The Sequence of Events during Fluid Accumulation in Acute Pulmonary Edema*

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MOST investigations of pulmonary edema have concentrated either on the initiating factors that lead to excess fluid leakage from the pulmonary capillaries or on the gross pathophysiology of the lung and whole animal. There is an intermediate process which is that of fluid movement and accumulation within the various spaces inside the lung. This process has received very little attention perhaps, as Visscher and his associates stated,16) due to the lack of good methods for seeing the edema process with precision.

A few direct and indirect studies of individual components of the process have been made such as the electron microscopic studies of Schulz11) on the thickening of the alveolar septum in edema and the all-or-none filling of individual alveoli deduced from the mechanical behavior of edematous lungs by Cook and co-workers.3)

In our studies we examined the histologic pattern of fluid filling by using rapid freezing of the inflated, living lung: a procedure that fixes the lung very quickly at a given point in time, thus permitting us to "see" the lung as it was in life.14)

METHODS

Our experiments were conducted on anesthetized dogs. We induced acute pulmonary edema by 1) elevation of pulmonary capillary hydrostatic pressure by the intravenous injection of alloxan. During a control and experimental period we made serial physiologic measurements (to be reported in detail elsewhere) after which we opened the thorax under positive pressure ventilation. A water resistance in the expiratory line prevented lung collapse in expiration and we adjusted the tidal volume so as not to exceed the peak transpulmonary pressure of the animal's

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spontaneous breathing. Thr right lower lobe hilum was exposed, cross-clamped at peak inflation, cut and the lobe removed from the chest and immediately frozen by inundating it with liquid propane cooled to \(-180^\circ\text{C}\). We placed the frozen lobe in a cryostat at \(-30^\circ\text{C}\) and cut blocks from the upper, middle and lower zones (relative to the animal’s position during the experiment) and fixed them by freeze-substitution.\(^{15}\) After nitrocellulose embedding we made thick and thin serial sections. We cut other specimens on a sliding microtome in the cryostat and examined them while still frozen.

**Results**

Five control dogs studied in the same manner as the edema dogs did not show excess fluid accumulation in any compartment of the lung. Fig. 1 is from a control lung. Quantitative measurements of total alveolar wall thickness (from one airspace across the alveolar septum to the next airspace) averaged 4.7 μ.

There were 21 dogs with various grades of acute pulmonary edema (9 by increased hydrostatic pressure and 12 by increased capillary permeability). Although the initiating factors were different in the two types of edema, the histologic pattern of fluid accumulation was the same. The first evidence of excessive fluid accumulation was collection of fluid in the connective tissue space around the blood vessels and airways (from about the level of the terminal bronchiole up to the hilum) (Fig. 2). This occurs before there is any alveolar filling.

Alveolar filling begins in scattered alveoli (Fig. 3). Individual alveoli appear to fill independently and are either completely filled by fluid or normal. Intermediate stages (such as half full) are infrequent. We do, however, see slight collections in the alveolar corners at any early stage. The fluid-filled alveoli appear to be at a reduced volume as evidenced by the folding of their

![Fig. 1. Control lung, 10 micra thick, fixed section. Random cuts through alveoli. Alveolar walls are smooth and flat. Inflation pressure approximately 10 cm. H₂O.](image-url)
Fig. 2. Earliest stage of visible fluid accumulation. Enlargement of interstitial connective tissue spaces around the blood vessels and airways from terminal bronchiolar level up to hilum. Some of the fluid is in thin-walled distended lymphatics, but most is free in the tissue space. The linear streaks in the interstitial fluid are due to ice crystal formation during freezing. At this stage alveoli are usually free of fluid and the alveolar walls appear normal.

Fig. 3. Early example of alveolar filling. Ten micra thick, fixed section. A few alveoli in center of field are completely filled with fluid while remainder appear normal. This specimen is from the group with increased capillary permeability edema in whom the edema fluid is free of red cells.

walls: a phenomenon seen only at low lung volume in normal lung.12) At this time (early edema) alveolar wall thickness in air-filled alveoli adjacent to fluid-filled ones averaged 5.5 μ.

Fig. 4 shows a more advanced stage with over half of the alveoli of the region shown filled with fluid, but again the same all-or-none pattern in individual alveoli. Fig. 5 shows a very advanced stage with almost all of the alveoli filled and at reduced volume. Alveolar wall thickness in the few air-filled alveoli remaining averaged 6.5 μ.

There are three additional important findings: 1) trapped air (bubbles) is not found except terminally when airway foaming occurs; 2) no fluid appears in alveolar ducts or larger airways until the alveoli are filled up; and 3) completely collapsed alveoli (atelectasis) are very infrequent.
Fig. 4. Moderate stage edema. Ten micra thick, fixed section. Alveolar walls congested in this example of edema due to increased capillary hydrostatic pressure. About half of the alveoli in this region are filled with fluid which contains some red cells. The edematous alveoli are at reduced volume (folding of their walls). Some of the air-filled alveoli show a small amount of fluid at the corners and have thickened walls. Note the absence of intermediate stages of filling.

Fig. 5. Advanced edema. Fifty-five micra thick, fixed section. All the alveoli in this region are filled with clear fluid (increased permeability edema) and are at decreased volume (folded walls). Atelectasis is very infrequent. Note that the airways (respiratory bronchioles) in upper right and lower left are free of fluid.

DISCUSSION

It is important first of all to recognize the existence of four separate spaces where excess fluid leaking out of the pulmonary capillaries may accumulate. The interstitial connective tissue space, well described by von Hayek, refers to the loose connective tissue space around blood vessels and airways larger than about 0.5 mm. diameter in man (terminal bronchioles, muscular pulmonary arteries and small veins) and in the interlobular connective tissue septa. The alveolar wall space includes both the intercellular and intracellular space outside the lumen of the pulmonary capillaries. Alveolar space is the lumen of the individual alveoli and airway space includes alveolar ducts,
respiratory bronchioles, terminal bronchioles and so on up to the trachea.

The first visible accumulation of excess fluid is in the interstitial space. This implies that there is a gradient of hydrostatic pressure from the site of fluid leakage to this space. Von Hayek, on the basis of anatomic studies, has already proposed a subatmospheric pressure in the space and Permutt and his coworkers\(^9\) have indirect evidence that markedly subatmospheric pressure may exist. Butler and his associates\(^1\) have evidence for a reduced pericapillary pressure in the alveolar walls themselves. An important experiment would be to attempt direct measurements of the interstitial connective tissue pressure and to follow the drainage path of fluid from the site of leakage to the interstitial space. Macklin\(^7\) and Drinker\(^4\) speculated on the movement of fluid along the alveolar septa. Our histologic evidence suggests that the early fluid movement is within the alveolar walls, not over the surface or through the airspaces, since there is no detectable fluid in the alveolar space at the time when the interstitial fluid appears.

The junctions of alveolar walls form a continuous connected path within the alveolar wall structure. It has been suggested that alveolar surface tension generates a reduced hydrostatic pressure at the alveolar corners because of the sharp curvature. We hypothesize that fluid leaking from the alveolar vessels flows into the junctional zones and thence along this natural drainage path into the interstitial connective tissue spaces without entering the alveolar spaces. The drainage of excess fluid from a mass of soap bubbles follows a similar pathway.

As the interstitial space fills to capacity fluid backs up and we begin to see measurable alveolar wall thickening. Our data on total alveolar wall thickness show that this process, so well seen by electron microscopy,\(^11\) is in absolute terms not very marked. The maximum increase in the blood-air pathway is about 1 µ, for each of the two sides of the alveolar wall. Theoretically, this increases the membrane component of the O\(_2\) diffusion pathway,\(^13\) but previous investigators’ work indicates that it is unlikely to significantly affect arterial oxygen saturation.\(^5\),\(^10\),\(^17\)

As the alveolar wall capacity is reached, fluid begins to overflow into the alveolar spaces. The discussion of curvature and surface tension in the preceding paragraphs implies that fluid will be seen first in the corners which is exactly where we do find it. The absence of trapped gas bubbles within alveolar edema fluid is strong evidence for an orderly process of alveolar filling from the bottom up. The lack of intermediate stages of filling is a new observation that supports the view that the main filling process is rapid and quantal in nature, that is, the continuum of whole lung edema consists of the individual all-or-none filling of discrete alveoli, each independently of its
neighbors.\textsuperscript{3)}

Fig. 6 summarizes the sequence of events as we see it. In the presence of fluid leakage in excess of the lymphatic drainage capacity the interstitial connective tissue spaces eventually fill to capacity (Fig. 6B). Fluid then accumulates in the alveolar walls, which, however, have only a small capacity to hold fluid. Fluid overflows into the alveolar corners but, because the filling is from the bottom up, the alveolar interfacial surfactant layer is lifted upward (Fig. 6C). The radius of curvature across the air-liquid interface decreases and by Laplace's equation there will be some critical interfacial tension and curvature at which the existing transpulmonary pressure will no longer be able to hold the alveolus at a stable configuration. The alveolus then changes rapidly to a new lower volume with a new interfacial curvature and tension.

Fig. 6. Schematic representation of sequence of events as the lung fills with edema fluid. A) Normal alveolar walls and no excess fluid in interstitial connective tissue spaces. B) Earliest stage. Leaking fluid flows first into the interstitial connective tissue space. The alveoli are fluid-free and the alveolar walls appear normal by light microscopy. C) Tissue spaces filled to capacity. Alveolar wall thickening becomes measurable and fluid begins to overflow into the alveolar space, notably at the corners where curvature is greatest. D) Quantal filling. Individual alveoli reach critical configuration at which existing inflation pressure can no longer maintain stability. Alveolar gas volume rapidly passes to a new much lower level (see inset graph). The volume deficit is absorbed by additional fluid filling or alveolar collapse depending on associated conditions such as alveolar surface tension and availability of fluid.
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(Fig. 6D). The actual final total volume (air and fluid) of an alveolus compared to its normal air volume at a given transpulmonary pressure will depend on the interfacial tension at the critical configuration and rapidity with which fluid in the alveolar wall, capillaries and adjacent alveoli can flow into the collapsing alveolar space. This picture of alveolar filling leads to another important question. Is the normal surface tension in an alveolus altered during edema formation? Unfortunately, the high surface tension reported in pulmonary edema fluid is not useful evidence. What we need is the actual interfacial tension in the individual alveoli. If the value is 10–20 dynes/cm. as Clements\(^2\) and Pattle\(^8\) believe, then quantal filling could occur without any significant change in that tension.

CONCLUSION

A sequence of events in the process of fluid accumulation in acute pulmonary edema have been presented. It is a working hypothesis that appears to account for the available data. It is a useful hypothesis in that it permits us to identify questions that need to be answered in future study. Two of the important questions are: What is the interstitial connective tissue pressure? What is the surface tension in individual alveoli, both normal and edematous?

REFERENCES