situation is based on reducing the vascular pressures. Typically, a diuretic, such as furosemide, is given to reduce the intravascular volume and, thereby, the intravascular pressures including Pc. The Pc needs to be lowered so that fluid filtration is less than the rate at which the fluid can be removed (lymph flow rate). Furosemide appears to also have a venodilatory effect that contributes to edema resolution by decreasing intravascular pressures.

Patients with congestive heart failure often have increased central venous pressure. As noted in previous discussion, increased CVP may not only enhance the formation of pulmonary edema but also impair the lung's ability to clear the excess fluid.

Negative Intrathoracic Pressure. Numerous case reports in the literature and animal experiments support the occurrence of pulmonary edema in the presence of active inspiratory maneuvers with a closed glottis, thereby generating transient, but large, decreases in intrathoracic pressure. Presumably, the negative intrathoracic pressure is transmitted to the interstitium and dramatically increases the hydrostatic pressure gradient enhancing movement of fluid out of the pulmonary circulation. These incidences can usually be managed expectantly, although some patients may require overnight treatment with an endotracheal tube and mechanical ventilation.

Resuscitation : Crystalloid vs. Colloid. The treatment and prevention of hypovolemia may require large amounts of replacement fluids to prevent hypoperfusion. A major goal of perioperative management is to maintain intravascular volume sufficient to protect the kidneys but insufficient to result in pulmonary edema. In the patient requiring large fluid infusions, the attainment of both goals is often difficult to accomplish. Controversy exists concerning the nature of the optimal replacement fluid. Clinical studies have provided directly opposing conclusions, probably due to the difficulty of measuring the various Starling forces accurately as well as the numerous variables that are difficult to control in these critically ill patients.

Some of these same benefits may also be derived by using hypertonic fluids. The rationale for this form of therapy is that intravascular resuscitation is accomplished by mobilizing interstitial fluid. The precise clinical indications for the use of these fluids is under continuing study.

Neurogenic Pulmonary Edema. This type of pulmonary edema is temporally related to a neurologic insult. Neurologic injury is associated with a hugh release of catecholamines, especially norepinephrine. These vasoactive hormones can cause a transient but extreme increase in the pulmonary capillary pressure. If the pressure spike is long enough or high enough, fluid leaks out in sufficient quantities to acutely overwhelm the anti edema safety factors[23]. Generally the capillary pressure spike resolves but the edema does not disappear as fast. There is also evidence for a pulmonary capillary permeability defect in acute neurologic injury[23]. Management of these patients includes adequate gas exchange and maintenance of low pulmonary vascular pressures.

Increased Airway Pressures. Laboratory studies have indicated that high levels of positive airway pressure or overinflation induces pulmonary edema by both raising capillary pressure and increasing permeability[3]. The edema formation appears to be related most closely to the peak airway pressure and whether the lung has suffered some other insult. Overinflation alone may also be a mechanism for increased permeability. The significance of these studies in critically ill humans requires elucidation.

Adult Respiratory Distress Syndrome. Much controversy surrounds the question of appropriate fluid management in pulmonary diseases such as ARDS where pulmonary microvascular permeability may be increased. Pulmonary edema associated with increases in permeability is often discussed outside any contributing effects of capillary pressure. In fact, increases in capillary pressure become even more important when permeability is increased. Pulmonary hypertension may be exacerbating lung water accumulation even in the presence of PCWP$<$20 mmHg. Thus, controlling pulmonary hypertension may be crucial to minimizing pulmonary edema in patients with increased capillary permeability such as those with ARDS. Many vasodilators have been tried with little success in ARDS. Recently inhaled nitric oxide (NO) has been administered to patients and has been shown to be an effective pulmonary vasodilator[24)25)]. There are potential advantages of an inhaled pulmonary vasodilator over an intravenous one. The inhaled vasodilator is delivered only to those alveoli that are ventilated. If perfusion to these alveoli is increased, the V/Q ratio should increase and gas exchange improve. Conversely, an intravascular vasodilator is delivered only to areas which are perfused but not necessarily ventilated or ventilated poorly. If perfusion increases in these areas it could result in

a decrease in the V/Q ratio (inhibition of HPV) and worsen hypoxemia.

Several studies suggest that minimizing pulmonary edema in patients with acute hypoxemic respiratory failure may improve outcome[4)~6)]. The reasons are most likely multifactorial. The primary method is to control intravascular volume, and therefore, capillary pressure, at the lowest level that still allows adequate left ventricular preload so that hypovolemia and tissue ischemia are avoided. This is usually attempted by monitoring PCWP. One drawback of this concept is the unreliability of PCWP to accurately track changes in left ventricular end diastolic volume.

Renewed interest in double dilution extravascular lung water measurements may contribute to fluid management in patients with ARDS. The dye curve can be used to calculate the "central blood volume" which appears to be an excellent measurement of preload[7)26)]. The amount of pulmonary edema may be minimized if fluid management is guided by repetitive measurements of central blood volume to prevent overhydration. Further the availability of bedside quantitative lung water measurements can alert the clinician when fluid therapy may need to be altered. Eisenberg et al studied patients with ARDS or sepsis who had initially large amounts of pulmonary edema[4)]. They found a better outcome in those patients in whom treatment was guided by EVLW measurements. Thus, direct measurements of preload volume and lung water content should minimize pulmonary edema formation and lead to shorter duration of mechanical ventilation, shorter ICU stays, fewer complications, and improved outcome.

Finally, another approach to reducing pulmonary edema in ARDS is to enhance its removal. We have demonstrated significant reduction of pulmonary edema in a animal model as a result of thoracic duct drainage[18)]. Investigators have noted substantial improvement in the pulmonary symptoms of patients with congestive heart failure following thoracic duct drainage. Other studies have demonstrated improvement in gas exchange following thoracic duct drainage in patients with ARDS associated with pancreatitis[27)]. These studies imply that patients who hemodynamically require an intravascular volume that also enhances pulmonary edema may benefit from thoracic duct drainage.

SUMMARY

Rational approaches to the prevention and treatment of pulmonary edema begin with a firm understanding of not only those factors which regulate fluid flux out of the capillary but also the removal of fluid from the interstitium. LAP or its estimate (PCWP) may not accurately reflect changes in the true capillary hydrostatic pressure (Pc) which represents the primary force driving fluid out of the capillary. The primary effect of permeability increase is to exaggerate the effect of increases in capillary pressure on edema production. Another confounding problem in critically ill patients may be increased central venous pressure which slows the maximal rate of lymph flow from the lungs and thereby impairing a key anti edema safety factor.

Preventing the development of significant amounts of pulmonary edema in critically ill patients may be associated with improved outcome. Thus techniques which allow precise monitoring at the bedside of preload volume and lung water content may be of benefit in the management of these critically ill patients.

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