World J. Surg. 11, 147–153, 1987

World Journal of Surgery

Pulmonary Edema: Current Concepts of Pathophysiology, Clinical Significance, and Methods of Measurement

Robert H. Demling, M.D.

Longwood Area Trauma Center, Harvard Medical School, Boston, Massachusetts, U.S.A.

By definition, pulmonary edema is simply excess fluid in the lung. The distribution of the fluid dictates the clinical significance of the edema. As far as a mechanism of edema formation, microvascular hydrostatic pressure remains the predominant Starling force. The lung interstitium is a major factor in determining both the amount of edema formed as well as the distribution. Increased permeability edema, with a more peripheral distribution of fluid as seen in the adult respiratory distress syndrome, may well be the result of interstitial matrix and basement membrane changes rather than simply more holes in the endothelial membrane. The significance of the edema, again, depends on its distribution, with perihilar interstitial fluid being much less significant than alveolar flooding. The relevance of the measurement of lung water, therefore, is dependent as much on where the water resides as on the absolute amount. The clinical applicability of methods that do not give information on distribution, therefore, is dependent on the clinician's understanding of the differences in distribution with various disease states and, therefore, the importance of the water in producing the pulmonary abnormalities.

Edema is a major component of pulmonary dysfunction, which can occur in the surgical patient. Current concepts as to the factors involved in lung edema formation, the physiological significance of the edema, and methods of measuring the amount of edema are discussed in this article.

Factors Involved in Edema Formation

Anatomically, the lung differs from other organs in that, in addition to the interstitium, a large potential water space (namely, the alveolar space) is present. Normally, little interstitial fluid flows into the alveolar space. This is because the alveolar epithelial barrier is nearly impermeable to macromolecules. Also, fluid crossing into the interstitium from the plasma space normally migrates toward the lymphatic opening in the interstitial space or, if excess fluid exceeds the pumping ability of the lymphatics, the fluid accumulates in the loose interstitial space around the larger vessels and airways. The reason for the fluid migration away from the alveolar septum is a result of a concentration gradient of interstitial pressure, which is more negative toward the hilum, as well as a more compliant interstitial space around the larger vessels compared to that at the septal level. Even in moderately severe edema, alveolar wall water content may be only modestly increased, while hilar interstitial fluid content will be increased many fold. This interstitial fluid collection will persist beyond the time at which the increased fluid transport from plasma has been corrected, as the fluid is slowly absorbed from this sequestered space. This explains the lag time of chest x-ray clearance of interstitial edema relative to the clinical improvement of the patient's gas exchange.

Much of the foundation of our current knowledge of the factors affecting the rate of fluid and protein crosing the plasma membrane into the interstitium was obtained nearly a century ago. Concepts were then refined by Starling, Landis, Pappenheimer, and others. Modifications have recently been made on these concepts based on new knowledge. It is important to emphasize that much of this research on edema formation was stimulated by the surgical problems of traumatic shock and resuscitation during the various wars of the time [1].

In 1896 [2], Starling had postulated the presence of pores of different sizes in the capillary wall to explain the transport of fluid and proteins across the capillary membrane into lymph. Evidence to support that these pores were in the junction between endothelial cells was presented by Chambers and Zweifach in the 1940's. After calculating the ratio of movement of various sized molecules across the capillaries in the hindlimb preparation, Pappenheimer presented, in 1947, the concept that uniform cylindrical pores with a radius of 30 to 45A°, confined to the intercellular junction, were present. Occasional large pores were also postulated to account for the larger macromolecules present in lymph. The "sieving" mechanism for macromolecules was, therefore, postulated. The amount of fluid crossing a microvessel at any one time was determined by the sum of the Starling forces, or the net driving pressure, times the conductance, or ease of water transport. This was presented in the following equation: $Qf = Kf[Pcap-Pi)-\sigma(COPcap-COPi)]$, where Qf is the net rate of fluid filtration, Kf is the coefficient describing the conductivity or ease of passage of water, Pcap and Pi are the microvascular and interstitial hydrostatic pressures, respectively, σ is the reflection coefficient, which measures the relative leakiness of the membrane to protein as compared with water, being nearly equal to one for protein and

Supported in part by NIH grants GM 31622 and HL 30068.

Reprint requests: Robert H. Demling, M.D., 75 Francis Street, Boston, Massachusetts 02115, U.S.A.

zero for small molecules, and COPcap and COPi are the microvascular and interstitial protein colloid osmotic pressures (COP), respectively. The importance of osmotic pressure on the filtration rate is reflected in the difference between plasma and interstitial values. An increase in water conductance in general means an increase also in the leakiness to protein. It was determined, therefore, that it was not necessary that a severe destruction of the membrane occur to allow for large increases in protein and fluid flow. An increase in pore size from 30–45A° to 100A° would essentially allow free flow of albumin and negate the protection of the oncotic gradient electrolyte. The special interest in protein transport was stimulated by the success of the treatment of traumatic shock during World War II with colloid solutions.

Microvascular Membrane

The anatomical term *capillary* has been replaced by the more physiological term *microvessel*, since it is now clear that fluid and protein also cross on either side of the anatomic capillary. Exchange vessels are, therefore, now generally termed microvessels [3]. Different microvessels have different permeability characteristics. The skin vessels are very nonpermeable, while lung vessels are modestly permeable, with interstitial protein being about 50% plasma. The splanchnic circulation is the most permeable to protein with interstitial albumin content being up to 90% of the plasma value as measured in thoracic duct lymph.

Maintenance of permeability characteristics appears to be a dynamic process. Endothelial cells seem to be able to regulate the permeability of the microvascular wall by controlling the nature and distribution of glycoprotein molecules within the water pathways or pores where fluid and protein cross [4]. It is not well established that albumin is necessary for the maintenance of vascular integrity, although small amounts of circulating albumin may be all that is necessary [5]. The mechanism by which albumin maintains membrane selectivity remains as yet undetermined. Current theories would suggest that albumin occupies space in the water channels thereby altering channel size. An alternative explanation would be related to the charge of the albumin repelling other like-charged macromolecules. Endothelial cell elongation and cell-cell adherence appears to be an energy-requiring process. Damage to the cells results in cell-cell separation and, therefore, an increase in protein permeability. Permeability properties are also dependent on the interstitium, however, as is described in the following section.

Interstitial Space

The Pappenheimer equation [6] and the principles of shock [7,8] and fluid management relative to colloid and permeability, do not identify the interstitium as having a major role in fluid and protein flux except for the generation of interstitial hydrostatic and oncotic pressure and their effect on the microvascular membrane. A major change in our current concepts of fluid balance is based on our new knowledge as to just how important the interstitium is in this process.

The interstitium is a complex network of collagen, elastic fibers, proteolgycans, and glycosaminoglycans [9]. The latter 2 components have the capability of swelling greatly when the tissue is hydrated. Included in the interstitium is the basement membrane, an important component of which is tissue fibronectin. Tissue fibronectin is the cement holding endothelial cells together [10]. There is no doubt that the compliance or viscosity of the interstitium is a very important determinant of fluid accumulation [11–13]. Oppenheimer et al. [13] recently demonstrated that a significant portion of increased lung transvascular to interstitial fluid flux is determined by the rate of water redistribution in the interstitium. Interstitial gel proteoglycans and glycosaminoglycans, in particular, hyaluronic acid, are now known to play a major role in fluid and protein flux. For example, proteoglycans in the glomerular basement membrane form the major barrier to protein filtration. These compounds appear to maintain tissue vascular permeability because of their viscosity effects. Hyaluronic acid solutions have very high viscosities because of their highly polymerized state. The large hyaluronic acid molecules also occupy a large volume, thereby inhibiting water and solute accumulation. Depolymerization of hyaluronic acid greatly decreases its viscosity [14]. Also, the small hyaluronic fragments competitively interfere with intermolecular interaction between the larger hyaluronate molecule leading to a further loss of viscosity and structure of the interstitium. Because of the very viscous matrix, only a portion of the interstitial space is available for equilibration with fluid and protein. The space not in equilibrium is known as the albumin-excluded volume [15]. Its size is felt to be dependent on the compactness of the interstitial gel or matrix. The albumin space is normally considerably smaller than the total interstitial space. Hydration of the gel by increased water content increases the space for protein and water distribution. This hydration process initially results in a redistribution of interstitial protein in a larger space, thereby initially decreasing interstitial oncotic pressure and increasing the plasma-interstitial oncotic gradient. Protein is then washed out with water by lymphatics, further decreasing the oncotic pressure and increasing the gradient, assuming no change in protein permeability. This washout process with an increasing oncotic gradient helps to neutralize the effect on fluid flux of an increase in microvascular hydrostatic pressure. This assumes that interstitial protein content can continue to decrease, thereby further increasing the oncotic gradient. Of course, the limit to this protective process is the minimal value for interstitial protein content that can be reached [16]. This process functions as long as an increase in interstitial space compliance or a decrease in lymphatic pumping ability does not occur.

Although the balance of Starling forces appears to be better maintained with hydration of the interstitium, edema formation may actually be accentuated if excessive edema occurs. The interstitium exhibits the property of stress relaxation. That is to say, the viscosity or stiffness of the matrix which helps to prevent edema accumulation is decreased as volume expansion occurs [17, 18]. This implies that fluid accumulation can become self-perpetuating if excessive edema is allowed to occur. The interstitial space can then become a reservoir for protein, and edema then becomes chronic with the extent limited only by the elastic limits of the soft tissues. The now-chronic edema, besides being more difficult to resolve, now appears to stimulate fibroblast activity with deposition of new collagen to again stiffen the matrix [18]. In the lung, however, as opposed to other tissues, the alveolar compartment will fill prior to an

extensive expansion of the matrix at the septal level. Chronic interstitial edema is seen, however, in disorders much as mitral stenosis, and interstitial pulmonary fibrosis can result from the chronic edema. It is incorrect to state that pulmonary edema is an innocuous complication of fluid overresuscitation, which is readily corrected. Alveolar edema can require several days to resolve, and changes in the interstitium can take even longer to resolve.

The adequacy of the balance of Starling forces can be misleading when referring to edema formation if, in fact, an additional variable, namely, changes in interstitial compliance, is present. A dehydration of the interstitium, despite a resulting increase in interstitial protein, may actually be a greater barrier to edema formation by decreasing interstitial space compliance. Dehydration of the gel, in turn, will increase the negative charge density, possibly acting as a further barrier. In the lung, gas diffusion would certainly be impaired in the presence of excess septal interstitial fluid.

Interstitial components also appear to play an important role in permeability edema. Enzymatic depolymerization of hyaluronic acid causes increased permeability in connective tissues. Recent studies have indicated the importance of molecular charge on solute flux. The sulfated glycosaminoglycans are heavily anionically charged molecules. Alphanaphthol thiourea causes a decrease in anionic charges in the lung and, in turn, an increase in permeability edema [19, 20]. Hyaluronic acid is known to be easily depolymerized by hydroxyl radicals. Hydroxyl radicals released from activated granulocytes are known to increase protein permeability. This process is inhibited by hydroxyl radical scavengers, superoxide dismutase and catalase. Fox et al. produced a lung permeability injury with phorbol myristate acetate which causes the release of oxygen radicals from granulocytes [19, 21] An increase in protein-rich lymph flow resulted, an effect that, in the past, has been attributed to an alteration at the endothelial cell membrane. These injured lungs also showed a severe depletion of the high molecular weight hyaluronic acid compared to controls. This interstitial effect may have been responsible for the increase in protein flux. Fibronectin, as previously stated, is a major component of the basement membrane. A depletion of plasma fibronectin has been shown to potentiate markedly the increase in lung permeability seen with sepsis. Data reported by Deno et al. [10] strongly suggest that plasma and tissue fibronectin are in equilibrium. A depletion of the tissue fibronectin may, therefore, play a major role in increased permeability.

The fact that the interstitium is involved with the process of protein transport is quite evident in the lung where a disruption in the normal pathway of interstitial fluid migration from the lung periphery to the hilar interstitium is seen with increased permeability. This is evident radiographically by the early appearance of alveolar flooding and the lack of airway interstitial fluid cuffing with permeability edema [22]. The compact matrix necessary at the septal level to produce a preferential flow of fluid to the looser matrix around larger vessels is most likely altered so as to impair this normal vent for septal fluid accumulation and lead to earlier involvement of the alveolar compartment [23].

Forces Affecting Fluid Transport

By far, the most important Starling force governing fluid transport is microvascular or capillary hydrostatic pressure (Pmv). The value for Pmv in the lung is somewhere between pulmonary artery (Ppa) and left atrial (Hla) pressures. The standard equation [24] for this calculation is Pmv = R (Ppa − Pla) + Pla, R being the fraction of total resistance on the venous side. In the normal lung, R is felt to be 0.4 or 40% of total resistance. It has been previously thought that the majority of the vascular resistance in the lung was present in the small arteries and arterioles with little decrease in pressure across the capillaries themselves. Recent lung micropuncture studies directly measuring capillary pressure [25] have indicated that 50% of the pressure drop across the normal pulmonary circulation occurs from the arterial end to the venous end of the capillary bed itself; therefore, Pmv is truly a mean pressure. This concept certainly holds true for the systemic microcirculation as well.

High pressure edema is characterized by vascular congestion, extravasation of red blood cells, and protein-poor edema fluid, since protein permeability is intact. The increased red blood cells are due to focal ruptures of capillaries and red cell diapedesis. Although more water crossed the membrane, protein flux remains restricted as protein permeability does not change significantly. The protective effect of the increased oncotic gradient is self-limiting in that the lowest level to which interstitial oncotic pressure can decrease appears to be 3 to 4 mm Hg. This protective response is less effective in the peripheral microcirculation because interstitial protein content is already quite low, thereby limiting the net buffering effect.

Although the decrease in plasma oncotic pressure from hypoproteinemia is in large part neutralized by a decrease in the interstitial value, we and others have recently described that plasma and, in turn, interstitial space protein depletion increases fluid flux [16, 26]. We have hypothesized that the protein washout from the interstitial space decreases the matrix viscosity, thereby increasing interstitial compliance and ease of water accumulation, an effect not related to oncotic pressure as previously described. Despite an increase in fluid flux, however, the resistance to flow through the interstitium to the lymphatic is also decreased and the increased lymphatic function can compensate for the increased fluid flux. Hypoproteinemia in systemic tissue leads to measureable edema as the changes in the matrix appear to be more significant and the lymphatic system is not as well developed as that in the lung [26].

The compliance of the interstitium will, in turn, dictate the rate of increase in interstitial hydrostatic pressure with fluid accumulation. The relationship between interstitial volume and pressure is not linear. Pressure changes very little until volume is near maximum. The eventual increase in interstitial pressure helps to decrease the rate of fluid flux. The lung interstitium is an exception to this process in that when a critical pressure is reached, the alveolar membrane integrity is altered, possibly due to alveolar cell separation, and interstitial fluid is vented into the low-resistance alveolar space.

Changes in Permeability

An increase in protein permeability, whether as a result of an increase in the number or in the size of the defects (pores) in the

membrane, or an altered interstitium markedly increases both fluid and protein transport into the interstitium. The ability of the membrane to maintain an oncotic gradient is decreased, although even with a severe change in permeability some oncotic gradient appears to exist. Of major importance is that even small changes in capillary hydrostatic pressure now produce very large changes in fluid and protein flux into the interstitium, thereby emphasizing, again, the importance of hydrostatic pressure.

Increased Surface Area

Another important determinant in the amount of fluid and protein flux is the vascular surface area available for exchange. An increase in surface area alone would increase the total fluid and protein exchange, but the characteristics of the fluid, in particular, the protein content, would remain constant assuming the Starling forces and permeability characteristics. Since this variable is frequently not totally controlled in experimental studies, the term *permeability surface area product* has been used to quantitate data. The term simply means that measured changes in water are due to permeability changes and/or surface area.

Significance of Lung Edema

The effect of increased water content on lung function depends on the location of the water and the other factors involved in the lung injury state. The distribution of lung water varies considerably at different stages of the lung injury process. Water distribution during edema formation is quite different from that in the resolution phase. This is particularly true with cardiogenic or high pressure edema in which, during edema formation, fluid initially in the alveolar septa not cleared by lymphatics ends up in the loose interstitial space or, if severe, in the alveolus. Impaired gas exchange and shunt fraction will correlate with the degree of alveolar flooding and, to a lesser extent, with the degree of fluid in the loose interstitium, where the main problem will be redistribution of blood flow and $\dot{V}/\dot{Q}$ mismatch. Loose interstitium edema is much slower to resorb due to its sequestration away from the lymphatic opening and, therefore, during the edema resolution phase, excess water will be evident even after impaired gas exchange has been resolved [27].

There is also a difference in distribution based on the type of edema. For example, in increased permeability edema (ARDS), the excess water is distributed more peripherally in the lung from the beginning with less gravitation to the loose interstitium. Impaired gas exchange can, therefore, be more severe relative to the amount of water present [22]. This process may well be the result of a disruption of the integrity of the interstitial matrix, either the gel or the supporting structures, so as to impair water movement from septa to loose interstitium.

The role of water in the lung dysfunction is also dependent on the other processes involved. With high-pressure edema, the major component is excess water during the formation phase, and there is an excellent correlation between impaired oxygenation and water content. In the case of many forms of ARDS, there is a poor correlation between water content and the degree of physiologic shunt [28, 29]. In the case of lung injuries primarily involving the aiways, such as smoke inhalation, water content increases only in extreme cases [27, 30]. In the acute phase of sepsis-induced ARDS, the mediator-induced broncho- and vasoconstrictor components of the injury process appear to play a significant role in the resulting hypoxia and increased work of breathing [31]. There appears to be a much better correlation between the degree of protein flux, i.e., the degree of permeability injury and the physiologic abnormalities.

Measurement of Pulmonary Edema

The concept of measuring lung water clinically assumes that an accurate measurement would be useful for the management of patients with lung dysfunction. In the case of the formation phase of high-pressure edema, this information could be quite useful, but probably less so during the resolution phase due to the perihilar water distribution. In the case of a number of forms of ARDS, the clinical usefulness of a measure of lung water remains in doubt [30, 31]. This information could, however, certainly be useful for clinical research purposes.

Assuming a need for lung water measurement, the criteria for the ideal method has been defined as one that is accurate, sensitive, reproducible, noninvasive, practical, and inexpensive. With regard to accuracy and sensitivity, it is believed that an increase in lung water, if over 30%, is required before a reliable detection of an increase can be made [32]. Also, interpretation of measurements will be affected with some techniques by lung gas volume, pulmonary blood volume, and blood flow distribution.

Although a number of methods are used in research models, there are really only 4 methods that have significant clinical potential. These are chest x-rays, soluble gas technique, double indicator dilution, and computed tomography. The external radioflux method, which detects the ratio of protein flux across the lung, i.e., permeability, is clinically applicable for detecting increased permeability to protein, but is less useful as a measure of water.

Chest X-ray

The chest x-ray remains the reference for comparison of methods of lung water measurement. This method achieves all the necessary criteria except for sensitivity. Also, accuracy is significantly affected by changes in lung volume, since interpretation is visual. In addition, the variability of the quality of bedside films, e.g., in the intensive care unit, remains a problem; however, this simple technique provides information on the distribution of water, which the other more complex methods do not [33, 34]. The distribution pattern can be very useful in making the diagnosis between high-pressure and increased permeability. Characteristics of high-pressure edema include inversion of the pulmonary vascular pattern, bronchovascular cuffs, increased heart size, and pleural effusion. Characteristics of increased permeability include absence of septal (Kerley's) lines, normal pulmonary vascular pattern, frequent air bronchograms, and infrequent perivascular cuffing, usually with normal heart size. Of course, a specific quantitation of the edema cannot be made with x-ray alone, simply a qualitative interpretation of change from normal.

Soluble Gas Method

In this method, the relative lung uptake of a soluble gas, usually acetylene, and an insoluble gas, usually helium, is measured [35]. The tissue volume, which includes capillary volume and any edema, is computed by the disappearance ratio of the soluble gas extrapolated to zero time.

Advantages of the method are that it does not require blood sampling, does not use radioactivity, can be used repeatedly, and, in addition to measuring lung volume, provides an estimate of cardiac output. Limitations include the need for the patient to be able to rebreathe the gas mixture, either on his/her own or through modification of the ventilator, and the requirement for a rapidly responding mass spectrometer or multichannel infrared analyzer (high initial cost and complexity). Also, inhomogeneity of ventilation and alveolar volume, in relation to lung tissue mass, accounts for considerable variability in normals, and is probably a greater source of error in patients with edema. Strict standardization of the rebreathing maneuver is required for reproducibility.

The method has been applied to the detection of pulmonary edema in animals and in humans. Studies in humans showed a wide scatter of normal values (biological variation) as well as considerable variation with lung volume [36]. In patients with clinically detected pulmonary edema, many had values within the normal range. Its clinical usefulness is yet to be determined.

Double Indicator Dilution

The double indicator dilution method for measuring lung water content has been available for more than 25 years without having any significant impact on the clinical measurement of lung water until the recent availability of heat as the diffusible indicator. Theoretical analyses and much experimental work have not completely solved the questions relating to diffusible indicators. There are problems of flow imitation (unperfused regions of lung) and diffusion limitation (large extravascular volumes).

The double thermodilution measurement of lung water content (actually thermal mass) is, however, being used clinically, and the correlation between indicator and postmortem gravimetric measurements of lung water is quite good [37, 38]. There is a tendency for the thermal lung mass to exceed the extravascular water volume. The thermodilution method fulfills several of the criteria for an ideal method. It is relatively inexpensive and portable, does not interfere with other aspects of patient care, can be used repeatedly, gives online data, and is reasonably accurate. A major problem is invasiveness because Swan-Ganz and special arterial catheters are necessary. This limits its use to ICU patients, but in that setting it may add useful information at a low cost.

Exclusion of the microcirculation by, for example, emboli or blood flow redistribution, will also affect the water determination, since the double indicators method depends on perfusion of the lung for determination of the extravascular fluid content [39, 40]. Positive pressure breathing may have unpredictable effects. In animal experiments using different types of acute lung injury, positive end-expiratory pressure (PEEP) may increase, decrease, or not affect the thermal dilution lung water content. Awareness of this variability is important because of the widespread use of PEEP in critical care units [41].

It is not clear whether measurement of lung thermal mass benefits patients because most studies have been made in patients with severe edema that can be readily detected by other procedures. It has been reported that changes in lung thermal mass may be an early sign of sepsis in burn patients, even before the x-ray shows unequivocal changes. This tends to confirm one of the quantitative chest x-ray study results, which was that clinical edema tended to occur before the chest film showed significant change. Results of several studies suggest that the accuracy of the thermal indicator dilution method depends on the type of edema. Clinical usefulness will also depend on the role and distribution of water in the disease being studied.

Computed Tomography

Computed tomography of the lung provides detailed information of volume and density of the lung with a resolution of approximately 1 cm^3. Accuracy of $\pm 2\%$ has been obtained in lung models, but larger errors occur in living animals and in humans [42].

Computed tomography is limited by the expensive, bulky equipment. It is unlikely that this drawback can be overcome so that the method can be used for critically ill patients. It is invasive in the sense that considerable radiation exposure is required, and there is no practical technique to distinguish between vascular congestion and lung water content. These problems may be overcome as experience accumulates.

Animal experiments suggest that computed tomography may have diagnostic value in distinguishing different types of pulmonary edema. Increased pressure edema resulted in greater increases in perihilar lung density, whereas oleic acid-induced acute lung injury caused patchy, lobular-shaped peripheral densities, and alloxan-induced acute lung injury gave a fairly uniform increase of density [42, 43].

External Radioflux Detection

Although the method was designed to measure the rate of tracer protein equilibration between plasma and lung interstitium, it does contain information about interstitial lung water content. In one configuration, the method measures local changes using a portable, focused, scintillation detector [44, 45]. In another configuration, a portable gamma camera is used to obtain a picture of the entire thorax [46–48]. The chest wall contribution to the external radioflux is a potential source of error, more so with lower energy isotopes (iodine) than with the higher energy isotopes (indium). With the focused scintillation detector, repositioning the probe for serial measurements can be a problem. The time to make a measurement is long in normal subjects (up to 1 hour or more), but in patients with suspected acute lung injury, the time decreases to 15 minutes.

The method is moderately invasive because radioactive isotopes must be injected intravascularly, and blood samples are needed for calibration purposes. The equipment is portable and only moderately expensive by current standards. The results are reproducible and ought to be sensitive for measuring

interstitial water content because intracellular water need not be detected, if the proper tracer is chosen.

Aside from the time to accumulate data, there is a significant time involved with computer calculation. Nevertheless, data could be available in time to be used in treating patients, particularly those in the at-risk group.

Recent studies [47, 49] in ARDS patients have indicated that changes in protein fluid precede changes in lung water by up to several days, and the correlation of protein flux with the degree of lung dysfunction is much better than that seen with lung water measurements.

Résumé

Par définition, l'oedème pulmonaire consiste simplement en un excès de liquide au niveau du poumon. La répartition de ce liquide donne sa signification clinique à l'oedème. En ce qui concerne le mécanisme de la formation de l'oedème, la pression hydrostatique microvasculaire reste la force prédominante de Starling. Le tissu interstitiel du parenchyme pulmonaire joue un rôle majeur en déterminant à la fois la quantité d'oedème formé et sa distribution. L'oedème par augmentation de la perméabilité avec une distribution plus périphérique du liquide comme elle est constatée dans le syndrome de détresse respiratoire de l'adulte peut être le résultat de modification de la membrane basale et de la matrice interstitielle plutôt que le résultat de la constitution de nombreux orifices dans la membrane endothéliale. Une fois encore la signification de l'oedème dépend de sa distribution, le liquide interstitiel péri-hilaire étant moins significatif que l'inondation alvéolaire. La valeur de la mesure de l'eau dans le poumon dépend plus de sa localisation que de sa quantité. L'applicabilité clinique des méthodes qui ne permettent pas de préciser la répartition de l'oedème dépend, de ce fait, de la connaissance par le clinicien des différences de distribution de l'oedème en fonction des différents états pathologiques.

Resumen

Por definición el edema pulmonar es simplemente un exceso de líquido en el pulmón. La distribución del líquido determina la significación clínica del edema. En cuanto al mecanismo de formación del edema, la presión hidrostática microvascular sigue siendo la fuerza primaria dentro de la ecuación de Starling. El intersticio pulmonar es el factor determinante principal, tanto del volumen de edema acumulado como de su distribución. El edema por permeabilidad aumentada, con una distribución más periférica del líquido, tal como se presenta en el síndrome de dificultad respiratoria del adulto, parece ser el resultado de cambios en la matrix intersticial y en la membrana basal, más que el simple aumento del número de orificios presentes en membrana endotelial. La significación clínica del edema depende de su distribución, y así el líquido intersticial perihiliar es bastante menos significativo que la inundación alveolar. Por consiguiente la pertinencia de la medición del agua pulmonar se refiere tanto a la ubicación del agua acumulada como a la cantidad absoluta. La aplicación clínica de métodos que no proveen información sobre distribución depende, por lo tanto, de la comprensión por parte del médico de las diferencias de distribución en las diversas condiciones clínicas y, por consiguiente, la importancia del agua en la producción de alteraciones pulmonares.

References

1. Crile, G. W.: An Experimental Research into Surgical Shock. Philadelphia, J.P. Lippincott, 1899
2. Starling, E.: On the absorption of fluids from the connective tissue spaces. J. Physiol. (Lond.) *19*:312, 1896
3. Renkin, E., Watson, P., Sloop, C.: Transport pathways for fluid and large molecules in microvascular endothelium of the dog's paw. Microvasc. Res. *14*:205, 1977
4. Schneeberger, E., Hamelin, M.: Interaction of serum proteins with lung endothelial glycocalyx: Its effect on capillary permeability. Am. J. Physiol. *247*:206, 1984
5. Curry, F.E.: Effect of albumin on the structure of the molecular filter at the capillary wall. Fed. Proc. *44*:2610, 1985
6. Pappenheimer, J., Soto-Rivera, A.: Effective osmotic pressure of the plasma proteins and other quantities associated with the capillary circulation in the hind limbs of cat and dogs. Am. J. Physiol. *152*:471, 1948
7. Hardaway, R.M.: Intensive study and treatment of shock in man. J.A.M.A. *199*:779, 1967
8. Shires, T., Brown, F., Canizarro, P., Sommerville, N.: Distributional changes in extracellular fluid during acute hemorrhagic shock. Surg. Forum *11*:115, 1960
9. Granger, H.G., Dhar, J., Chen, H.I.: Structure and function of the interstitium. In Proceedings of the NIH Workshop On Albumin, J.J. Agours, A. Rene, editors, Washington, D.C., U.S. Goverment Printing Office, 1975
10. Deno, C., Saba, T., Lewis, E.: Kinetics of endogenously labelled plasma fibrinectin: Incorporation into tissues. Am. J. Physiol. *245*:564, 1983
11. Taylor, A.E., Gibson, W.H., Granger, H.F., Guyton, A.C.: The interaction between intracapillary and tissue forces in the overall regulation of interstitial fluid volume. Lymphology. *6*:192, 1973
12. Day, T.D.: The permeability of interstitial connective tissue and the nature of the interfibrillary substance. J. Physiol. *117*:1, 1952
13. Oppenheimer, L., Unruh, H., Skoog, C., Goldberg, H.: Transvascular fluid flux measured from intravascular water concentration changes. J. Appl. Physiol. *54*:64, 1983
14. Comper, W.D., Laurent, T.C.: Physiological function of connective tissue polysaccharides. Physiol. Rev. *58*:255, 1978
15. Parker, J., Falgout, H., Parker, R.: The effect of fluid volume loading on exclusion of interstitial albumin and lymph flow in the dog lung. Circ. Res. *45*:440, 1979
16. Kramer, G.C., Harms, B.A., Gunther, R., Renkin, E., Demling, R.H.: The effects of hypoproteinemia on blood to lymph fluid transport in sheep lung. Circ. Res. *49*:1173, 1981
17. Granger, H., Laine, G., Barnes, G., Lewis, R.: Dynamics and control of transmicrovascular fluid exchange. In Edema, N. Staub, A. Taylor, editors, New York, Raven Press, 1984, pp. 189–228
18. Comper, W.D.: Interstitium. In Edema, N. Staub, A. Taylor, editors, New York, Raven Press, 1984, pp. 229–263
19. Fox, R., Harada, R., Tate, R., Repine, J.: Prevention of thiourea-induced pulmonary edema by hydroxyl radical scavengers. J. Appl. Physiol. *55*:1456, 1983
20. Parker, J., Martin, D., Rutile, G.: Prevention of free radical mediated vascular permeability increase in lung using superoxide dismutase. Chest *83*:525, 1983
21. Fox, R., Fox, W.: Demethylsulfoxide prevents hydroxyl radical mediated depolymerization of hyaluronic acid. Ann. N.Y. Acad. Sci. *411*:14, 1983
22. Ilne, E., Pistolesu, M., Miniati, M., Guitini, C.: The radiologic distinction of cardiogenic and noncardiogenic edema. A.J.R. *144*:1, 1985
23. Unruh, H., Goldberg, N., Oppenheimer, L.: Pulmonary interstitial compartments and tissue resistance to fluid flux. J. Appl. Physiol. *57*:1512, 1984
24. Staub, N.C.: Pathogenesis of pulmonary edema. Am. Rev. Respir. Dis. *109*:358, 1974
25. Bhattacharya, J., Staub, N.C.: Direct measurement of microvas-

cular pressures in the isolated perfused dog lung. Science *210*:327, 1980
26. Kramer, G., Harms, B., Demling, R.H., Renkin, E.: Mechanism of redistribution of plasma protein following acute protein depletion. Am. J. Physiol. *243*:803, 1982
27. Zumsteg, T., Havill, A., Gee, M.: Relationships among lung extravascular fluid compartments with alveolar flooding. J. Appl. Physiol. *53*:267, 1982
28. Brigham, K., Snell, J., Marshall, S., Harris, T.: Indication of dilution of lung water and vascular permeability in humans: Effects of pulmonary vascular pressure. Circ. Res. *44*:523, 1979
29. Staub, N.C., Hogg, J.C.: Conference report of a workshop on the measurement of lung water. Crit. Care Med. *8*:752, 1980
30. Transbaugh, R., Elings, V., Christensen, J., Lewis, F.: Effect of inhalation injury on lung water accumulation. J. Trauma *23*:597, 1983
31. Demling, R.H.: Role of prostaglandins in acute pulmonary microvascular injury. Ann. N.Y. Acad. Sci. *384*:517, 1982
32. Ohkuda, K., Ohnuki, T., Koike, K., Nitta, S., Nakada, T.: Quantitative assessment of water content on human lung: A study on open lung biopsy specimen. Tohuku J. Exp. Med. *138*:299, 1982
33. Milne, E.N.C.: Correlation of physiologic findings with chest roentgenenology. Radiol. Clin. North Am. *11*:17, 1973
34. Pistolesi, M., Guintini, C.: Assessment of extravascular lung water. Radiol. Clin. North Am. *16*:551, 1978
35. Friedman, M., Kaufman, S.H., Wilkings, S.A., Jr.: Analysis of rebreathing measurements of pulmonary tissue voulume in pulmonary edema. J. Appl. Physiol. *48*:66, 1980
36. Overland, E.S., Gupta, R.N., Huchon, G.J., Murray, J.F.: Measurement of pulmonary tissue volume and blood flow in persons with normal and edematous lungs. J. Appl. Physiol. *51*:1375, 1981
37. Lewis, F.R., Elings, V.B., Hill, S.L., Christensen, J.M.: The measurement of extravascular lung water by thermal-green dye indicator dilution. Ann. N.Y. Acad. Sci. *384*:394, 1982
38. Lewis, F.R., Elings, V.B., Sturm, J.A.: Bedside measurement of lung water. J. Surg. Res. *27*:250, 1979
39. Beckett, R.C., Gray, B.A.: Effect of atelectasis and embolization on extravascular thermal volume of the lung. J. Appl. Physiol. *53*:1614, 1982
40. Carlile, P.V., Gray, B.A.: Type of lung injury influences and the thermo-dye estimation of extravascular lung water. J. Appl. Physiol. *57*:680, 1984
41. Lowery, D.D., Carlile, P.V., McCurdy, H.T., Gray, B.A.: Effect of PEEP on the thermodilution measurement of edema in focal and diffuse lung injury. Am. Rev. Respir. Dis. *129*:A94, 1984
42. Hedlund, L.W., Vock, P., Effman, E.L.: Computed tomography of the lung. Radiol. Clin. North Am. *21*:775, 1983
43. Hedlund, L.W., Effman, E.L., Bates, W.M., Beck, J.W., Goulding, P.L., Putnam, C.E.: Pulmonary edema: A CT study of regional changes in lung density following oleic acid injury. J. Comput. Assist. Tomogr. *6*:939, 1982
44. Gorin, A.B., Weidner, W.J., Demlin, R.H., Staub, N.C.: Noninvasive measurement of pulmonary transvascular protein flux in sheep. J. Appl. Physiol. *45*:225, 1978
45. Gorin, A.B., Kohler, J., Denardo, G.: Noninvasive measurement of pulmonary transvascular protein flux in normal man. J. Clin. Invest. *66*:869, 1980
46. Kanazawa, M., Vanschai, S., Hussein, A., Scott, M., Leew, G.D.: Noninvasive measurement of lung water distribution and capillary-permeability in man. Clin. Sci. *61*:2, 1981
47. Sugerman, H.J., Tatum, J.L., Burke, T.S., Strash, A.M., Glauser, F.L.: Gamma scintigraphic analysis of albumin flux in patients with acute respiratory distress syndrome. Surgery *95*:674, 1984
48. Tatum, J.L., Burke, T.S., Sugerman, H.J., Strash, A.M., Hirsch, J.I., Fratkin, M.J.: Computerized scintigraphic technique for the evaluation of adult respiratory distress syndrome: Initial clinical trials. Radiology *143*:237, 1982
49. Sturm, J.A., Wisner, D.H., Oestern, H.-S., Kant, C.J., Tscherne, H., Creutzig, H.: Increased lung capillary permeability after trauma: A prospective clinical study. J. Trauma *26*:409, 1986