Role of Pulmonary Lymphatics in Chronic Pulmonary Edema

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Clinically, the development of pulmonary edema is frequently associated with an elevation of left atrial pressure. However, overt pulmonary edema does not always occur with such pressure elevations, even when the plasma oncotic pressure is greatly exceeded. It is conceivable that a dilatation of the pulmonary lymphatic system might remove fluid from the lung and prevent, or delay, the development of overt pulmonary edema. In experimental studies on the dog, it has been demonstrated that lymph flow from the lungs increased with an acute elevation of the pulmonary venous pressure; however, the quantity of lymph was small and apparently ineffective in preventing the development of pulmonary edema. The critical question, however, of the extent of the pulmonary lymph flow in chronic pulmonary edema remained unanswered. It was the purpose of the current study to determine what role, if any, the lymphatics play in the prevention of chronic pulmonary edema.

Methods

Mongrel dogs were used in this study. The animals were anesthetized with intravenous sodium pentobarbital (29 mg./Kg.), and a side-to-side 5 to 15-min. aorticocaval anastomosis was made immediately below the renal vessels by approximating and suturing the aorta and vena cava. Dogs not surviving more than one month were excluded from the study. Thirty animals not included in the experimental group were used for preliminary observation and development of techniques. Ten dogs, initially weighing between 8.6 and 14 Kg., with an aortocaval anastomosis, comprised the experimental group, and three of the dogs had a supplementary arteriovenous fistula between the left carotid artery and external jugular vein to overload the heart further and hasten the development of edema. Preliminary studies demonstrated that it was difficult to obtain an anastomosis of the exact size that would result in the appearance of pulmonary edema after the operation unless the dogs were further challenged by giving desoxycorticosterone trimethylacetate and a salt-enriched diet. Nine of the experimental group were placed on 50 mg. of the steroid a week and approximately 6 Gm. of salt per day.

The animals were closely observed for clinical signs of congestive failure as evidenced by subcutaneous edema, ascites, weight gain, dyspnea, or lethargy. When these signs were apparently well developed in seven of the dogs, or as in the case of three dogs, they failed to appear after prolonged observation, the animals were anesthetized with intravenous pentobarbital (29 mg./Kg.), and lymph from the lungs was collected by a technique recently developed in this laboratory. The method consists of introducing a 3-inch long plastic tube into the right 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. Cannulation of the artificial chamber allowed collection of right duct lymph. The thorax was opened, and respirations were maintained by intermittent positive pressure. Left atrial pressures were recorded by inserting a small-bore plastic tube, attached to a manometer, into the left atrial appendage. After the data were collected and lung biopsies were obtained, the respirator was stopped. Necropsy was performed immediately. Pulmonary edema was estimated by the gross appearance of the lungs, histological sections, the per cent of fluid in small lung biopsies, and the ratio of the lung weight to body weight (LW/BW).
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Results

Seven of the ten animals exhibited signs of congestive failure as evidenced by peripheral edema, ascites, dyspnea, or weight gain. The remaining three dogs did not demonstrate any of these clinical signs. All of the animals that had clinical signs of failure had aortico-caval anastomoses that were 7 mm. in diameter or more at necropsy, whereas in the remaining group the diameters were 6 mm. or less. Five of the dogs with clinical evidence of failure were placed on the desoxycorticosterone regime within one month after the formation of the aortico-caval anastomosis and showed definitive signs of fluid retention within the next one to two months. Of the two remaining dogs in the "clinical failure group," one did not require any steroid and developed ascites in approximately three months, and the other animal was placed on the steroid regime 11 months after the operation and went into overt failure within 15 days (fig. 1).

The lymph flow varied from the normal flow of 4 ml./hr. to a maximum of 111 ml./hr. All of the animals with increased flows had large lymphatics in the region of the right lymphatic duct near its entrance into the right subclavian vein. Seven of the dogs had flows that represented a 300 to 2,800 per cent increase over the normal flow of 4.2 ml./hr., and three of the dogs actually had unprecedented levels of over 100 ml./hr. (fig. 2).

At necropsy, it was seen that all of the dogs had cardiomegaly, as evidenced by heart weight/body weight ratio greater than 0.009.° The dogs that were clinically free of failure (nos. 691, 692, and 689) had no gross evidence of fluid in the lungs or any ascites, pericardial, pleural, or tracheal fluid (fig. 3), whereas the remaining animals had gross pulmonary edema and varying amounts of ascites, pericardial, pleural, and tracheal fluid.

All of the dogs, including the three animals that were clinically free of failure, demonstrated some degree of pulmonary edema by the lung weight to body weight method (fig. 2). A ratio of 1.40 was the upper limit of normal. Likewise, the majority of animals had more than 7% per cent fluid/lung biopsy mass which was considered the upper limit of normal.

Discussion

Drinker had shown that nearly all of the lymph from the lungs of the dog drained into the right lymphatic duct,10 which empties into the junction of the right subclavian and right external jugular veins. These channels are normally minute delicate structures which are quite difficult to cannulate. Drinker was able to collect lymph from 20 per cent of the dogs.3 However, by creating an artificial chamber within the jugular vein, in the vicinity of the entrance of the lymph channels, we were able to avoid difficult microscopic cannulation procedures and successfully collect lymph in 90
per cent or more of the dogs. With this method of lymph collection, the earlier studies of Warren and Drinker, demonstrating an increase in right duct flow with an increase in pulmonary venous pressure, were confirmed. It was apparent, however, that the absolute increase in lymphatic flow was too small to remove fluid from the lung effectively in acute pulmonary edema.

This current study is concerned with the role of the pulmonary lymphatic system in chronic pulmonary edema. Previous workers experienced considerable difficulty in sustaining an elevated left atrial pressure over a long period of time. We attempted to produce chronic pulmonary edema by creating arteriovenous fistulae in the abdomen (aorticocaval) and occasionally in the neck (left carotid-jugular), thereby avoiding entrance into the thoracic cavity and possibly disturbing the pulmonary lymphatic system. Although such a procedure would produce the desired edematous state, the size of the anastomosis was found to be very critical, either producing failure within too short a period of time or no gross evidence of failure at all. By loading these animals, which had arteriovenous fistulae, with desoxycorticosterone trimethylacetate and salt, it was possible to produce pulmonary edema over a period of weeks without entering the chest. At least two factors appeared to influence the development of the edematous state: (1) shunt size and (2) duration of the steroid regime. Accordingly, all dogs with anastomoses 7 mm. or more that were placed on the steroid regime within one month after the operation were in overt congestive failure within two to three months (fig. 1).

Five of the seven dogs that demonstrated gross evidence of fluid retention had an increase in size of the complex of right duct lymph channels and excessively high lymph flows. Only two dogs with gross evidence of fluid retention had small lymph flows, presumably because insufficient time had elapsed before they were sacrificed. Accordingly, these dogs did not show the microscopic picture of severe pulmonary edema that was seen in the remaining dogs with gross evidence of edema (fig. 2).

The correlation between the right duct lymph flow and the precise degree of pulmonary edema as measured by either the lung weight to body weight or the per cent fluid/lung biopsy mass was not impressive. On the other hand, when the lymph flow was plotted against the left atrial pressure, a fairly good correlation was obtained. It is of further interest that the data of a previous study revealed that when the left atrial pressure was acutely raised to approximately 41 cm. H₂O, the right duct lymph flow was increased only.

**FIGURE 3**

Gross autopsy findings of the experimental animals.

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<th>Dog#</th>
<th>Gross evidence of pulmonary edema</th>
<th>Cardiac enlargement</th>
<th>Ascites (ml)</th>
<th>Pericardial fluid (ml)</th>
<th>Pleural fluid (ml)</th>
<th>Frothy tracheal fluid</th>
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*HW/BW > .009

**FIGURE 4**

Relationship of the pulmonary lymph flow to the left atrial pressure.
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Photograph of the entrance of the right duct into the venous circulation in dogs with chronic congestive failure. The umbilical tape has pulled the external jugular vein away so as to expose the right duct. The portion of the duct next to the vein contains some blood. Beyond this point, the translucent right duct (the width of which is indicated by the double arrow) just contains lymph and is difficult to visualize. Note that the right duct is approximately the size of the internal jugular vein seen near the top of the photograph joining the external jugular vein.

Large increases in the size of the right duct lymphatics were observed in those animals with increased right duct lymph flow. Figure 5 demonstrates the tremendous enlargement the lymph ducts can undergo with time. These large lymphatics contrast sharply with the much smaller lymphatics seen in normal dogs (fig. 6) or those with acute pulmonary edema.

It is apparent that the pulmonary lymphatic drainage system is capable of expansion over a period of time. Under the conditions imposed in this experiment, the minimal period observed for such expansion was approximately one and a half months. The expansion appeared to be related to a chronic elevation of the left atrial pressure in that far greater "acute" left atrial pressure elevations failed to develop the large lymph vessels and the huge lymph flows seen in the chronic experiment. It is conceivable, therefore, that the expansion of the pulmonary lymphatic drainage system may act as a compensatory mechanism permitting removal of fluid from the lungs and thereby preventing otherwise fatal pulmonary edema.

Summary

Previously small increases in canine pulmonary lymph flow found in acute pulmonary venous hypertension were ineffective in preventing fatal pulmonary edema. Our objective was to determine if functional expansion of the pulmonary lymphatic system could occur over a period of time and possibly aid in preventing critical pulmonary edema. Chronic heart failure was successfully induced in ten dogs by creating an aorticeaval anastomosis and administering desoxytocicosterone trimethylacetate and a salt-rich diet. Pulmonary lymph flow was obtained at the time of sacrifice by tapping an isolated lymph-collecting chamber produced in the right external jugular vein. Gross increases in pulmonary lymph flow, varying from 300 to 2,800 per cent over the normal flow of 4 ml./hr., were found in 7 of the 10 dogs. These observations indicate that important functional expansion of the pulmonary lymph drainage can occur over a period of time, and such expansion may occur as a compensatory mechanism for the prevention of overt pulmonary edema.

Circulation Research, Volume XI, December 1968
References


Book Reviews


This monograph opens with a chapter by I. H. Page entitled, "The Mosaic Theory of Hypertension." It is an excellent review of the nervous, endocrine, cardiovascular, and renal factors responsible for an elevation of blood pressure. Each of these factors is covered in greater detail by the other 40 participants, and the discussions are also recorded. The last few chapters pertain to the drug therapy of essential hypertension. The newer adrenergic blocking drugs (guanethidine and bretylium), as well as the saluretic drugs, are adequately described.


This includes the 20 papers which were presented at the Seventh Annual Scientific Meeting of the Houston Neurological Society. The following major topics were discussed: anatomy of blood vessels of the brain, occlusive diseases, intracerebral hemorrhage, and subarachnoid hemorrhage. The chapter on changes in cerebral blood flow resulting from vascular occlusion contains some helpful schema on the probable train of events resulting from stenosis of cerebral arteries and hypertensive encephalopathy and on the causation of cerebral thrombosis. There is an abundance of reports on clinical material, and the discussion of each report has been recorded.


The emphasis of this monograph is on chemical agents which increase coronary blood flow. The clinically useful coronary vasodilators (nitrites, papaverine, xanthines, and khellin) are discussed, as well as all other agents which are not clinically useful but have been shown to increase coronary blood flow. The coverage of coronary vasodilators is encyclopedic, complete with documentation from the literature.

The monograph includes a critical analysis of methods for measurement of changes in the lumen of the coronary vessels. The clinical methods for success in antianginal therapy are also included. However, the coverage of other aspects of the coronary circulation is rather poor. There is no section on anatomy; the discussion of the vasocostrictor effect of pituitrin is limited to half a page, and there is no mention of chemical agents that elicit reflexes from the coronary vessels (Bezold-Jarisch reflex). The author has strictly confined his monograph to vasodilators of the coronary bed.
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_Circ Res._ 1962;11:966-970
doi: 10.1161/01.RES.11.6.966

_Circulation Research_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
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