Influence of Airway Pressures on Edema in the Isolated Dog’s Lung

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POSITIVE pressure ventilation is used widely in the treatment of pulmonary edema, but mechanisms which explain its effect have not been investigated since 1938. In the experiments described here, the influence of inflation and of airway pressures upon fluid accumulation in isolated lung tissue was studied.

Methods

In anesthetized (sodium pentobarbital, 25 mg./Kg.), heparinized (2 mg./Kg.) dogs under positive pressure ventilation, the left lower lobe was excised after occluding the lobar pulmonary artery; the lobe, while in the collapsed state, was weighed on a balanced scale. At the same time, the right lower lobe was excised, placed on the balance and trimmed so that the two lobes had identical weights. The hemoglobin content of the excised right lobe was assumed to represent the blood content of the left lower lobe before perfusion. The cannulated pulmonary vessels of the left lower lobe were connected with a system of adjustable reservoirs which permitted perfusion with blood obtained from the femoral artery of a donor dog at any desired level of nonpulsatile inflow or outflow pressures. The rate of spillover from the venous reservoir could be measured before the blood was returned to the donor dog's femoral vein. In some experiments, the lobe was perfused with pulsatile pressure directly from the donor's femoral artery. T-connections close to the inflow and outflow canulae permitted registration of the pulmonary arterial and venous pressures. Infra-red heat lamps controlled the temperature of the blood in the perfusion reservoirs; occasional stirring prevented sedimentation. The lung preparation was mounted on a wire-mesh platform which was suspended from a lever connected to a bonded strain gauge, permitting continuous weight registration. The registration system recorded changes in weight of 1.0 gram or more.

At the beginning of an experiment, the blood reservoirs were changed while the airway pressure remained atmospheric. In most of the experiments, the perfused lobe was then inflated with air at various static pressures or ventilated with intermittent positive-negative pressure. In five preparations, the lobes were not inflated, but remained collapsed; when such collapsed lobes had gained weight they were homogenized and their hemoglobin content was compared with control specimens. Blood hemoglobin content was measured at the beginning and at the end of perfusion. The blood content of control and edematous lobes could thus be compared, and weight gain due to increased blood content could be distinguished from weight gain caused by accumulation of edema fluid.

Results

Fluid Accumulation in the Collapsed Lung

When the blood conduits were suddenly opened with the reservoirs at “normal” pressures (arterial reservoir, 15 to 20 mm. Hg; venous reservoir, 0 to 3 mm. Hg), the weight of the lobe increased steeply within 15 seconds; after this initial “step,” the lung weight reached a stable plateau within a few minutes which did not vary when the experimental conditions were kept constant. The blood flow through the perfused lobe changed in the same stepwise direction as the lung weight and amounted to 130 to 300 ml./min. Edema accumulation in the perfused lobe was apparent when the lung weight, at constant perfusion pressures, showed a continuous weight gain without reaching a plateau. When fluid accumulation was present, the blood flow through the collapsed lobes did not usually decrease (and vascular resistance did not increase) until the lobe had gained about 100 per cent of its control weight.

Fluid accumulation in the perfused lobe...
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Table 1

<table>
<thead>
<tr>
<th>Experiment no.</th>
<th>Lobe weight (Gm.)</th>
<th>Weight gain</th>
<th>Hb content (Gm.)</th>
<th>Blood Hb (Gm.% before</th>
<th>Blood holdup of exp. lobe after perfusion</th>
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<tr>
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<td>Exp.†</td>
<td>Control†</td>
<td>Exp.†</td>
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<td>49.0</td>
<td>19.0</td>
<td>1.57</td>
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</tr>
</tbody>
</table>

*Control = right lower lobe of equal weight before perfusion.
†Exp. = left lower lobe after perfusion with abnormal pressures.

was always observed when the outflow pressure was above 20 mm. Hg and the inflow pressure above 35 mm. Hg. At higher pressure gradients, edema formed at more rapid rates, in proportion with the increase of gradient or of outflow pressure. In several preliminary experiments, when lobes were perfused directly from a femoral artery, the discharge of edema fluid from the lobar bronchus was related to the mean arterial pressure and was not influenced by pulsatile characteristics of flow or pressure. Edematous lobes sometimes gained 150 per cent of their control weight, although no attempt was made to produce "maximal" pulmonary edema. In two experiments, outflow pressures below 20 mm. Hg resulted in fluid accumulation (fig. 1). When normal perfusion pressures were restored after episodes of pulmonary edema, the weight of the perfused lobe decreased more slowly than it had risen, never descending to the control weight (except when the osmotic pressure of the perfusion blood was increased intentionally). Irrespective of the magnitude of fluid accumulation, the airways of collapsed lobes did not discharge fluid of any kind, unless extremely high pressures were reached, when frank blood issued from the bronchus.

The question arose whether fluid accumulation in a collapsed lobe was due to interstitial hemorrhage or other blood trapping, or whether it was due to edema. Table 1 compares the hemoglobin content of edematous, perfused lobes with the hemoglobin content of nonperfused control lung tissue taken from the same animal. It is evident that blood holdup accounted for only about 10 per cent of the total weight gain of edematous lobes. In one instance (experiment 7), the increased blood content in the perfused lobe amounted to 12.4 Gm.; in this experiment there was frank hemorrhage from the airways which did not exist in the other preparations.

Influence of Inflation and of Airway Pressure upon Pulmonary Edema

When collapsed lobes were perfused with abnormal pressures, fluid did not issue from the airways even when the lobes continued to gain weight. In 24 experiments, the lobes were rapidly inflated with the least positive pressure needed for inflation (usually between 15 and 25 cm. H2O) while perfusion with abnormal pressures continued. Inflation changed the appearance of the lobes to the typical consistency and pink color of normally ventilated lungs. Within a few minutes after inflation, when the airway was at atmospheric pressure or slightly above, fluid began to issue from the bronchi. The initial color of the fluid was blood-tinged, but soon became clear and foamy, having the typical appearance of pulmonary edema. Inflation of the lobe or variation of the static airway pressure did not influence the rate of fluid accumulation when other factors were constant (fig. 2). After edema fluid had started to issue from the bronchi, increases of the airway pressure to levels ranging from 5 to 40 cm. H2O arrested the fluid discharge from the airway, but the lobe gained weight in proportion to the amount of fluid which would have issued from the airway at atmospheric airway pressure.
Figure 1

Changes of lobe weight as influenced by perfusion pressures, inflation, and airway pressure. (PAP) inflow pressure; (PVP) outflow pressure. Note weight registration slope, denoting fluid accumulation after increase of (PVP). Artifacts of lobe weight at 11 and 12 minutes.

In three experiments, isolated lobes were perfused with abnormal pulsatile pressures while ventilated with intermittent positive or positive-negative pressures. Intermittent ventilation resulted in cyclic changes of the blood content and bronchial fluid discharge to an extent which seemed to preclude accurate, continuous registration of lobe weight. In these experiments, the previously reported relationship between airway pressure and pulmonary vascular resistance was confirmed. "Pulmonary edema" was not prevented by intermittent positive pressure ventilation, as indicated by the increased lobe weights after periods of perfusion with abnormal pressures, and by the appearance of bronchial discharge whenever the pressure in the airway was kept below 5 cm. H₂O for more than two minutes.

Discussion

Experimental pulmonary edema has often been studied as an end result, but its evolution has been followed only in a few studies mentioned below. Born recorded the weight of isolated rabbit lungs which were perfused with modified saline solutions. Cook et al. studied ventilation mechanics during experimental pulmonary edema in dogs; prolonged congestion produced a striking decrease in lung compliance, but the influence of airway pressure on pulmonary edema was not investigated. Analysis of edematous lungs with the methods of ventilation mechanics have not established unequivocal criteria which would identify or measure the development of pulmonary edema because changes of airway resistance and of lung compliance can be caused not only by edema and congestion, but also by decreases of the pulmonary or systemic blood volumes and pressures. Aviado and Schmidt followed the development of pulmonary edema by recording differential radioactivity of lung tissue when perfused with tagged red cells and albumin. This method dissociated pulmonary congestion from transudation. "Lung opacity" has also been used as a criterion, but it seems doubtful whether this measurement can distinguish between pulmonary edema and congestion.

Positive pressure ventilation is a universally accepted treatment for pulmonary edema. Barach, Martin, and Eckman attributed the effect of positive pressure not only to tamponade of the great veins (with resulting decreases of cardiac output, systemic arterial
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pressure, and load on the left heart), but also to "a direct opposing physical force in the external capillary wall, tending to counteract the tendency to ooze serum." Although Alt- schule11 questioned the existence of such a direct physical force and explained the therapeu tic effect of positive pressure breathing in terms of reduced cardiac load, a recent re view12 gives full currency to the earlier con cepts of Barach, Martin, and Eckman.

Fluid accumulation in isolated perfused lungs was recorded here by means of electrical weight registration. Hemoglobin measurements in control and edematous specimens showed that blood contributed only about 10 per cent of the accumulated fluid and that the other 90 per cent of the weight gain was, therefore, explained by accumulation of transudate. The appearance of the fluid discharge from the airways of inflated lungs during perfusion with abnormal pressures was additional evidence in favor of this interpretation.

Isolated lobes could be perfused for pro longed periods at normal pressures without the occurrence of the characteristic weight slope denoting pulmonary edema. As soon as the perfusion pressures were increased to abnormally high levels, fluid started to accumulate in the perfused lobes, as is evident from the slope of the weight registration. Fluid continued to accumulate as long as abnormal pressures were maintained; the rate of edema formation could be varied at will by changes of the reservoir levels, but was not influenced by the presence or absence of air in the alveoli. This is an interesting fact because the literature does not contain information about edema in atelectatic lung tissue.

When intermittent, instead of static, infla tion was used, the trace of lobe weight reflected not only accumulation of edema fluid, but also fluctuations of blood content, and was therefore difficult to interpret. However, edema could be measured from the weight gain and fluid discharge of the lobe during perfusion. Preliminary experiments indicated that the intermittent character of positive airway pressure did not influence the rate of edema formation.

If the direct physical force exerted by posi tive airway pressure upon the alveolar wall would retard transudation of fluid from the lung capillaries, it should have been possible to demonstrate this effect in the system described here. However, inflation of collapsed lungs or increased static positive airway pressure did not change the rate of fluid accumulation, although fluid discharge from the airway was completely arrested with relatively low static airway pressures. The data suggest that airway pressure per se does not influence edema formation, but that positive airway pressure may have shifted the accumulating transudate from the alveoli into the interstitial or intracellular13 spaces of the lung. We are forced to conclude that positive pressure ventilation counteracts clinical pulmonary edema by indirect mechanisms: it decreases the blood volume of the lesser circulation, cardiac output, and cardiac load by venous tamponade or by decreasing systemic resistance;14 it may dilate the airways; and it can improve alveolar gas exchange. A direct physical effect of airway pressure upon transudation in lung tissue was not evident in our experiments.

Summary

The left lower lobe of anesthetized, hepa rinized dogs was excised, weighed, and cannu lated. Another lobe of the same dog was excised for control purposes. The cannulated lobe was perfused by a system of adjustable reservoirs which was fed with fresh blood from a donor dog. The perfused lobe was mounted on an electronic balance so that weight changes could be recorded together with the pressures in the inflow and outflow conduits and in the bronchus. When the perfusion pressures were varied within normal limits, the weight of the lobes reached stable plateaus. Abnormally high perfusion pressures caused a continuous, steady increase in lobe weight, which was evident from the slope of the weight registration. Blood holdup in the lobe was measured by comparing the hemoglobin content of the control lobe with that of the experimental specimen taken at the end of an experiment. Blood holdup accounted for

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only about 10 per cent of the weight increase of edematous lobes. Initial observations were made in collapsed lobes; in the course of some experiments these lobes were inflated and the static airway pressures were then kept at varying levels.

Irrespective of the perfusion pressures, transudate did not issue from the airway as long as the lobe was collapsed. Abnormal perfusion pressures caused the accumulation of fluid, which continued as long as the perfusion pressures were constant. The rate of transudation was determined by the perfusion pressures and was not influenced by inflation of the collapsed lobe nor by variations of the static airway pressure. When a collapsed lobe had become edematous and was then inflated, transudate issued from the airway. Increases of the static airway pressure did not decrease the rate of fluid accumulation, but only confined the transudate to the lung and prevented its discharge from the airway.

Acknowledgment

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References

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