TIME LAG BETWEEN PULMONARY CONGESTION AND PULMONARY EDEMA IN DOGS

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The time course of pulmonary congestion and pulmonary edema was examined using a gravimetric method in 19 open-chest anesthetized dogs. Balloon catheters in the left atrium (LA) were inflated to elevate LA pressure more than 25 mmHg. The dogs were divided into 4 groups (G) according to the duration of the elevated LA pressure: G.1 (n = 6) as control; G.2 (n = 4) for 15 minutes; G.3 (n = 4) for 30 minutes; and G.4 (n = 5) for 60 minutes. Although no significant increase of extravascular lung water content (an indicator of pulmonary edema) was observed in G.2 (4.97 ± 0.85 g/kg) and G.3 (4.46 ± 0.96) compared with G.1 (4.02 ± 0.88), a significant increase was observed in G.4 (6.81 ± 1.21 , $p < 0.05$). Residual pulmonary blood content (an indicator of pulmonary congestion) was significantly increased in G.2, 3 and 4 compared with G.1. By light and electron microscopes, pulmonary congestion was revealed in G.2, whereas interstitial pulmonary edema was demonstrated only in G.4.

Thus, it was concluded that pulmonary congestion occurred within 15 minutes, but pulmonary edema occurred 30 to 60 minutes after left atrial pressure was elevated more than 25 mmHg. This time lag may be an important factor in explaining the discrepancy between the elevated left atrial pressure and the clinical manifestation of pulmonary edema.

It is well known that cardiogenic pulmonary edema develops when the left atrial pressure (LAP) rises above 25 mmHg.¹ But it is occasionally observed that the elevated LAP does not always result in the clinical manifestation of pulmonary edema. For instance, even when the mean pulmonary arterial wedge pressure (nearly equal to LAP) rises more than 25 mmHg during exercise in patients with valvular heart disease² or ischemic heart disease,³ symptoms and signs of pulmonary edema are not infrequently absent.

The reason for this discrepancy still remains unclear.

Pulmonary edema, as defined by Visscher and colleagues,⁴ is a pathological state in which there is abnormal extravascular water storage in the lung. This definition is commonly used by both physicians and pathologists. On the other hand, the term of pulmonary congestion, which has characteristics of dyspnea on effort, orthopnea and pulmonary rales, is widely used clinically,⁵ but there is difficulty in making a pathological definition. In the present study we have selected the pathological definition of pulmonary congestion as being pulmonary vascular engorgement,⁶ i.e., an increased volume of blood within dilated vessels in the lung.⁷

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According to these definitions, the acute elevation of LAP leads to the elevation of pulmonary venous pressure, which results in pulmonary congestion (pulmonary venous engorgement) with subsequent development of pulmonary edema (excess of extravascular lung water).⁶ The sequence of liquid accumulation in the lung during pulmonary edema has thoroughly been investigated using light microscopy by Staub et al.⁸ However, little information is available either concerning the time course of the accumulation of extravascular lung water after the abrupt increase in LAP or about the pathological sequence between pulmonary congestion and pulmonary edema,⁹ especially its very early stages.

According to our experiences, it was assumed that the discrepancy between the elevated LAP and the clinical manifestation of pulmonary edema mentioned above is possibly due to the time lag between pulmonary congestion and pulmonary edema or between elevated LAP and the increase of extravascular lung water. The present study was attempted to confirm this hypothesis using direct quantitative measures of extravascular lung water content and pulmonary blood content using a modified Pearce's method¹⁰⁻¹² and pathological examination by light and electron microscopes. Subjects were dogs with left atrial hypertension produced by balloon inflation.

MATERIALS AND METHODS

1. Animal preparation

Observations were made on 19 mongrel dogs of both sexes weighing 11.9 ± 3.0 kg (mean $\pm$ SD, range 7.5 – 19.5). Each animal was anesthetized with pentobarbital sodium (25 mg/kg iv) and the supplemental anesthetic was given, as required, during the experiment. The animals were ventilated with room air through a cuffed endotracheal tube using a Harvard Respirator at a constant volume (15 ml/kg) and at a rate of 12 to 14 cycles/min which maintained $Paco_2$ in about 35 mmHg.

To measure pulmonary arterial pressure (PAP) and cardiac output (CO), an 8-F balloon-tipped thermo-dilution catheter was inserted through the right internal jugular vein into the pulmonary artery. A polyethylene catheter was placed in the abdominal aorta through a femoral artery to measure arterial pressure and arterial blood gas. After the chest was opened by median sterno-

tomy, a polyethylene catheter was placed into the left atrium through the atrial appendage to measure left atrial pressure (LAP). A balloon catheter (Foley catheter) was positioned in front of the mitral valve and distal (downstream) to the left atrial catheter.

Pressures (aortic, left atrial and pulmonary arterial) were measured through the fluid-filled catheters using transducers. All hemodynamic parameters were recorded using a direct writing recorder. CO was measured by the thermodilution method (5 ml of iced saline solution injected into the right atrium) and triplicate measurements were taken and averaged.

2. Study protocol

After control data (PAP, LAP, CO) were obtained from each animal, the left atrial balloon was inflated with water to elevate the mean LAP higher than 25 mmHg. Data were then collected again 5 minutes after a steady state had been reached. LAP was held constant by increasing or decreasing the amount of water in the left atrial balloon catheter.

The 19 dogs were divided into four groups. Group 1 (6 dogs) served as sham controls without elevation of LAP and the remaining others underwent inflation of the left atrial balloon to elevate LAP. According to the duration of the elevated LAP, the 13 dogs were divided into Group 2 ($n = 4$), Group 3 ($n = 4$) and Group 4 ($n = 5$) with 15-, 30-, and 60-minute durations, respectively.

3. Measurement of extravascular lung water

The extravascular lung water content (Qwl) and the residual pulmonary blood content (Qb) were determined using the modified direct method of Pearce.¹⁰⁻¹² The procedure was as follows.

At the end of each experiment, the dogs were injected with KCL into the left atrium. Immediately after the animals were dead, both pulmonary hili were clamped and the lungs were removed. The blood was not allowed to drain from the lobal vessels because the pulmonary blood volume was to be measured precisely. Approximately 2–4 cm of bronchi were removed and the lungs were weighed. A few small cubes were then obtained from both upper and lower lobes of the bilateral lungs for pathological examination. Water was added to the rest of the lungs for homogenization and the resultant lung homogenate was weighed. Hemoglobin determinations were made on the dog blood and the

TABLE I HEMODYNAMIC DATA BEFORE AND AFTER INFLATION OF THE LEFT ATRIAL BALLOON

		Group 1	Group 2	Group 3	Group 4
LAP (mmHg)	before	6.6 ± 4.2	8.9 ± 3.7	9.4 ± 4.0	11.3 ± 2.8
	after		35.1 ± 4.7*	31.0 ± 4.5*	31.6 ± 6.5*
PAP (mmHg)	before	18.9 ± 2.3	17.5 ± 2.8	21.9 ± 4.0	20.0 ± 2.6
	after		39.6 ± 9.4**	36.6 ± 2.6**	39.6 ± 6.3**
CO (L/min)	before	1.71 ± 0.32	1.73 ± 0.69	1.68 ± 0.77	1.53 ± 0.24
	after		0.67 ± 0.17***	1.17 ± 0.53***	0.78 ± 0.15***

Values represent mean ± SD.

Abbreviations: LAP = mean left atrial pressure; PAP = mean pulmonary arterial pressure;

CO = cardiac output

Before vs after: * $p < 0.01$; ** $p < 0.02$; *** $p < 0.05$

TABLE II QUANTITATIVE DATA OF DIRECT METHOD

	Group 1	Group 2	Group 3	Group 4
Qlb (g/kg)	8.93 ± 1.51	12.80 ± 1.22 ⁺	11.30 ± 1.01*	14.70 ± 1.29 ^{++☆☆}
Qb (g/kg)	3.76 ± 0.84	6.60 ± 0.56 ⁺⁺	5.70 ± 1.51**	6.61 ± 1.65 ⁺
Qwl (g/kg)	4.02 ± 0.88	4.97 ± 0.85	4.46 ± 0.96	6.81 ± 1.21 ^{++☆☆}
dQl (g/kg)	1.16 ± 0.10	1.23 ± 0.18	1.15 ± 0.33	1.28 ± 0.17

All values are mean ± SD and expressed as a function of total body weight.

Abbreviations: Qlb = weight of wet lung; Qb = residual pulmonary blood content; Qwl = extravascular lung water content; dQl = bloodless dry weight of the lung

Group 1 vs Group 2, 3 or 4: * $p < 0.01$; ** $p < 0.02$; + $p < 0.005$; ++ $p < 0.001$

Group 2 vs Group 4: ☆ $p < 0.05$

Group 3 vs Group 4: ☆☆ $p < 0.02$; ☆☆☆ $p < 0.005$

centrifuged homogenate supernant using a CO oximeter (IL 282). The water content of both the homogenate and the blood were determined by drying the samples to a constant weight in an 80°C oven. Qwl, Qb and the bloodless dry weight of the lung (dQl) was calculated using the equation of Noble¹⁰ and Selinger¹²

Qwl, Qb and dQl were expressed as a function of total body weight (g/kg). We evaluated Qwl as the indicator of pulmonary edema and Qb as that of pulmonary congestion.

4. Histological examination

From apical and diaphragmatic lobes of both lungs, 3 × 3 × 3 cm cubes were excised for examination by light microscope. They were placed in 10% formalin solution for 72 hours. The samples for light microscopy were dehydrated in ethanol, cleared in xylene, embedded in paraffin, and stained with hematoxylin and eosin.

Samples for transmission electron microscopy (1 × 1 × 1 mm cube) were removed from the same sites as those taken for light microscopy. They were fixed in 2% glutaraldehyde in 0.15M cacodylate buffer, pH 7.4, for 30 minutes in a vacuum and then placed in the same solution for an additional 24 hours at 4°C. The materials were postfixed in 1.0% OsO₄ for 1 hour, dehydrated in ascending concentrations of ethanol and propylene oxide, and were then embedded in Epon 812. Thin sections were doubly stained with uranyl acetate and lead citrate and viewed using a JOEL JEM 1200 EX electron microscope at an accelerating voltage of 80 kV.

5. Statistics

All results are expressed as mean ± SD. Differences in mean values were analyzed by the paired or unpaired t-test as appropriate. P value < 0.05 was considered significant.

Fig.1. Light micrographs.

- 1-1 Lung, Group 1 (control). Br = bronchiole, PV = pulmonary blood vessel, AS = alveolar space (H & E, $\times 100$)
- 1-2 Lung, Group 2 (15 minutes after elevation of the left atrial pressure). Note packed red blood cells in the pulmonary capillaries (H & E, $\times 150$).
- 1-3 Lung, Group 3 (30 minutes). Perivascular lymphatic (Ly) was dilated and perivascular area was loose, adding to the findings of pulmonary congestion (H & E, $\times 150$).
- 1-4 Lung, Group 4 (60 minutes). Note the dilatation of the lymphatic (Ly) and interstitial edema in the peri-bronchovascular area (H & E, $\times 80$)

Fig.2. Electron micrographs.

- 2-1 Lung, Group 1. Int = interstitium, Cap = capillary, AS = alveolar space (x6000)
- 2-2 Lung, Group 2. Alveolar septum was intact, except for an increased number of the pinocytotic vesicles in the endothelium (End) of capillary (x12000)
- 2-3 Lung, Group 3. Note the vesicles (V) in the thick portion of alveolar septum and intact capillary except for the packed red blood cells (x5000).
- 2-4 Lung, Group 4. Edematous change was found in the subepithelium of the alveolar duct and bronchiole. AS = alveolar space, Br = bronchiole, SMC = smooth muscle cell (x3000)

RESULTS

1. Hemodynamic results

The hemodynamic results for each group are given in Table I. There were no significant differences among the four groups with respect to mean left atrial pressure (LAP), mean pulmonary arterial pressure (PAP) and cardiac output (CO) at the start of each experiment. After inflation of the left atrial balloon, there was a significant increase in LAP ($p < 0.01$) and PAP ($p < 0.02$), and a significant decrease in CO ($p < 0.05$) from the base-line values in each of Groups 2, 3 and 4. However, there were no significant differences in these parameters among these three groups when the left atrial balloon was inflated.

2. Quantitative data of direct method

The quantitative results of direct method in each group are displayed in Table II. According to the equation of Selinger,¹² the weight of the wet lung (Qlb) consists of three components: extravascular lung water content (Qwl), residual pulmonary blood content (Qb), and the blood-less dry weight of the lung (dQl).

After inflation of the left atrial balloon, Qlb significantly increased in Groups 2, 3 and 4 in comparison to the Group 1 value ($p < 0.005$, $p < 0.01$ and $p < 0.001$, respectively). Qb also significantly increased in Groups 2, 3 and 4 compared to the Group 1 value ($p < 0.001$, $p < 0.002$ and $p < 0.005$, respectively), suggesting that pulmonary congestion occurred within 15 minutes. However, there was no significant difference in Qb among Groups 2, 3 and 4.

On the other hand, no significant increase of Qwl was observed in Groups 2 and 3 compared with Group 1, while a significant increase was observed in Group 4 ($p < 0.05$), suggesting that pulmonary edema occurred 30 to 60 minutes after inflation. Qwl in Group 4 also increased significantly compared with Group 2 ($p < 0.05$) and Group 3 ($p < 0.02$). There was no significant difference in dQl among four groups (Table II).

3. Pathological analysis

Macroscopically, the control lungs were orange-pink in color. Little blood flow from vessels when they were cut, but neither fluid nor foam was found in the airways. In contrast with the control, the lungs with high LAP were dark red-purple, heavy, firm and plethoric. Even in group 4, there was some foam in the large air-

ways. On slicing the lung, considerably more blood flowed from the vessels in Groups 2, 3 and 4 than in Group 1. Although pinky foam could not be expressed from the smaller airways in Group 2, it could be in Group 3 and it spontaneously flowed out in Group 4.

In light microscopy, the alveoli and alveolar ducts were well inflated and the airways clear in the control lung (Group 1). There was no evidence of excess fluid in the perivascular and peribronchial connective tissue spaces and no alveolar fluid was present. The alveolar walls were smooth and flat (Fig. 1-1). The Group 2 lung with 15 minutes duration of LAP elevation exhibited distended veins and capillaries with red blood cells; however there was no finding of interstitial edema or alveolar edema (Fig. 1-2). The Group 3 lung (30 minutes) showed that, in addition to the finding of pulmonary congestion, the perivascular connective tissue was loose and perivascular lymphatics were dilated (Fig. 1-3). In Group 4 (60 minutes), interstitial edema was evident around bronchioles and small vessels of the lung. Dilated lymphatics and pulmonary congestion were also observed (Fig. 1-4).

By electron microscopy of the control lung, the pulmonary capillaries were seen to be incorporated eccentrically into the alveolar septum. This created two distinct aspects to the alveolar-capillary interface — a thin portion and thick portion. There were some pinocytotic vesicles in the capillary endothelial cells (Fig. 2-1). In Group 2, lungs had intact alveolar septum except for an increased number of the pinocytotic vesicles in the capillary endothelial cells (Fig. 2-2). Lungs in Group 3 showed that the larger vesicles were present in the thick portion of the alveolar septum; however, the thin portion and the endothelial cells were intact, resembling the very early stage of interstitial pulmonary edema (Fig. 2-3). In Group 4, an edematous change in the subepithelial space of the alveolar ducts and bronchioles was observed (Fig. 2-4).

Both light and electron microscopic findings indicated no remarkable difference either between the right and left lungs or between the upper and lower lobes.

DISCUSSION

We have demonstrated in the present study that, in dogs, pulmonary congestion occurred within 15 minutes, but interstitial pulmonary edema occurred 30 to 60 minutes after left atrial

pressure (LAP) was elevated more than 25 mmHg. Although it was difficult to differentiate clearly between pulmonary congestion and pulmonary edema, we define the former as a state with increased volume of blood within dilated pulmonary vessels, that reflects an increase in pulmonary blood content (Qb). The latter is defined as a state with abnormal extravascular water storage in the lung, that reflects an increase in extravascular lung water content (Qwl).

A significant increase of Qb compared with the control group was observed in the 15-minute group (Group 2) as well as the 30-minute and 60-minute groups. In contrast, a significant increase of Qwl was observed in the 60-minute group (Group 4), and not in the 15- or 30-minute (Group 3) groups (Table II).

Levine and his associates⁶ have previously differentiated pulmonary congestion with edema from pulmonary congestion alone. They obtained measurements of pulmonary blood volume (PBV) and pulmonary extravascular water volume (PEV) in dogs, using the double indicator dilution technique (Evans blue dye and tritiated water). Conclusions were that, in the presence of pulmonary congestion alone, the PBV was increased but PEV remained normal, and when pulmonary edema supervened PEV increased significantly, while PBV showed no further change from the values determined during pulmonary congestion.

Levine et al.¹³ have also demonstrated that, in dogs with left atrial hypertension created by means of a left atrial balloon and volume overload, the rate of accumulation of lung water determined by the same method was non-linear with respect to time. Water accumulated in the lungs slowly during the first half hour and more rapidly during the second half hour. These findings were generally consistent with ours.

Using the double indicator techniques (thermal – green dye), Slutsky and Higgins⁹ have recently shown that, when left atrial hypertension was produced by left atrial balloon in dogs, pulmonary blood volume (PBV) initially increased while extravascular lung water (EVLW) increased slowly at first, and then more rapidly as time progressed. A significant absolute change in EVLW was found during 30–60 minutes, while PBV increased immediately after LAP elevation. In spite of different quantitative methods, the consistent result occurred in both our and their studies, i.e., that the time lag was present between the increases in PBV and EVLW. However, there

is only a difference that PBV gradually decreased in their study. The reason for it is unclear.

Normally, the fluid transferred from capillary to interstitial space moves along the alveolar septum into the perivascular connective tissue and flows into the lymphatic channels. When LAP elevates, it is considered that the normal process of fluid movement is merely accentuated.⁵ When LAP abruptly increases more than 25 mmHg, an imbalance of Starling forces is induced and liquid should instantly move out of the capillary into the interstitial space. Since the alveolar wall interstitium is continuous with the wider and more compliant space surrounding terminal bronchioles, small arteries and small veins, the liquid is accumulated in the latter space, where lymphatics first appear.¹⁵ Thus, liquid accumulation in the lung is determined by the net flux between the vascular and interstitial spaces (which is determined by the classic Starling equation) and the rate of lymphatic drainage.¹⁴ In this sense, the lymphatics play a key role in removing liquid from the interstitial space of the lung.

Therefore, there are two possible mechanisms that are responsible for the time lag between pulmonary congestion and pulmonary edema, or the discrepancy between the elevated LAP and the increase of extravascular lung water. They are (1) lymphatic drainage from the lung and (2) the capacity of the interstitial space, which is composed of the alveolar wall interstitium and the loose connective tissue (interlobular septa, perivascular and peribronchial). Both are important early protective mechanisms which prevent alveolar flooding, i.e., pulmonary edema, accommodating excessive extravascular lung water and maintaining normal gas exchange. Lymphatics have enormous reserves as lymph flow can increase 20 times the normal value¹⁶ and can also dilate with increasing interstitial fluid. Loose connective tissue around bronchi and vessels can also hold large volumes of excessive free interstitial fluid and accommodate them to protect the alveolar epithelium from disruption and subsequent alveolar edema.¹⁷ In addition, the expansible thick portion of the alveolar wall septum and an increased washout of interstitial protein due to augmented lymph flow also play important roles in preventing alveolar flooding.

Thus, even if a lot of fluid enters into the interstitial space from capillaries because of the acute increase of LAP, pulmonary edema,

especially alveolar edema, does not immediately occur — owing to the various protective mechanisms mentioned above. Then, a time lag exists between the elevated LAP and the increase of extravascular lung water, i.e., pulmonary edema.

Although we did not measure the lymph flow in the present study, Parker et al.¹⁸ have described that, in sheep with chronic lymph fistula, it took at least 1 hour for lymph flow to be stabilized during progressive elevation of LAP thus suggesting the capacity and reserve of the lymphatic drainage.

Our explanation of the time lag between pulmonary congestion and pulmonary edema was confirmed by pathological examinations of the lung. Using light and electron microscopes, lungs in Group 2 (15 minutes duration with elevated LAP) showed only pulmonary congestion; those of Group 3 (30 minutes duration) was in very early stage of interstitial pulmonary edema in addition to the finding of pulmonary congestion; and those of Group 4 (60 minutes duration) showed established interstitial pulmonary edema (Fig. 1-1, 2, 3, 4 and Fig. 2-1, 2, 3, 4).

The morphological changes in both hemodynamic and alloxan-induced pulmonary edema have been studied by Staub and colleagues⁸ using the rapid freezing technique and light microscopy. Swelling of the connective tissues around the vessels and airways had occurred before the alveolar septums were expanded. Our findings were similar to theirs in respect to the morphology; however, they had not demonstrated the time course of the change of extravascular lung water in pulmonary edema.

Based upon the study of Staub and his associates, Ingram and Braunwald¹⁴ have recently divided the accumulation process of the fluid in pulmonary edema into three stages. In Stage 1 there is no measurable increase in interstitial fluid volume, since the fluid volume transferred from pulmonary capillary to the interstitium is nearly equal to the lymphatic outflow volume. But when the pumping capacity of the lymphatics is approached or exceeded, excess liquid begins to accumulate in the more compliant interstitial compartment surrounding bronchioles, arterioles and venules. This is designated as Stage 2. With further increments in filtered load, early alveolar edema (Stage 3a) and alveolar flooding (Stage 3b) result. Accordingly, our findings of pulmonary congestion in Group 2 might resemble Stage 1 and the findings in Group 3 might correspond to the early stage of interstitial pulmonary edema.

The established interstitial pulmonary edema (Group 4) could correspond to Stage 2.

Electron microscopic alterations at the alveolar level in pulmonary edema have been reported by Cottrell et al.¹⁹ They showed that, in hemodynamic pulmonary edema, the interstitial fluid collected only in the collagen-containing portions, i.e., the thick portions of the alveolar septum. This finding is similar to our finding in Groups 3 and 4 in which there were vesicles in the thick portions of the alveolar septum (Fig. 2-3,4). They have also described pinocytotic vesicles in the endothelial cells of capillaries in the control state, similar to the findings in our control group (Fig. 2-1). On increase in vesicle number was noted in the stage of pulmonary congestion (Fig. 2-2), suggesting the increased liquid transferred from capillaries to the interstitium.

In our study, several problems should be pointed out. According to the reported clinical studies, elevated LAP was accompanied by increased cardiac output in patients with heart disease during exercise testing^{2,3}. In our study, cardiac output decreased while LAP increased, as in the clinical cases of acute mitral stenosis or acute left ventricular failure. Therefore, our experimental findings could not be easily applied to the phenomena in cardiac patients during exercise. However, the degree of elevation of LAP induced by exercise is similar to that induced by balloon inflation in the left atrium, and the duration of exercise, usually within 15 minutes, is too short to increase extravascular lung water. Thus, the clinical implication of our study is to be considered as follows: the time lag between pulmonary congestion and pulmonary edema is an important factor in explaining the clinical event, namely the discrepancy between the elevated LAP and the clinical manifestation of pulmonary edema.

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