Pulmonary Edema and Elevated Left Atrial Pressure: Four Hours and Beyond

R. E. Drake and M. F. Doursout

Department of Anesthesiology, University of Texas Medical School at Houston, Houston, Texas 77030

Cardiogenic pulmonary edema is caused by the increase in left atrial pressure when the left heart fails. The increased pressure causes rapid fluid accumulation within the lung interstitial spaces. However, over the following days to weeks, additional fluid may accumulate due to the deposition of excess lung connective tissue.

Pulmonary edema is one of the most serious consequences of left ventricular cardiac failure. When the left ventricle fails or when the mitral valve fails, left atrial pressure (LAP) may increase substantially. The resulting increase in pulmonary capillary pressure (Pc) forces excess fluid filtration through the pulmonary capillary walls and into the lung tissue. At first, the fluid collects within the lung interstitial space. If LAP exceeds a critical level of ~25 mmHg, the volume of edema fluid will overwhelm the capacity of the interstitial spaces and fluid will flood the airways and alveoli (8). This airway edema directly interferes with gas exchange, and it can kill the patient. However, many people live for months or years with modestly elevated LAP (<25 mmHg). We believe that sustained, subcritical LAP elevations lead to two phases of change in the lungs. The first phase is the acute edema that develops in the first few hours of elevated LAP. The second phase concerns the effect of long-term (7 days or more) increases in LAP below the critical level. This review deals with the acute phase and long-term phase changes in the lung caused by modestly elevated LAP.

The acute phase of pulmonary edema has been the subject of intense investigation for many years. In 1896, Starling (7) laid the foundation for our current understanding of pulmonary edema with his famous fluid filtration equation. The equation relates the rate of fluid filtration through the capillary wall ($J_v$) to the pressures across the capillary wall and to the filtration characteristics of the capillary membrane. The current form of the equation is

$$J_v = K_f \left[ \frac{P_c - P_if - \sigma(P_c - P_if)}{G_{10}} \right]$$

where $P_c$ and $P_if$ are the pulmonary capillary and interstitial fluid hydrostatic pressures, respectively, $Pc$ and $P_if$ are the plasma and interstitial fluid colloid osmotic pressures, respectively, $K_f$ is the membrane fluid filtration coefficient, and $\sigma$ is the membrane reflection coefficient to protein. Normally there is an imbalance in the pressures across the pulmonary capillary membrane, and fluid slowly filters from the pulmonary capillaries into the lung tissue (3). This fluid flows through the tissue space and into nearby lymphatic vessels. The lymphatic vessels drain the fluid to veins within the neck.

Investigators have performed hundreds of studies on the changes in the factors in the Starling equation and on lymph flow in response to increased $P_c$. The results of these studies have lead to the concept illustrated in Fig. 1. The solid line that figure represents capillary filtration rate, and the dashed line represents lymph flow. The two lines are superimposed on the left of the figure because, in steady-state conditions, lymphatic vessels remove fluid from the lung at the same rate that fluid filters from the capillaries. As soon as $P_c$ is increased, filtration rate increases to a peak. Then, as fluid collects within the lung tissue, $P_if$ increases and $\Pi_if$ decreases. These changes act to decrease filtration, and they account for the slow decrease in filtration rate indicated by the solid line in Fig. 1. As shown by the dotted line in the figure, lymph flow increases slowly after the increase in $P_c$. Because filtration rate increases rapidly and lymph flow is much slower to increase, filtration rate exceeds lymph flow and fluid accumulates within the lung at a rate equal to the difference in filtration rate minus lymph flow rate. However, filtration rate slowly decreases and lymph flow slowly increases until the two rates eventually match each other. Thus a new steady-state fluid balance is attained after several hours of elevated $P_c$. However, the lung fluid volume is increased by the amount of fluid that collects during the time in which filtration rate exceeds lymph flow.

The time course of the changes in Fig. 1 is important. Investigators have consistently reported that changes in lymph flow filtration rate, lung weight, $P_if$, and $\Pi_if$ are completed within the first 4 h of elevated $P_c$. Thus it appears that the acute phase of edema fluid accumulation is completed within the first 4 h of elevated $P_c$.

**Holding capacity of the lung interstitial matrix**

Small increases in lung fluid usually do not directly interfere with gas exchange because the fluid remains within the lung interstitial space (8). Generally, the lung interstitial space can hold ~30 ml of excess fluid per 100 g of wet lung tissue (8, 11). The mechanism by which the fluid is held within the interstitial space is unknown. However, this characteristic of the lung tissue is probably due, in part, to the ability of the lung connective matrix to absorb fluid (11). This absorptive property of the matrix is mainly due to glycosaminoglycan molecules, which can imbibe far more than their weight in fluid (1, 5). Bhattacharya et al. (1) showed that rabbit lung extravascular fluid volume was significantly correlated with lung
patients with heart disease. Activated LAP may cause increased lung connective tissue in patients with chronic heart disease (10). The mechanism of the fibrosis in patients with chronic heart disease is complicated by factors that may influence the production of connective tissue. For example, some investigators believe that activation of the renin-angiotensin-aldosterone system may lead to fibrosis in patients with chronic heart failure. Also, the drugs used to treat heart failure may cause pulmonary fibrosis. Thus other factors besides elevated LAP may cause increased lung connective tissue in patients with heart disease.

The lungs of patients with chronically elevated LAP

Any heart disease that leads to increased LAP will cause some degree of pulmonary edema. In addition, increased lung connective tissue (pulmonary fibrosis) is common in patients with chronic heart disease (10). The mechanism of the fibrosis would be difficult to investigate in patients, because most chronic heart disease is complicated by factors that may influence the production of connective tissue. For example, some investigators believe that activation of the renin-angiotensin-aldosterone system may lead to fibrosis in patients with chronic heart failure. Also, the drugs used to treat heart failure may cause pulmonary fibrosis. Thus other factors besides elevated LAP may cause increased lung connective tissue in patients with heart disease.

Of the various forms of left heart failure, mitral valve failure probably most closely approximates pure LAP elevation. Investigators first reported pulmonary fibrosis in patients with mitral valve stenosis in the 1930s. Between 1936 and 1970, many investigators used histological evidence to document the fibrosis in patients. In 1936, Parker and Weiss (6) were among the first investigators to document the fibrosis. Their study included 10 adult patients with mitral valve stenosis resulting from childhood rheumatic heart disease. All of the patients showed signs of pulmonary congestion, and they had frequent episodes of respiratory distress. Parker and Weiss found histological evidence of increased collagen and edema fluid within the alveolar walls. In the lungs of some of the subjects, Parker and Weiss (1) were surprised to find “no appreciable amount of edema in the airways,” but they found a considerable amount of edema fluid within the lung tissue.

Some investigators have speculated that the increased lung connective tissue in patients with chronic heart disease may be a typical response to the persistence of edema fluid in almost any organ (2, 13).

Possible mechanism for the lung changes with chronically elevated LAP: the persistent edema hypothesis of pulmonary fibrosis

Recently discovered evidence concerning the interaction between cells and the surrounding extracellular matrix suggests a mechanism by which edema may lead to pulmonary fibrosis. Fibroblasts secrete several enzymes that degrade established matrix, and they constantly produce new matrix molecules. Studies with cultured fibroblasts show that the balance between synthesis and degradation is tightly regulated (4). This regulation is mediated via direct cellular contact with surrounding matrix molecules. Integrin receptors that bind specific sites on components of the extracellular matrix appear to be key in transmitting information about the extracellular environment into the cytoplasm. When fibroblasts are grown in collagen gels, synthesis of collagenase is upregulated and collagen synthesis is suppressed. On the other hand, collagen synthesis is upregulated and collagenase synthesis is downregulated in fibroblasts that are not in contact with collagen (4). Synthesis and degradation of other components of the extracellular matrix such as glycosaminoglycans seem to be regulated in the same way as collagen (12).

Cellular contact with the extracellular matrix may also regulate synthesis of cytokines that influence production of extracellular matrix. For example, transforming growth factor-β (TGF-β) synthesis is upregulated in mammary epithelial cells grown on plastic, but it is downregulated in cells grown on basement membrane matrix (9). This is important because investigators have shown that TGF-β can cause cellular proliferation and can induce cells to produce extracellular matrix. Thus Streuli et al. (9) have proposed that TGF-β plays an important role in a feedback mechanism to regulate the amount of extracellular matrix in a tissue.

We speculate that the following mechanism may lead to excess lung fluid in animals or patients with chronically ele-
vated LAP. Normally, fibroblasts within the lung interstitium are in contact with the surrounding connective tissue fibers. Fibroblast production of connective tissue and of enzymes that degrade connective tissue is modulated via this fibroblast-to-connective tissue contact. Thus in the normal lung (Fig. 2, left) the synthesis and degradation of connective tissue are balanced. When LAP is increased, a small amount of edema fluid accumulates in the first 4 h of elevated pressure. This fluid is held within the interstitial space by the normal absorptive capacity of the interstitial connective tissue. However, as the connective tissue gel swells with the excess fluid, the tissue fibers are forced apart. Consequently, cells located within the tissue must lose contact with some of the surrounding connective tissue fibers (Fig. 2, middle).

If the recent findings on cultured cells can be extrapolated to cells within lung tissue, then lung cells respond to the change in their local environment by proliferating and producing additional connective tissue (Fig. 2, right). As this new connective tissue is deposited within the interstitial space, it must absorb some of the excess fluid and thereby reduce Pif. The decreased Pif probably tilts the balance of pressures across the capillary membrane (the Starling pressures) in favor of increased filtration. As a result, more fluid should accumulate within the lung tissue. If this mechanism is correct, there are two phases of edema fluid accumulation in response to elevated LAP. The first phase is the fluid that accumulates within the first 4 h. The second phase is the fluid that accumulates as a result of the increase in connective tissue.

Because lung connective tissue (particularly glycosaminoglycans) is very effective in absorbing fluid, large amounts of edema fluid could accumulate during the second phase of edema formation. However, the fluid should not flood the alveoli because the fluid would be held within the interstitial matrix. If the fluid is prevented from entering the alveoli, it probably has little direct effect on gas exchange within the lung (8). On the other hand, the fluid and increased connective tissue would probably affect the mechanical properties of the lung.

Nettelbladt et al. (5) found a significant increase in lung hyaluronan and increased lung fluid within 24 h after they administered bleomycin to rats. Thus the lung is capable of rapid production of glycosaminoglycan. We believe that increased lung connective tissue and phase two edema could reach significant levels within the first few days of elevated LAP.

Evidence for lung changes during prolonged LAP elevation in animals.

Owing to the lack of studies in which investigators have elevated LAP for >24 h, there is not much evidence on increased connective tissue or phase two edema in animals with chronically elevated LAP. However, a study by Erdmann and his associates (3) did address this issue in two sheep. Those investigators placed balloons into the left atria of these sheep and, after the sheep recovered from the surgery for several days, they inflated the balloons to increase LAP. Most of their study was focused on the changes in lung fluid and lymph flow that occurred over the first 4 h of elevated LAP. They observed that lymph flow plateaued within the first 4 h of elevated LAP. To test if lung fluid was steady after 4 h, they maintained LAP elevated for 14 days.
vated for 14 days in two sheep. After 14 days, they determined the lung extravascular fluid volume and lung tissue dry weight for each sheep. They compared the ratio of extravascular fluid-to-dry tissue weight for those sheep to the ratios for sheep in which they had elevated LAP for only 4 h. The extravascular fluid dry weight ratios after 2 wk of elevated LAP were almost exactly the same as the ratios for the sheep with acute LAP elevation.

At face value, the Erdmann et al. (3) data seem to contradict the persistent edema hypothesis because they seem to show that lung fluid is no higher after 2 wk of elevated LAP compared with 4 h of elevated LAP. However, according to the persistent edema hypothesis, dry lung tissue weight should be increased due to the increase in connective tissue within the lung after a prolonged period of elevated LAP. Dry tissue weight may also be increased due to an increase in the lung cell population. With the persistent edema hypothesis, lung fluid should be increased because of the increase in connective tissue. As such, lung extravascular fluid volume would be increased in proportion to the increase in connective tissue. Because both lung dry tissue weight and lung extravascular fluid would be increased, the extravascular fluid-to-dry tissue weight ratio might remain almost unchanged during a prolonged period of elevated LAP.

In Fig. 3, we plotted lung extravascular fluid and lung dry weight data from Erdmann et al. (3). As shown in the figure, lung dry weight and extravascular fluid were each ~75% higher after 14 days vs. 4 h of elevated LAP. Thus the Erdmann et al. (3) data seem to support rather than contradict the hypothesis that lung extravascular fluid is increased in association with an increase in lung connective tissue during prolonged increases in LAP. If the analysis in Fig. 3 is correct, a large amount of edema fluid accumulated in the Erdmann et al. sheep long after the first 4 h of elevated LAP.

This work was supported by Grant HL-64941 from the National Heart, Lung, and Blood Institute.

References