Cardiopulmonary Effects of Pulmonary Venous Hypertension with Special Reference to Pulmonary Lymphatic Flow

By Erwin R. Rabin, M.D., and Edward C. Meyer, M.D.

The development of pulmonary edema in mitral stenosis is often attributed to increased left atrial pressure. Moreover, pulmonary edema is commonly observed in patients with high left atrial pressure from any cause. It is remarkable, however, that pulmonary edema does not necessarily occur even at left atrial or pulmonary "capillary" pressure considerably above plasma oncotic pressure.\(^1\)\(^2\)

Experimentally, no exact relationship has been observed between increased left atrial pressure and pulmonary edema.\(^3\) Paine and his associates\(^4\) reported that pulmonary edema as established by gross and histologic examination occurred in dogs at left atrial pressures between 30 and 50 mm. Hg; it was not a constant finding until the left atrial pressure exceeded 50 mm. Hg, twice the plasma oncotic pressure.\(^5\)

Harrison and Liebow\(^5\) observed that pulmonary edema, as judged by the ratio of lung weight to body weight, was produced in dogs with induced intracranial hypertension, but only "in those animals where the left atrial pressure is maintained above 20 cm. H\(_2\)O for more than 15 minutes."\(^6\) Other investigators\(^6\)\(^7\) have also stressed the importance of increased left atrial pressure as one factor in the development of pulmonary edema, but little quantitative information is available with respect to this relationship and on the role that other factors may play in preventing the formation of edema.

Several explanations may be considered for the absence of pulmonary edema under some circumstances when the pulmonary capillary pressure exceeds oncotic pressure: (1) A change in the walls of the small vessels or in the walls of the alveoli may block the filtration of fluid at capillary pressures above plasma oncotic pressure; (2) An expanded system of pulmonary lymphatics may remove fluid as it is produced in pulmonary edema. Although it has been demonstrated experimentally that pulmonary lymphatic flow increases during the development of pulmonary edema,\(^8\) the quantitative relationship of increased left atrial pressure to pulmonary lymph flow has not been studied previously.

An estimate of pulmonary lymphatic flow may be obtained in the dog by measurement of lymph flow from the right lymphatic duct. According to Drinker,\(^9\) lung lymph with the exception of that from the apical segment of the left upper lobe drains into the right lymphatic duct. Lymph from the heart and pleura also drains into the right lymphatic duct, but this contribution can be assumed to be constant in amount. Therefore, any variation of flow observed in the right lymphatic duct can be ascribed to variation in pulmonary lymphatic flow, provided no communication exists between the right lymphatic and thoracic duct.

The aim of this report is to present functional and anatomical studies in dogs with acutely induced or chronically maintained elevation of left atrial pressure, with special attention to the quantitative relationships of left atrial pressure to pulmonary lymphatic flow and pulmonary edema.
Methods

Mongrel dogs were used in this study. These weighed between 10 and 20 Kg. at the start of the experiment. Left atrial pressure was raised by a method devised by Ellison and associates with only slight modification. Supravalvular stenosis was produced by placing a nylon snare through the interatrial septum and, in purse-string fashion, around the outside of the left atrium above the mitral valve. It was found desirable to enclose the No. 60 nylon line in a tube of No. 160 polyethylene which dulled the cutting tendency of the nylon while retaining the tensile strength of the latter. The ends of the snare, enclosed in a polyethylene cannula, were passed through the fourth intercostal space and sutured to the subcutaneous tissue of the chest wall. Several weeks later, after the dogs had recuperated, the ends of the snare were easily recovered by a small superficial chest wall incision.

On pulling up both ends of the snare to varying degrees, left atrial mean pressure could be controlled acutely at any level desired between the normal of —2 to +7 mm. Hg, and a maximum elevation of 60 mm. Hg (fig. 1). In one series of experiments acute left atrial pressure elevation was usually maintained for 10-minute intervals and then restored to normal. In a second series chronic elevation of the left atrial pressure was produced gradually over a period of several weeks to 1 month by repeated “pull-ups” spaced at intervals of 1 to 2 weeks. Intravenous injection of sodium pentobarbital (30 mg./Kg.) was used for anesthesia. Prophylactic injections of penicillin (600,000 units per day) and streptomycin (0.2 Gm. per day) were continued for 6 days after thoracotomy and for several days after “pull-up” procedures.

A series of 15 dogs was used for the study of acute elevation of left atrial pressure, and a second group of 15 dogs comprised the series for the study of chronic left atrial pressure elevation. An additional 30 dogs, not part of the experimental groups, were used in developing the technic for the production of chronic supravalvular stenosis and for various preliminary observations. In 15 of these 30 dogs the tightened snare gradually eroded through the atrial myocardium resulting in relief of the imposed stenosis. Several times the intact nylon snare was pulled completely through the heart and out of the chest without any ill effect on the dog. The only finding observed when the animal was sacrificed was a linear scar in the atrium along the path of the erosion. The other 15 dogs developed bacterial endocarditis with large fibrous vegetations adherent to the exposed nylon in the left atrium. Staphylococci were smeared and cultured from 2 of these vegetations; one of the vegetations contained gram negative rods.

Cannulation of the right lymphatic duct in the neck outside the chest cavity was carried out according to the method developed by Drinker. Communication between the right lymphatic and the thoracic duct was evident if lymph from the right lymphatic duct was chylous; if no communication existed the lymph was clear. Communication was tested by injection of Evans blue dye into a
Relationship of right lymphatic duct flow to acute elevation of left atrial pressure for 1 of 5 dogs studied. Lower half of graph represents left atrial pressure. Upper half represents lymph flow from the right lymphatic duct.

Results

Acute Elevation of Left Atrial Pressure

The relationship of right lymphatic duct flow to left atrial pressure is demonstrated in Figure 2 for 1 of 5 dogs studied. Observations were similar in 4 other dogs (Table 1). Control values for right lymphatic duct flow at normal left atrial mean pressure of −2 to +7 mm Hg in the various animals ranged between 15 and 90 mg/min. Eight lymphatic duct flow at left atrial mean pressure below 25 mm Hg was less than, or remained unchanged, from control flows. A prompt increase of right lymphatic flow was observed in association with left atrial mean pressures above 25 mm Hg. It was interesting to note that, in animals whose left atrial mean pressure was acutely raised above 30 mm Hg for measured directly with the aid of a modified London cannula. Cardiac output was estimated by the direct Fick principle and also according to the Stewart-Hamilton dye method. Oxygen content of the blood was determined by the Van Slyke manometric method. Dye was injected into the right atrium and dye content of blood withdrawn from a cannula in the femoral artery was determined with a Waters cuvette and electronic circuit modified for Fox green dye, or in later experiments with the aid of the Colson infra-red phototube system. Lymph from the right lymphatic duct was weighed on an analytical balance and expressed as mg/min, whereas lymph from the thoracic duct was measured in a graduated cylinder and expressed as ml/min. Lymph samples from both ducts were collected at 10-minute intervals.

Necropsy was performed on all animals. The lungs were inflated with 10 per cent formalin poured into the trachea and allowed to fix for several days. Blocks of lungs were taken from the periphery, middle, and hilar regions. No blocks were taken from the lingular segment which was usually adherent to the heart and chest wall from the previous thoracotomy. Lung sections were stained with hematoxylin and eosin. Additional lung sections were stained for elastic tissue and iron.

Additional artery, systemic arterial and venous pressures and electrocardiogram were recorded on a 6-channel Sanborn instrument. Pulmonary arterial pressure was obtained with a Cournand catheter and left atrial pressure was measured directly with the aid of a modified London cannula.
Table 1

Range of Right Lymphatic Duct Flow at Indicated Left Atrial Mean Pressures in Five Dogs.

<table>
<thead>
<tr>
<th>Left atrial pressure (mm Hg)</th>
<th>Right lymphatic duct flow (mg/min.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>-2 to 7</td>
<td>20-70</td>
</tr>
<tr>
<td>15 to 25</td>
<td>15-50</td>
</tr>
<tr>
<td>30 to 50</td>
<td>30-90</td>
</tr>
<tr>
<td></td>
<td>(708)</td>
</tr>
<tr>
<td>Dog no.</td>
<td>15-60</td>
</tr>
<tr>
<td></td>
<td>(156)</td>
</tr>
</tbody>
</table>

In the 5 dogs, variations in left atrial pressure did not affect thoracic duct flow. The latter at normal and elevated left atrial pressures ranged between 0.4 and 1 ml./min. No gross evidence of blood was observed in lymph from the thoracic duct at high left atrial pressure.

Mean left atrial pressure of 50 mm. Hg was maintained in 8 dogs (the 5 dogs in which lymph flow was measured and 3 additional animals) for periods of 30 minutes with only slightly reduced systemic arterial pressure, normal systemic venous pressure, and without electrocardiographic abnormalities. Left atrial pressure elevation of this degree for periods longer than 30 minutes, however, resulted in pulmonary edema. Loud rales became audible over both lung fields, and foamy fluid was noted to drip from the tracheal tube. Hypoxia was evident as arterial blood became dark and the tongue cyanotic. This was followed by evidence of myocardial ischemia (QRS and T-wave changes). Systemic venous pressure rose and systemic arterial pressure declined to shock levels, and the animal died within a few minutes. Necropsy revealed small sero-sanguineous pleural effusions and marked pulmonary edema and congestion in all 8 animals, with average value for LW/BW of 2.34 per cent, and a range of 1.89 to 2.99 per cent. The dog would recover if the snare were released before severe pulmonary edema became apparent.

Systemic arterial pressure uniformly fell as left atrial pressure rose. This was observed in more than 40 dogs. If the snare were "pulled-up" maximally systemic pressure dropped sharply from approximately 120 mm. Hg to below 40 mm. Hg and systemic arterial pulse pressure approached zero (fig. 1). During the production of acute left atrial pressure elevation, an initial sharp decline in systemic arterial pressure was usually followed by a gradual recovery, whereupon it remained stable at a point slightly below the mean at normal left atrial pressure (fig. 1).

The relationship of pulmonary artery pressure to acute elevation of left atrial mean pressure, as observed in 5 dogs, is demonstrated in figure 3. Elevation of left atrial mean pressure

Figure 3

Relationship of pulmonary arterial mean pressure to acute elevation of left atrial mean pressure observed in 5 dogs. Determinations on individual animals are connected.
The relationship of cardiac output to acute elevation of left atrial pressure observed in 5 dogs. Determinations on individual animals are connected. From 0 to 10 mm Hg was accompanied by only a slight rise in pulmonary arterial mean pressure; pulmonary arterial pressure rose 1 mm Hg for a corresponding 2 mm Hg elevation of left atrial pressure. The increase in pulmonary arterial pressure became more pronounced when the mean pressure in the left atrium exceeded 15 mm Hg. At left atrial mean pressure between 15 and 40 mm Hg pulmonary arterial pressure rose 1 mm Hg for a corresponding 1 mm Hg elevation of left atrial pressure. At left atrial mean pressures above 45 mm Hg the rise in pulmonary arterial pressure was even more pronounced although only a few observations were made in that range.

The relationship of cardiac output to acute elevation of left atrial pressure, as observed in 5 dogs, is recorded in figure 4. At left atrial mean pressure between 0 and 15 mm Hg cardiac output was only slightly less than that at normal left atrial pressure. At left atrial mean pressure between 25 and 40 mm Hg the decrease in cardiac output was more significant. It was 30 to 50 per cent less than the volume obtained at normal left atrial pressure.

The relationship of pulmonary vascular resistance to acute elevation of left atrial pressure, observed in 5 dogs, is demonstrated in figure 5. Pulmonary vascular resistance declined sharply with left atrial pressures between 0 and 15 mm Hg. At left atrial mean pressure between 25 and 40 mm Hg pulmonary vascular resistance gradually rose to or higher than the value obtained at normal left atrial pressure.

The relationship of hematocrit to left atrial pressure elevation is demonstrated in figure 6 for 1 of 7 dogs studied. Observations were similar in 6 other dogs studied. Three control hematocrits obtained at normal left atrial pressure varied 1 to 4 hematocrit units with the average variation less than 2 units for the group of 7 animals. After a 10-minute period of acute left atrial pressure elevation, hematocrit readings increased 4 to 8 units with an average increase of 6½ units. The hematocrit did not fall immediately when left atrial pressure was restored to normal, and in some instances it continued to rise. After 1 hour at normal left atrial pressure the hematocrit was almost always lower than the values recorded at high left atrial pressure. Generally, it remained higher than the initial values obtained at normal left atrial pressure.
Table 2

Left Atrial and Pulmonary Arterial Mean Pressure, Pulmonary Vascular Resistance, and Some Measurements of Cardiac Output Before and After Chronic Supravalvular Mitral Stenosis for Periods of 1 to 10 Months in 15 Dogs.

<table>
<thead>
<tr>
<th>Dog no.</th>
<th>Chr. Group A*</th>
<th>Chr. Group B*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Left atrial pressure (mm. Hg)</td>
<td>Pul. arterial pressure (mm. Hg)</td>
</tr>
<tr>
<td></td>
<td>b</td>
<td>a</td>
</tr>
<tr>
<td>776</td>
<td>3</td>
<td>15</td>
</tr>
<tr>
<td>893</td>
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<td>15</td>
</tr>
<tr>
<td>803</td>
<td>3</td>
<td>15</td>
</tr>
<tr>
<td>845</td>
<td>5</td>
<td>24</td>
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<td>814</td>
<td>2</td>
<td>12</td>
</tr>
<tr>
<td>844</td>
<td>-1</td>
<td>23</td>
</tr>
<tr>
<td>664</td>
<td>2</td>
<td>17</td>
</tr>
<tr>
<td>753</td>
<td>4</td>
<td>12</td>
</tr>
<tr>
<td>678</td>
<td>2</td>
<td>14</td>
</tr>
<tr>
<td>681</td>
<td>2</td>
<td>21</td>
</tr>
</tbody>
</table>

Chronic Group A* consists of 10 animals that were sacrificed in good clinical condition. Chronic Group B* consists of 5 animals that expired 1 to 2 days after left atrial pressure was elevated to between 30 and 40 mm. Hg. Pressure recorded before final "pull-up" is listed in parentheses.

Chronic Elevation of Left Atrial Pressure

Table 2 lists left atrial pressure, pulmonary arterial pressure, and some measurements of cardiac output and pulmonary vascular resistance before and after chronic stenosis for periods of 1 to 10 months as observed in 15 dogs. Ten of these 15 dogs, designated hereafter as Chronic Group A, were sacrificed in good clinical condition; the remaining 5 dogs with chronic stenosis, designated hereafter as Chronic Group B, expired 1 to 2 days after left atrial mean pressure was elevated by a second or third "pull-up" to between 30 and 40 mm. Hg.

In the 10 dogs comprising Chronic Group A, left atrial mean pressure before chronic stenosis was -3 to +5 mm. Hg and after stenosis was 10 to 23 mm. Hg. Pulmonary arterial mean pressure before stenosis was 9 to 18 mm. Hg and after stenosis rose to 20 to 34 mm. Hg. In 4 animals of Chronic Group A, measurements of cardiac output after stenosis were only slightly less than those prior to stenosis (see table 2).

Figure 7 demonstrates left atrial and pulmonary arterial pressure in 1 of 15 dogs during the production of chronic supravalvular stenosis and for 10 months thereafter. Records of the other dogs in the chronic groups were similar in the zig-zag but generally upward trend of left atrial pressure after repeated "pull-ups" of the snare. Elevated left atrial and pulmonary arterial pressures produced by pulling up and fixing both ends of the snare were usually much lower when measured several weeks after "pull-up." Chronically
Elevated left atrial and pulmonary arterial pressures diminished slightly over a period of several months.

Systemic venous pressure, recorded in the femoral vein, remained normal after chronic stenosis. In 3 dogs of Chronic Group A, pressure was recorded when the catheter was withdrawn from the right atrium into the inferior vena cava to determine if any stenosis of this vessel had been produced inadvertently upon tightening the snare. No sudden increase of pressure was observed. Ascites was never noted in the chronic group. The only physical sign was a harsh diastolic murmur heard best at the apex of the heart which was confirmed in 1 dog by means of a phonocardiogram.

Right lymphatic duct cannulations were performed in 5 dogs of Chronic Group A. Three of these had no communication between right lymphatic and the thoracic duct as established by the criteria mentioned previously. Left atrial mean pressure in the 3 animals was between 15 and 20 mm. Hg. Right lymphatic flow did not exceed that measured in control dogs with normal left atrial pressure (15 to 90 mg./min.).

At necropsy, no fluid was present in either the pleural or peritoneal cavity in the 10 dogs of Chronic Group A. The pericardial sac was adherent but easily separated from the heart. Neither right ventricular hypertrophy nor dilatation of any marked degree was evident. The lungs were grossly normal except for adhesions about the polyethylene cannulas which involved the lingular segment of the left lung. Healed infarcts of the spleen or kidney were noted in 4 of the 10 dogs in this group. The extent of the supravalvular stenosis produced...
PULMONARY LYMPHATIC FLOW

was marked (fig. 8). The diameter of the stenotic aperture measured from 3 to 7 mm.

Microscopic examination revealed no changes in the pulmonary vessels or alveolar walls of the 10 dogs comprising Group A. Neither pulmonary edema nor congestion was observed with average value for LW/BW of 1.05 per cent, and a range of between 0.89 and 1.38 per cent. The only positive finding consisted of foci of iron-containing pigment usually in macrophages in the interstitial tissue surrounding bronchi and bronchioles in 6 animals in Group A. In 2 of these 6 dogs, large amounts of iron were present in macrophages in the interstitial tissue and distal air spaces. Only minute amounts of iron positive pigment were seen in the lungs of a control series of 5 animals that had been snared but not "pulled-up."

A multicolored vinylite bronchovascular corrosion cast of the lung was made in 1 dog of Chronic Group A (Dog No. 845) to determine if any enlargement of the bronchial venous system had developed. This dog had an elevated left atrial mean pressure of 20 to 25 mm. Hg for a 3-month period prior to sacrifice (table 2). The cast was prepared by a technic identical to that used by Vidone and Liebow.38 In this specimen there is evidence of an expanded venous collateral circulation. This consists of several elements: (A) Transpleural. There are newly formed collateral venules joining pulmonary veins through adhesions on the lateral and mediastinal aspects. These drain respectively into a series of left intercostal veins and into a left pericardiophrenic vein. Interestingly, these are all on the left side, the side of operation, except for several small vessels which traverse the mediastinum from right to the left to drain into the plexus that ultimately enters the left pericardiophrenic vein. Those on the right side connect directly with branches of small pulmonary veins, 1 mm. or less, in the right upper and middle lobes. (B) Enlarged Presumably Pre-existing Bronchial Venules. One of these venules enters the azygos vein as a bridge from a major right middle lobe pulmonary vein and the other receives bronchial veins from the region of the left main bronchus, and left mediastinal pleura, as described above.

At necropsy, in the 5 dogs of Chronic Group B, small serosanguineous pleural effusions were present. Severe supravalvular stenosis was apparent. The diameter of the stenotic aperture measured between 3 and 7 mm. On microscopic examination marked pulmonary edema and congestion were observed.

Simultaneous Cannulation of Right Lymphatic and Thoracic Duct

Right lymphatic duct cannulation was successfully performed in 16 dogs. Six of these 16 had chylous right duct lymph suggesting communication with the thoracic duct. Flow of lymph from the right lymphatic duct was much greater in the 6 dogs that demonstrated communication, 100 to 250 mg./min. as compared to 15 to 90 mg./min. when no communication was evident. In 2 of the 6 dogs with communication, it was interesting to note that chyle disappeared from the right lymphatic duct on advancing the cannula down the thoracic duct to approximately the level of the third rib. It was assumed that communication was interrupted by this maneuver.

Pressure was recorded in the right lymphatic and thoracic ducts in 5 dogs. The pressure transducer completely obstructed the ducts while the pressure was measured. Three of the 5 dogs had no communication between the right lymphatic and the thoracic duct. In
these 3, right lymphatic duct mean pressure varied initially between 3 and 5 mm. Hg and gradually increased and remained at 10 mm. Hg over a 10-minute period. Thoracic duct mean pressure varied initially between 9 and 14 mm. Hg and gradually increased and remained at about 18 mm. Hg over a 10-minute period. The only difference observed in 2 dogs demonstrating communication was a slightly higher initial mean pressure in the right lymphatic duct, 5 to 7 mm. of Hg.

At necropsy, investigation of lymphatic anatomy was carried out. The right lymphatic duct arose from a node within the pleural space at the right cupola. Some of the afferent branches of this node were traced to the hilum of the lung on either side. The thoracic duct lay retropleurally in the thorax several cm. from the vertebral column. In 2 dogs with cloudy right lymphatic duct lymph, a large branch of the thoracic duct crossed above the region of the arch of the aorta and drained into the node in the right cupula. On gross examination in 1 dog, an additional lymphatic channel of comparable size to the right lymphatic duct appeared to drain the lung. This channel entered the azygos vein, whereas the right lymphatic duct drained into the junction of the right external jugular and subclavian veins, as is usually observed.

Discussion

Warren and Drinker\(^9\) demonstrated an increase in right lymphatic duct flow after pulmonary veins were compressed in a dog with an open chest. Lung lymphatic flow not only increased in quantity but promptly became sanguineous. Pulmonary arterial pressure rose to high levels as pulmonary veins were compressed. These general observations were confirmed in our study with an intact animal. More specifically, it would appear from our data that in acute experiments transudation of fluid across the pulmonary capillary membrane into the interstitial space occurred according to Starling's hypothesis,\(^9\) i.e., as soon as capillary pressure exceeded plasma oncotic pressure. The accumulation of a large amount of fluid in the interstitial space and the transfer of it across the alveolar membrane into the distal air sacs did not occur readily when left atrial pressure was only slightly above the presumed normal plasma oncotic pressure. The production of manifest pulmonary edema with signs of hypoxia was observed only after a considerable elevation of left atrial pressure was maintained for a period of half an hour or more in an otherwise normal dog.

Within the framework of our present experiment the removal of fluid via pulmonary lymphatics was small in amount and of little effect in preventing pulmonary edema induced by acute elevation of left atrial pressure. Maximum flow from the right lymphatic duct barely exceeded 0.3 ml./min., although the possibility exists that other lymph channels in addition to the right lymphatic duct drain the lung. Even if several channels were present, the amount of fluid that could be removed during the development of pulmonary edema would probably be little more than several ml./min.

The relationship of pulmonary lymphatic flow to chronic left atrial pressure elevation could not be completely evaluated. It was our intent to study pulmonary lymphatic flow at chronic left atrial mean pressure in the range of 25 to 40 mm. Hg, but we were unable to sustain left atrial mean pressure above 25 mm. Hg in any dog in our chronic group. The animals that were "pulled-up" to left atrial mean pressure between 30 and 40 mm. Hg and presumably sustained these high levels were found dead in their cages with pulmonary edema 1 to 2 days after tightening the snare.

The increase in hematocrit observed after a short period of high left atrial pressure suggested that a sizeable quantity of plasma was transferred from the blood into the interstitial space of the lung. Another indication that this may have occurred was our observation that right lymphatic duct flow remained elevated for as long as 1 hour after left atrial pressure had been restored to normal. The transfer of red blood cells across the pulmonary capillary membrane also occurred at high left
atrial pressures. Lymph from the right lymphatic duct became grossly sanguineous. The hematocrit of the lymph, however, never exceeded 2 per cent. It seems reasonable to assume that the number of red blood cells was small in comparison to the amount of plasma transferred across the capillary membrane in order to account for the increase in hematocrit observed in the blood.

The relationship of pulmonary vascular resistance to the distending pressure in the pulmonary capillary bed has been the subject of several recent reports. Borst and his associates demonstrated that pulmonary vascular resistance decreased as left atrial pressure was raised. These observations were made in dogs whose left lungs were perfused to maintain a constant pulmonary arterial pressure. A small change in a low left atrial pressure had a marked effect on pulmonary vascular resistance, whereas this effect was progressively less at higher left atrial pressure. Caxillill and her group reported similar findings in cats of which the left lungs were perfused at constant volume inflow. Our results in intact animals were substantially the same at low left atrial pressure up to 15 mm. Hg. In our study, however, at higher left atrial pressure pulmonary vascular resistance gradually rose to or higher than the value obtained at normal left atrial pressure. This observation is of interest since it can be interpreted as confirmatory that presumably reflex arteriospasm can occur when the pressure in the left atrium is critically increased.

The functional and anatomical changes often noted in lungs of patients with mitral stenosis have not been previously observed in experimental mitral stenosis. Similarly these changes, except for some hemosiderosis, were not observed in our chronic group, and this was puzzling since the degree of supravalvular stenosis present at necropsy was particularly marked. Several possible explanations are apparent. The dogs with supravalvular stenosis had functional mitral valves and therefore did not have any mitral regurgitation which invariably accompanies mitral stenosis to some degree in man. Secondly, our animals were observed for only one year or less; they were kept at rest in their cages and their pulmonary arterial pressures were not extremely high. Patients develop pulmonary arterial hypertension, increased pulmonary vascular resistance and fibrous intimal narrowing of small pulmonary arteries usually over a 10- to 20-year period. During this time they usually maintain full activity which necessarily demands a larger pulmonary blood flow probably with higher peaks of pulmonary arterial pressure than if they were to remain at rest, and these factors may play an important role in the pathogenesis of subsequent pulmonary alterations.

Rucker and his associates reported massive ascites after tightening a ligature around the mitral valve. However, Hamilton from this same group reported that when the inferior vena cava was carefully dissected away from the right atrial wall before the snare was placed, ascites did not occur. Under these circumstances there was no obstruction of the inferior vena cava. Our experience would confirm this point. Care was exercised to identify the inferior vena cava and the ligature was placed above and to the side of it. Ascites and other signs of right heart failure were not observed in any of our dogs in the chronic group.

**Summary**

Acute elevation of left atrial pressure could be precisely controlled at any desired level up to a mean of 60 mm. Hg in dogs with an intact thorax. The following observations were made in a series of 15 dogs. Right lymphatic duct flow did not increase at acutely elevated left atrial mean pressure below 25 mm. Hg, whereas flow increased to 4-fold at mean pressure above 25 mm. Hg. The total amount of lymph at maximum flow, however, was only 0.3 ml./min. Lymph flow remained elevated for as long as 1 hour after left atrial pressure was restored to normal. Elevation of left atrial pressure did not affect lymph flow in the thoracic duct. Pulmonary edema did not occur readily at left atrial mean pressure.
elevated only slightly above plasma oncotic pressure. The production of pulmonary edema was observed only after a considerable elevation of left atrial pressure above plasma oncotic pressure was maintained for a period of one half hour or more in an otherwise normal dog. The hematocrit increased significantly after a 10-minute period of high left atrial pressure. Pulmonary vascular resistance decreased sharply as left atrial mean pressure was raised from 0 to 15 mm Hg. The resistance gradually rose as left atrial pressure was raised to between 15 and 30 mm Hg. Pulmonary arterial pressure uniformly rose and cardiac output uniformly declined with increasing left atrial pressure.

Chronic elevation of left atrial pressure was achieved in 15 dogs. Left atrial mean pressure varied from 10 to 23 mm Hg. These dogs were followed up to 10 months and the following observations were made. Right lymphatic duct flow did not increase at chronically elevated left atrial mean pressure below 25 mm Hg. Flow was not studied at higher pressures since we were unable to sustain left atrial mean pressure above 25 mm Hg in any dog in our chronic group. The animals that were brought to left atrial mean pressure between 30 and 40 mm Hg and in whom these high levels were presumably maintained were found dead in their cages with pulmonary edema 1 to 2 days after tightening the snare. Many of the usual functional and structural changes often found in lungs of patients with mitral stenosis, except for hemosiderosis, were not observed in our experimental animals although the extent of the supravalvular stenosis produced was marked. Pulmonary arterial pressure rose slightly and cardiac output declined slightly. No change was noted in pulmonary vascular resistance. Ascites and other signs of right sided failure were not encountered.

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