Paroxysmal Pulmonary Edema Induced by Intravenous Chloroform.* (25744)

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During other investigations(1), a new method was developed for the production of paroxysmal pulmonary edema in rabbits. This method, consisting of intravenous injection of chloroform, is also effective in dogs. Chloroform has direct depressant effect on the myocardium. This basic observation of MacWilliam(2) was confirmed and extended by others, and extensively reinvestigated by Orth *et al.*(3). The extensive literature on chloroform is summarized in 3 reviews(4,5,6), which deal with history, physiology, and pharmacology of this drug.

Method. Thirty male albino rabbits weighing about 2 kg each and 11 male mongrel dogs weighing 14 and 18 kg were used. The method was based on slow intravenous administration of chloroform in intact unanesthetized animals, properly restrained. In the rabbit, the marginal ear vein was used; in dog the saphenous vein. Preliminary investigations, concerned with speed of administration and effective dosage, demonstrated that best results would be obtained by slow (60-120 min) intravenous injection of 0.1 cc/kg using a graduated Luer-Lock syringe. Larger doses or faster injections cause rapid death in most animals without formation of edema. Smaller doses gave variable results. In some experiments, saline solution (approximately 100 cc/kg) was injected by rapid (less than 5 min) or slow (more than 30 min) infusion, to overload the circulation. This was done either before, during, or after injection of chloroform. This technic, however, did not result in more severe pulmonary edema than chloroform alone. ECG was recorded throughout each experiment using bipolar limb leads, augmented "unipolar" limb leads, and 2 precordial leads (V_4R and V_4). Standardization was 1 MV = 1.5 cm (Fig. 1 and 2). Animals which did not die spontaneously were sacrificed 60 minutes after injection of chloroform, to examine the lungs. Evaluation of pulmonary edema was based on determination of lung-body (L/B) index (weight of lung in g divided by total body weight in g times 100). Average normal value of L/B index is approximately 0.50 in the rabbit and between 0.7 and 0.8 in the dog. An index higher than 1 in either species is evidence of pulmonary edema(1).

Results. Results are summarized in Table I. Average survival time was very close in the 2 species, *i.e.*, about one-half hour. However, 6 out of 11 dogs survived one hour, while only 7 out of 25 rabbits survived one hour.

Immediate response to injection of chloroform was characterized by short period of excitement and struggle, followed by transitory vagal effect on heart and respiration, *i.e.*, bradycardia and bradypnea. No evident anesthetic effect was observed with this dose, but animals appeared depressed and, with few exceptions, remained still. Then, respiration became shallow and labored, and tachycardia occurred. Representative electrocardiograms are presented in Fig. 1 and 2. Terminal pulmonary edema was characterized by appearance of bloody foam from mouth and nostrils, followed by a few gasping respirations, one or 2 generalized convulsions, and death.

At post mortem, essential findings were in lungs, which appeared markedly congested, with various amounts of foam in trachea and bronchi. Average lung-body index was 1.06 for rabbits and 1.33 for dogs. In 25 rabbits, liver-body index was also determined. Normally this index varies between 3.5 and 4.5 as

TABLE I. Results of Chloroform.

Species	No.	Avg survival time, min.	No. surviving at 60 min.	Avg lung/body index	Avg liver/body index
Rabbits	25	32	7	1.06	4.69
Dogs	11	37.5	5	1.33	

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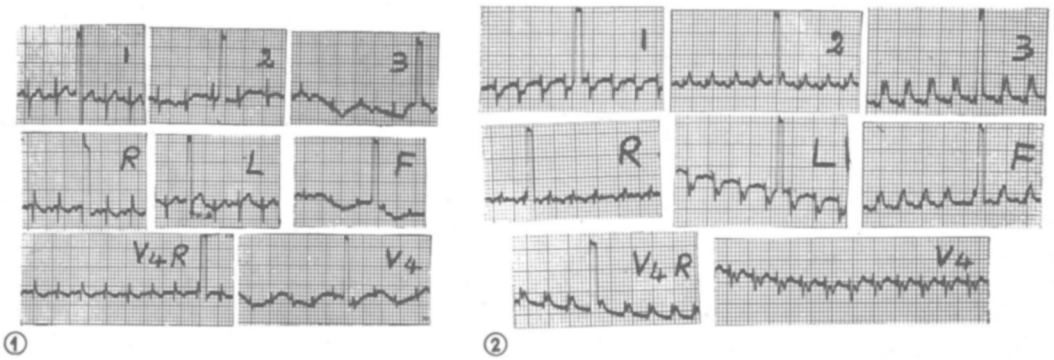

FIG. 1. Normal electrocardiogram in a rabbit. The extremity leads (1, 2, 3, R, L, F) and 2 precordial leads (V_4R and V_4) are recorded. Standardization is 1 MV = 1.5 cm.

FIG. 2. Same rabbit as in Fig. 1. Electrocardiogram taken 19 min. after intrav. inj. of 0.1 cc/kg of chloroform, showing a pattern of "acute cor pulmonale."

ascertained by previous determinations. An index higher than 4.5 is interpreted as evidence of congestion of liver, and this occurred in all animals. The heart stopped in diastole but appeared normal, except for deep cyanotic hue. Large clots were present in cardiac chambers. Serial sections in 2 rabbits failed to reveal microscopic alterations. Other organs appeared normal.

Intracardiac pressure tracings in dogs revealed gradual decrease of systolic pressures either in both ventricles or only in the left. Later, end-diastolic pressure of both ventricles and mean pressure of left atrium rose. In final stage of most experiments, left ventricular systolic pressure further decreased while that of the right either remained at the same level or rose slightly. Left atrial pressure showed a gradual rise, attaining levels of from 20 to 26 mm Hg (Table II).

The authors believe that pulmonary edema was caused by depressing action of chloroform on myocardium, as demonstrated by Orth *et al.*(6) both in isolated hearts and in intact animals. The results indicate that, by using slow intravenous injections, the primary vagal effect of the drug is minimized and its direct depressing effect on the heart is increased. In final stage, left ventricular depression is greater than the right, pressure in pulmonary capillaries becomes greater than the colloid osmotic pressure of the blood and transudation into the alveoli results.

TABLE II. Intracardiac Pressures (mm Hg) Following I.V. Chloroform in a Dog.

Min. after inj.	0	15	30	45
LV	90/5	70/7	60/8	50/10
LA (mean)	8	10	12	22
RV	20/4.5	22/8	18/8	30/12

Summary. 1) A method for production of acute pulmonary edema in unanesthetized rabbits and dogs, consisting of slow (60-120 min) intravenous injection of chloroform (0.1 cc/kg) is presented. 2) Pulmonary edema, as determined by lung-body (L/B) index, occurred in all animals and was accompanied by congestion of liver. 3) Measurements of intracardiac pressures suggest that pulmonary edema is due to relatively greater drop in left than in right ventricular pressure, causing increased pressure in capillaries of lung. 4) Results are believed due to direct depressant effect of chloroform on the myocardium.

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