Effect of Lung Denervation on Pulmonary Hypertension and Edema

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With collaboration of Robert W. Frykman and John Ognanovich

Under conditions of high pulmonary artery pressure and flow produced in dogs by a controlled systemic artery shunt, pulmonary edema occurred after denervation of the lung at arterial pressures that were tolerated without edema before denervation. Left atrial pressures were not altered by the shunt, which involved only one segment of lung. Observation of animals with shunts for 1½ to 10 months showed that denervation apparently did not affect the incidence of arteriosclerosis.

That vasomotor reactions in the pulmonary circulation have little physiologic importance has been widely taught. On the other hand, sympathetic nerve stimulation, hypoxia, or a sudden increase of pulmonary arterial pressure and flow have provoked increases of blood flow resistance easily interpreted as due to arteriolar constriction. Moreover, in experimental pulmonary hypertension persisting 2 weeks or more, the initial pathologic change observed in the pulmonary arterioles is muscular medial hypertrophy, suggesting that these vessels have been actively contracting. While the arteriolar muscle may act autonomously in response to stretching, abundant vasomotor nerves are present, making it plausible that a nervous reflex is involved. In the experiments to be described, we have tested the effect of denervating the pulmonary vessels when they are subjected to unusually high pressure and flow.

Materials and Methods

After a series of preliminary trials of various methods were performed in 11 young dogs weighing 10 to 15 Kg. The first 8 were anesthetized with pentobarbital and the last 3 with Pentothal sodium. They were connected by endotracheal tube to a cylinder type respirator, which exerted positive air pressure never exceeding 15 mm Hg during % of the cycle, and atmospheric pressure during the remainder. Alveolar carbon dioxide varied between 3 and 4 per cent with the respirator settings used. The operative preparation is shown in figure 1. The upper segment of the upper lobe was sacrificed for cannulations, and observations were made on the lower or lingular segment which represents about 6 per cent of both lungs by weight. Each upper lobe segment normally has a separate main artery and vein. A shunt of left brachial artery blood into the left pulmonary artery was made at the level of the pericardial reflection, with only the minimal dissection distal to this point required for insertion of cannulas. No anticoagulant was given the animal. Nerve supply of the lingular segment remained visibly intact. The venous cannula orifice was near the opening into the left atrium of the vein from the superior segment of the upper lobe. The artery to this segment was cannulated, perpendicular to the main artery, for measurement of upper lobe shunt pressure, which was regulated by constriction of the lower lobe branch with an adjustable tourniquet. Observations on the innervated lingular segment at various shunt pressures were made. If pulmonary edema had not developed, the shunt was occluded for about 5 min. and the vein, with occasional small accessory veins, artery, and branch of this segment, was dissected completely free of all adventitial structures, including nerves, lymphatics, and a branch of the bronchial artery, which was tied only proximally. The shunt was reopened for further observations. Lymphatics drained visibly as the pressure rose. The 5 mm bronchial cannula was left open, and air escaped with each inflation, so that as soon as any froth appeared in the bronchus it was detected. In 4 experiments, at the onset of edema, blood was drawn for measurement of plasma proteins, to compare with a sample drawn before the procedure started. The maximum decrease was 0.3 Gm. per cent, and in 2 dogs there was a slight increase, indicating that there was probably no consistent change in plasma osmotic pressure. The amount of saline injected during experiments was limited to less than 20 ml.
Delayed effects of denervation were looked for in 9 survivors of 20 young full-grown animals weighing 10 to 15 Kg. in which the systemic artery shunt entered only the left lower lobe, comprising about 26 per cent of both lungs by weight. In 3 of these dogs the lobe was completely removed and reanastomosed; in the other 6, the hilus was stripped, with division and reanastomosis of the bronchus in 3 of these. Blood flow was measured after opening the shunt, and at times when biopsies were taken, using an electromagnetic flowmeter similar to one described by Denison, Spencer, and Green,7 calibrated on excised shunt vessels perfused with saline. Pulmonary artery mean pressure was measured through a cannula inserted 1 cm. distal to the anastomosis, and the circular flowmeter electrode block was applied without compression just proximal to this point. Flow measurements were considered acceptable only when the shunt pressure was unchanged by application of the meter, and when the same 0 reading could be obtained by occluding the shunt distal and proximal to the meter, before and after repeated measurements. Histologic evaluation of lung biopsies was made by methods previously described.5

RESULTS

Immediate Effect of Denervation. In order to obtain data comparing lung tolerance to the same arterial pressures before and after denervation in the same animal, we drew on the information obtained in preliminary experiments, to judge approximately the maximum pressure the innervated segment would tolerate without becoming edematous. The actual level of pressure, the engorged appearance of the parenchyma, and an increase of surface fluid, were the signs observed. The guess was correct in six instances, listed in table 1.

Pressure was maintained at the indicated level for 5 to 20 min. in innervated lungs, was shut off while the segment was denervated, and was then slowly brought up toward the same level after denervation. If edema then developed, pressure rapidly rose even higher without further constriction of the lower lobe tourniquet. The pressures listed after denervation in the table are those at which edema began to appear. Left atrial mean pressure was measured 0 to 2 mm. Hg by opening the shunt, and was never above 6 mm. Hg.

When the first bit of colorless froth appeared in the bronchial cannula, large amounts of increasingly blood fluid rapidly followed unless the shunt was promptly closed. When the first edema fluid appeared, shunt pressure rapidly rose toward the aortic level, which simultaneously began to fall, due probably to extensive loss of fluid and blood. The end point at which pulmonary edema was recorded was therefore clearcut.

In the 5 remaining acute experiments, edema occurred at a pressure of 74 mm. Hg in one innervated segment, and at pressures of 76, 70, 60 and 75 in denervated segments, where pressures had not been raised equally high before denervation. In these 4 dogs the pressures used in innervated lungs were maintained 15 to 30 min. after denervation before raising them higher to produce edema. In the preliminary experiments, in which respiratory and osmotic

![Diagram of operated preparation.](http://circres.ahajournals.org/)

<table>
<thead>
<tr>
<th>Dog</th>
<th>Before denervation</th>
<th>After denervation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Shunt (mm. Hg)</td>
<td>Left atrial (mm. Hg)</td>
</tr>
<tr>
<td>820</td>
<td>50</td>
<td>4</td>
</tr>
<tr>
<td>842</td>
<td>58</td>
<td>0</td>
</tr>
<tr>
<td>856</td>
<td>54</td>
<td>0</td>
</tr>
<tr>
<td>945</td>
<td>58</td>
<td>*</td>
</tr>
<tr>
<td>950</td>
<td>90</td>
<td>5</td>
</tr>
<tr>
<td>975</td>
<td>82</td>
<td>4</td>
</tr>
</tbody>
</table>

* No venous cannula inserted.
pressures were uncontrolled, edema appeared in 17 denervated segments at an average pressure of 51 mm. Hg, and in 1 innervated segment at a pressure of 62. Pressures tolerated without edema in 7 innervated segments averaged 67.

Chronic Effect of Denervation. In 9 surviving animals of 20 with shunts into denervated left lower lobes, observations of pressure and flow were made at intervals from 1 1/2 to 10 months after operation (table 2). Three animals developed arteriosclerosis, with a questionable medial hypertrophy of a few arterioles appearing in 1 of these, and moderate and severe changes in the other 2. According to our previous experience, 7 out of 18 dogs with comparable operative shunt pressures in innervated left lower lobes developed vascular lesions after similar periods of time.5

The lobe in the animal with severe changes (dog 3, table 2) had been completely removed and reanastomosed, while the bronchus but not the vein was divided in the other 2 (dogs 2 and 6). Veins appeared to be freely patent at the time of biopsy in dog 3, but some narrowing undoubtedly was present. The sections showed no evidence of venous hypertension, however. Venules and capillaries were normal, and arterioles showed severe changes. Shunt pressure equaled aortic pressure, 125 mm. Hg.

TABLE 2.—Shunt Pressures and Flow after Chronic Systemic-Pulmonary Shunts with Denervation

<table>
<thead>
<tr>
<th>Dog no. and weight (Kg.)</th>
<th>Time (mo.)</th>
<th>Press (mm. Hg)</th>
<th>Flow (ml/min.)</th>
<th>Lung biopsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Op.</td>
<td>30</td>
<td>750</td>
<td>—</td>
</tr>
<tr>
<td>2</td>
<td>4 1/2</td>
<td>25</td>
<td>1000</td>
<td>—</td>
</tr>
<tr>
<td>3</td>
<td>Op.</td>
<td>30</td>
<td>500</td>
<td>—</td>
</tr>
<tr>
<td>4</td>
<td>5 1/2</td>
<td>—</td>
<td>—</td>
<td>Severe sclerosis</td>
</tr>
<tr>
<td>5</td>
<td>Op.</td>
<td>45</td>
<td>1600</td>
<td>—</td>
</tr>
<tr>
<td>6</td>
<td>Op.</td>
<td>35</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>7</td>
<td>Op.</td>
<td>44</td>
<td>900</td>
<td>—</td>
</tr>
<tr>
<td>8</td>
<td>Op.</td>
<td>30</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>9</td>
<td>Op.</td>
<td>32</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>10</td>
<td>Op.</td>
<td>30</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>11</td>
<td>1 1/2</td>
<td>8</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

Eleven other animals intended for chronic study died with pulmonary edema within 2 days after operation. Large amounts of fluid were formed, causing asphyxia and shock. The same shunt was well tolerated in a previous study using innervated lung.5 In 3 dogs in the present experiment, venous anastomoses contributed to the development of edema by causing partial venous obstruction. In the others, unmeasured increases of shunt pressure and flow associated with activity on recovery from anesthesia may well have precipitated the fatal edema. Left atrial pressures measured in 4 animals were elevated only 0 to 2 mm. Hg when the shunt was opened, but some left heart failure may have occurred later, when flow increased. Flow measurements repeated at intervals in 2 survivors (table 2) showed a decrease of resistance several months after operation. The other single measurements only serve to indicate high flow rates except in dog 3.

DISCUSSION

Pulmonary edema, clinically and experimentally, is usually associated with elevation of pulmonary venous pressure. Experiments in which edema occurs with elevation of arterial pressure alone have not, so far as we know, been previously described. In our experiments it has been possible to avoid an elevation of left atrial pressure while maximally increasing arterial flow, by confining the increased flow to a very small segment of lung. What the venous pressure at various levels within the small segment under test may have been is unknown. There seemed to be no way of measuring this pressure without changing it. We learned in the preliminary experiments that under conditions of high flow, the slightest venous kinking or occlusion was followed immediately by edema; for this reason we abandoned retrograde insertion of tiny venous pressure cannulae from the atrium, gave up suspending lobes on scales for...
detection of edema, and compromised on stripping the vein instead of dividing and reanastomosing it for more certain denervation.

Pressure measurements in systemic-pulmonary shunts are more difficult than they are in the normal circulation, because of the larger kinetic energy factor involved. The blood flow through the shunt is often in the range of the basal cardiac output of the animal, while the outside diameter of the pulmonary artery just past the anastomosis is only 5 to 6 mm., compared to an aortic diameter about twice as great. Since linear flow velocity is proportional to the square of the radius, flow in the shunt is about 4 times as fast as in the aorta. Hence the slightest change of axis of the pressure measuring cannula causes wide variations in the pressure record. There is also a great deal of turbulence in the flow. These observations cast doubt on the accuracy of all absolute values for pressure measurements made during high flow through the shunt. The comparative measurements shown in table 1, however, should be less affected. When the pulmonary vessels react by pathologic thickening, or when for any reason flow is reduced, pressures are again easily determined in the same location.

The effect of dividing the lymphatics was thought to be minimized by not tying them off. They drained freely, clear fluid at first, becoming bloody when edema developed. Division of the bronchial artery has no known effect other than to decrease response to vasomotor nerve stimulation.3 The shunt blood was always fully oxygenated, so that hypoxic effects were avoided.

To summarize our data and reconcile them with some related observations, the hypothesis may be considered that the passive distensibility of pulmonary arterial vessels in response to large increases in blood flow has an upper limit where active vasomotor regulation comes into effect. It may be further supposed that most previous studies of pulmonary resistance have not imposed an arterial load greater than the limit of passive arterial distensibility before testing for vasomotor activity. Some experiments have raised arterial pressure in such a way that left atrial pressure has also been increased, thus obscuring knowledge of arterial pressures that are tolerable in the presence of normal atrial pressure, and reaching the stage of pulmonary edema before reaching the limit of passive arterial dilation.6

Afferent nerve impulses, probably arising from the pulmonary arterioles have been demonstrated in vagal fibers.9 Together with the sympathetic vasoconstrictor nerves, they provide an anatomic basis for postulating an autonomic vasomotor reflex. Unlike the peripheral vasomotor mechanism, a pulmonary reflex does not ordinarily participate in control of flow or pressure, but may operate when pulmonary artery pressure is increased by a factor of 4 or 5, as in fetal life or with left to right shunts, and serve chiefly to protect capillaries from excessive arterial pressure. While there is definitely a greater susceptibility to edema with high arterial pressure after the denervation procedure, there might be some protection against development of arteriosclerosis, if normally a contraction of the arteriolar muscle, activated through its nerve supply, produces further resistance and still higher pressure. Our data do not support this idea, but more extensive long-term observations may reveal some measurable chronic effect of denervation.

SUMMARY

Segments of dog lungs were subjected to high pressure and flow of systemic arterial blood through the pulmonary artery, before and after denervation, which was performed by stripping the hilus down to pulmonary artery, vein, and bronchus. Edema occurred in 6 dogs after denervation at arterial pressures tolerated without edema for 5 to 20 min. before denervation. In 28 other experiments edema occurred at various arterial pressures, generally higher in innervated segments. Left atrial pressures were not elevated.

In longer term observations, 3 of 9 dogs with left lower lobe systemic artery shunts developed arteriosclerosis within 1½ to 10
months after denervation, compared to 7 of 18 dogs with innervated lungs observed in a previous study. Eleven other dogs in the denervated group died with pulmonary edema shortly after operation.

**SUMMARY IN INTERLINGUA**

Segmentos de pulmones canin esseva subjicit a alte nivellos de pression e fluxo de systemic sanguine arterial in le arteria pulmonar ante e post disnervation que eseva effectuate per disnudar le hilo usque a pulmonar arteria, vena, e broncho. Edema occurreva in 6 canes post disnervation a pressiones arterial que eseva tolerate sin edema durante 5 a 20 minutas ante le disnervation. In 28 altere experimentos, edema occurreva a varie pressiones arterial que eseva generalmente plus alte in segmentos non disnervate. Le pressiones sinistro-atrial non eseva elevate.

In studios plus durative, 3 ex 9 canes con derivationes de arteria systemic del lobo sinistro-inferior disveloppava arteriosclerosis intra 1½ e 10 menses post le disnervation. Isto es a comparar con le mesme effecto observate in un previe studio in 7 ex 18 canes con pulmones non disnervate. Dece-un altere canes in le grupo disnervate moriva con edema pulmonar brevemente post le operation.

**REFERENCES**

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