THE PATHOGENESIS OF PULMONARY EDEMA INDUCED BY SILVER NITRATE

COMMUNICATION I. THE REASON FOR CIRCULATORY DISTURBANCES IN PULMONARY EDEMA

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Numerous clinical and laboratory observations have shown that pulmonary edema is usually associated with grave circulatory disorders.

In many kinds of toxic pulmonary edema, there is nothing to explain the circulatory disturbances or their relation to the cause of the edema. As an example, we may consider pulmonary edema induced by adrenalin [10,11, 12, 14], ammonium chloride [8, 13], silver nitrate [4,5], and alloxan [7, 9].

In the present investigation, an attempt has been made to find the reason for the circulatory disturbances occurring in pulmonary edema induced by silver nitrate.

METHOD

Adult dogs of both sexes were used. After being fixed to a vivisection table for 30-40 minutes, all the animals received a subcutaneous injection of 0.01 g/kg of morphine hydrochloride. A 0.4% aqueous solution of silver nitrate was freshly prepared for the experiment, and 3.2 mg/kg were injected intravenously.

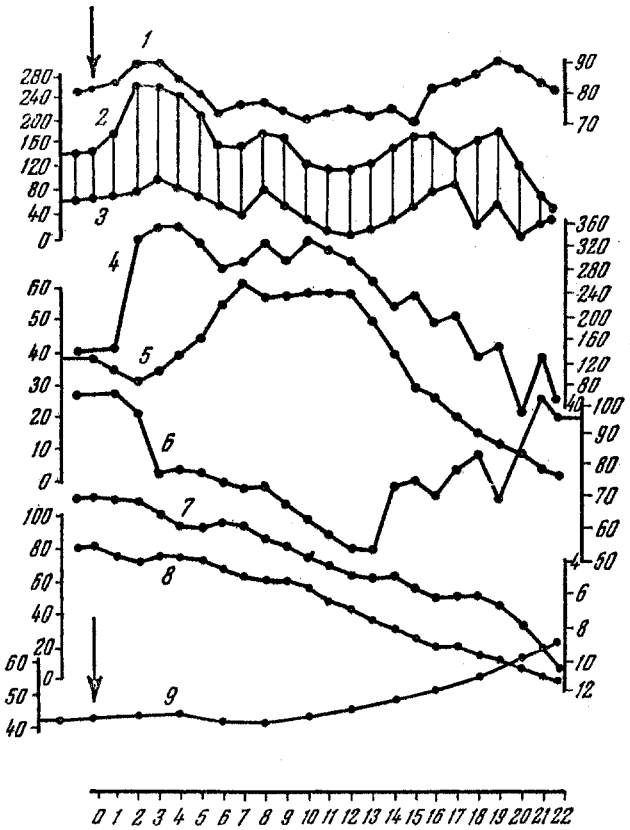
The arterial pressure, the pressure in the right ventricle or pulmonary artery as obtained by a catheter, and the respiration, were recorded on a kymograph. In addition, measurements of the pressure in the inferior vena cava were made (by catheterization) and of the arterial oxygen saturation as determined by a photoelectric oxyhemoglobinometer.

In some experiments, additional recordings of the pressure in the left atrium were made after opening the thorax and introducing a cannula into the auricular appendage. In some of the dogs, erythrocyte volume was measured with a hematocrit.

After the animals had died, a macroscopic and microscopic examination of the viscera was made. Measurements were made of the ratio of the lung weight of the body and heart, as well as of the ratio of the weight of the dry residue to that of the moist pulmonary tissue. In all, 24 experiments were carried out on 24 dogs. To establish normal weight indices, the corresponding measurements were made on 7 control animals, killed by an electric current.

RESULTS

After the injection of silver nitrate, all the animals died within 11-30 minutes, with clear signs of pulmo-



Change of certain hemodynamic and other indices in response to injection of silver nitrate (arrow shows moment of injection). Curves, from above downwards: 1) pressure in inferior vena cava in mm of water; 2-3) pressure in right ventricle, in mm water (systolic and diastolic); 4) pressure in pulmonary artery in mm water; 5) respiration rate, per minute; 6) pressure in left auricle in mm water; 7) pressure in common carotid artery in mm mercury; 8) percentage oxygen saturation of arterial blood, arbitrary units (an increase in the number denotes a reduction in the percentage saturation); 9) erythrocyte volume (hematocrit number).

nary edema. After 1-2 minutes from the beginning of the injection, serious circulatory disturbances occurred, as well as changes in many of the other indices measured.

The figure shows graphically the average values for each recorded quantity. The results of all the experiments are referred to a single time scale which represents the average survival time.

It can be seen from the figure that after the injection, there was a marked increase of pressure in the pulmonary artery. Equally sudden was the fall in pressure in the left auricle. The great reduction in the oxygen saturation of the arterial blood, the increase in respiration rate, and the thickening of the blood (as indicated by the hematocrit number) all of which signs indicate the developments of edema, occurred somewhat later.

Postmortem and microscopical examination showed that in all cases there was a severe pulmonary edema and hyperemia.

Table 1 shows the average values of figures for the weight changes in the lungs.

From the results obtained it can be seen that the pulmonary edema following the intravenous injection of silver nitrate is associated with severe circulatory disorders.

Four basic mechanisms may be concerned in their development: a) the circulatory disturbance may developed as a result of left ventricular failure; b) it may result from the edema (pressure on the pulmonary vessels by the accumulation of exudate); c) silver nitrate alters the physical properties of the blood, and may produce clots within the vessels [2, 5, 6]; possibly therefore, the chief cause of the pulmonary congestion is the formation of emboli in the branches of the pulmonary artery; d) finally, it may be that the circulatory disturbance is due to spasm of the pulmonary vessels. Thus, it is known that solutions of silver nitrate may constrict the vessels of isolated organs [3] and the mesenteric vessels of the frog [1].

We have excluded left ventricular failure as a cause, because of the low pressure in the left auricle. A reduced output from the left ventricle with increased work by the right (see figure) is scarcely possible without a raised pressure in the left auricle. In our experiments, on the contrary, after injecting the silver nitrate solution the pressure in the left auricle was reduced.

Circulatory disturbances could not be brought about by the edema which develops, because they occur too rapidly after the injection. In most experiments, even one minute after the beginning of the injection, there has been a considerable increase in pressure in the pulmonary artery (see figure), and sometimes the effect occurs after only 12-15 seconds. It is hard to imagine that by this time the edema could have developed sufficiently for the accumulated exudate to cause any appreciable pressure on the pulmonary vessels.

Secondly, at the time of the maximum pressure increase in the pulmonary artery, the frequency of

TABLE

Ratio of Lung Weight to Body and Heart Weight, and Ratio of Dried Lung Residue to Raw Lung Weight

Animal	Number of animals	Ratio of lung weight, in g to body weight, in kg (M ± m)	Ratio of lung weight to heart weight, in g (M ± m)	Dried lung residue as % of weight of raw tissue (M ± m)
Experiment	20*	38,55±1,60	4,68±0,25	13,40±0,35
Control	7	9,35±0,83	0,96±0,05	20,10±20,41

* Four experiments in which artificial respiration was used are not included.

respiration, oxygen saturation of arterial blood, and hematocrit number, all of which indicate the extent of the edema, have not yet shown any appreciable change (see figure).

A. M. Kotovshikov [5] considered the possibility of the pressure in the pulmonary artery being raised after silver nitrate injections, through the action of a large number of embolisms in the pulmonary circulation containing dense masses of changed blood. He concluded that the possibility of embolism formation depends on the amount of silver nitrate injected. With comparatively large doses, clots of coagulated blood could be observed under the microscope, and he thought that these could give rise to embolisms . He found no such clots with small doses.

The amounts of silver nitrate which we used for producing pulmonary edema corresponded approximately to those which did not cause blood changes in A. M. Kotovshikov's experiment, and were considerably smaller than those which caused blood changes which could be observed microscopically. Also, after the intravenous injection, microscopical examination revealed no trace of metabolisms.

From what has been described, it may be supposed that embolisms of the pulmonary circulation are not the cause of the profound circulatory disturbances observed. However, these could be fully accounted for by spasm of the pulmonary vessels.

In our opinion, spasm of the pulmonary vessels is the principal cause of the circulatory disturbance resulting from intravenous injection of silver nitrate in dogs.

SUMMARY

Experiments were performed on dogs in which silver nitrate solution was injected intravenously to induce acute pulmonary edema. Recordings were made of arterial and venous pressure, pressure in the left auricle and pulmonary artery, respiration, arterial blood oxygen saturation, and hematocrit ratio. Postmortem determinations were made of lung weight, ratio of body to heart weight, and ratio of dried to raw lung tissue.

The pulmonary edema which developed was accompanied by acute circulatory disturbances; these were not the direct effect of the edema, nor did they result from the denaturing effect of silver nitrate on the blood, nor from left ventricular failure. It was thought that the circulatory disorders resulted from spasm of the pulmonary vessels.

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