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Differentiation of Pulmonary Congestion and Edema in the Rat, Induced by Epinephrine, and Their Modification by Various Procedures.* (29821)

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Various techniques have previously been designed to measure shifts of blood in the pulmonary circuit and to attempt to determine the relative degrees of pulmonary edema and congestion when present. The methods used in this study were designed to determine how the changes in wet lung weight were related to the directional shifts of blood within the pulmonary circuit and the relative extent of pulmonary edema formation. The modification of these parameters by several agents was studied.

Methods. Sprague-Dawley albino rats usually weighing over 400 g were divided into 9 experimental groups of 8 animals per group. A tracheotomy was performed on each animal after anesthesia with ether or pentobarbital (40-50 mg/kg). Pressure was monitored from the femoral artery using a polyethylene cannula connected to a Statham pressure transducer and a Sanborn recorder. Epinephrine, 0.01%, was infused through a femoral vein at a rate adjusted to give maximum mean systemic arterial pressures for each rat, free of irregularities. The length of infusion varied from 25 to 35 minutes for each group of animals during which time approximately one milliliter of solution was infused. At the end of each experiment, the animals were sacrificed by removing the arterial cannula to allow hemorrhage and opening the chest to prevent intrathoracic pressure. The lungs were immediately removed and their wet weight recorded. Drying of the lungs was accomplished by placing them under a lamp at a temperature of 50°C until a constant weight was attained.

Some of the experiments were modified by giving each animal a single intraperitoneal dose of atropine sulfate (5 mg/kg) 10 to 20 minutes prior to beginning the epinephrine infusion. In other experiments a Physiograph small animal respirator was used to supply an inspiratory pressure of 15 cm of water at a rate of 70 inspirations per minute and an inspiratory-expiratory ratio of 1:2, respectively; expiration was passive.

Wet lung weight to animal body weight ratios and wet lung weight to dry lung weight ratios were calculated for each experimental animal. These ratios were then totaled for each experimental group and the arithmetic mean and standard deviation (SD) were calculated for each group.

Computations. An accepted method for determining the extent of pulmonary edema and congestion is the index of the wet lung weight to body weight ratio(1). Various increments above control level in this ratio indicate a progressive increase in degree of pulmonary edema and/or congestion. It is often difficult to separate the relative extent of the two conditions. Guyton and Lindsey(6) used a method for determining relative increases in the amount of edema fluid formation in the lungs. Using wet lung weight to dry lung weight ratios they were able to establish an index of edema fluid formation. They based

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their findings on the results of measurements of wet and dry blood weights. It was found that the ratio of wet to dry blood weight was the same as the ratio of wet to dry lung weight for normal animals. This meant that any variation in the amount of blood sequestered in the lungs would not change the wet to dry lung weight ratio. However, edema fluid formation would be reflected as an increase in the ratio and its relative amount could be determined.

Using these principles, a method was formulated for quantitating the amount of edema fluid formation for the purpose of separating increases in the wet lung weight to body weight ratio into 2 different components, namely, that part due to edema fluid formation and the part due to congestion (blood).

The wet to dry lung weight ratio can be expressed as grams of wet lung weight per kilogram of body weight, to grams of dry lung weight per kilogram of body weight. This does not change the value of the ratio in any way. In this form the ratio becomes more useful for determining the quantitative difference in increase of wet lung weight between control and experimental groups. This may be accomplished as shown by the equation:

$$\frac{\text{Experimental}}{\text{g WLW/kg BW}} - \frac{\text{Controls}}{\text{g WLW/kg BW}} = \frac{\text{Difference}}{\text{g WLW/kg BW}}.$$
$$\frac{\text{g DLW/kg BW}}{\text{g DLW/kg BW}} - \frac{\text{g DLW/kg BW}}{\text{g DLW/kg BW}} = \frac{\text{g DLW/kg BW}}{\text{g DLW/kg BW}}.$$

Subtracting the control ratio from the experimental and solving the equation for the numerator of the difference will yield the amount of increase in the wet lung weight specifically due to an increase in edema fluid formation. Since this expression is in the same mathematical form as the index of wet lung weight to body weight it may be subtracted directly. Any remaining increase in the wet lung to body weight index, over the control value, can be attributed to accumulation of blood in the lungs.

Results. Maximum mean systemic pressures attained, free of irregularities, varied from 165 to 210 mmHg with the majority in the range of 180 to 195 mmHg. The pressure ranges attained were comparable for the various experimental groups. Table I and Fig. 1 present the wet lung weight to body weight ratios and wet lung weight to dry lung weight ratios for the controls and various experimental procedures.

TABLE I

Experimental group	WLW/kg BW ratio Mean	SD	WLW/DLW ratio Mean	SD
Pentobarbital control	4.37	.28	5.07	.17
Pentobarbital-Epi.	5.92	.77	5.07	.62
Pentobarbital-Epi.-atropine	4.76	.45	4.91	.47
Pentobarbital-P.P.B.	5.21	1.04	5.65	.69
Ether control	4.40	.27	5.24	.20
Ether-epinephrine	7.80	1.70	7.17	1.30
Ether-Epi.-atropine	7.80	2.68	6.17	1.44
Ether-Epi.-P.P.B.	7.00	2.80	6.86	1.60
Ether-Epi.-P.P.B.-atropine	4.60	1.00	5.41	.55

Discussion. It can be seen from the accompanying table and chart that the various procedures and drug combinations resulted in a considerable modification of the wet lung to animal body weight ratios and wet lung to dry lung weight ratios. A study of these differences and ratios provides a means of estimating the relative extent of edema fluid or congestion development.

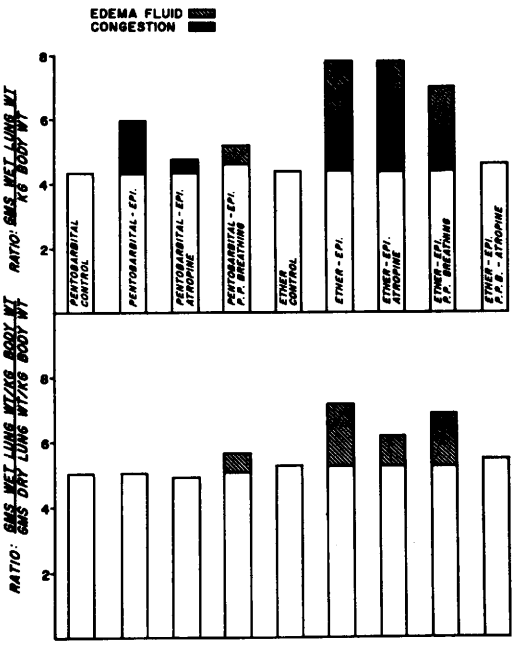

FIG. 1. Ratios of wet lung weight to body weight and wet lung weight to dry lung weight resulting from various experimental procedures.

Several related factors are apparent upon inspection of Table I and Fig. 1 which show the results of each experimental group. It can be seen that rats anesthetized with pentobarbital developed a considerable degree of congestion when infused with epinephrine; however, edema fluid formation was not evident except for a small amount found in one group where positive pressure breathing was used. Atropine apparently had a considerable effect in reducing edema fluid formation in one group of rats anesthetized with ether. Reports have indicated that atropine causes an increase in heart rate resulting in an increased cardiac output in the dog(2) and also in man(5). This effect of atropine could explain, in part, the decrease in congestion noted in the group of rats anesthetized with pentobarbital. In contrast to this finding, it can be seen in one group of rats anesthetized with ether that atropine apparently contributed to increased congestion. No explanation for this paradox is suggested.

Positive pressure breathing invariably reduced or prevented congestion in each experimental group where it was used. It can be seen that this effect is much greater in rats anesthetized with pentobarbital than in those anesthetized with ether, except in one experimental group where atropine was used concomitantly with positive pressure breathing in rats anesthetized with ether. In the latter case, the combined use of these 2 agents completely prevented the development of pulmonary edema or congestion. It can also be noted that neither atropine nor positive pressure breathing had any effect when each agent was used alone in rats anesthetized with ether. The effect of positive pressure breathing to reduce congestion in the lungs as shown in these experiments is supported by the work of Fenn *et al*(4).

The congestive effects of epinephrine have long been known. There is still some disagreement among investigators about the action of epinephrine on the pulmonary vascular system(2,3,7). It can be stated that epinephrine has far greater pharmacological action on the systemic circulation than on the pulmonary circulation. However, it is by this greater action on the systemic circulation that the resultant effect of pulmonary congestion occurs along with formation of pulmonary edema(8).

Summary. 1. Infusion of epinephrine, intravenously, into rats at a rate which maintained the mean arterial pressure at the maximum level that could be attained free of cardiac irregularities for 25-35 minutes resulted in formation of marked pulmonary edema and congestion in most animals anesthetized with ether and in congestion only in animals anesthetized with pentobarbital. 2. A method is presented for differentiating quantitatively between the relative amount of edema and congestion developed. 3. Positive pressure breathing invariably reduced or prevented the congestive effects of epinephrine in the lungs in rats anesthetized with ether and those anesthetized with pentobarbital. 4. Atropine reduced congestion in rats anesthetized with pentobarbital and apparently aggravated congestion in rats anesthetized with ether. 5. The combined use of atropine and positive pressure breathing prevented the development of pulmonary edema or congestion in rats anesthetized with ether.

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