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Hypoxia and Edema of the Perfused Isolated Canine Lung* (33796)

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In view of the persistence of the concept that hypoxia may play a role in the production of lung edema suggested by Maurer (1) and Drinker (2–4), a direct study has been made of the effects of variations in oxygen saturation of the blood on rates of weight gain in the isolated perfused canine lung.

Methods. Portions of the lungs of dogs removed after anesthetization with sodium pentobarbital (30 mg/kg) were suspended on a Strain gauge torsion balance, after cannulation of the pulmonary artery and the trachea. The connecting tubing was suspended to the arm and fulcrum of the balance and weights placed on a counterpoise pan to allow continuous measurement of changes in weight of the lung to be made to an accuracy of 1 g, following the method of Stish *et al.* (5). Besides lung weight, measurements were also made continuously of pulmonary artery perfusion pressure and pulmonary blood flow rate. Periodic measurements of blood oxygen saturation were made in some experiments using a Gilford densitometer with blood withdrawn from the pulmonary vein collecting system. Heparinized autologous

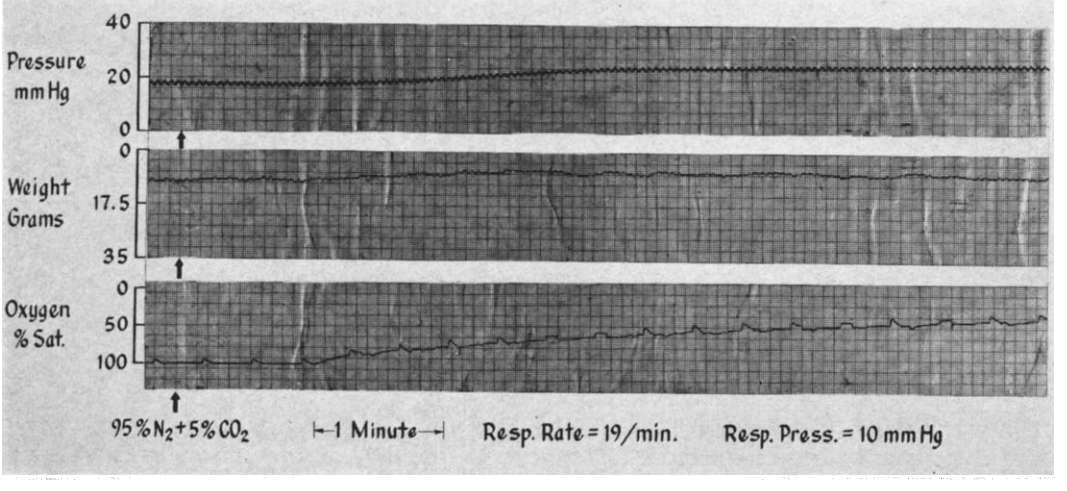

FIG. 1. Associated with the decline in oxygen saturation, there is an initial rise in pulmonary artery pressure and a decline in lung weight. Blood flow was kept constant.

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whole blood was employed for perfusion. The left atrium was trimmed off from the pulmonary veins and blood allowed to flow through a large collecting funnel leading to a collecting cylinder from which it was pumped to a temperature controlled reservoir. From the latter it was delivered to the pulmonary artery by a sigmamotor pump at controlled rates. The lungs were ventilated with appropriate gas mixtures, as indicated in the description of the experiments, using a Harvard respiration pump.

Figure 1 shows a continuous record over a number of minutes at constant blood flow, of the pulmonary artery pressure, the lung weight changes and the oxygen saturation, following a change in the ventilation mixture from 20% O_2 + 75% N_2 + 5% CO_2 to 95% N_2 + 5% CO_2. It will be noted that associated with the decline in oxygen saturation to about 70% there is a rise in pulmonary artery pressure and a decline in lung weight of about 3.5 g. The decrease in lung weight is to be ascribed to arterial vasoconstriction. After the initial changes, both the pressure and weight become stabilized. When the pressure is raised by increasing the rate of delivery of blood, as shown in Fig. 2, there is an increase in lung weight over the first 30–60 sec, after which the weight remains constant unless the threshold for edema is exceeded in which case there is a continuous gain in weight

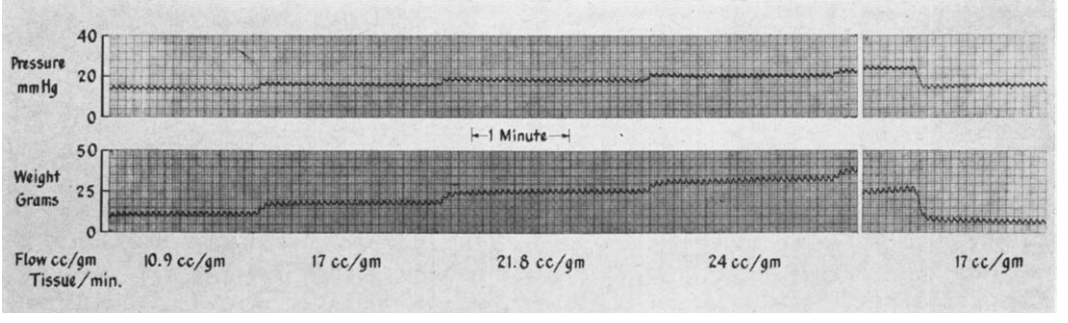

FIG. 2. The pressure and weight of the lung stabilize within 30 sec when flow is increased to values below the edema threshold level. When flow was increased to 24 ml/g, which exceeded the threshold for the particular lung, it showed a continuous gain in weight. When the flow was returned to 17 ml/g, the weight returned to a lower level and became constant.

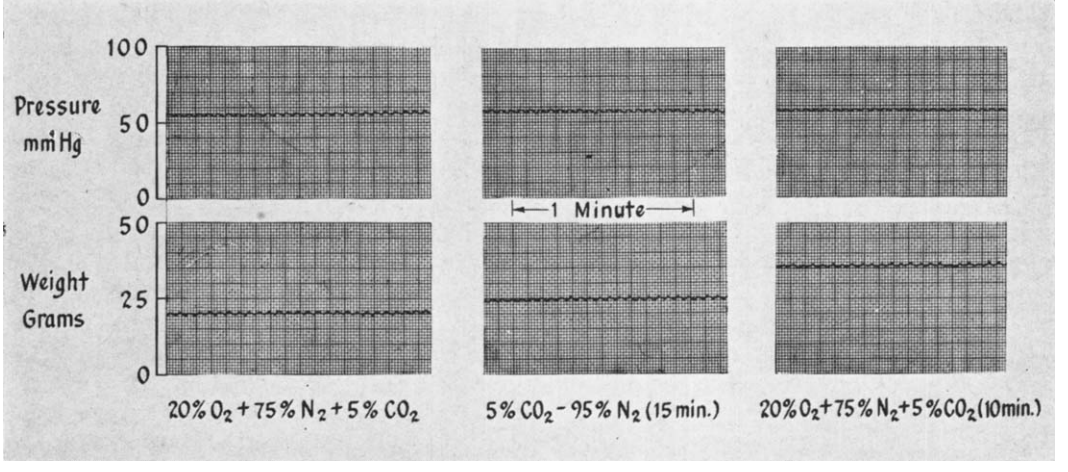

FIG. 3. The slope of the weight line remained unchanged when the lung was ventilated with 95% N_2 + 5% CO_2 for 15 min at a perfusion rate and pressure just below the threshold for edemogenesis.

TABLE I. Effect of Hypoxia on Rate of Sustained Lung Weight Gain.

Lung no.	(flow/g; ml/min)	PA pressure (mm Hg) 75% N_2, 20% O_2, 5% CO_2	95% N_2, 5% CO_2	75% N_2, 20% O_2, 5% CO_2	Rate of sustained wt. gain[a] 75% N_2, 20% O_2, 5% CO_2	95% N_2, 5% CO_2	75% N_2, 20% O_2, 5% CO_2	Duration of 95% N_2, 5% CO_2 (min)	% Saturation during hypoxia
10B	57	51	47	47	16.0	0	12.0	11.0	26
6B	102	81	83	80	20.0	20.0	20.0	15.0	20
11B	105	37	42	36	16.0	16.0	16.0	13.0	25
7B	107	55	57	54	3.6	3.6	3.6	15.0	23
1B	175	77	80	78	10.9	10.9	10.9	9.0	32
12B	215	51	54	50	8.0	6.0	8.0	20.0	19
2B	305	55	58	54	6.6	4.0	4.0	37.5	10
5B	407	91	87	89	28.6	28.6	24.0	8.0	35
Mean					13.7	11.1	12.3		

[a] (g/5 min/10 g of dry lung tissue).

which occurred at 24 ml/g/min in this case. The rate of gain in weight that occurs following the vascular adjustment phase is employed as a measure of the rate of edema formation. The weight changes due to pressure changes are rapidly reversible by reversing the pressure conditions. The changes due to edema formation are only very slowly reversible.

Experimental Results. In seven lungs experiments were performed in which measurements were made of rates of lung weight gain at various blood flow rates while they were ventilated, first with 20% O_2 + 75% N_2 + 5% CO_2, second with 95% N_2 + 5% CO_2 and finally again with the first gas mixture. Figure 3 presents graphically the record of the perfusion pressure and the lung weights during portions of an experiment when the pressures were below the threshold values for edemogenesis in the lung in question. It may be noted that the lung weight was constant during each of the three periods. The differences in weight in the three periods are due to the fact that in intervening periods, which are not shown, the lung had been exposed to flows and pressures above the threshold for edema production.

Table I presents a summary of the relevant data from eight experiments in which the pulmonary blood flow rates were duplicated precisely in the control, nitrogen, and second control periods, at levels producing pressures which caused edema. It was decided to compare the rates of edema formation at identical flows rather than at identical pulmonary artery pressures because hypoxia is known to produce changes in pulmonary arterial resistance as already shown in Fig. 1. During the hypoxic situation there is usually, but not invariably, an increase in arterial resistance which might make capillary pressures lower, at constant arterial pressures and thus might mask an edemogenic effect of the hypoxia. It is shown that at blood oxygen saturations between 10 and 32% there is no evidence that hypoxia increases the rate of lung weight gain. The differences between the means are not statistically significant. In no case was the rate higher under hypoxia than

under the first control oxygenation condition. In one instance in the second oxygenation period the weight gain was slightly lower.

Additional experiments were performed in which the thresholds of pulmonary artery pressure at which edema began to be formed were determined and it was found, as shown in Fig. 4, that in 20 out of 21 trials on seven lungs the pulmonary artery pressure necessary to produce edema was either the same or higher in the hypoxic than in the normal oxygenation condition.

Experiments were also performed on 12 dogs which were intact except that they were placed on a left atrial–femoral artery bypass. The left atrial blood was passed through an oxygenator before being returned fully saturated to the femoral artery to be distributed via the aorta to the entire body. In the hypoxia group the lungs were ventilated with 95% N_2 + 5% CO_2 for 45 min and oxygen saturation in the left atrial blood fell to 42%,

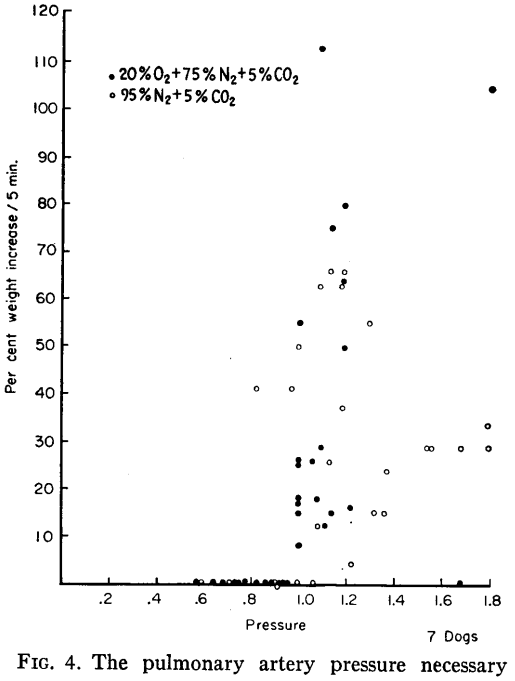

FIG. 4. The pulmonary artery pressure necessary to produce edema when the lung was ventilated with 20% O_2 + 75% N_2 + 5% CO_2 was taken as 1. The pressures necessary to produce the same rate of lung weight gain when ventilated with 95% N_2 + 5% CO_2, divided by the control pressures are shown on the graph.

on the average, the range being from 20 to 50%. A control series was carried out in which the bypass was established and the lungs were ventilated with room air for the same time. The lungs were excised and wet and dry weights were determined and compared in the two series, employing the ratios of lung weights to wet heart weight and to total body weights for comparison. The results indicated that 45 min to exposure to such low oxygen saturations did not increase the wet weights of the lungs, referred either to heart or body weights of the animals. In fact, the mean values for the ratios were slightly but not significantly lower in the low oxygen as compared with the normal oxygen groups. These experiments were performed primarily to give evidence that the totally isolated lungs did not behave differently from the lungs in the whole body, with the nervous system intact and with the blood passing through the entire body before being returned to the lungs.

Discussion and Conclusions. There is renewed interest in the possible effects of hypoxia upon pulmonary capillary permeability to protein in connection with the pathogenesis of high altitude pulmonary edema (6). This study was initiated partly to test the question of whether hypoxia of degrees compatible with survival of an animal did or did not induce pulmonary edema while pressure conditions were held constant. The results reported indicate that hypoxia at even lower levels of oxygen tension do not promote pulmonary edemogenesis. Haddy *et al.* (7) found that pulmonary edema occurred in intact dogs breathing low oxygen mixtures only when left atrial pressure was elevated. They ascribed the edemogenic effect of hypoxia in the intact dog to left ventricular failure with its consequent hydrodynamic pressure effects.

There is also a possible effect of hypoxia in the intact animal which would involve the liberation of vasoactive substances which might influence pulmonary capillary filtration pressure. Edema might be induced by pulmonary venoconstriction by such agents. Kuida *et al.* (8) showed that the pulmonary capillary pressure as measured by the pulmo-

nary artery wedge method in the bovine is increased at high altitude in brisket disease. Aviado (9) showed an increase in pulmonary artery wedge pressure in hypoxia in dogs. Gilbert *et al.* (10) have demonstrated that epinephrine, norepinephrine, histamine, and 5-hydroxytryptamine at appropriate dose levels cause pulmonary venoconstriction in isolated perfused lungs and could therefore under some circumstances induce pulmonary edema.

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Prevention of Drop in Adrenocortical Activity in the 7-Day-Old Rat by Pretreatment with ACTH* (33797)

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It has been recently established that the neonatal rat responds to certain stressors with increased plasma corticosterone (1–3). The response is high at birth, diminishes to a low value by day 7, and then progressively increases, reaching the adult-type response by day 21. This biphasic pattern of corticosterone production has also been demonstrated after treatment with ACTH (4, 5).

An important question that can be raised is why the adrenal cortex fails to respond in the 7-day-old rat? Since hypophysectomy leads to a decreased sensitivity of the adrenal cortex to ACTH (6), we argued that a relative lack of ACTH might be the responsible factor and could lead to the decreased steroidogenic response to ACTH (7). On the basis of such reasoning, the following experiment was designed to test this hypothesis: neonatal rata were primed with ACTH in beeswax-oil on day 5 of age and tested with ACTH in 1% albumin on day 7.

Materials and Methods. In all experiments female Purdue-Wistar rats and their litters were maintained under normal colony conditions: a light schedule of 13 hr light and 11 hr dark (lights went on at 7:00 a.m.), a temperature range of 72–74°F, and a relative humidity of 45–55%. Food and water were given *ad libitum*. The morning on which the litters were found was designated as day 1. On this day all litters were reduced to 6 female pups and were not disturbed until day 5.

At 3:30 p.m. on day 5 the litters were removed, weighed, and marked, and given a single (subcutaneous) injection of either 2, 5, or 10 IU of ACTH[2] suspended in 0.1 ml of beeswax-oil[3] (8–10) or the vehicle alone.

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[2] The ACTH was obtained through the courtesy of Dr. James W. Bastian, Armour Pharmaceutical Co., Kankakee, Ill.

[3] The beeswax-oil vehicle was obtained through the courtesy of Dr. Robert Kroc, Warner-Chilcott Laboratories, Morristown, N. J.