Some Observations on the Role of the Lymphatics in Experimental Acute Pulmonary Edema

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Although the role of the lymphatics in pulmonary edema is a subject of considerable interest,1–9 experimental observations in this area have been hampered by the lack of a simple and reliable means of collecting right duct lymph.10 A technique was recently developed in this laboratory by which the total right duct lymph flow in the dog can be easily measured, thus eliminating the problems inherent in the cannulation of one of many minute channels.11–13

The method consists of introducing a 3-inch-long plastic tube into the external jugular vein in the vicinity of the entrance of the multiple small lymphatic vessels and securing the tube in place at either end to create an artificial chamber between the vein wall and the outside of the tube, at the same time allowing continuity of the venous return to the heart through the tube. Cannulation of the artificial chamber allows collection of right duct lymph and eliminates the tedious and often impossible task of cannulating the individual minute lymphatic vessels (fig. 1).

To study the possible role of the lymphatics in the genesis of pulmonary edema, a series of experiments was conducted in which the pulmonary venous pressure was elevated, simulating mitral stenosis or left ventricular failure, and the effect on right duct and thoracic duct lymph was observed. In addition, the glutamic oxalaeetic and pyruvic transaminase levels were measured in the right duct and thoracic duct to obtain possible information on the distribution and levels of the enzymes in the respective ducts in this experiment, as well as possible hepatocellular involvement due to "backward failure."7

Methods

Thirteen dogs were anesthetized with pentobarbital sodium (29 mg./Kg.). Respirations in the open-chest dogs were maintained by intermittent positive pressure. The right duct lymph was obtained by the method described, and the thoracic lymph was obtained by conventional cannulation of the thoracic duct. In seven dogs, the thoracic duct was ligated just above the diaphragm. A Foley catheter was inserted into the left atrium. A small-bore plastic tube attached to a manometer was inserted into the left atrial appendage or the superior vena cava for the measurement of the blood pressure. The Foley catheter balloon was inflated and maintained at the level of distention that resulted in an increase in the left atrial and pulmonary venous pressure to approximately 30 mm. Hg. Lymph was collected from the thoracic and right duct at 15-minute intervals from the start of the experiment until the animals died. Lymph pressures were obtained by vertically positioning the polyethylene cannula draining the artificial chamber created in the right external jugular vein and recording the level of lymph. Total protein,14 glutamic oxalaeetic,15 and glutamic pyruvic transaminase16 were measured in the lymph collected.

In five experiments, the fluid content of the parenchymal portions of the lung was obtained by weighing small biopsied samples of lung, heating them to 60 C. for 24 hours and reweighing. The remaining weight was expressed as dry tissue weight (grams) per total biopsy weight (grams) and, when subtracted from 100, was considered as the per cent fluid per lung biopsy.

Results

Right Duct and Thoracic Duct Dynamics

The following sequence generally occurred after elevation of the left atrial pressure. Inflation of the left atrial balloon to the point...
LYMPHATICS IN PULMONARY EDEMA

Artificial chamber method for the collection of right duct lymph. See text.

at which the left atrial pressure was maintained at 30 mm. Hg resulted in a change in color of the lung from a salmon pink to a bright red, presumably due to engorged pulmonary capillaries. There was an initial increase in thoracic duct flow within 15 to 30 minutes (average 26 minutes) in the seven dogs in which the thoracic duct was not tied off just above the diaphragm. In the remaining seven experiments in which the thoracic duct was ligated, no significant thoracic duct flow occurred except in two animals where subsequent dissection revealed unoccluded thoracic duct channels near the diaphragm. Ligation of these additional vessels abolished the thoracic duct flow. After the initial increase in the flow of thoracic lymph, an increase was also noted in the lymph flow from the right duct approximately 38 minutes after inflation of the left atrial balloon. Both flows progressively increased, provided that the left atrial pressure was kept at approximately 30 mm. Hg.

Approximately 30 minutes after the onset of increase in right lymphatic flow, pulmonary edema gradually became apparent as manifested principally by increased moisture in the lungs, heaviness of the lungs, and oozing from the cut end of the lung biopsy samples. As the degree of edema became more pronounced and the lymphatic flows continued to increase, blood appeared in the right duct lymph, and a sponge applied to the surface of the lung stained red. Approximately 60 to 90 minutes after inflation of the left atrial balloon, the animals died in acute pulmonary edema.

At the time of peak flow (usually at the time of death), the average right duct flow was 2.8 ml./15 min. compared with 0.8 ml./15 min. just prior to inflation of the left atrial balloon. The average thoracic duct peak flow was 11.1 ml./15 min. compared with 3.0 ml./15 min. just prior to inflation of the left atrial balloon (see table 1).

Pre- and postatrial balloon inflation changes in pressure of lymph were not significant (see table 1). The pressures in the right duct were always higher than those in the superior vena cava. It is of interest that the superior vena cava pressure was not significantly affected by the elevation of the left atrial pressure.

Figure 2 illustrates a typical experiment showing the effect on lymph flow of pulmonary edema induced by increase in left atrial pres-
Effect of removal of left atrial obstruction on lymph flow.

When the balloon was inflated, lymph flow increased in both thoracic and right ducts, until the dog died of acute pulmonary edema 60 minutes after inflation of the left atrial balloon. If the balloon had to be deflated, as was frequently necessitated by the appearance of marked bradycardia and arrest, the thoracic and right duct flows decreased within the 15-minute period of collection, and the dogs would not die of pulmonary edema (fig. 3).

The total protein of the right duct lymph averaged 4.56 Gm./100 ml. (S.D. - 0.88) preinflation of the atrial balloon and averaged 5.33 Gm./100 ml. (S.D. - 0.86) postinflation of atrial balloon. The mean difference produced by inflation was 0.78 Gm./100 ml. (S.D. - 0.84). The probability of this difference occurring by chance is less than 0.05.

Changes in Fluid Content of Lungs with Elevation of Left Atrial Pressure

In the course of these experiments, an attempt was made to correlate the changes in the fluid content of lung tissue with the elevation of left atrial pressure. Multiple lung biopsies permitted one to obtain the per cent fluid per tissue weight. Figure 4 illustrates control biopsies of 77.3 and 77.2 per cent fluid

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| **Thoracic duct**                       |
| **Before inflation**                    |
| **After inflation**                     |
| 0.20 ± 0.055                            | 0.74 ± 0.107 |
| 33 ± 15.4                              | 37 ± 15.8    |

*Thirteen dogs.
†Seven dogs.
‡S.E. mean.
§Peak flow.

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Changes in fluid content of the lung biopsies with fluctuation of the left atrial pressure.

per tissue weight. With subsequent increase in left atrial pressure, the per cent fluid increased to 79.1 at the first 15-minute biopsy and gradually continued to increase until the final biopsy. In other experiments it was noted that shortly after a decrease of a previously elevated left atrial pressure, the per cent fluid per tissue weight diminished accordingly (fig. 5).

Enzyme Studies

The lymph collected from the right duct and thoracic duct was analyzed for glutamic oxalacetic transaminase and glutamic pyruvic transaminase. Table 2 depicts the relationship of the average levels of these enzymes in the right and thoracic duct at the time of the collection of the initial samples after thoracotomy, the samples just prior to and immediately after obstruction, and the terminal samples. The glutamic pyruvic transaminase in both right and thoracic ducts was essentially unchanged with a slight terminal elevation.

On the other hand, the glutamic oxalacetic transaminase content of fluid from the right duct was markedly elevated in the initial sample after thoracotomy, probably due to the
surgical trauma to the chest wall. With the manipulation of the left atrium involved in insertion of the balloon, an increase in the glutamic oxaloacetic transaminase content of the right duct was observed. After the left atrial flow was partially obstructed, a further increase was obtained. The terminal value, although still elevated over normal values, was slightly decreased. In contrast to the rapid and marked increase in glutamic oxaloacetic transaminase in the fluid of the right duct, that of the fluid in the thoracic duct rose slowly, although the terminal value was considerably elevated.

Discussion

These studies demonstrated that elevation of the left atrial pressure to 30 mm. Hg resulted in an increase in the right duct lymph flow in approximately 38 minutes. Critical pulmonary edema became apparent within the next 30 minutes; the animals died in pulmonary edema.

In addition, these studies demonstrated that elevation of the left atrial pressure was followed by an increase of thoracic duct flow. That the flow was abolished by thoracic duct ligation at the diaphragm indicates that a shunt from the right duct to the thoracic duct above the diaphragm was not a factor in the increased thoracic duct flow. Likewise, the failure of the superior vena cava pressure to increase with the elevated left atrial pressure indicates that "backward failure" via the right heart is an unlikely cause of the increased thoracic duct flow.

The slight increase in the pulmonary tissue content of fluid after prolonged elevation of left atrial pressure suggests that such acute elevation of left atrial pressure cannot be compensated for by any significant degree of tissue hydration. Rather, an escape of fluid from the lung tissue to the tracheobronchial tree and lymph channels ensues. Since the quantitative increase in lymph is small, it is suggested that the lymphatic system is unable to function significantly to relieve the excess of fluid that collects in the engorged lung after marked elevation of left atrial pressure in the acute experiment. As a result, the fluid "overflows" into the tracheobronchial tree. At autopsy, approximately 30 cc. of fluid was found in the trachea in these experiments. In other words, with a marked acute elevation in left atrial pressure, the parenchymatous portion of the lungs quickly becomes engorged, tolerating only a slight increase in fluid content, with resultant overflow, principally into the tracheobronchial tree and, to a lesser extent, into the lymphatic channels. These events, however, may have no relevance to an elevation of pulmonary venous pressure occurring gradually over a long period of time, wherein the compensatory mechanisms, especially lymphatic drainage, may expand, preventing the occurrence of alveolar flooding. Further experiments concerning the role of the lymphatics in chronic pulmonary edema are in progress.

The marked increases in the glutamic oxaloacetic transaminase in the right duct and the modest levels in the thoracic duct until the end of the experiments demonstrate the effectiveness of the right duct in funneling the enzymes from the heart and lungs. The pyruvic transaminase levels were essentially unchanged, suggesting that the acute conditions imposed by the nature of this experiment did not affect the integrity of the liver cells.

Summary

Lymph was collected from the right duct and thoracic duct of 13 dogs in which acute pulmonary edema was produced by partial obstruction of the left atrium by means of a balloon. Elevation of left atrial pressure to 30 mm. Hg resulted in an increase in thoracic duct flow within 30 minutes, followed by an increase in right duct flow within the next 15 minutes. Critical pulmonary edema became manifest approximately 30 minutes after the onset of increased right duct flow, and the dogs died in pulmonary edema approximately 90 minutes after inflation of the left atrial balloon, unless the left atrial pressure was reduced. The per cent of fluid in serial lung biopsies increased in the first biopsy taken 15 minutes after the elevation of left atrial press-
sure to 30 mm Hg, and the increase was sustained, resulting in engorgement of the lungs unless the left atrial pressure was decreased. The small absolute increase in lymph from the right duct suggests that the lymphatics are unable to function significantly to relieve the pulmonary edema produced in these acute experiments, resulting in an overflow of fluid into the tracheobronchial tree. Glutamic oxalacetic transaminase showed marked increases in the lymph from the right duct but only modest increases in the lymph from the thoracic duct throughout the experiments. Pyruvic transaminase in lymph from the right and thoracic ducts was relatively unchanged.

References
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